Clinical Study Protocol

A Phase I/II, Multicenter, Open-Label, Single-Dose, Dose-Ranging Study to Assess the Safety and Tolerability of ST-920, an AAV2/6 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.
7000 Marina Blvd.
Brisbane, CA 94005
(628) 252-7545

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7000 Marina Blvd.
Brisbane, CA 94005
+1 628 252 7545

Medical Monitor: Cristobal Passalacqua, M.D.
Phone: +1 917 322 9524
CPassalacqua@sangamo.com

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Amendment 6: February 11, 2021

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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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DocuSigned by Cristobal Passalacqua
Cristobal Passalacqua | I approve this document 6/8/2022 | 08:11 PDT
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6/8/2022 | 08:45 PDT

Cristobal Passalacqua, M.D.
Medical Monitor
Senior Medical Director, Clinical Sciences
Sangamo Therapeutics, Inc.

Date

DocuSigned by Bettina Cockroft
Bettina Cockroft | I approve this document 6/8/2022 | 10:48 PDT
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6/8/2022 | 10:48 PDT

Bettina Cockroft, M.D., M.B.A
Protocol Review Committee Chairperson
Senior Vice President & Chief Medical Officer
Sangamo Therapeutics, Inc.

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

α-Gal A	Alpha-galactosidase A
AAV	Adeno-associated virus
ACE	Angiotensin converting enzyme
AE	Adverse event
AFP	Alpha fetoprotein
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ApoE	Apolipoprotein E
ARB	Angiotensin receptor blocker
AST	Aspartate transaminase
BPI	Brief Pain Inventory
BSC	BioSafety Committee
CCoA	Clinical Certificate of Analysis
cDNA	Complementary deoxyribonucleic acid
CMR	Cardiovascular magnetic resonance
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
ddPCR	Droplet digital polymerase chain reaction
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
GC	Genome copy
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GLA	The gene Galactosidase alpha
GLAKO	*GLA* knockout
GLAKO/Gb3Stg	*GLA* knockout with overexpression of Gb3 synthase
GLP	Good laboratory practice
hAAT	Human α-1-antitrypsin
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HEENT	Head, eyes, ears, nose, and throat

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS (CONT.)

hGLA	Human *GLA*
HIV	Human immunodeficiency virus
IATA	International Air Transport Association
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IND	Investigational New Drug
IRB	Institutional review board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
LDH	Lactate dehydrogenase
LGE	Late gadolinium enhancement
LVH	Left ventricular hypertrophy
LVMI	Left ventricular mass index
Lyso-Gb3	Globotriaosylsphingosine
LTFU	Long-term follow-up
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MLHF-Q	Minnesota Living With Heart Failure Questionnaire
MPS	Mucopolysaccharidosis
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MSSI	Mainz Severity Score Index
NASH	Non-alcoholic steatohepatitis
NHP	Non-human primate
NIH	National Institutes of Health
NOAEL	No-observed-adverse-effect level
NT-proBNP	N-terminal pro-hormone B-type natriuretic peptide
NYHA	New York Heart Association
OHR	Office for Human Research
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction
PFT	Pulmonary function test
QOL	Quality of life
qPCR	Quantitative polymerase chain reaction
RNA	Ribonucleic acid
RSI	Reference safety information
SAE	Serious adverse event
SAP	Statistical analysis plan
Sf9/rBV	Sf9 insect cell/recombinant baculovirus
SFN	Small fiber neuropathy
SMC	Safety Monitoring Committee
ST-920PC	ST-920 parent construct

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS (CONT.)

SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
UACR	Urine albumin to creatinine ratio
ULN	Upper limit of normal
UPCR	Urine protein to creatinine ratio
vg	Vector genome
WHV	Woodchuck hepatitis virus
WPRE	Woodchuck hepatitis virus posttranscriptional regulatory element
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, an AAV2/6 Human Alpha Galactosidase A Gene Therapy in Subjects with Fabry Disease	
Sponsor	Sangamo Therapeutics, Inc.
Investigational Product	ST-920 is an adeno-associated virus (AAV) 2/6 vector that encodes a human alpha galactosidase A (α-Gal A; hGLA) cDNA.
Study Sites	Approximately 20 to 30 sites worldwide
Study Design	Multicenter, open-label, single dose, dose-ranging study
Study Rationale	Fabry disease is an X-linked lysosomal storage disease caused by mutations in the *GLA* gene, which encodes the lysosomal enzyme alpha galactosidase A (α-Gal A). Deficiency 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. Thus, there is a need for alternative therapies that address the unmet needs in Fabry disease. Gene therapy with AAV vectors has 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 at least eight years for hemophilia B.

<table>
<tr><td></td><td>The proposed study uses ST-920, a recombinant AAV2/6 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, and also to recombinant α-Gal A, an approved ERT. The ST-920 construct encodes a liver-specific promoter, the human α-1-antitrypsin (hAAT) promoter and includes liver-specific regulatory elements. In addition, AAV2/6 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 AAV2/6 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 which may be associated with biweekly ERT. The goal of ST-920 is to provide stable, long-term production of α-Gal A at therapeutic levels in patients with Fabry disease. Importantly, the constant production of α-Gal A in humans should enable reduction and potentially clearance of Fabry disease substrates Gb3 and lyso-Gb3.</td></tr>
<tr><td>Objectives and Endpoints</td><td>
<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td colspan="2">Primary</td></tr>
<tr><td>• To assess safety and tolerability of ST-920</td><td>• Incidence of treatment-emergent adverse events (TEAEs)
Additional safety evaluations will include:
o Routine hematology, chemistry, and liver tests, vital signs, electrocardiogram (ECG) and echocardiogram (ECHO)
o Serial alpha fetoprotein (AFP) testing and magnetic resonance imaging (MRI) of liver (or equivalent imaging modality) to monitor for liver mass</td></tr>
<tr><td colspan="2">Secondary</td></tr>
<tr><td>• To assess α-Gal A activity and the presence of its substrates in plasma over time</td><td>• Change from baseline at specific time points over the 1-year study period in:
o α-Gal A activity in plasma
o Gb3 and lyso-Gb3 levels in plasma</td></tr>
<tr><td>• To assess impact of ST-920 on ERT administration required for subjects on ERT</td><td>• Change from baseline at specific time points over the 1-year study period in:
o Frequency of ERT infusion</td></tr>
<tr><td>• To assess the impact of ST-920 on renal function</td><td>• Change from baseline at specific time points over the 1-year study period in:
o Estimated glomerular filtration rate (eGFR) using the CKD-EPI formula</td></tr>
<tr><td>• To assess the impact of ST-920 on cardiac function and left ventricular hypertrophy</td><td>• Change from baseline at specific time points over the 1-year study period in:
o Ejection fraction, global longitudinal strain, left ventricular mass index (LVMI), left ventricular systolic function measured by cardiac magnetic resonance imaging (CMR)</td></tr>
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	• To evaluate ST-920 vector DNA shedding over time	• ST-920 vector clearance measured by level of vector genome in blood (plasma), saliva, urine, stool, and semen (if applicable)
	Exploratory	
	• To assess clinical impact of ST-920 on Fabry disease	• Change from baseline at specific time points over the 1-year study period in: o Late gadolinium enhancement (LGE), native myocardial T1 values and T2 mapping measured by cardiac MRI (CMR) o High sensitivity troponin T, N-terminal pro-hormone B type natriuretic peptide (NT-proBNP) and other cardiac biomarkers o Minnesota Living With Heart Failure Questionnaire (MLHF-Q) summary score o Urine protein to creatinine ratio (UPCR) and urine albumin to creatinine ratio (UACR) 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 o Pulmonary function o Audiologic function
	• To assess α-Gal A activity over time in skin	• Change from baseline at specific time points over the 1-year study period in: o α-Gal A activity measured in skin
	• To assess the presence of Gb3 inclusion levels in skin in ERT-naïve and ERT-pseudo-naïve subjects (defined as not having received ERT treatment during the 6 months prior to baseline) and selected subjects previously on migalastat	• Change from baseline at specific time points over the 1-year study period in: o Gb3 inclusion levels measured in skin in ERT-naïve and ERT-pseudo-naïve subjects and selected subjects previously on migalastat
	• To assess the presence of α-Gal A substrates in urine for all subjects over time	• Change from baseline at specific time points over the 1-year study period in: o Gb3 and lyso-Gb3 levels in urine for all subjects over time

	• To assess immune response to AAV2/6	• Measurement of antibodies to AAV2/6 • Assessment of cell-mediated immune response to AAV2/6
	• To assess immune response to α-Gal A	• Measurement of immune response to α-Gal A
	• To assess the impact of ST-920 on Gb3 inclusion in the kidney (via kidney biopsy) in ERT-naïve and ERT-pseudo-naïve subjects and selected subjects previously on migalastat	• Percent reduction from baseline at Week 24: Gb3 inclusion in the kidney (assessed by kidney biopsy) in ERT-naïve and ERT-pseudo-naïve subjects and selected subjects previously on migalastat
Study Population	Adult male and female subjects who are ≥ 18 years of age with a documented diagnosis of Fabry disease based on the established criteria for Fabry disease.	
Number of Subjects	Up to 48 subjects will be enrolled in this study.	
Inclusion & Exclusion Criteria	**Inclusion Criteria** 1. ≥18 years of age 2. Signed, written informed consent 3. Diagnosis of Fabry disease 4. One or more of the following symptoms: i) cornea verticillata, ii) acroparesthesia, iii) anhidrosis, iv) angiokeratoma 5. Subjects who are on ERT or are ERT-naïve or are ERT-pseudo-naïve (defined as not having received ERT treatment during the 6 months prior to baseline). For subjects receiving ERT, ERT must have been administered at a stable dose and regimen for at least 6 months (defined as not having missed more than 3 doses of ERT during the 6 months prior to consent). 6. Subjects on migalastat (Galafold™) must agree to withdraw migalastat prior to Baseline and, if non-responder to migalastat (based on clinical and/or biochemical assessments), undergo an incisional skin biopsy and kidney biopsy. 7. Male subjects must 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. 8. Female subjects must refrain from egg donation from the time of ST-920 administration until all the samples are negative for AAV2/6 after administration of ST-920. 9. Subjects must agree to use a highly effective form of contraception from the time of ST-920 administration until a minimum of 90 days after ST-920 administration and, for male subjects, a minimum of 3 consecutive semen samples are negative for AAV2/6 after administration of ST-920. Highly effective birth control methods include: a. a documented vasectomy or permanent sterilization	

	b. condom c. combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal or transdermal) d. progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable) e. intrauterine device (IUD) f. intrauterine hormone-releasing system (IUS) g. sexual abstinence is acceptable only as true abstinence and when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception 10. Subject must be fully vaccinated (as per the Centers for Disease Control and Prevention (CDC) definition in the US and as per local guidelines in other countries) for COVID-19 at least one month prior to dosing Additional inclusion criteria for: Cohorts 1-4b: 11. Male subjects with classical Fabry disease as defined by < 5% α-Gal A activity in either plasma or leukocytes. a. For male subjects who do not have documented diagnostic α-Gal A activity, a blood sample will be taken to measure α-Gal A activity (in plasma). For subjects who are on ERT, this blood draw must be taken at least 13 days after their last ERT infusion (trough). b. If the subject's α-Gal A activity is > 5% and the subject is on ERT, this level of enzyme activity may be due to residual α-Gal A activity from the last ERT infusion. In this case, the diagnosis of classical Fabry disease may be confirmed if the following three criteria are fulfilled: i. two or more documented symptomatic characteristics outlined in inclusion criterion #4. If there is documented clustered periumbilical angiokeratoma, this symptom alone is sufficient as it is a pathognomonic sign of classical Fabry disease; ii. a mutation that is indicative of classical Fabry (i.e. listed in a database, such as http://dbfgp.org); and iii. the α-Gal A activity at trough is below the lower limit of the normal range of the assay. Female cohort: 12. Female subjects with a documented mutation that is indicative of classical Fabry (i.e., listed in a database, such as http://dbfgp.org) and treatment (ERT and/or migalastat) is clinically indicated Renal and Cardiac cohorts: 13. Symptomatic Fabry disease defined for male subjects by <30% α-Gal A activity in either plasma or leukocytes and for female subjects based on genetic test results consistent with Fabry pathogenic mutation, or in the case of novel mutations a first-degree male family member with Fabry disease with the same mutation AND Renal cohort: 14. Screening eGFR value between 40-90 mL/min/1.73 m²

15. Linear negative eGFR slope (estimated from at least 3 serum creatinine values within 18 months, including the value obtained during screening visit) of ≥ 2 mL/min/1.73 m²/year

Cardiac cohort:

16. Left ventricular hypertrophy (LVH) in 2D echocardiography or CMR defined as an end diastolic septum and posterior wall thickness ≥12 mm with no other explanation for LVH, OR presentation with cardiac changes indicative of disease progression such as decreased global longitudinal strain on 2D strain echocardiography or low native T1 mapping on CMR

Exclusion Criteria

1. Positive neutralizing antibodies to AAV6
2. Intercurrent illness expected to impair evaluation of safety or efficacy during the observation period of the study
3. eGFR <40 mL/min/1.73m^2
4. Active infection with hepatitis A virus (HAV ribonucleic acid [RNA] positive), active or occult hepatitis B virus infection (positive HBV-DNA or anti-HBc positive), active infection with hepatitis C virus (HCV RNA positive), infection with the human immunodeficiency virus (HIV) as measured by quantitative polymerase chain reaction (qPCR), or active or latent infection with tuberculosis (TB) measured by quantiferon test
5. Breastfeeding at screening or breastfeeding during required period of contraception
6. History of liver disease such as clinically significant steatosis, fibrosis, non-alcoholic steatohepatitis (NASH) and cirrhosis, biliary disease within 6 months of informed consent; except for Gilbert's syndrome
7. Elevated circulating serum AFP
8. For subjects receiving ERT, recent or recurrent hypersensitivity reaction manifested by significant infusion reaction to ERT treatment within 6 months prior to consent
9. One or more of the following:
    a. Albumin ≤ 3.5 g/dL
    b. Total bilirubin > upper limit of normal (ULN) and direct bilirubin ≥ 0.5 mg/dL
    c. Alkaline phosphatase (ALP) > 2.0 x ULN
    d. Alanine aminotransferase (ALT) > 1.5 x ULN
10. Current or history of systemic IV or oral immunomodulatory agents, or biologics or steroid use in the past 6 months prior to consent (topical and inhaled treatment are allowed, [e.g., for asthma or eczema]). Occasional use of systemic steroid may be allowed based on discussion and agreement with the Medical Monitor.
11. Contraindication to use of corticosteroids
12. History of malignancy, except for non-melanoma skin cancer and localized prostate cancer treated with curative intent
13. Recent history of alcohol or substance abuse. The use of marijuana may be considered on an individual basis with discussion and agreement from the Medical Monitor.
14. Participation in investigational interventional drug or medical device study throughout the duration of this study and within the last 3 months prior to consent (with the exception of implantable loop recorders as in the RaILRoAD trial)
15. Prior treatment with a gene therapy product

	16. Known hypersensitivity to components of ST-920 formulation 17. Any other reason that, in the opinion of the Site Investigator or Medical Monitor, would render the subject unsuitable for participation in the study, including but not limited to risk of COVID-19 infection Additional exclusion criteria for: Cohorts 1- 4, female and renal cohort: 18. Subjects who meet New York Heart Association (NYHA) Class III and IV Renal cohort: 19. History of renal dialysis or transplantation 20. History of acute kidney insufficiency in the 6 months prior to screening 21. Angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy initiated within 4 weeks prior to screening or changed ACE inhibitor or ARB dose in the 4 weeks prior to screening 22. Urine protein to creatinine ratio (UPCR) > 0.5 g/g who are not being treated with an ACE inhibitor or ARB Cardiac cohort: 23. Significant cardiac fibrosis defined as having more than 3 segments full thickness of late gadolinium enhancement on CMR 24. Any contraindications to CMR as per local hospital/institution guidelines 25. Angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy initiated within 4 weeks prior to screening or changed ACE inhibitor or ARB dose in the 4 weeks prior to screening 26. NHYA Class IV
Concomitant Medications	All medications are permitted with limited exceptions. The use of potentially hepatotoxic agents including herbal supplements may be allowed based on discussion and agreement with the Medical Monitor. For subjects receiving ERT, ERT must have been administered at a stable dose and regimen (defined as not having missed more than 3 doses of ERT during the 6 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. Subjects who are ERT-naïve or ERT pseudo-naïve (defined as not having received ERT treatment in the 6 months prior to baseline) may not initiate treatment with ERT during the study period, unless dictated by clinical circumstances and following discussion with the Sponsor Medical Monitor. Subjects may not initiate treatment with migalastat (Galafold™) during the study period.

Dose and Rationale for Dose Selection

The doses being evaluated were selected based on preclinical studies in mice and monkeys and cumulative safety data from ongoing Sangamo clinical studies that use the same AAV 2/6. Several dose levels may need to be studied to identify a safe and tolerable therapeutic dose. The dose levels for this dose escalation study are as noted in Table 1. Dose escalation to the next dose level will be decided by the Safety Monitoring Committee (SMC) upon review of safety data from the previous cohort. Other data derived from other Sangamo-sponsored clinical trials that use *in vivo* AAV2/6 based therapy may be considered as well, and based on the recommendation of the SMC, which will comprise external subject matter experts, the study Medical Monitor, Sponsor's Drug Safety Lead, and Site Investigators as appropriate (as described in the SMC charter).

From preclinical experiments with ST-920 in a mouse model of Fabry disease, it is anticipated that supraphysiological levels of enzymatic activity need to be achieved in the blood (at least 8 times the normal enzymatic activity), at steady state, in order to lead to a full reduction of substrate accumulation in the main target organs (kidneys and heart).

In addition, depending on the enzyme activity and safety data of the subjects dosed, the SMC may recommend a dose escalation to one of the doses listed in Table 1.

No dose given to subjects will exceed 5.00E+13 vg/kg (by qPCR) without a substantial amendment.

Table 1: Dose by Cohort

Cohort	AAV[1] Dose (vector genomes [vg]/kg) qPCR[2]
1	0.50E+13
2	1.00E+13 or 3.00E+13
3	3.00E+13 or 5.00E+13
4	5.00E+13

[1]AAV = adeno-associated virus, [2]quantitative PCR

A droplet digital PCR (ddPCR) test method is being developed to determine the level of vector genome (vg) titers for ST-920. The nominal genome copies (vg/mL) are not changing; a new method (ddPCR) to evaluate the nominal genome copies is being implemented and will replace the qPCR method. Once fully implemented, drug product released using the initial qPCR assay or the new ddPCR assay will be used in Study ST-920-201. See Section 7 for additional details.

Treatment Plan

Up to 48 subjects may be enrolled in this overall study. Initially, recruitment will be limited to male subjects meeting criteria for inclusion during dose escalation. Once a safe and tolerable dose is selected, recruitment will be extended via dose expansion to a broader patient population. Once cohort expansion is initiated, subjects will undergo assessments which will determine the most appropriate expansion cohort for their enrollment.

During dose escalation, treatment of the first 2 subjects will be staggered so that the second subject cannot be infused until the first subject has been observed for at least 2 weeks. After any 2 subjects in a cohort have been dosed, safety data from these 2 subjects will be reviewed by the SMC. Dose escalation to the next dose cohort and dose

	expansion cannot occur until at least 4 weeks of safety data are available after the second subject in the preceding cohort has been dosed, and safety data from this cohort has been reviewed by the SMC. The SMC will recommend whether it is safe to escalate the dose or add subjects to the dose cohort at the same dose level. Once a cohort's data has been reviewed and dose escalation has been endorsed, additional subjects may be infused at any time in the same cohort, as per protocol. Two male subjects with classical Fabry disease will be dosed in Cohort 1. Following the SMC recommendation to dose escalate to Cohort 2, which is subdivided into Cohort 2a (subjects who are antibody-positive to α-Gal A) and Cohort 2b (subjects who are antibody-negative to α-Gal A), 2 male subjects with classical Fabry disease will be dosed and safety data from these 2 subjects will be reviewed by the SMC. After SMC review, up to an additional 8 (4 subjects in Cohort 2a and 4 subjects in Cohort 2b) subjects may be recruited into Cohort 2 and if dose escalation is recommended, recruitment of subjects into Cohort 3 may commence. Dosing may continue in Cohort 2 until all 10 subjects have been dosed, unless it is concluded during the SMC review that it is more appropriate to dose in Cohort 3 rather than continuing dosing at the Cohort 2 dose level. Dosing in Cohort 3 and the remainder of Cohort 2 can be concurrent. Following the SMC recommendation to dose escalate to Cohort 3, which is subdivided into Cohort 3a (subjects who are antibody-positive to α-Gal A) and Cohort 3b (subjects who are antibody-negative to α-Gal A), 2 male subjects with classical Fabry disease will be dosed and safety data from these 2 subjects will be reviewed by the SMC. After SMC review, up to an additional 8 (4 subjects in Cohort 3a and 4 subjects in Cohort 3b) subjects may be recruited into Cohort 3 and if dose escalation is recommended, recruitment of subjects into Cohort 4 may commence. Dosing may continue in Cohort 3 until all 10 subjects have been dosed, unless it is concluded during the SMC review that it is more appropriate to dose in Cohort 4 rather than continuing dosing at the Cohort 3 dose level. Dosing in Cohort 4 and the remainder of Cohort 3 can be concurrent. Following the SMC recommendation to dose escalate to Cohort 4, which is subdivided into Cohort 4a (subjects who are antibody-positive to α-Gal A) and Cohort 4b (subjects who are antibody-negative to α-Gal A), 2 male subjects with classical Fabry disease will be dosed and safety data from these 2 subjects will be reviewed by the SMC. After SMC review, up to an additional 8 subjects may be recruited into Cohort 4. Dosing may continue in Cohort 4 until all 10 subjects have been dosed, unless it is concluded during the SMC review that it is more appropriate to select a dose for dose expansion. Dosing in dose expansion and the remainder of Cohorts 3 and/or 4 can be concurrent. The dose considered to be tolerable and safe will be utilized in the dose expansion cohorts. After dose escalation has been completed, dose expansion will commence where up to 6 subjects will be enrolled into each of the dose expansion cohorts, which include patients with classical Fabry disease who are antibody-positive to α-Gal A, patients with classical Fabry disease who are antibody-negative to α-Gal A, female patients (female cohort) and patients who meet criteria for the renal (renal cohort) and cardiac (cardiac cohort) inclusion and exclusion criteria. The dose for the expansion cohorts may be reassessed if there are emerging safety considerations.

	Anti α-Gal A Ab positive cohort: Up to 6 male subjects with classical Fabry disease who are antibody-positive to α-Gal A will be enrolled. **Anti α-Gal A Ab negative cohort**: Up to 6 male subjects with classical Fabry disease who are antibody-negative to α-Gal A will be enrolled. **Female cohort:** Up to 6 female subjects with classical Fabry disease will be enrolled. **Renal cohort:** Up to 6 male or female subjects with symptomatic Fabry disease with a linear negative eGFR slope (estimated from at least 3 historical serum creatinine values [within 18 months, including the value obtained during screening visit]) of ≥ 2 mL/min/1.73 m²/year will be enrolled. **Cardiac cohort**: Up to 6 male or female subjects with symptomatic Fabry disease with cardiac involvement, defined as either LVH in 2D echocardiography or CMR (end diastolic septum and posterior wall thickness ≥ 12 mm) with no other explanation for LVH OR cardiac changes indicative of disease progression such as decreased global longitudinal strain on 2D strain echocardiography or low native T1 mapping on CMR will be enrolled. Subjects who have had a cardiovascular event in the 6-month period before screening may be excluded at the discretion of the Investigator. For all dose escalation and dose expansion cohorts, subjects who received ERT prior to study participation will continue to receive ERT during the study and remain on their current dose and regimen per standard of care unless they undergo ERT withdrawal. For subjects on ERT, baseline testing of enzyme and substrate levels will be coordinated such that samples will be taken on 2 separate occasions in the morning at trough, defined as 14 days (± 1 day) after the previous ERT infusion. An additional time point will have been taken previously during the screening period, so as to have 3 time points to assess the residual activity of α-Gal A at trough prior to the gene therapy administration. These 3 samples must be taken at trough, and preferably at the same time during the day (e.g. in the morning) to minimize the impact of non-specific factors on enzyme activity. Based on Sangamo's prior clinical experience with the AAV2/6 vector, an ALT elevation (suggestive of an immune reaction to the viral capsid) may be observed. Subjects will be closely monitored for ALT elevation throughout the study and the protocol-defined treatment (or treatment at the discretion of the Investigator and agreed upon with the Medical Monitor) with corticosteroids may be initiated in response. Dose selection and guidance are provided in Appendix 3 of the protocol. ST-920 will be administered via IV infusion while the subject is in the healthcare facility, where the subject will remain for observation for at least 24 hours after completion of the ST-920 infusion. During infusion, only light foods such as jello or apple sauce or liquids may be consumed. The subject will be discharged when all vital signs are stable and any adverse events (AEs) have resolved or the subject is considered stabilized as per Investigator judgment. 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. The 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 tests will be assessed twice weekly during the first 20 weeks after ST-920 infusion, then weekly for four weeks (Weeks 21-24), and monthly thereafter to coincide with study visits (Weeks 28-52). Liver tests may be conducted remotely and analyzed locally or centrally. Blood samples for liver tests will be drawn 2-4 days apart when possible. For the first week they will be drawn on Day 2 and 2-4 days later. Day 8 visit will be the first Week 2 blood draw. If there is a need to initiate treatment with corticosteroids because of elevated ALT, liver enzymes will continue to be assessed at least twice a week until normalization and then per protocol thereafter analyzed locally or centrally.
Dose Escalation	For the first 2 subjects in each cohort, treatment will be staggered so that each subsequent subject will not be infused until the preceding subject has been observed for at least 2 weeks. After the first 2 subjects, the subsequent subjects in the same dose cohort can be infused at any time if the safety data from the first 2 subjects is deemed satisfactory by the SMC. A decision to dose escalate to the next dose level will not occur until at least 4 weeks after the 2 subjects in the preceding cohort have been dosed and the safety data from the 2 subjects in the prior cohort has been reviewed by the SMC. Dosing and dose escalation will be paused if any of the stopping rules are met. In such an event, the SMC will be convened 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.
Dose Expansion	The dose deemed to be tolerable and safe will be utilized in the expansion cohorts.
ERT Withdrawal	The ultimate goal of ST-920 treatment is to abrogate the need for ERT by using an 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 activity of α-Gal A and substrates (Gb3 and lyso-Gb3) compared to baseline. During dose escalation, 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: • Are ≥ 4 weeks post-administration of ST-920. • Are medically stable and can tolerate temporary discontinuation of ERT in the judgment of the Site Investigator. • Agree to increased safety monitoring and additional lab testing until ERT Withdrawal Follow-Up visit (Appendix 2).

	Initiation of the dose expansion phase of the study assumes that a safe and tolerable dose of ST-920 has been achieved. At this point, ERT withdrawal will be implemented for all subjects who are in the expansion cohorts and have achieved supraphysiological (above normal range) plasma α-Gal A for 8 weeks ± 2 weeks, at the discretion of the investigator. ERT withdrawal assumes a complete stop in ERT administration rather than a "dose-down" or dose reduction. ERT does not need to be restarted after the ERT Withdrawal Follow-Up visit. However, ERT may be re-initiated at any time based on clinical circumstances or at the judgment of the Site Investigator. After ERT withdrawal, in order to assess whether a subject has received a suboptimal dose, evidence of a lack of response will be primarily based on α-Gal A activity and lyso-Gb3 substrate levels, which will be tested on a regular basis (refer to Appendix 2 for a full list of assessments and schedule of events). Plasma α-Gal A activity below the normal range, or plasma lyso-Gb3 levels, will be part of the criteria used by the Site Investigators to determine lack of response (and need for reinstitution of ERT).
Study Duration	The duration of study participation will be up to 84 weeks for each subject divided into up to 8 weeks for screening, up to 24 weeks for baseline, and 52 weeks follow-up after dosing. Accrual is planned for 48 months. Subjects will be encouraged to participate in an additional separate long-term follow-up study (of 4 years) for a total of at least 5 years from infusion.
Safety Monitoring Committee & Stopping Rules	An SMC with appropriate medical and scientific expertise was appointed to provide safety oversight for the study. The SMC is comprised of external subject matter experts, the study Medical Monitor, Sponsor's Drug Safety Lead, Study Biostatistician, and Site Investigators as appropriate. The SMC will periodically meet during the study and provide recommendations to the Sponsor concerning dosing. The SMC will also convene at any time if an emergent safety issue emerges during the study or one of the stopping rules are met. These include: • 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, with the exception of non-melanoma skin cancers and localized prostate cancer treated with curative intent 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, ST-920. All data will be evaluated to determine whether changes should be made to the study or if accrual should be continued or halted. 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. Relevant data from other trials sponsored by Sangamo may be shared with the SMC to expand the clinical experience, particularly as it relates to safety and dose, and such data can be used by the SMC to inform its recommendations for the present study. The SMC may also recommend changes to the dose and enrollment of cohorts based on cumulative safety data from this and other Sangamo sponsored clinical trials that use *in vivo* AAV2/6 based therapy. When no further enrolling or dosing decisions are required of the SMC, the SMC will no longer meet on a regular basis. The Sponsor will continue to review the subject safety data on an ongoing basis.
Safety Monitoring and Mitigation Plan	Elevation of liver enzymes has been observed in other trials using AAV 2/6. Therefore, liver tests (aspartate transaminase [AST], alanine transaminase [ALT], bilirubin, alkaline phosphatase [ALP], and gamma-glutamyl transferase [GGT]) will be monitored closely throughout the study. These will be performed twice weekly during the first 20 weeks after ST-920 infusion, weekly for four weeks (Weeks 21-24), and then monthly thereafter to coincide with study visits (Weeks 28-52) in all subjects, and may be conducted remotely. If there is a need to initiate corticosteroid treatment as a result of elevated liver enzymes, liver enzymes will continue to be assessed at least twice a week until normalization and then per protocol thereafter analyzed locally or centrally.
Sample Size	This is a Phase I/II dose-escalation study with up to 48 subjects. 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 52 weeks 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	The primary objective of this study is to evaluate the safety and tolerability of ST-920. All statistical summaries will be descriptive in nature. All subjects who receive any portion of the ST-920 infusion will be included in the analyses. All analyses, summaries, and listing will be generated using SAS version 9.4 or later. Further analysis details will be provided in the statistical analysis plan (SAP). **Primary Safety Analyses** TEAEs will be summarized overall and by dose and cohort. For each subject, the maximum reported severity of each AE will be used in the summaries by severity grade. In addition, summaries of all SAEs and AEs related to study treatment will be provided. For other safety evaluations, 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.

Secondary Analyses

At each sampling time point, the actual value and the change from baseline for α-Gal A, Gb3 and lyso-Gb3, eGFR, ejection fraction, global longitudinal strain, LVMI and left ventricular systolic function will be summarized by dose and cohort using descriptive statistics and plotted over the 1-year study period by dose and cohort. Similar summaries will also be provided for ERT naïve/ERT pseudo-naïve subjects, and separately for ERT subjects (migalastat subjects will be grouped with either the ERT naïve/ERT pseudo-naïve subjects, or with the ERT subject, based on the clinical response determined by the Investigator at Screening).

For subjects who undergo ERT withdrawal, changes from pre- to post- ERT withdrawal in the frequency and dose of ERT infusions will be evaluated and summarized using annualized total dose and number of infusions. Duration of ERT withdrawal may also be analyzed.

Clearance of ST-920 measured by vector genomes in the different samples (plasma, saliva, urine, stool, and semen, if applicable) will be summarized over time by dose and cohort.

Exploratory Analyses

Data permitting, the following exploratory endpoints and their change from baseline summaries by dose and cohort will be provided at each sampling time point over the 1-year study period:

- LGE, native myocardial T1 values and T2 mapping measured by CMR
- High-sensitivity troponin T, NT-proBNP and other cardiac biomarkers
- MLHF-Q summary score
- UPCR and UACR
- 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
- α-Gal A activity measured in skin
- Gb3 inclusion levels measured in skin in ERT-naïve and ERT-pseudo-naïve subjects and selected subjects previously on migalastat
- Gb3 and lyso-Gb3 levels in urine for all subjects over time
- Pulmonary function over time
- Audiologic function over time

Data permitting, summaries of percent reduction from baseline at Week 24 by dose and cohort will be provided for:

- Gb3 inclusion in the kidney (assessed by kidney biopsy) in ERT-naïve and ERT-pseudo-naïve subjects and selected subjects previously on migalastat

Summaries by dose and cohort will be provided for the following exploratory endpoints at each sampling time point:

- Measurement of antibodies to AAV2/6
- Assessment of cell-mediated immune response to AAV2/6
- Measurement of immune response to α-Gal A

1. INTRODUCTION

1.1 Fabry disease

Fabry disease is an X-linked lysosomal storage disease caused by mutations in the *GLA* gene, which encodes the lysosomal enzyme alpha galactosidase A (α-Gal A). Deficiency 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. 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 enzyme replacement therapy (ERT) using recombinant α-Gal A, 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 frequent 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. Thus, there is 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 and safely deliver therapeutic transgenes to the liver, with reports of stable levels of transgene expression at least out to eight years for hemophilia B (Nathwani et al. 2018; Muhuri et al. 2022).

The proposed study uses ST-920, a recombinant AAV2/6 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, and also to recombinant α-Gal A, an approved ERT. 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 which may be associated with biweekly ERT. 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. Importantly, the constant production of α-Gal A in humans should enable reduction and potentially clearance of Fabry disease substrates Gb3 and lyso-Gb3.

1.2 ST-920 Molecular Design and Construction

ST-920 consists of the ST-920 hGLA expression cassette (3321 bp) that includes liver-specific regulatory elements that drive expression of a hGLA transgene (Figure 1). The hGLA transgene is under the control of an enhancer and hepatic control region from the human apolipoprotein E (ApoE) gene and the human α-1-antitrypsin (hAAT) promoter. The ApoE enhancer and hAAT promoter are specifically and highly active in the liver, the intended target tissue, but inactive in non-liver cell and tissue types, thus preventing hGLA expression and activity in non-target tissues. A modified chimeric intron (HBB-IGG) has been added as this sequence has been shown to increase transgene expression. The hGLA transgene comprises a codon-optimized hGLA construct, including the native *GLA* signal peptide; the secreted α-Gal A has the same amino acid sequence as the native protein and an approved recombinant α-Gal A enzyme replacement therapy (agalsidase beta, Fabrazyme®)

ST-920 contains a mutated form of the woodchuck hepatitis virus (WHV) posttranscriptional regulatory element (WPREmut6). WPREmut6 is a 592-bp DNA sequence containing the promoter region of WHV X protein followed by a truncated form of the X protein itself (WPRE, Zufferey et al. 1999) with point mutations in the putative promoter region and start codon of the X protein open reading frame to prevent X protein expression (mut6, Zanta-Boussif et al. 2009). The poly A sequence is a derivative of the bovine growth hormone polyadenylation signal. The addition of the WPREmut6 element led to increased α-Gal A protein production. Indeed, greater potency was noted with ST-920 compared to ST-920 parent construct (ST-920PC, that lacks the WPREmut6 element).

The ST-920 AAV vector is packaged with capsid serotype AAV2/6 using a Sf9 insect cell / recombinant baculovirus (Sf9/rBV) expression system.

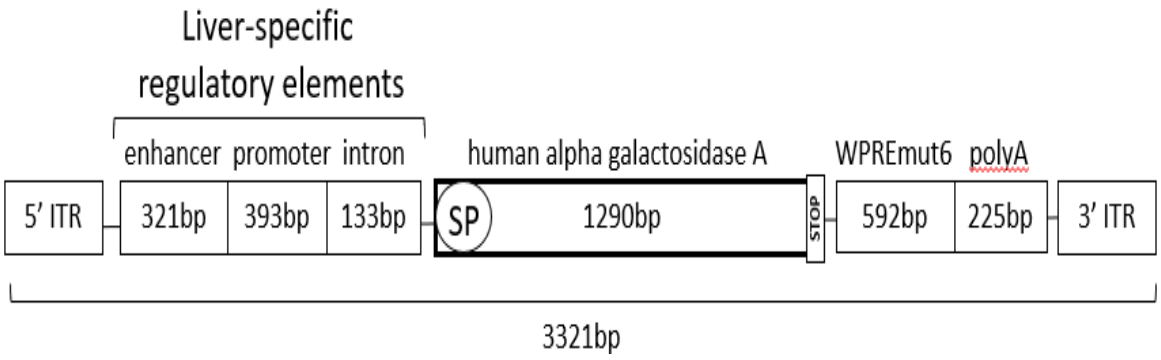


Figure 1: Schematic of the ST-920 hGLA AAV Cassette

Transcription of the human GLA transgene is driven from a liver-specific regulatory element consisting of an enhancer, promoter and intron. The enhancer is a derivative of the human ApoE gene enhancer and hepatic control region, the promoter is the human α-1-antitrypsin promoter, and the intron is the chimeric HBB-IGG intron. The WPREmut6 is derived from the promoter region and a truncated form of the woodchuck hepatitis virus X protein. The poly adenylation signal is derived from the bovine growth hormone polyA sequence. SP refers to the endogenous hGLA signal peptide. Sizes of the various elements are shown as is the entire size of the cassette (3321 bp).

1.3 Nonclinical Studies

The nonclinical evaluation included 3 *in vitro* and 10 *in vivo* studies. The *in vivo* studies were conducted as components of combination endpoint studies that included pharmacology, pharmacokinetics, AAV vector biodistribution and/or vector shedding, and toxicology. Mouse and cynomolgus monkey were selected as relevant species for evaluation. In addition, two mouse models of Fabry disease were used to assess potential changes on the biomarkers of the disease.

Some changes implemented during the nonclinical development were the:

1) introduction of ST-920 which harbors a WPREmut6 element in the cDNA but is otherwise identical to ST-920PC. Based on improvements in α-Gal A activity related to the WPREmut6 element, ST-920 was selected for clinical development.
2) use of Sf9 cells instead of HEK293 for manufacturing.

These changes were bridged *in vitro* and *in vivo* using head to head comparison studies.

Details of all studies are provided in the Investigator Brochure.

1.3.1 Pharmacology

1.3.1.1 *In Vitro* Pharmacology

The pharmacological activity of ST-920 and ST-920PC was evaluated *in vitro* using various mouse, cynomolgus monkey and human primary cell and cell lines system.

α-Gal A activity was measured in cell supernatant and hGLA messenger ribonucleic acid (mRNA) levels were assessed in cell pellets. ST-920 and ST-920PC were either produced in

HEK293 cells or in a Sf9 baculovirus cell system. Several doses were evaluated (up to multiplicities of infection of 2.00E+6 vg/cell).

Overall, dose-dependent, high levels of secreted and pharmacologically active α-Gal A were measured. α-Gal A cellular uptake via the mannose-6 -phosphate receptor pathway was confirmed. ST-920 had similar or higher activity when compared to ST-920PC (up to 2-fold more activity in cynomolgus primary hepatocytes, up to 4-fold more activity in human primary hepatocytes and 7-fold more activity in human HepG2 cells), supporting the selection of ST-920 for clinical development.

The observed lower potency in the Sf9/rBV material can likely be attributed to the differences in the VP1:VP2:VP3 capsid ratios for AAV produced in mammalian cells (such as HEK293) and insect cells (such as Sf9).

1.3.1.2 *In Vivo* Pharmacology Studies

1.3.1.2.1 Studies Conducted in 2 Mouse Models of Fabry Disease

Early nonclinical studies evaluated ST-920PC. The pharmacodynamic activity of ST-920PC was evaluated in 2 mouse models of Fabry disease including the GLA knockout (GLAKO) and GLAKO/Gb3Stg (GLA knockout with overexpression of Gb3 synthase) mouse models, due to similarities in natural history between these mice and the human disease. In both models, Gb3 and lyso-Gb3 (α-Gal A substrates) accumulate in plasma and organs/tissues. In addition, GLAKO/Gb3Stg mice display a renal phenotype similar to that seen in patients.

The mice received an IV dose administration of ST-920PC at levels ranging from 2.00E+11 to 5.00E+13 vg/kg. The animals were monitored for 2 to 3 months. Material was either produced in HEK293 cells or in a Sf9 insect cell/rBV expression system.

Overall, in both models, dose-dependent, sustained, supraphysiological levels of plasma human (h)GLA activity were measured. Supraphysiological levels of hGLA activity were also achieved in the liver, heart and kidney along with a reduction in the tissue levels of disease substrates, Gb3 and lyso-Gb3.

In GLAKO animals given 5.00E+13 vg/kg dose levels (Sf9 insect cells, comparable to clinical material), plasma hGLA activity was up to 700-fold the normal levels. Gb3 levels were generally reduced by 80% or more in the liver, heart and kidney compared to untreated animals.

However, in GLAKO/Gb3Stg that display a renal phenotype, this reduction in Gb3 did not lead to an improvement in pathology of this organ. Presumably, by the time of dosing (2 to 3 months of age), these animals had already developed severe kidney damage.

1.3.1.2.2 Studies Conducted in Wild Type Mice

Human α-Gal A enzyme expression/activity in plasma and liver was evaluated in five studies conducted in wild type (WT) mice.

Male and female C57BL/6 mice were given an IV dose administration of ST-920 or ST-920PC at levels ranging from 5.00E+11 to 1.50E+14 vg/kg. The animals were monitored for up to 90 days. The material was produced in HEK293 cells or Sf9/rBV insect cells.

In summary, hGLA protein was detected in liver of these mice via a human GLA-specific western blot. Dose-related supraphysiological levels of plasma α-Gal A activity (endogenous plus human α-Gal A activity) were measured by Day 7 and maintained to Day 90.

Consistent with *in vitro* data, plasma and liver α-Gal A levels were higher in animals administered ST-920PC manufactured in HEK293 cell versus Sf9 cell system (up to 21-fold higher).

In addition, the presence of the WPREmut6 element in ST-920 led to greater plasma and liver α-Gal A activity compared to ST-920PC. Animals administered ST-920 or ST-920PC at the 2.00E+12 vg/kg dose level had plasma α-Gal A levels up to 70- and 11-fold of normal, respectively. In these animals, liver α-Gal A activity was up to 35- and 8-fold that of normal, respectively.

ST-920 and ST-920PC pharmacological activity was evaluated in a head-to-head comparison study using Sf9/rBV material. Greater activity was noted with ST-920, up to 7-fold higher α-Gal A plasma and liver activity compared to ST-920PC at the 5.00E+13 vg/kg dose level.

In a Good Laboratory Practice (GLP) 3-month toxicology study, plasma α-Gal A activity increased in a dose-dependent manner in WT mice treated with ST-920 and remained stable over the 3-month study duration. The mean plasma α-Gal A activity was higher (~2- to 5-fold at the 1.50E+14 vg/kg dose) in male mice compared to female mice, which is consistent with lower vector genome copy levels in female mice. The lower level of AAV transduction in female mouse liver has been observed in previous Sangamo studies using AAV2/6 vectors and has been reported by others (Nietupski et al., 2011; Davidoff et al., 2003).

1.3.1.2.3 Study Conducted in Nonhuman Primates (Cynomolgus Monkeys)

A GLP 2-month pharmacology and toxicology study was conducted following administration of a single IV dose of ST-920PC at 6.00E+12, 1.00E+13, 3.00E+13, or 6.00E+13 vg/kg to male cynomolgus monkeys (n=3/group). To mitigate a possible immune response to ST-920PC and/or human GLA, animals received rituximab (10 mg/kg; IV) prior to study drug administration and methylprednisolone (10 mg/kg; intramuscular) daily throughout the study. An additional group received ST-920PC at the highest dose (6.00E+13 vg/kg) but no immunosuppression administration. The ST-920PC lot used in this study was manufactured in a GMP clinical manufacturing process using the Sf9/rBV cell platform comparable to the manufacturing process for the Phase I/II clinical study.

Circulating α-Gal A protein levels and plasma α-Gal A activity were generally detected by Day 7, with protein levels and activity peaking between Days 7 and 21, and no clear dose response. Animals administered ST-920PC without immunosuppression generally had lower

levels of α-Gal A protein and activity than animals administered ST-920PC with immunosuppression. The lack of clear dose response and rapid clearance of α-Gal A activity and protein levels is likely related to an immune reaction against human α-Gal A in the monkey. Despite the reduced levels of human α-Gal A, some animals sustained high levels of human α-Gal A (activity and protein). In one high dose animal (6.00E+13 vg/kg, IV) levels of 193 nmol/hr/mL were measured on Day 56 while levels in vehicle treated animals were undetectable (<10 nmol/hr/mL). α-Gal A activity was measured in the liver and spleen tissue of all animals at necropsy.

In summary, circulating α-Gal A activity was measured in cynomolgus monkeys following administration of ST-920PC. The transient nature of this response in several animals was likely related to an expected immune response to the human α-Gal A enzyme (human protein administered to an animal).

1.3.2 Pharmacokinetics

All 10 *in vivo* studies conducted in this program included various gene therapy-related pharmacokinetics evaluations.

Plasma AAV2/6 pharmacokinetic analysis following ST-920PC IV administration to C57BL/6 mice and cynomolgus monkeys showed a dose-dependent increase in vector copy numbers. Half-life ranged from 19.3 to 31.2 hours for cynomolgus monkeys receiving an immunosuppression regimen, 16 hours for cynomolgus monkeys not receiving the immunosuppression regimen, and approximately 7 hours in both male and female C57BL/6 mice.

ST-920 or ST-920PC vector copies were evaluated by quantitative polymerase chain reaction (qPCR) in the liver from mouse and monkey studies to gauge liver exposure to test compound and/or compare exposure between material manufactured in HEK293 cells at Sangamo or Sf9/rBV process at Brammer Bio. Levels of vector copies in the liver increased with dose and higher levels were found with HEK293 material compared to Sf9/rBV material. Evaluation of vector copies in testes showed no detectable levels in 3-month GLAKO mouse study and very low levels in the 2-month monkey study. Evaluation of vector copies in ovaries and testes showed low levels in the 3-month C57BL/6 mouse study.

In situ hybridization studies measuring levels of hGLA DNA construct in the liver showed a dose-response relationship in mouse and monkey hepatocytes and confirmed transfer of DNA to the nuclei. The high dose (5.00E+13 vg/kg) in the mouse yielded a range of 28% to 58% positive staining cells, and the high dose (6.00E+13 vg/kg; with immunosuppression) in the monkey study yielded a range of 61% to 73% positive staining cells. Another monkey (without immunosuppression) yielded 49% positive staining cells.

Samples for vector shedding analysis were evaluated by a qPCR method in the 3-month C57BL/6 mouse study and in the 2-month monkey study. There was no measurable amount of ST-920 vector at 3 months in any of the urine, semen, and feces samples tested in the mouse study. In the monkeys, low levels of hGLA vector were measured in the saliva, urine- and feces

of some ST-920 treated animals up to Day 4 (urine) or Day 14 (saliva, feces). At Day 60, no hGLA vector levels were detected in these biological fluids.

To supplement ST-920 tissue biodistribution and shedding analysis, data from the Sangamo SB-913 IND (BB17006) for mucopolysaccharidosis II (MPS II) were included in ST-920 IND since the same AAV6 capsid proteins are present in both compounds and similar manufacturing processes were employed. In the GLP 6-month pharmacology and toxicology study evaluating SB-913, the following tissues and biological fluids were evaluated for the presence of the vector: liver, brain, heart, kidney, lung, spleen, intestines, testes, urine, semen and feces. A qualified qPCR analysis method was used. This study showed liver tropism and rapid shedding. No vector was detected in semen.

Overall, the PK evaluation confirmed hepatic tropism of ST-920, liver-specific production of human α-Gal A, secretion in the blood stream and distribution to secondary tissues. Rapid ST-920 clearance from the blood stream and other biological fluids (shedding) was observed. No ST-920 vector was detected in semen.

1.3.3 Toxicology

Four studies characterized the ST-920/ST-920PC toxicology profile including a 3-month single-dose study with ST-920PC in a Fabry disease mouse model (GLAKO mice), a 4-week and 3-month GLP study with ST-920 in C57BL/6 mice, and a 2-month GLP study with ST-920PC in cynomolgus monkeys. All ST-920 and ST-920PC studies administered test compound via a single-dose IV administration.

Overall, ST-920 and ST-920PC were well tolerated in a Fabry disease mouse model (GLAKO), WT (C56BL/6) mice and cynomolgus monkeys.

In GLAKO mice, there were no adverse findings related to a single IV administration of ST-920PC up to 5.00E+13 vg/kg, the highest dose level tested. In the GLP C57BL/6 mouse studies, the no-observed-adverse-effect level (NOAEL) was ≥ 1.50E+14 vg/kg, the highest dose tested. In the GLP monkey study, ST-920-related findings were limited to animals that did not receive an immunosuppression treatment (6.00E+13 vg/kg). These findings consisted of increases in lymphoid cellularity in lymphoid tissues and spleen and were likely consistent with an immune response related to hGLA and/ or AAV2/6 administration. In this study, the NOAEL was 6.00E+13 vg/kg, with or without the immunosuppressive regimen, the highest dose level tested.

1.3.4 Nonclinical Conclusion

The studies in the Fabry disease mouse models, WT mice and immunosuppressed cynomolgus monkeys, demonstrate the feasibility of safely producing durable and potentially efficacious levels of α-Gal A after treatment with ST-920.

No adverse effects were noted in the mice at dose levels up to 1.50E+14 vg/kg and in the monkeys at dose levels up to 6.00E+13 vg/kg, the highest dose levels given, respectively.

Therefore, the clinical starting dose of 0.50E+13 vg/kg is supported by a 30-fold safety dose multiple in mice and 12-fold safety dose multiple in monkeys.

Measurable levels of α-Gal A are expected in subjects at a dose of 0.50E+13 vg/kg based on the marked pharmacodynamic response noted in the Fabry disease mice given 2.00E+12 vg/kg.

1.4 Clinical Experience with AAV Gene Therapy and AAV2/6 Serotype

Several AAV-mediated cDNA gene transfer Phase I and II studies have reported clinical study data and are currently enrolling in Phase III studies, using IV administration. Onasemnogene abeparvovec-xioi (ZOLGENSMA [AveXis 2019]), an AAV9-based gene therapy treatment, is approved in the United States for pediatric patients ≤ 2 years with spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 (SMN1) and has been found to cause aminotransferase (aspartate transaminase [AST]/alanine transaminase [ALT]) elevations. An 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, AAV-associated elevation of liver enzymes have been observed at vector doses ranging from 5.00E+11 vg/kg to 6.00E+13 vg/kg, with variable amount of losses in factor protein expression (Manno et al. 2006, Nathwani et al. 2014). Based on Sangamo's prior clinical experience with AAV2/6 vector, an ALT elevation (suggestive of an immune reaction to the viral capsid) may be observed. Subjects will be closely monitored for ALT elevation (Appendix 1) throughout the study and the protocol-defined treatment (or treatment at the discretion of the Investigator and agreed upon with the Medical Monitor) with corticosteroids may be initiated in response. Dose selection and guidance are provided in Appendix 3 of the protocol.

As of the data cut on 14 February 2022, six male patients with classic Fabry disease had been dosed in study ST-920-201: 2 patients in Cohort 1 (dose 0.50E+13 vg/kg), 2 patients in Cohort 2 (dose 1.00E+13 vg/kg) and 2 patients in Cohort 3 (dose 3.00E+13 vg/kg). Eleven treatment-related AEs, all mild, were reported: Cohort 1 Subject 1 anemia, thrombocytosis, rash; Cohort 2 Subject 1 fever (twice); Cohort 3 Subject 1 fever, frequent bowel movements, abdominal pain, fatigue, headache, and myalgia. No treatment-related serious AEs were reported. No subject experienced liver enzyme elevations requiring steroid treatment (for further details, refer to the Investigator Brochure).

1.5 Rationale for ST-920 Dose Selection

The rationale for ST-920 dose selection was based on:

i. Nonclinical pharmacology and safety studies administering AAV2/6 at IV doses ranging from 0.50E+13 to 1.50E+14 vg/kg to mice and cynomolgus monkeys with ST-920PC (Sangamo Studies TX17-GLA-019 and TX17-GLA-020) and ST-920 (Sangamo Studies TX18-GLA-031, TX18-GLA-032, and TX19-GLA-050) resulting in pharmacodynamic activity at the lowest dose tested and no adverse events (AEs) related to administration up

to the highest dose tested. These studies included concomitant assessments of the pharmacology, PK/biodistribution and toxicology.

ii. Cumulative safety data from similar ongoing clinical studies that use the same AAV2/6 (ClinicalTrials.gov Identifiers: NCT03041324, NCT02702115, and NCT03061201).

iii. Administration of a safe and potentially active starting dose.

Based on the nonclinical safety and pharmacodynamic mouse data, the proposed clinical dose range is 0.50E+13 to 5.00E+13 vg/kg, with a starting dose of 0.50E+13 vg/kg. The doses proposed were well tolerated in other Sangamo clinical studies.

1.6 Targeted Patient Population

Subjects who satisfy all inclusion/exclusion criteria will be enrolled into one of the 4 treatment dose cohorts. The targeted patient population of this study will be male and female subjects ≥18 years of age with a documented diagnosis of Fabry disease (Arends et al. 2017). Cohorts 1, 2, 3, and 4 include males with classical Fabry disease defined by plasma and/or leukocyte α-Gal A activity and one or more characteristics of classical Fabry disease among cornea verticillata, acroparesthesia, anhidrosis and angiokeratoma. Female cohort includes females with classical Fabry defined as a documented *GLA* mutation and one or more characteristics of classical Fabry disease among cornea verticillata, acroparesthesia, anhidrosis and angiokeratoma. Renal cohort includes both males and females with symptomatic Fabry disease with a linear negative eGFR slope (estimated from at least 3 historical serum creatinine values [within 18 months, including the value obtained during screening visit]) of ≥ 2 mL/min/1.73 m²/year. Cardiac cohort includes both males and females with symptomatic Fabry disease, with cardiac involvement. 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). Therefore, females will be included in the Female cohort once an appropriate dose is determined in a homogeneous population of classical Fabry disease males to mitigate the possibility that biochemical or clinical heterogeneity confounds any responses to ST-920, specifically the α-Gal A levels produced by the cDNA.

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 recombinant α-Gal A 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 ST-920 include insertion mutagenesis (carcinogenicity), vertical and horizontal transmission and off-target effects.

Mitigation strategies are in place for each potential risk and are described in the Investigator Brochure. Additional risks and related mitigation strategies are listed below.

1.7.1 Vertical and Horizontal 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 must agree to use a highly effective form of contraception (e.g., true sexual abstinence, documented vasectomy, 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. Female subjects must agree to use a highly effective form of contraception (described in Inclusion Criteria 9), and they must refrain from egg donation from the time of ST-920 administration until all the samples are negative for AAV2/6 after administration of ST-920.

ST-920 vector shedding has been shown in animal and human studies and is generally cleared in bodily fluids by 2 months post dose administration. Results from the first six subjects of ST-920-201 show that the AAV6 vector is not detectable after 2-8 weeks post-dosing. To mitigate any potential risks to other individuals or the environment from vector shedding, subjects are instructed to avoid the contact of their body fluids or excrements with other individuals or the environment, and maintain hygiene and cleanliness of their hands and the environment within an appropriate time period after receiving treatment; items to be disposed after coming in contact with the body fluids or excrements of subjects should be sealed in disposable garbage bags. For details, refer to the Laboratory Manual.

1.7.2 Off-Target Effects

Because the viral vector construct includes a liver-specific promoter for the *GLA* 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 will be followed for a total of 52 weeks (-2 weeks/+ 1 month) post-ST-920 infusion in this study. Subjects will also be encouraged to participate in an additional, optional separate long-term follow-up study (of 4 years) for a total of up to 5 years from infusion to facilitate detection of potential delayed AEs associated with ST-920 treatment.

1.7.3 Humoral Immune Response to AAV

As described in Section 1.3.3 of this protocol, in the GLP C57BL/6 mouse studies, the no-observed-adverse-effect level (NOAEL) was ≥ 1.50E+14 vg/kg, the highest dose tested. In the GLP monkey study, ST-920PC-related findings were limited to animals that did not receive an immunosuppression treatment (6.00E+13 vg/kg). There were no adverse findings related to a single IV administration of ST-920PC up to 5.00E+13 vg/kg, the highest dose level tested, hence risk mitigation strategies are not needed.

Patients treated with ST-920 are expected to develop a humoral antibody response against the AAV capsid. An enzyme-linked immunosorbent assay has been developed to detect anti-AAV6 total antibodies from patient serum post-dose throughout the study. This anti-AAV6 antibody assay has been validated and sample analysis will follow FDA and EMA recommended tiered immunogenicity testing approach to confirm a positive response.

1.7.4 Development of Neutralising Anti-Human α-Gal A Antibodies

Subjects treated with ST-920 carry a similar risk of developing an antibody response to the treatment as with other biologic interventional therapies. Two validated assays following FDA and EMA guidelines on immunogenicity assessment, total antibody and neutralizing antibody assays, are in place to assess and monitor treatment-elicited antibody response to transgene expressed α-Gal A.

1.7.5 Vector-induced Hepatitis and Loss of α-Gal A Expression

As described in Section 1.4 of this protocol, based on Sangamo's prior clinical experience with AAV2/6 vector, an ALT elevation (suggestive of an immune reaction to the viral capsid) may be observed. Subjects will be closely monitored for ALT elevation throughout the study and the protocol-defined treatment (or treatment at the discretion of the Investigator and agreed upon with the Medical Monitor) with corticosteroids may be initiated in response. Corticosteroid dose selection and guidance are provided in Appendix 3.

1.7.6 Transduction of Extra-Hepatic Tissues

As stated in the Investigator Brochure, ST-920 includes a liver-specific promoter for the *GLA* gene and liver-specific enhancers, therefore, the transgene should only be expressed in the liver, thus limiting the risk of off-target effects. Off-target effects were not observed in nonclinical studies where supraphysiological concentrations of produced enzyme were attained. Subjects will be closely followed for up to 5 years after ST-920 administration, with standard safety monitoring, described in Protocol ST-920-LT01, Appendix A, Schedule of Events.

1.7.7 Corticosteroids to Suppress Immune Hepatitis

Based on Sangamo's prior clinical experience with AAV2/6 vector, it is possible that an ALT elevation (suggestive of an immune reaction to the viral capsid) may be observed. Subjects will be closely monitored for ALT elevation throughout the study and the protocol-defined treatment (or treatment at the discretion of the Investigator and agreed upon with the Medical Monitor) with corticosteroids may be initiated in response. The corticosteroid dosing regimen and tapering schedule are provided in Appendix 3.

1.7.8 Insertional Mutagenesis and/or Tumorigenesis

The consensus in the gene therapy field is that insertional mutagenesis and carcinogenic risks associated with AAV gene therapy vectors is low. AAV vectors predominantly persist as episomal structures and integration frequency of AAV is estimated to be very low. There are no attributes of ST-920 that indicate that this AAV6 vector has unique properties that increase

oncogenic risk. ST-920 hGLA expression is driven by a liver specific promoter/enhancer and lacks the strong viral promoters which are associated with increased carcinogenicity risk. While insertional mutagenic risk cannot be completely excluded, the overall weight of the evidence indicates the risk is low.

The balance between benefit and (theoretical) risk should be weighed, and long-term monitoring for potential hepatocellular carcinogenicity will be key. The clinical plan includes monitoring for hepatocellular carcinoma (HCC)/liver masses by magnetic resonance imaging (MRI) or equivalent imaging modality at 24 weeks and at 1 year post ST-920 administration. In addition, the long-term safety of ST-920 will be evaluated as part of the long-term follow-up (LTFU, 4 years) study for 5 years from ST-920 infusion. This will include serial alpha fetoprotein (AFP) testing and liver imaging to monitor for potential liver masses at Months 12, 24, 36, and 48 (± 2 months).

1.7.9 Exposure to Supraphysiological Levels of α-Gal A

Nonclinical studies administered ST-920 IV to mice at doses up to 1.50E+14 vg/kg and assessed plasma α-Gal A activity over 3 months. Plasma α-Gal A activity increased in a dose-dependent manner in mice treated with ST-920 and remained stable over the 3-month study duration. Overall, supraphysiological levels of α-Gal A activity (up to ~4,100-fold in male and ~2,200 in female mice at 3 months) were observed in plasma, compared to those in vehicle control group. No ST-920 treatment-related adverse effects were seen and the NOAEL was considered to be ≥1.50E+14 vg/kg, the highest dose tested. These results support safety of supraphysiological levels of plasma α-Gal A activity.

1.7.10 Risks of Kidney Biopsy

For subjects who are ERT-naïve or ERT-pseudo-naïve (defined as not having received ERT treatment during the 6 months prior to baseline) and selected subjects previously on migalastat who the Principal Investigator, in conversation with the Sponsor Medical Monitor, considers a non-responder to migalastat based on clinical and/or biochemical assessments, a kidney biopsy will be performed at baseline and after 6 months of dosing. The risks associated with this procedure include bleeding and infection. The bleeding is usually minor but can be severe in rare cases, requiring surgery to stop the bleeding. Management will be based on local guidelines. Infection will be treated based on standard of care. There is a low risk of puncturing adjacent organs; to reduce this risk, the procedure is guided by ultrasound. Local anesthesia and pain medication during and after the procedure will be based on local guidelines, considering potential risks of adverse reactions to such medications.

1.7.11 Risks of Skin Biopsy

Skin biopsy will be performed using incisional or punch biopsy techniques. All biopsies will result in a scar. Some scars may be raised, which is more likely if the biopsy is taken on the upper body. Scars fade gradually. The biopsy will be done in non-exposed areas of the skin such as the abdomen.

1.7.11.1 Risks of Incisional Skin Biopsy

Incisional skin biopsy may produce discomfort, which will be mitigated by local anesthesia. A minor burning sensation may occur when the freezing is injected, but usually subsides in a few seconds. Skin biopsies may also be associated with bleeding, which will be managed by applying pressure and a bandage. Complete healing of the wound may take weeks.

In addition to these risks of bleeding and scarring, there can be bruising, infection, and an allergic reaction to topical antibiotics. These risks will be mitigated by keeping the area clean and covering the site with a breathable bandage.

1.7.11.2 Risks of Punch Biopsy

Punch skin biopsy may produce discomfort, which will be mitigated by local anesthesia. A minor burning sensation may occur when the freezing is injected, but usually subsides in a few seconds. Skin biopsies may also be associated with bleeding, which will be managed by applying pressure and a bandage. Complete healing of the wound may take weeks.

In addition to these risks of bleeding and scarring, there can be bruising, infection, and an allergic reaction to topical antibiotics. These risks will be mitigated by keeping the area clean and covering the site with a breathable bandage.

1.7.12 Risks of Liver Biopsy

Liver biopsy will be required in the presence of a liver mass > 2 cm and elevated AFP (described in Section 6.2.8). The bleeding is usually minor but can be severe in rare cases, requiring surgery to stop the bleeding. Management will be based on local guidelines. Infection will be treated based on standard of care. There is a low risk of puncturing adjacent organs; to reduce this risk, the procedure is guided by ultrasound. Local anesthesia and pain medication during and after the procedure will be based on local guidelines, considering potential risks of adverse reactions to such medications.

1.7.13 Risks Associated with DNA Impurities

To control for residual host cell DNA in the Sangamo gene therapy manufacturing process, benzonase is added to the cell harvest prior to purification as a mitigation strategy to prevent residual DNA being larger than 200 base pairs. The benzonase enzyme digests all forms of nucleic acid by hydrolyzing with high efficiency (nearly 99.95%) unencapsidated nucleic acid oligomers into smaller nucleotide fragments of <10 base pairs in length. Due to high efficiency of benzonase treatment, there is a high probability that the total amount of residual host cell DNA observed is within the expected size range, thus posing no concern based on current regulatory guidance. Finally, Sangamo is characterizing potentially encapsidated DNA with both short and long read next generation sequencing for any nucleotides greater than 200 base pairs and to date has not found any unexpected areas of concern. All DNA sequences detected are process related and found in extremely low percentages of total encapsidated nucleic acids.

1.7.13 Risks Associated with Replication Competent AAV

ST-920 employs a replication defective AAV vector and persistence in bodily fluids is not anticipated past 60 days based on animal data. The risk associated with the generation of a replication competent AAV in the manufacturing process is very low, based on the presence of engineering and analytical controls that are implemented during the manufacture and release of the ST-920 drug product. The manufacturing process is designed to make use of two separate baculovirus infected insect cells (BIICs), namely Helper and Vector BIICs. The Helper BIIC contains a plasmid that provides rep/cap genes while Vector BIIC contains a plasmid that provides ITR, transgene and regulatory elements. This strategy allows for separating the ITR region from rep/cap elements thereby de-risking the possibility of producing a replication competent AAV during the manufacture of the ST-920 drug product. In addition, the control strategy includes a lot release test for the detection of a replication competent AAV. A negative test result for this assay is required for the lot release, confirming that the AAV drug product is replication deficient.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess safety and tolerability of ST-920	• Incidence of treatment-emergent adverse events (TEAEs) Additional safety evaluations will include: o Routine hematology, chemistry, and liver tests, vital signs, electrocardiogram (ECG) and echocardiogram (ECHO) o Serial alpha fetoprotein (AFP) testing and MRI of liver (or equivalent imaging modality) to monitor for liver mass
Secondary	
• To assess α-Gal A activity and the presence of its substrates in plasma over time	• Change from baseline at specific time points over the 1-year study period in: o α-Gal A activity in plasma o Gb3 and lyso-Gb3 levels in plasma
• To assess impact of ST-920 on ERT administration required for subjects on ERT	• Change from baseline at specific time points over the 1-year study period in: o Frequency of ERT infusion
• To assess the impact of ST-920 on renal function	• Change from baseline at specific time points over the 1-year study period in: o Estimated glomerular filtration rate (eGFR) using the CKD-EPI formula
• To assess the impact of ST-920 on cardiac function and left ventricular hypertrophy	• Change from baseline at specific time points over the 1-year study period in: o Ejection fraction, global longitudinal strain, left ventricular mass index (LVMI), left ventricular systolic function measured by cardiac magnetic resonance imaging (CMR)
• To evaluate ST-920 vector DNA shedding over time	• ST-920 vector clearance measured by level of vector genome in blood (plasma), saliva, urine, stool, and semen (if applicable)
Exploratory	
• To assess clinical impact of ST-920 on Fabry disease	• Change from baseline at specific time points over the 1-year study period in: o Late gadolinium enhancement (LGE), native myocardial T1 values and T2 mapping measured by cardiac MRI (CMR) o High sensitivity troponin T, N-terminal pro-hormone B type natriuretic peptide (NT-proBNP) and other cardiac biomarkers

	○ Minnesota Living With Heart Failure Questionnaire (MLHF-Q) summary score ○ Urine protein to creatinine ratio (UPCR) and urine albumin to creatinine ratio (UACR) ○ Biomarkers of renal function in urine ○ Neuropathic pain measured by the Brief Pain Inventory (BPI) ○ Frequency of pain medication use ○ Gastrointestinal (GI) symptoms measured by the GI symptoms rating scale ○ Mainz Severity Score Index (MSSI) ○ Quality of life (QOL) patient-reported outcome measured by the SF-36 questionnaire ○ Pulmonary function ○ Audiologic function
• To assess α-Gal A activity over time in skin	• Change from baseline at specific time points over the 1-year study period in: ○ α-Gal A activity measured in skin
• To assess the presence of Gb3 inclusion levels in skin in ERT-naïve and ERT-pseudo-naïve subjects (defined as not having received ERT treatment during the 6 months prior to baseline) and selected subjects previously on migalastat	• Change from baseline at specific time points over the 1-year study period in: ○ Gb3 inclusion levels measured in skin in ERT-naïve and ERT-pseudo-naïve subjects and selected subjects previously on migalastat.
• To assess the presence of α-Gal A substrates in urine for all subjects over time	• Change from baseline at specific time points over the 1-year study period in: ○ Gb3 and lyso-Gb3 levels in urine for all subjects over time
• To assess immune response to AAV2/6	• Measurement of antibodies to AAV2/6 • Assessment of cell-mediated immune response to AAV2/6
• To assess immune response to α-Gal A	• Measurement of immune response to α-Gal A
• To assess the impact of ST-920 on Gb3 inclusion in the kidney (via kidney biopsy) in ERT-naïve and ERT-pseudo-naïve subjects and selected subjects previously on migalastat	• Percent reduction from baseline at Week 24: ○ Gb3 inclusion in the kidney (assessed by kidney biopsy) in ERT-naïve and ERT-pseudo-naïve subjects and selected subjects previously on migalastat

Any samples collected from consenting subjects may be used for future research objectives. Such future research objectives may include analysis of biomarkers of severity of disease, response to therapy (e.g., cytokines, soluble cell surface proteins, soluble receptors), additional measures of

α-Gal A activity/protein levels, correlation with functional improvements, as well as determination of AAV virus inhibition, function, immunogenicity, or pharmacodynamics (e.g., antibodies, soluble receptors, AAV viral receptor inhibitors, cytokines, co-existing alternate serotype antibodies). For further details, refer to the Study Reference Manual.

3 STUDY DESIGN

3.1 Overview and Rationale

This is a Phase I/II, multicenter, open-label, single-dose, dose-ranging study with a dose escalation phase potentially enrolling 4 cohorts representing 4 dose levels. Up to 48 subjects who are ≥ 18 years of age and who satisfy all inclusion/exclusion criteria are eligible to be enrolled in the overall study. Initially, recruitment will be limited to male subjects meeting criteria for inclusion during dose escalation. Once a safe and tolerable dose is selected, recruitment will be extended via dose expansion to a broader patient population. Once dose expansion is initiated, subjects will undergo assessments which will determine the most appropriate expansion cohort for their enrollment.

During dose escalation, treatment of the first 2 subjects will be staggered so that the subsequent subject cannot be infused until the preceding subject has been observed for at least 2 weeks. After any 2 subjects in a cohort have been dosed, safety data from these 2 subjects will be reviewed by the Safety Monitoring Committee (SMC). Dose escalation to the next dose cohort and dose expansion cannot occur until at least 4 weeks of safety data are available after the second subject in the preceding cohort has been dosed, and data from this cohort has been reviewed by the SMC. The SMC will recommend whether it is safe to escalate the dose or to add subjects to the dose cohort at the same dose level. Once a cohort's data has been reviewed and dose escalation has been endorsed, additional subjects may be infused at any time in the same cohort, as per protocol.

Two male subjects with classical Fabry disease will be dosed in Cohort 1. Following the SMC recommendation to dose escalate to Cohort 2, which is subdivided into Cohort 2a (subjects who are antibody-postive to α-Gal A) and Cohort 2b (subjects who are antibody-negative to α-Gal A), 2 male subjects with classical Fabry disease will be dosed and safety data from these 2 subjects will be reviewed by the SMC. After SMC review, up to an additional 8 (4 subjects in Cohort 2a and 4 subjects in Cohort 2b) subjects may be recruited into Cohort 2 and if dose escalation is recommended, recruitment of subjects into Cohort 3 may commence. Dosing may continue in Cohort 2 until all 10 subjects have been dosed, unless it is concluded during the SMC review that it is more appropriate to dose in Cohort 3 rather than continuing dosing at the Cohort 2 dose level. Dosing in Cohort 3 and the remainder of Cohort 2 can be concurrent.

Following the SMC recommendation to dose escalate to Cohort 3, which is subdivided into Cohort 3a (subjects who are antibody-positive to α-Gal A) and Cohort 3b (subjects who are antibody-negative to α-Gal A), 2 male subjects with classical Fabry disease will be dosed and safety data from these 2 subjects will be reviewed by the SMC. After SMC review, up to an additional 8 (4 subjects in Cohort 3a and 4 subjects in Cohort 3b) subjects may be recruited into Cohort 3 and if dose escalation is recommended, recruitment of subjects into Cohort 4 may commence. Dosing may continue in Cohort 3 until all 10 subjects have been dosed, unless it is

concluded during the SMC review that it is more appropriate to dose in Cohort 4 rather than continuing dosing at the Cohort 3 dose level. Dosing in Cohort 4 and the remainder of Cohort 3 can be concurrent.

Following the SMC recommendation to dose escalate to Cohort 4, which is subdivided into Cohort 4a (subjects who are antibody-positive to α-Gal A) and Cohort 4b (subjects who are antibody-negative to α-Gal A), 2 male subjects with classical Fabry disease will be dosed and safety data from these 2 subjects will be reviewed by the SMC. After SMC review, up to an additional 8 subjects may be recruited into Cohort 4. Dosing may continue in Cohort 4 until all 10 subjects have been dosed, unless it is concluded during the SMC review that it is more appropriate to select a dose for dose expansion. Dosing in dose expansion and the remainder of Cohorts 3 and/or 4 can be concurrent.

The dose considered to be tolerable and safe will be utilized in the dose expansion cohorts. After dose escalation has been completed, dose expansion will commence where up to 6 subjects will be enrolled into each of the dose expansion cohorts, which include patients with classical Fabry disease who are antibody-positive to α-Gal A, patients with classical Fabry disease who are antibody-negative to α-Gal A, female patients (female cohort) and patients who meet criteria for the renal (renal cohort) and cardiac (cardiac cohort) inclusion and exclusion criteria. The dose for the expansion cohorts may be reassessed if there are emerging safety considerations.

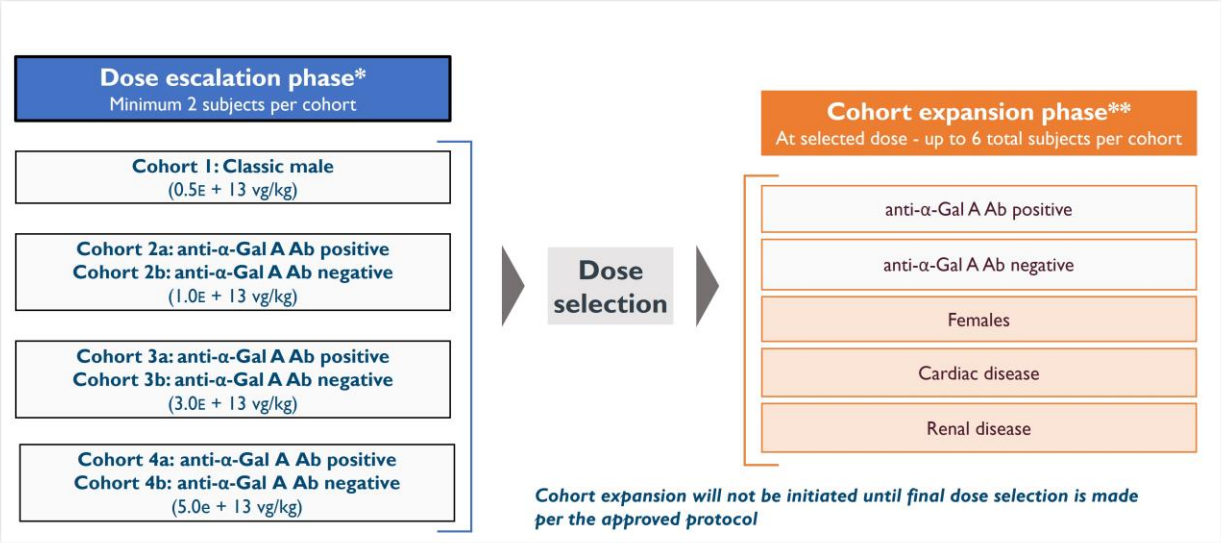
Anti α-Gal A Ab positive cohort: Up to 6 male subjects with classical Fabry disease who are antibody-positive to α-Gal A will be enrolled.

Anti α-Gal A Ab negative cohort: Up to 6 male subjects with classical Fabry disease who are antibody-negative to α-Gal A will be enrolled.

Female cohort: Up to 6 female subjects with classical Fabry disease will be enrolled.

Renal cohort: Up to 6 male or female subjects with symptomatic Fabry disease with a linear negative eGFR slope (estimated from at least 3 historical serum creatinine values [within 18 months, including the value obtained during screening visit]) of ≥ 2 mL/min/1.73 m²/year will be enrolled.

Cardiac cohort: Up to 6 male or female subjects with symptomatic Fabry disease with cardiac involvement, defined as either left ventricular hypertrophy (LVH) in 2D echocardiography or CMR (end diastolic septum and posterior wall thickness ≥ 12mm) with no other explanation for LVH OR cardiac changes indicative of disease progression such as decreased global longitudinal strain on 2D strain echocardiography or low native T1 mapping on CMR will be enrolled. Subjects who have had a cardiovascular event in the 6-month period before screening may be excluded at the discretion of the Investigator.



*Safety and efficacy data of each cohort was/will be reviewed by a safety monitoring committee (SMC) prior to dose escalation.
** The dose for the expansion cohorts may be reassessed if there are emerging safety considerations.

Figure 2: Schema of Study Enrollment: Dose Escalation and Expansion

For all dose escalation and expansion cohorts, subjects who received ERT prior to study participation will continue to receive ERT during the study and remain on their current dose and regimen per standard of care unless they undergo ERT withdrawal. For subjects on ERT, baseline testing of enzyme and substrate levels will be coordinated such that samples will be taken on 2 separate occasions in the morning at trough, defined as 14 days (± 1 day) after the previous ERT infusion. An additional time point will have been taken previously during the screening period, so as to have 3 time points to assess the residual activity of α-Gal A at trough prior to the gene therapy administration. These 3 samples must be taken at trough, and preferably at the same time during the day (e.g. in the morning) to minimize the potential impact of non-specific factors on enzyme activity.

Based on Sangamo's prior clinical experience with the AAV2/6 vector, an ALT elevation (suggestive of an immune reaction to the viral capsid) may be observed. Subjects will be closely monitored for ALT elevation throughout the study and the protocol-defined treatment (or treatment at the discretion of the Investigator and agreed upon with the Medical Monitor) with corticosteroids may be started in response to ALT elevation. Dose selection and guidance are provided in Appendix 3 of the protocol.

For this Phase I/II study, the sample size of 2 subjects prior to a potential dose escalation was chosen based on:

a) consideration of optimum benefit/risk of the one-time administration of ST-920 to subjects due to the known development of an immune response against AAV6, and hence inability to treat the same subject again with AAV6 if efficacy is not achieved

b) recruitment feasibility in this orphan disease population, Fabry disease being a rare inherited X-linked metabolic disease:

i) approximately 30-40% of subjects are expected to screen fail due to the presence of AAV6 neutralizing antibodies
ii) only male subjects with classical Fabry disease will be recruited during dose escalation and, to ensure that any residual enzyme level does not interfere with the measurement of enzyme levels produced by the cDNA transgene, either ERT-naïve subjects or subjects on a stable dose and regimen (defined as not having missed more than 3 doses of ERT during the 6 months prior to consent) or ERT-pseudo-naïve subjects who have previously been on ERT but have not received ERT treatment during the 6 months prior to baseline, will be allowed in the study

c) ability to detect any safety signal

This sample size of 2 subjects per cohort will provide a 28% chance of observing at least one AE for events with a ≥15% incidence. In addition, for an expanded cohort of 6 subjects (2 + 4), the sample size of 6 subjects will provide a 62% chance of observing at least 1 AE for events with a ≥15% incidence.

Safety and tolerability of ST-920 infusion in each cohort will be assessed by incidence of TEAEs and serious AEs (SAEs). Other safety assessments will include monitoring liver tests for any AAV-associated elevation of liver enzymes, clinical laboratory tests (chemistry, hematology, urinalysis), vital signs, AAV clearance from tissues including plasma, urine, saliva, stool and semen (if applicable). Safety data from 24 subjects treated in the Sponsor's studies with AAV2/6 have, to date, not identified any dose limiting safety concerns with treatment of subjects at the starting dose proposed in this study. Therefore, 2 subjects per dose during the escalation is believed appropriate to limit the number of subjects who may be exposed to a suboptimal dose, and to maximize treatment of subjects at the dose that will optimize the benefit risk assessment**.** This is particularly pertinent, considering that it is very unlikely that a subject could be retreated with this technology should they not experience efficacy at the dose tested.

The rationale for a two-week staggering interval between the first 2 subjects in a cohort and four weeks between dose cohorts is based on the experience that the Sponsor has acquired from other gene therapy programs using AAV2/6. There was no evidence of acute or subacute adverse effects in preclinical studies with this product or similar products using AAV2/6. Based on safety data from preclinical studies using ST-920 and similar products, as well as clinical studies using similar products, a two-week staggering interval between first two subjects in a cohort provides adequate time to assess any acute or subacute AEs in this study (for further details, refer to the Investigator Brochure).

ST-920 will be administered via intravenous infusion while the subject is in the healthcare facility, where the subject will remain for observation for at least 24 hours after completion of the ST-920 infusion. During infusion, only light foods such as jello or apple sauce or liquids may be consumed. The subject will be discharged when all vital signs are stable and any AEs have resolved or the subject is considered stabilized as per Investigator judgment.

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. The 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 tests will be assessed twice weekly during the first 20 weeks after ST-920 infusion, then weekly for four weeks (Weeks 21-24), and monthly thereafter to coincide with study visits (Weeks 28-52). Liver tests may be conducted remotely and analyzed locally or centrally. Blood samples for liver tests will be drawn 2-4 days apart when possible. For the first week they will be drawn on Day 2 and 2-4 days later. Day 8 visit will be the first Week 2 blood draw. If there is a need to initiate treatment with corticosteroids because of elevated ALT, liver enzymes will continue to be assessed at least twice a week until normalization and then per protocol thereafter analyzed locally or centrally (Appendix 3).

A four-week staggering interval between dose cohorts will allow for appropriate time to collect safety data for the first two subjects in each cohort for the Safety Monitoring Committee to review and make recommendations to the Sponsor as to whether to dose-escalate, dose-de-escalate or add a cohort.

The duration of study participation will be up to 84 weeks for each subject divided into up to 8 weeks for screening, up to 24 weeks for baseline, and 52 weeks follow-up after dosing. Accrual is planned for 48 months.

The proposed evaluation period in this study is 52 weeks after ST-920 administration. This one-year safety evaluation of the study includes physical evaluation, ECG, ECHO, and hearing test, in addition to other routine clinical tests and biochemical safety evaluation (for further details, refer to Section 6 and Appendix 1). The 52-week 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 52 weeks, subjects will be encouraged to participate in an additional separate long-term follow-up study (of 4 years) for a total of at least 5 years from infusion for long term safety and durability of response monitoring.

3.2 Screening Period

The objective of the screening visit is to identify subjects who meet the stated inclusion and exclusion criteria and who are willing and able to participate in the study. After informed consent, screening may take up to approximately 8 weeks and may be performed across several visits.

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 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 and clinical symptoms for male subjects. For females the diagnosis will be made based on mutation and clinical symptoms.

A sample will be taken during the screening period to measure baseline levels of enzyme and substrate levels. Two more samples for baseline levels of enzyme and substrate will be taken during the baseline period (see Section 3.3), so as to have 3 time points to assess the residual activity of α-Gal A prior to the gene therapy administration. For subjects on ERT, testing of enzyme and substrate levels will be coordinated such that samples will be taken at trough, defined as 14 days (± 1 day) after the previous ERT administration, and preferably at the same time during the day (e.g. in the morning) to minimize the potential impact of non-specific factors on enzyme activity.

3.3 Baseline Period

Baseline assessments and procedures outlined in the Schedule of Events (Appendix 1) will be performed within 12 weeks prior to ST-920 infusion. The duration may be extended to 24 weeks for subjects whose visits are impacted by delays due to COVID-19. In subjects receiving ERT, assessments including α-Gal A levels, and Gb3 and lyso-Gb3 and immunogenicity samples will be taken at ERT trough levels, defined as 14 days (± 1 day) after the previous ERT administration. Two samples will be taken at baseline on 2 different days in the morning. For subjects not on ERT, two samples will be taken at baseline on 2 occasions with at least 14 days (± 1 day) between the 2 occasions. Documentation of dosing should be recorded in the electronic case report form (eCRF) and administration of all ERT should be obtained and recorded in the ERT Administration Log.

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. All activated sites will be asked to communicate subject status at their site to the Sponsor on at least a weekly basis. A summary of subject status across the study will be shared with each site at least on a weekly basis. Significant safety information will be communicated to sites as described in Section 9.5. This will allow both the Sponsor and the study sites to be up -to -date on current potential treatment slots available based on subjects in screening, and on safety data.

As an additional assurance that a site cannot dose a subject when they should not, the vials required for the treatment are shipped to the study site only after the subject's baseline assessment visit.

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.

The doses being evaluated were selected based on preclinical studies in mice and monkeys and cumulative safety data from ongoing Sangamo clinical studies that use the same AAV2/6. Several dose levels may need to be studied to identify a safe and tolerable therapeutic dose. The dose levels for this dose escalation study are as noted in Table 1. Dose escalation to the next dose level will be decided by the SMC upon review of safety data from the previous cohort. Other data derived from other Sangamo-sponsored clinical trials that use *in vivo* AAV2/6-based therapy may be considered as well, and based on the recommendation of the Safety Monitoring Committee (SMC), which will be composed of external subject matter experts, the study Medical Monitors, Sponsor Drug Safety Lead and Site Investigators as appropriate (as described in the SMC charter).

From preclinical experiments with ST-920 in a mouse model of Fabry disease, it is anticipated that supraphysiological levels of enzymatic activity need to be achieved in the blood (at least 8 times the normal enzymatic activity), at steady state, in order to lead to a full reduction of the substrate accumulation in the main target organs (kidneys and heart).

In addition, depending on the enzyme activity and safety data of the subjects dosed, the SMC may recommend a dose escalation to one of the two doses listed in Table 1. However, no dose given to subjects will exceed 5.00E+13 vg/kg (by qPCR) without a substantial amendment.

Table 1: Dose by Cohort

Cohort	AAV[1] Dose (vector genomes [vg]/kg)
	qPCR[2]
1	0.50E+13
2	1.00E+13 or 3.00E+13
3	3.00E+13 or 5.00E+13
4	5.00E+13
[1]AAV = adeno-associated virus, [2]quantitative PCR	

A droplet digital PCR (ddPCR) test method is being developed to determine the level of vector genome (vg) titers for ST-920. The nominal genome copies (vg/mL) are not changing; a new method (ddPCR) to evaluate the nominal genome copies is being implemented and will replace the qPCR method. Once fully implemented, drug product released using the initial qPCR assay or the new ddPCR assay will be used in Study ST-920-201. See Section 7 for additional details.

For the first 2 subjects in each cohort, treatment will be staggered so that each subsequent subject will not be infused until the preceding subject has been observed for at least 2 weeks. After the first 2 subjects, the subsequent subjects in the same dose cohort can be infused at any time if the safety data from the first 2 subjects is deemed satisfactory by the SMC.

A decision to dose escalate to the next dose level will not occur until at least 4 weeks after the 2 subjects in the preceding cohort have been dosed and the safety data from the 2 subjects in the prior cohort has been reviewed by the SMC.

Safety and tolerability of the ST-920 infusion will be assessed by the incidence of TEAEs and SAEs. Other safety assessments will include monitoring liver tests for any AAV-associated elevation of liver enzymes, clinical laboratory tests (chemistry, hematology, urinalysis), vital signs, AAV clearance from tissues including plasma, urine, saliva, stool and semen (if applicable). Preliminary bioactivity and efficacy will be assessed by evaluating any change from baseline of α-Gal A levels and Gb3 and lyso-Gb3 substrate levels over time. For those subjects on ERT, these samples will be taken at trough ERT levels (with trough defined as 14 days [± 1 day] after the previous ERT administration). In relation to symptomatic efficacy, we will be assessing any changes in Fabry-specific symptoms including GI symptoms, neuropathic pain, and lack of sweating with exercise which will be informative as markers of efficacy in subjects who are treatment naïve and in subjects who withdraw from ERT after ST-920 infusion.

Dosing and dose escalation will be paused if any of the study stopping rules are met (refer to Section 3.5). In such an event, the SMC will be convened to provide recommendations to dose de-escalate, or to discontinue the study. 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.

The dose deemed to be tolerable and safe will be utilized in the expansion cohorts.
All subjects will be asked to return to the study site for a follow-up visit 7 ± 1 days after ST-920 infusion. See the Schedule of Events (Appendix 1) for a list of assessments and procedures performed on Day 8. Thereafter, study visits are scheduled as described in the Schedule of Events (Appendix 1).

Subjects will be followed for a total of 52 weeks (-2 weeks/+ 1 month) post-ST-920 infusion in this study. Subjects will be encouraged to participate in an additional, optional separate long-term follow--up study (4 years) for a total of at least 5 years from infusion.

3.5 Study Stopping Rules

An SMC with appropriate medical and scientific expertise was appointed to provide safety oversight for the study. The SMC is comprised of external subject matter experts, the study Medical Monitor, Sponsor's Drug Safety Lead, Study Biostatistician, and Site Investigators as appropriate. The SMC will periodically meet during the study and provide recommendations to the Sponsor concerning dosing. The SMC will also convene at any time if an emergent safety issue emerges during the study or one of the stopping rules are met. These include:

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

- Development of a malignancy, with the exception of non-melanoma skin cancers and localized prostate cancer treated with curative intent

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 development of the investigational product, ST-920.

All data will be evaluated to determine whether changes should be made to the study or if accrual should be continued or halted. 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.

Relevant data from other trials sponsored by Sangamo may be shared with the SMC to expand the clinical experience, particularly as it relates to safety and dose, and such data can be used by the SMC to inform its recommendations for the present study.

The SMC may also recommend changes to the dose and enrollment of cohorts based on cumulative safety data from this and other Sangamo sponsored clinical trials that use *in vivo* AAV2/6-based therapy. When no further enrolling or dosing decisions are required of the SMC, the SMC will no longer meet on a regular basis. The Sponsor will continue to review the subject safety data on an ongoing basis.

3.6 Enzyme Replacement Therapy Withdrawal (any time after Week 4)

The ultimate goal of ST-920 treatment is to abrogate the need for ERT by using an 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. During dose escalation, subjects on ERT may 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. The ERT withdrawal can only be considered after a period of four weeks, in order to allow enough time for transduction of the target liver cells.

Subjects who undergo ERT withdrawal will be closely monitored for any AEs, vital signs, any changes in safety laboratory evaluations, including liver tests and activity of α-Gal A and substrates (Gb3 and lyso-Gb3) compared to baseline (Appendix 2).

During dose escalation, 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:

- Are ≥4 weeks post-administration of ST-920.
- Are medically stable and can tolerate temporary discontinuation of ERT in the judgment of the Site Investigator.

- Agree to increased safety monitoring and additional lab testing until ERT Withdrawal Follow-Up visit (Appendix 2).

Initiation of the dose expansion phase of the study assumes that a safe and tolerable dose of ST-920 has been achieved. At this point, ERT withdrawal will be implemented for all subjects who are in the expansion cohorts and have achieved supraphysiological (above normal range) plasma α-Gal A for 8 weeks ± 2 weeks, at the discretion of the investigator.

ERT withdrawal assumes a complete stop in ERT administration rather than a "dose-down" or dose reduction.

Study visits associated with ERT withdrawal may occur concurrently or independently of regular scheduled study visits, but should be combined with regular scheduled study visits whenever possible to reduce study burden. When combined, assessments associated with ERT withdrawal (Appendix 2) that are duplicated at the regular scheduled study visits (Appendix 1) should be waived. The ERT Withdrawal Follow-Up visit (visit where a clinical assessment is performed by the Site Investigator to determine whether ERT should be reinitiated in the subject) will occur at Week 12 after ERT withdrawal visit (Appendix 2), but it can occur earlier at the discretion of the Site Investigator, if clinically indicated.

ERT does not need to be restarted after the ERT Withdrawal Follow-Up visit. However, ERT may be re-initiated at any time based on clinical circumstances or at the judgment of the Site Investigator. After ERT withdrawal, in order to assess whether a subject has received a suboptimal dose, evidence of a lack of response will be primarily based on α-Gal A activity and lyso-Gb3 substrate levels in plasma, which will be tested on a regular basis (refer to Appendix 2 for a full list of assessments and schedule of events). Plasma α-Gal A activity below the normal range, or plasma lyso-Gb3 levels, will be part of the criteria used by the Site Investigators to determine lack of response (and need for reinstitution of ERT).

ERT withdrawal may be repeated if previously unsuccessful, provided this is done at least 12 weeks after the previous attempt if the subject is willing, and at the discretion of the Site Investigator and after consultation with the Sponsor.

3.6.1 ERT Withdrawal Monitoring

ERT Withdrawal Monitoring visits will take place following the ERT Withdrawal visit. ERT Withdrawal Monitoring visits should be combined with regular scheduled visits whenever possible to reduce study burden. ERT Withdrawal Monitoring visits may be conducted remotely.

See the ERT Withdrawal Schedule of Events (Appendix 2) for a list of assessments and procedures performed during the ERT Withdrawal Monitoring Visits.

3.6.2 ERT Withdrawal Follow-Up

The ERT Withdrawal Follow-Up visit will occur at Week 12 ± 2 days after the ERT withdrawal visit (Appendix 2), but it can occur earlier at the discretion of the Site Investigator, if clinically

indicated. If clinically indicated, ERT may be re-initiated at any time based on clinical circumstances or at the judgment of the Site Investigator.

See the ERT Withdrawal Schedule of Events (Appendix 2) for a list of assessments and procedures performed during the ERT Withdrawal Follow-up Visit.

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

An End of Study (EOS) visit will be conducted at Week 52 (-2 weeks/+1 month) for final assessments, detailed in the Schedule of Assessments (Appendix 1). At the EOS visit, subjects will be encouraged to participate in a separate long-term follow-up study where subjects will be followed for at least 4 years. Subjects will be followed for a total of up to 5 years from infusion. Informed consent will be obtained prior to participating in the long-term follow-up study.

4. SUBJECT SELECTION

4.1 Inclusion Criteria

1. ≥18 years of age
2. Signed, written informed consent
3. Diagnosis of Fabry disease
4. One or more of the following symptoms: i) cornea verticillata, ii) acroparesthesia, iii) anhidrosis, iv) angiokeratoma
5. Subjects who are on ERT or are ERT-naïve or are ERT-pseudo-naïve (defined as not having received ERT treatment in the 6 months prior to baseline). For subjects receiving ERT, ERT must have been administered at a stable dose and regimen for at least 6 months (defined as not having missed more than 3 doses of ERT during the 6 months prior to consent).
6. Subjects on migalastat (Galafold™) must agree to withdraw migalastat prior to Baseline and, if non-responder to migalastat (based on clinical and/or biochemical assessments), undergo an incisional skin biopsy and kidney biopsy.
7. Male subjects must 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.
8. Female subjects must refrain from egg donation from the time of ST-920 administration until all the samples are negative for AAV2/6 after administration of ST-920.
9. Subjects must agree to use a highly effective form of contraception from the time of ST-920 administration until a minimum of minimum of 90 days after ST-920 administration and, for male subjects, 3 consecutive semen samples are negative for AAV2/6 after administration of ST-920. Highly effective birth control methods include:
    i. a documented vasectomy or permanent sterilization
    ii. condom
    iii. combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal or transdermal)
    iv. progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable)
    v. intrauterine device (IUD)
    vi. intrauterine hormone-releasing system (IUS)

vii. sexual abstinence is acceptable only as true abstinence and when in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

10. Subject must be fully vaccinated (as per the Centers for Disease Control and Prevention (CDC) definition in the US and as per local guidelines in other countries) for COVID-19 at least one month prior to dosing

Additional inclusion criteria for:

Cohorts 1-4b:

11. Male subjects with classical Fabry disease as defined by < 5% α-Gal A activity in either plasma or leukocytes
    a. For male subjects who do not have documented diagnostic α-Gal A activity, a blood sample will be taken to measure α-Gal A activity (in plasma). For subjects who are on ERT, this blood draw must be taken at least 13 days after their last ERT infusion (trough).
    b. If the subject's α-Gal A activity is > 5% and the subject is on ERT, this level of enzyme activity may be due to residual α-Gal A activity from the last ERT infusion. In this case, the diagnosis of classical Fabry disease may be confirmed if the following three criteria are fulfilled:
        i. two or more documented symptomatic characteristics outlined in inclusion criterion #4. If there is documented clustered periumbilicial angiokeratoma, this symptom alone is sufficient as it is a pathognomonic sign of classical Fabry disease;
        ii. a mutation that is indicative of classical Fabry (i.e. listed in a database, such as http://dbfgp.org); and
        iii. the α-Gal A activity at trough is below the lower limit of the normal range of the assay.

Female cohort:

12. Female subjects with a documented mutation that is indicative of classical Fabry (i.e., listed in a database, such as http://dbfgp.org) and treatment (ERT and/or migalastat) is clinically indicated

Renal and Cardiac cohorts:

13. Symptomatic Fabry disease defined for male subjects by <30% α-Gal A activity in either plasma or leukocytes and for female subjects based on historical genetic test results consistent with Fabry pathogenic mutation or in the case of novel mutations a first-degree male family member with Fabry disease with the same mutation

AND

Renal cohort:

14. Screening eGFR value between 40-90 mL/min/1.73 m²
15. Linear negative eGFR slope (estimated from at least 3 historical serum creatinine values [within 18 months, including the value obtained during screening visit]) of ≥ 2 mL/min/1.73 m²/year

Cardiac cohort:

16. LVH in 2D echocardiography or CMR defined as an end diastolic septum and posterior wall thickness ≥12 mm with no other explanation for LVH, OR presentation with cardiac changes indicative of disease progression such as decreased global longitudinal strain on 2D strain echocardiography or low native T1 mapping on CMR

4.2 Exclusion Criteria

1. Positive neutralizing antibodies to AAV6
2. Intercurrent illness expected to impair evaluation of safety or efficacy during the observation period of the study
3. eGFR <40 mL/min/1.73m^2
4. Active infection with hepatitis A virus (HAV RNA positive), active or occult hepatitis B virus infection (positive HBV-DNA or anti-HBc positive), active infection with hepatitis C virus (HCV RNA positive), infection with the human immunodeficiency virus (HIV) as measured by quantitative polymerase chain reaction (qPCR), or active or latent infection with tuberculosis (TB) measured by quantiferon test
5. Breastfeeding at screening or breastfeeding during required period of contraception
6. History of liver disease such as clinically significant steatosis, fibrosis, non-alcoholic steatohepatitis (NASH) and cirrhosis, biliary disease within 6 months of informed consent; except for Gilbert's syndrome
7. Elevated circulating serum AFP
8. For subjects receiving ERT, recent or recurrent hypersensitivity reaction manifested by significant infusion reaction to ERT treatment within 6 months prior to consent
9. One or more of the following:
    a. Albumin ≤ 3.5 g/dL
    b. Total bilirubin > upper limit of normal (ULN) and direct bilirubin ≥ 0.5 mg/dL
    c. Alkaline phosphatase (ALP) > 2.0 x ULN
    d. Alanine aminotransferase (ALT) > 1.5 x ULN
10. Current or history of systemic intravenous (IV) or oral immunomodulatory agents, or biologics or steroid use in the past 6 months prior to consent (topical and inhaled treatment are allowed, [e.g., for asthma or eczema]). Occasional use of systemic steroid may be allowed based on discussion and agreement with the Medical Monitor.
11. Contraindication to use of corticosteroids
12. History of malignancy, except for non-melanoma skin cancer and localized prostate cancer treated with curative intent
13. Recent history of alcohol or substance abuse. The use of marijuana may be considered on an individual basis with discussion and agreement from the Medical Monitor.
14. Participation in investigational interventional drug or medical device study throughout the duration of this study and within the last 3 months prior to consent (with the exception of implantable loop recorders as in the RaILRoAD trial)
15. Prior treatment with a gene therapy product
16. Known hypersensitivity to components of ST-920 formulation
17. Any other reason that, in the opinion of the Site Investigator or Medical Monitor, would render the subject unsuitable for participation in the study, including but not limited to risk of COVID-19 infection.

Additional exclusion criteria for:
Cohorts 1-4, female, and renal cohort:
18. New York Heart Association (NYHA) Class III and IV

Renal cohort:
19. History of renal dialysis or transplantation
20. History of acute kidney insufficiency in the 6 months prior to screening
21. Angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy initiated within 4 weeks prior to screening or changed ACE inhibitor or ARB dose in the 4 weeks prior to screening
22. Urine protein to creatinine ratio (UPCR) > 0.5 g/g who are not being treated with an ACE inhibitor or ARB

Cardiac cohort:
23. Significant cardiac fibrosis defined as having more than 3 segments full thickness of late gadolinium enhancement on CMR
24. Any contraindications to CMR as per local hospital/institution guidelines
25. Angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy initiated within 4 weeks prior to screening or changed ACE inhibitor or ARB dose in the 4 weeks prior to screening
26. NYHA Class IV

5. INFORMED CONSENT

Informed consent must be obtained from the subject 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. 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 (Appendix 1, Appendix 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 health care facility for the ST-920 infusion. ST-920 will be injected using a peristaltic pump or IV infusion pump (see Study Pharmacy Manual). During infusion, only light foods such as jello or apple sauce or liquids may be consumed. 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 health care facility for at least 24 hours after completion of ST-920 infusion for observation and will be discharged when all AEs have resolved or the subject is considered stabilized as per Investigator judgment 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 participation will continue to receive ERT during the study and remain on their current dose and regimen per standard of care unless they undergo ERT withdrawal (Section 3.6). For subjects on ERT, baseline testing of enzyme and substrate levels will be coordinated such that samples will be taken on 2 separate occasions in the morning at trough, defined as 14 days (± 1 day) after the previous ERT administration. A third sample will have been taken during the screening period to provide α-Gal A trough levels at 3 time points to assess the residual levels of α-Gal A prior to the gene therapy administration.

The actual date should be recorded for all procedures and the Site Investigator should make every effort to perform procedures at the scheduled nominal dates outlined in the Schedule of Events (Appendix 1). Planned safety and laboratory assessments may be collected at additional time points following conversation between the Site Investigator and Medical Monitor based on emerging clinical events. The change in timing for any planned study assessments must be approved and documented by the Sponsor, but this will not constitute a protocol amendment where they are considered needed for safety reasons. The addition of any new study assessments to the protocol required for any ongoing and new subjects would constitute an amendment.

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. Sites should perform a review of the medical records and collect all eGFR values within 18 months prior to screening. 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, sex, 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 and Immune Response to α-Gal A

The level of neutralizing antibodies to AAV6 will be measured at screening to assess the subject's pre-existing immune response to AAV6. Subjects who tested positive for neutralizing antibodies to AAV6 are not eligible to participate in this study. If dosing is not completed within 12 weeks of sample collection for neutralizing antibodies to AAV6 the serum neutralization assay to AAV6 should be repeated. Immune response to α-Gal A will be measured to assess the effect of anti-α-Gal A antibodies on therapy efficacy and outcome. It is important to collect the screening and baseline samples for immune response to α-Gal A at trough (14 days ± 1 day) after the previous ERT administration) to reduce interference from ERT. For details, refer to the Laboratory Manual.

6.1.6 Concomitant Medications

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

6.1.6.1 Vaccines

Live attenuated vaccines (for any infection) should not be prescribed within two weeks prior to and up to 20 weeks after ST-920 infusion.

6.1.6.1.1 COVID-19 Vaccine

ST-920 is to be administered no earlier than 4 weeks after any dose of a COVID-19 vaccine dose, including booster doses. For subjects who have been dosed with ST-920, the COVID-19 vaccine booster can be administered as of 4 weeks following ST-920 infusion.

The COVID-19 vaccine should not be administered if the subject is receiving corticosteroids in response to an ALT elevation; it may be administered 7 days following discontinuation of the corticosteroids.

COVID-19 vaccines using an adenoviral vector are not contraindicated.

All subjects participating in this study are encouraged to be up to date with their COVID-19 vaccination status, including boosters.

6.1.7 ERT Clinical Assessment

A clinical assessment of the need for ERT must be conducted at the ERT Withdrawal Follow-Up visit if a subject withdraws from ERT. The Site Investigator should determine if chronic ERT infusions will be resumed or if the subject may continue without ERT, and indicate the decision on the appropriate eCRF. The assessment will be made based on the clinical judgment of the Site Investigator and in consultation with the Medical Monitor, taking into account all information available (which may include but is not limited to AEs, clinical laboratory testing, α-Gal A levels, substrate levels, pain assessment, and other available data). The ERT Clinical Assessment may be completed again at any time post-ERT withdrawal if there is a clinically significant change in the status of the subject's ERT administration.

6.1.8 ERT Administration Log

The frequency of ERT administration will be studied before and after administration of ST-920. Each dose of ERT given to the subject from the time of screening will be recorded on the ERT Administration Log, including date and time of start and stop of ERT infusion. At each indicated visit, documentation of all ERT administration since the last visit must be obtained and confirmed. An assumed standing schedule (e.g., every other week) should not be used.

6.1.9 Diagnostic α-Gal A Activity

If available, diagnostic α-Gal A activity results in plasma or leukocytes obtained prior to the study may be used.

For subjects who do not have a documented diagnostic α-Gal A activity, a blood sample should be taken to measure α-Gal A activity in plasma. For those subjects who are on ERT, this blood draw must be taken at least 13 days after their last ERT infusion during trough.

For details, refer to the Laboratory Manual.

6.2 Safety/Tolerability Assessments

6.2.1 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; as well as cardiovascular, dermatologic, respiratory, GI, musculoskeletal, and neurologic systems. For details, refer to the Study Reference Manual.

6.2.2 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.

6.2.3 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

Analyses will be done centrally unless local analyses is necessary with Sponsor agreement.

6.2.4 Adverse Events

AEs 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.

6.2.5 Liver Panel

Liver panel will include assessment of ALT, AST, gamma-glutamyl transferase (GGT), total and direct bilirubin, ALP, lactate dehydrogenase (LDH), albumin, and total protein levels. Since monitoring of liver enzymes is important 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 (Appendix 1), may be conducted remotely, and analyzed centrally or locally. 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.

6.2.6 12-Lead Electrocardiogram

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

6.2.7 Echocardiogram

Standard 2-dimensional Doppler 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. An ECHO taken within 6 months of

consent in the study may be used to determine subject eligibility on a case-by-case basis at the discretion of the Site Investigator and the Medical Monitor.

6.2.8 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 (Appendix 1) to screen and monitor for the potential development of liver masses. An MRI of the liver can be replaced by an abdomen CT-scan or any equivalent imaging technology (like ultrasound) in case the subject has a contraindication to MRI (for example history of hip replacement). Parameters adapted to the search for a liver mass will be applied to any imaging modality.

Any subject with an elevated AFP and MRI mass suspicious for HCC or greater than 2 cm will undergo liver biopsy (Appendix 4). For details, refer to the Study Reference Manual and the Imaging Guidelines. An MRI, or equivalent imaging technology, taken within 6 months of consent in the study may be used to determine subject eligibility on a case-by-case basis at the discretion of the Site Investigator and the Medical Monitor.

6.2.9 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.

6.2.10 Vector Genome Polymerase Chain Reaction

Plasma, saliva, urine, stool, and semen (if applicable) samples will be analyzed by qPCR to determine clearance of ST-920 vector genomes. Each type of sample (plasma, saliva, urine, stool, semen [if applicable]) should be collected until 3 consecutive specimens of that sample type are reported as negative or undetectable for vector genome. For details, refer to the Laboratory Manual.

6.2.11 COVID-19 Assessments

Subjects will be assessed and monitored for COVID-19 as outlined in Appendix 7. Importantly, 2 negative PCR tests will be required before the subject can be infused with ST-920. The first test can be done 10-14 days prior to planned dosing and the second test should be done 2-3 days prior to planned dosing. For details, refer to Appendix 7.

In case of a positive result, COVID-19 standard of care according to the individual site's guidelines will be initiated and the next steps will be discussed between the Investigator and the Sangamo Medical Monitor.

6.2.12 Pregnancy Testing

Female subjects who are women of childbearing potential will have a pregnancy test performed at the timepoints specified in Schedule of Events (Appendix 1, Appendix 2). Serum pregnancy tests will be performed at screening and sent to the central laboratory. At other visits, a urine pregnancy test should be performed by the local laboratory. A serum pregnancy test will be performed by the central laboratory in the event of a positive or equivocal urine pregnancy test result.

6.3 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 activity measurements may be conducted. 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, plasma or urine 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 Total Protein and Albumin to Creatinine Ratios

The kidneys are the organs most severely affected over the long-term course of Fabry disease, thereby leading to kidney disease as a major complication of Fabry disease. It would be most informative to show any reduction in Gb3 inclusion in the kidneys, however it is likely that most of the subjects enrolled in this Phase I/II study will be on ERT at baseline, and it may be challenging to see a meaningful change in Gb3 inclusion in the kidneys while on ERT or during a short period after ERT withdrawal. We also want to reduce subject burden as much as possible.

Therefore, we will instead be monitoring for any change in kidney function over time by calculating the glomerular filtration rate (eGFR), and total protein and albumin to creatinine ratios. For details, refer to the Study Reference Manual.

6.4.2 Kidney biopsy

For those subjects who are ERT-naïve or ERT-pseudo-naïve (defined as has not having received ERT treatment during the 6 months prior to baseline) and selected subjects previously on migalastat who the Principal Investigator, in conversation with the Sponsor Medical Monitor, considers a non-responder to migalastat based on clinical and/or biochemical assessments, any meaningful reduction in Gb3 inclusion in the kidneys from baseline would be informative and potentially indicative of clinical benefit. Kidney biopsies will thus be performed on ERT-naïve or ERT-pseudo-naïve subjects and selected subjects previously on migalastat only, which will be on a voluntary basis for Cohort 2 and mandatory for subsequent cohorts unless contraindicated by a Site Investigator or physician. Kidney biopsies should be performed as per local hospital/institution guidelines. For details, refer to the Laboratory Manual.

6.4.3 Cardiac MRI

Fabry disease can be associated with significant cardiac complications. Gb3 accumulates in the microvasculature, causing ischemic damages that can result in cardiovascular disease. Cardiovascular manifestations of Fabry disease include left ventricular hypertrophy (LVH), aortic and mitral regurgitation, conduction defects, coronary artery disease, hypertension, and aortic root dilation resulting in arrhythmia, palpitation, angina, dyspnea, or syncope. CMR will be used in all subjects to assess cardiac function and LVH by measuring ejection fraction, left ventricular global longitudinal strain, left ventricular systolic function and LVMI. It will also be used to evaluate changes over time in LGE, native myocardial T1 values and T2 mapping. Results from CMR performed within 6 months prior to consent can be used for screening or baseline if the patient fulfills the requirements within the Imaging Guidelines; for details, refer to the Imaging Guidelines.

6.4.4 Cardiac Biomarkers

For all subjects, high sensitivity troponin T, N-terminal pro-hormone B-type natriuretic peptide (NT-proBNP), and other cardiac biomarkers, will be measured to assess the clinical impact of ST-920 on cardiac manifestations of Fabry disease. High-sensitivity troponin T is a biomarker for staging cardiomyopathy progression (Seydelmann et al. 2016) and may also be used to monitor subjects for transient myocarditis. NT-pro-BNP is a marker of early cardiac involvement and cardiomyopathy progression (Coats et al. 2013; Cammarata et al. 2018). For details, refer to the Study Reference Manual.

6.4.5 Minnesota Living With Heart Failure Questionnaire (MLHF-Q) Summary Score

Heart failure is one of the cardiac manifestations of Fabry disease. (Seydelmann et al. 2016) The MLHF-Q is a health-related quality of life questionnaire for patients living with heart failure. It includes 21 items rated on six-point Likert scales. It provides a summary score (total score with

range 0-105, from best to worst quality of life), as well as scores for physical (8 items, range 0-40) and emotional (5 items, range 0-25) dimensions of heart failure. (Bilbao et al. 2016) For subjects in the Cardiac cohort, the MLHF-Q summary score will be used to measure quality of life. For details, refer to the Study Reference Manual.

6.4.6 Skin Biopsy

Progressive Gb3 accumulation in dermal fibroblasts can lead to skin lesions and small fiber neuropathy (SFN) responsible for paraesthesias of extremities, hypohydrosis, and GI symptoms. Skin biopsies will be performed in ERT-naïve and ERT-pseudo-naïve subjects and selected subjects previously on migalastat to monitor any changes in substrate accumulation in skin tissues to evaluate any potential impact of ST-920 on any substrate reduction in skin tissues. α-Gal A may also be measured in skin biopsies to determine any tissue uptake of the enzyme in all subjects. Of note is that special considerations may need to be taken into account for female patients based on variable patterns of X chromosome inactivation. For details, refer to the Study Reference Manual and Laboratory Manual.

6.4.7 Pain Assessments: Frequency of Pain Medication Use and Short Form Brief Pain Inventory

Fabry disease can cause pain and burning in the hands and feet (acroparesthesia). This study will assess the frequency of pain medication use and will use the short form BPI to measure pain. For details, refer to the Study Reference Manual.

6.4.8 Quality of Life

Patients with Fabry disease have a lower QOL than the general population. The SF-36 v2 questionnaire will be used to assess QOL in this study. For details, refer to the Study Reference Manual.

6.4.9 Gastrointestinal Symptoms Rating Scale

Fabry disease frequently causes GI symptoms such as abdominal pain, diarrhea, constipation, nausea, and vomiting. The GI Symptom Rating Scale will be used to assess GI symptoms. For details, refer to the Study Reference Manual.

6.4.10 Mainz Severity Score Index (MSSI)

The MSSI is a clinical scoring system developed to assess overall disease severity in each subject by recording which organs or systems are affected and applying a weighting based on impact of organ involvement and their contribution to the morbidity of the disease. The MSSI is composed of four sections that cover general, neurological, cardiovascular and renal signs and symptoms of Fabry disease. MSSI will be recorded to assess any change in Fabry disease progression over time. For details, refer to the Study Reference Manual.

6.4.11 Pulmonary Function Tests

Fabry disease may be associated with pulmonary complications such as airway narrowing and capillary blockage. Pulmonary function tests (PFTs) are a common method for evaluating respiratory function and will be conducted in this study. For details, refer to the Study Reference Manual. Pulmonary function tests taken within 6 months of consent in the study may be used to determine subject eligibility on a case-by-case basis at the discretion of the Site Investigator and the Medical Monitor.

6.4.12 Audiologic Evaluation

Patients with Fabry disease may experience audiologic symptoms such as tinnitus, vertigo, and progressive hearing loss. Subjects in this study will receive audiologic evaluations to monitor any hearing loss. For details, refer to the Study Reference Manual.

6.5 Immunogenicity

Immune responses to both the AAV6 capsid and the α-Gal A enzyme will be assessed by measuring total antibodies and/or neutralizing antibodies. Samples for cell-mediated immunogenicity will also be collected and stored for future analysis.

6.6 Future Research

Any samples collected from consenting subjects may be used for future research which may include analysis of biomarkers of renal function and severity of disease, response to therapy (e.g., cytokines, soluble cell surface proteins, soluble receptors), additional measures of α-Gal A activity/protein levels, correlation with functional improvements, as well as determination of AAV virus inhibition, function, immunogenicity, or pharmacodynamics (e.g., antibodies, soluble receptors, AAV viral receptor inhibitors, cytokines, co-existing alternate serotype antibodies).

7 INVESTIGATIONAL PRODUCT AND OTHER STUDY MEDICATIONS

7.1 ST-920

ST-920 is a recombinant AAV vector, AAV2 serotype 6 (AAV2/6), encoding human GLA cDNA.

Each lot of ST-920 is formulated at approximately 1.00E+13 vg/mL measured by qPCR in phosphate buffered saline (PBS) containing $CaCl_2$, $MgCl_2$, NaCl, Sucrose and Kolliphor (Poloxamer) P 188, filled at volumes of 5 mL or 10 mL into vials, and stored at ≤-65°C. The vials of ST-920 are labeled and have an aluminum seal with a flip-top.

A ddPCR test method is being developed to determine the level of vector genome (vg) titers for ST-920 and will replace the current qPCR method once fully implemented. The nominal genome copies (vg/mL) in the investigational product are not changing, just the method by which they are measured. The Investigational Product tested using the qPCR method that is within the approved shelf life will be used in ST-920-201 study until fully depleted. Clinical batches tested using ddPCR method will be used to support the ongoing ST-920-201 study. The Quality dossier

with the ddPCR data will be submitted for review prior to the introduction of the ddPCR material into ST-920-201.

7.1.1 Inventory, Storage, and Handling of the Drug Product

The investigational product required for subject treatment will be shipped to the study center with dry ice and temperature monitoring device and will be required to be stored at ≤-65°C (with temperature monitoring) prior to the scheduled infusion.

A Clinical Certificate of Analysis (CcoA) will accompany each investigational product shipment. The vials will have a label affixed containing the following information: vector identity, lot number, concentration, volume, storage conditions, manufacturer, date of manufacturing, Sponsor, and "Caution: For investigational use only."

Subject-specific kits, in the quantities required based on the subject's weight and cohort, will be prepared for shipment to the facility where IP infusion will take place. Kit labels will contain the following additional information: subject ID number, protocol number, and quantity.

The study center is required to maintain complete records of all study products received during the course of this study, as well as of labeled product that is dispensed. At the conclusion or termination of this study, return or destruction of all drug supplies must be pre-approved and coordinated with the Sponsor (Refer to the Pharmacy Manual for additional details).

The Site Investigator agrees not to supply labeled product to any person other than study personnel and subjects in this study.

7.1.2 ST-920 Administration

ST-920 will be administered by IV infusion using a peristaltic pump or IV infusion pump. ST-920 should be prepared by a research pharmacy at or near the health care facility and will be administered through an IV catheter at a controlled speed while monitoring the subject's vital signs (heart rate, blood pressure, respiratory rate, 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.

Following ST-920 infusion transient fever, chills, and/or nausea may occur. All subjects must be pre-medicated with acetaminophen 650 mg and diphenhydramine hydrochloride (Benadryl®) 25-50 mg by mouth or IV, or equivalent as per site practice, approximately one hour prior to the administration of ST-920. Post- infusion fever and/or chills can be treated with antipyretics not exceeding the maximum recommended daily dose and following guidance on the applicable product label. If fever and/or chills recur or persist for 24 hours, an evaluation to rule out infection should be conducted.

7.1.3 Precautions

ST-920 is an investigational product, and there is a potential risk of infusion reactions. Emergency medical equipment must be available during the infusion in case the subject has a

severe infusion reaction. 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).

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).

All medications are permitted with limited exceptions. The use of potentially hepatotoxic agents including herbal supplements may be allowed based on discussion and agreement with the Medical Monitor.

For subjects receiving ERT, ERT must have been administered at a stable dose and regimen (defined as not having missed more than 3 doses of ERT during the 6 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 (Section 3.6). Administration of all ERT should be obtained and recorded in the ERT Administration Log.

Subjects who are ERT-naïve or ERT-pseudo-naïve (defined as not having received ERT treatment in the 6 months prior to baseline) may not initiate treatment with ERT during the study period, unless dictated by clinical circumstances and following discussion with the Sponsor Medical Monitor. Subjects may not initiate treatment with migalastat (Galafold™) during the study period.

Treatment with prednisone or other equipotent steroid and pre-treatment with acetaminophen and diphenhydramine hydrochloride should also be recorded on the concomitant medications page.

8 SAFETY AND POTENTIAL RISKS

Study ST-920-201 is planned as the first-in-human study to assess the safety and tolerability of ST-920. There are currently no identified risks with ST-920. Potential risks associated with ST-920 include immune reaction to the vector and/or transgene, off-target effects, insertional mutagenesis (carcinogenesis), and risk of horizontal and vertical transmission. For details refer to current version of the Investigator Brochure.

9 SAFETY MONITORING AND ADVERSE EVENTS

9.1 Definitions

9.1.1 Adverse Event

An 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.

A medically important event (i.e., an AE that may not result in death, be life-threatening, or require hospitalization, but may be considered serious when, based upon appropriate medical judgment, the AE may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above; examples of such medical events include but are not limited to allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalizations.)

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 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. Further assessments may be done if indicated for evaluating and monitoring the AE(s).

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 non-invasive 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 an outcome and not an AE. 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 or designee.

Relationship to Study Treatment

The relationship of the AE to the investigational drug and corticosteroids if administered 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 or the corticosteroid if there is not a reasonable possibility that the event has been caused by the product under investigation or the corticosteroid. 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 or the corticosteroid 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 or the corticosteroid, must be reported immediately to Sponsor's designee, Medpace Clinical Safety, on an SAE Report form within 24 hours of the Site Investigator's awareness.

MedPace Clinical Safety SAE Report Notification:
Email: Medpace-safetynotification@medpace.com
Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3 or +49 89 89 55 718 44
Fax: +1-866-336-5320 or +49 89 89 55 718 104

Completion Guidelines of the SAE Report Form should be referred to when completing the SAE Report Form. Medpace Clinical Safety will query the Site Investigator regarding any further information or documentation that is required for a complete case report. Follow-up reports must be submitted within 24 hours from the time that the additional information becomes available. All SAEs must be followed with appropriate medical management until resolved or stabilized.

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

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 Reporting

Pregnancies of female subjects and pregnancies of male subjects' partners occurring during this study are to be reported to Medpace Clinical Safety on the Pregnancy Reporting Form, as per reporting details above in Section 9.4. 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.

9.7 Overdose Reporting

Overdose refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. For this study, administration of the investigational medicinal product, ST-920, in excess of the protocol defined dose is required to be reported within 24 hours of awareness, regardless of whether the overdose is associated with clinical sequelae. The Investigator must complete an Overdose Report Form and submit to Medpace Clinical Safety, as per Section 9.4 above.

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/ Medicines and Healthcare products Regulatory Agency [MHRA] or equivalent), Site Investigator, or Sponsor.

Subjects who, after dosing, 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

Elevation of liver enzymes has been observed in other trials using AAV2/6. Therefore, liver tests (AST, ALT, bilirubin, alkaline phosphatase, and GGT) will be monitored closely throughout the study.

These will be performed twice weekly during the first 20 weeks after ST-920 infusion, weekly for four weeks (Weeks 21-24), and then monthly thereafter to coincide with study visits (Weeks 28-52) in all subjects, and may be conducted remotely.

If there is a need to initiate corticosteroid treatment as a result of elevated liver enzymes, liver enzymes will continue to be assessed at least twice a week until normalization and then per protocol thereafter analyzed locally or centrally.

10.3 Safety Monitoring Committee

An SMC with appropriate medical and scientific expertise was appointed to provide safety oversight for the study. The SMC is comprised of external subject matter experts, the study Medical Monitor, Sponsor's Drug Safety Lead, study Biostatistician, and Site Investigators as appropriate. The SMC will periodically meet during the study and provide recommendations to the Sponsor concerning dosing. The SMC will also convene at any time if an emergent safety issue emerges during the study or one of the stopping rules are met. These include:

- 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, with the exception of non-melanoma skin cancers and localized prostate cancer treated with curative intent

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, ST-920.

All data will be evaluated to determine whether changes should be made to the study or if accrual should be continued or halted. 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.

Relevant data from other trials sponsored by Sangamo may be shared with the SMC to expand the clinical experience, particularly as it relates to safety and dose, and such data can be used by the SMC to inform its recommendations for the present study.

The SMC may also recommend changes to the dose and enrollment of cohorts based on cumulative safety data from this and other Sangamo sponsored clinical trials that use *in vivo* AAV2/6-based therapy.

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 subject treatment, follow-up and safety.

When no further enrolling or dosing decisions are required of the SMC, the SMC will no longer meet on a regular basis. The Sponsor will continue to review the subject safety data on an ongoing basis.

11 STATISTICAL ANALYSES

11.1 Determination of Sample Size

This study will enroll up to 48 subjects (2 subjects in each of Cohorts 1, 2, 3, and 4 with potential enrollment of 4 additional subjects in Cohorts 1, 2a, 2b, 3a, 3b, 4a, and 4b, plus up to 6 subjects in each of the anti α-Gal A Ab positive, anti α-Gal A Ab negative, female, renal, and cardiac cohorts). 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 the 52 weeks 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

The primary objective of this study is to evaluate the safety and tolerability of ST-920. All statistical summaries will be descriptive in nature. All subjects who receive any portion of the ST-920 infusion will be included in the analyses. All analyses, summaries, and listing will be generated using SAS version 9.4 or later. Further analysis details will be provided in the statistical analysis plan (SAP).

11.2.1 Analysis of the Conduct of the Study

Enrollment, major protocol violations, and discontinuations from the study will be summarized by dose and 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 and cohort.

11.2.2 Primary Safety Analyses

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 TEAEs will be evaluated to address the primary endpoint of this study. A TEAE is any AE with an onset 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 and cohort. For each subject, the maximum reported severity of each AE will be used in the summaries by severity grade. In addition, summaries of all SAEs and AEs related to study treatment will be provided.

Additional safety evaluations will include:

- Routine hematology, chemistry, and liver tests, vital signs, ECG and ECHO
- Serial AFP testing and MRI of liver (or equivalent imaging modality) to monitor for liver mass.

For other safety evaluations, 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.

11.2.3 Secondary Analyses

At each sampling time point, the actual value and the change from baseline for plasma α-Gal A activity, Gb3 and lyso-Gb3, eGFR, ejection fraction, global longitudinal strain, and LVMI and left ventricular systolic function will be summarized by dose and cohort using descriptive statistics and plotted over the 1-year study period by dose and cohort. Similar summaries will also be provided for ERT naïve/ERT pseudo-naïve subjects, and separately for ERT subjects (migalastat subjects will be grouped with either the ERT naïve/ERT pseudo-naïve subjects, or with the ERT subject, based on the clinical response determined by the Investigator at Screening).

For subjects who undergo ERT withdrawal, changes from pre- to post-ERT withdrawal in the frequency and dose of ERT infusions will be evaluated and summarized using annualized total dose and number of infusions. Duration of ERT withdrawal may also be analyzed.

Clearance of ST-920 measured by vg in the different samples (plasma, saliva, urine, stool, and semen, if applicable) will be summarized over time by dose and cohort.

11.2.4 Exploratory Analyses

Data permitting, the following exploratory endpoints and their change from baseline summaries by dose and cohort will be provided at each sampling time point over the 1-year study period:

- LGE, native myocardial T1 values and T2 mapping measured by CMR
- High sensitivity troponin T, NT-proBNP and other cardiac biomarkers
- MLHF-Q summary score
- UPCR and UACR
- 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
- α-Gal A activity measured in skin

- Gb3 inclusion levels measured in skin in ERT-naïve and ERT-pseudo-naïve subjects and selected subjects previously on migalastat
- Gb3 and lyso-Gb3 urine for all subjects over time
- Pulmonary function over time
- Audiologic function over time

Data permitting, summaries of percent reduction from baseline at Week 24 by dose and cohort will be provided for:

- Gb3 inclusion in the kidney (assessed by kidney biopsy) in ERT-naïve and ERT-pseudo-naïve subjects and selected subjects previously on migalastat

Summaries by dose and cohort will be provided for the following exploratory endpoints at each sampling time point:

- Measurement of antibodies to AAV2/6
- Assessment of cell-mediated immune response to AAV2/6
- Measurement of immune response to α-Gal A

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APPENDIX 1: SCHEDULE OF EVENTS

PROCEDURE	Screening	Baseline (a)	Health Care Facility		Day	Week																ETV
					8	2	4	6	8	12	16	20	24	28 *	32 *	36	40*	44 *	48*	52 EOS	
	(w/in 8 weeks of Baseline)	(w/in 12 weeks prior to ST-920 infusion)	Day 1	Day 2	(+/- 1 day)	(+/-2 days)				(+/-1 week)			(+/-2 weeks)	(+/-1 week)					(-2 weeks/+ 1 month)		
Informed Consent	X																				
Medical History	X																				
Inclusion/Exclusion	X																				
Demographics	X																				
Fabry Gene Sequencing (b, c)	X																				
Infectious Disease Screening	X																				
Neutralizing Antibodies to AAV2/6 (d)	X																				
Physical Examination	X	X	X	X	X		X		X	X			X			X				X	X
Vital Signs (e)	X	X	X	X	X	X	X	X	X	X	X	X	X			X				X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory (f)	X	X	X (g)	X		X	X	X	X	X	X	X	X			X				X	X
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ERT Administration Log	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver Panel (h)	X	X (i)	X (g)	X									X	X	X	X	X	X	X	X	X
12-Lead ECG	X	X			X								X							X	X
ECHO (b)	X																			X	X
MRI of Liver (b, j)	X												X							X	X
eGFR (k)	X	X			X		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Diagnostic α-Gal A Testing (l)	X																				
α-Gal A Testing in Blood (m)	X	X (n)				X (o)							X	X	X	X	X	X	X	X	X
Gb3 and lyso-Gb3 Testing (m)	X	X (n)				X (o)							X	X	X	X	X	X	X	X	X
Iron panel (p)		X																			
Biomarkers of Renal Function in Urine	X	X							X	X			X			X				X	X

APPENDIX 1: SCHEDULE OF EVENTS (continued)

PROCEDURE	Screening	Baseline (a)	Health Care Facility		Day	Week															ETV
					8	2	4	6	8	12	16	20	24	28 *	32 *	36	40 *	44 *	48 *	52 EOS	
	(w/in 8 weeks of Baseline)	(w/in 12 weeks prior to ST-920 infusion)	Day 1	Day 2	(+/- 1 day)	(+/-2 days)				(+/-1 week)			(+/-2 weeks)	(+/-1 week)						(-2weeks /+1 month)	
Protein and albumin to Creatinine Ratio in Urine	X	X								X			X			X				X	X
Cardiac MRI (CMR) (q)	X	X											X							X	X
Blood samples for high sensitivity troponin T, NT-proBNP, and other cardiac biomarkers		X							X	X			X			X			X	X	X
Minnesota Living With Heart Failure Questionnaire (MLHF-Q) (r)		X											X							X	X
Circulating AFP	X						X		X	X			X							X	X
Skin Biopsy (s)		X											X							X	X
PT, PTT & INR (t)		X											X								
Kidney biopsy (t)		X											X								
Frequency of Pain Medication Use	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Short Form Brief Pain Inventory (BPI)		X								X			X			X				X	X
QOL (SF-36 Questionnaire)		X											X							X	X
GI Symptoms Rating Scale		X											X							X	X
Mainz Severity Score Index		X											X							X	X
PFTs (b)	X	X											X							X	X
Audiologic Evaluation		X																		X	X
Vector Genome PCR in Blood (Plasma)				X (12 hr post-infusion)																	

APPENDIX 1: SCHEDULE OF EVENTS (continued)

Vector Genome PCR in Blood (Plasma), Saliva, Urine, Stool and Semen (u)		X			X	X	X		X	X	X	X	X			X				X	
AAV Immunogenicity (v)		X					X	X		X			X			X				X	
Immune response to α-Gal A (m)	X	X					X		X	X	X		X			X				X	X
Future Research (optional) (w)	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ST-920 Infusion			X																		
COVID-19 Assessment (x)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (if applicable) (y)	X	X	X				X		X	X	X	X	X	X	X	X	X	X	X	X	X

* 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.

a) For subjects in screening or baseline whose visits are impacted by the COVID-19 situation, the duration of baseline can be extended up to 24 weeks without having to be screen -failed. The Investigator will discuss with Sangamo Medical Monitor to decide which tests need to be repeated to continue in the study on a case-by-case basis.

b) Assessments including ECHO, PFTs, and MRI of liver performed within 6 months of consent may be used for evaluation of inclusion/exclusion criteria on a --case-by-case basis at the judgment of the Site Investigator. Further, genetic marker analysis including Fabry disease gene sequencing will not be repeated as these will not change over time.

c) The assay will be performed on blood or saliva samples. If available, gene sequencing results obtained prior to the study may be used.

d) If dosing is not completed within 12 weeks of sample collection, the serum neutralization assay to AAV6 should be repeated.

e) Vital signs include height, weight, systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. For frequency, refer to the Study Reference Manual. Baseline weight obtained 2-4 weeks prior to ST-920 infusion should be used for dose calculation.

f) Clinical laboratory tests include hematology, urinalysis, and serum chemistry.

g) On Day 1, clinical laboratory tests and liver panel should be drawn prior to ST-920 infusion.

h) Liver panel does not need to be drawn as a separate sample if Clinical Laboratory Tests are obtained at the same visit. Liver panel (including assessment of AST, ALT, GGT, total and direct bilirubin, ALP, LDH and albumin) and total protein levels will be performed twice weekly from Week 1 through Week 20 after ST-920 infusion, weekly for four weeks (Weeks 21, 22, 23, 24 [±2 days]) and then monthly thereafter. Samples may be drawn tandemly for ALT, AST, ALP, and total bilirubin at either local or central labs with results to be utilized for decision on corticosteroid treatment. Liver tests may be conducted remotely and analyzed locally or centrally. If there is a need to initiate treatment with corticosteroids because of elevated ALT, liver enzymes will continue to be assessed at least twice a week until normalization and then per protocol thereafter analyzed locally or centrally.

i) The liver panel test for the baseline visit will be performed within 7-14 days of planned ST-920 dosing.

j) MRI or equivalent imaging modality for detection of liver masses.

k) eGFR calculated by creatinine levels in blood using the CKD-EPI formula.

l) This assay will be performed on plasma. If available, α-Gal A activity documentation obtained prior to the study may be used (plasma and leukocyte results are acceptable). For subjects who do not have a documented α-Gal A activity for diagnosis, a blood sample should be taken to measure plasma α-Gal A activity. For those subjects who are on ERT, this blood draw must be taken at least 14 days (± 1 day) after their last ERT infusion.

m) For subjects on ERT, α-Gal A, immune response to α-Gal A, Gb3 and lyso-Gb3 samples should be obtained at trough, defined as 14 days (+/- 1 day) after the previous ERT administration, and should be taken at the same time of the day (i.e. morning) as the subsequent enzyme and substrate samples in the study.

n) 2 samples will be taken at baseline on 2 different occasions at least 13 days apart (for subjects on ERT, preferably at the same time during the day [e.g. in the morning] and at ERT trough levels, defined as 14 days [± 1 day] after the previous ERT administration).

o) Samples will be taken every 2 weeks during the first 20 weeks after ST-920 infusion. For substrates analysis in urine, whether naive or on ERT, all samples should be collected in the morning (morning void). Samples may be collected remotely.

p) Iron panel will include iron, ferritin, total iron binding capacity, transferrin saturation and hepcidin

q) CMR can be done at screening or baseline. Results of a CMR completed within 6 months prior to consent can be used for screening or the baseline measure unless the parameters do not meet imaging guidelines. For all subjects, CMR will include LGE, T1 and T2 mapping.

r) These assessments will be performed only for subjects enrolled in cardiac cohort.

s) Unless contraindicated by a Site Investigator or physician.

t) Kidney biopsies will be voluntary for Cohort 2 and mandatory for subsequent cohorts and performed on ERT-naïve or ERT-pseudo-naïve subjects (defined as not having received ERT treatment during the 6 months prior to baseline) and selected subjects previously on migalastat who the Principal Investigator, in conversation with the Sponsor Medical Monitor, considers a non-responder to migalastat based on clinical and/or biochemical assessments only, unless contraindicated by a Site Investigator or physician. In subjects who will have a kidney biopsy, PT, PTT & INR will be done locally prior to kidney biopsy to ensure blood coagulation is normal.

u) Each type of sample (blood, saliva, urine, stool, semen [if applicable]) should be collected until 3 consecutive specimens of that sample type are reported as negative or undetectable for vector genome.

v) Samples for AAV immunogenicity will be taken at baseline, and Weeks 4, 12, 24, 36, and 52 to measure total antibodies to AAV6. Additional samples for cell-mediated immunogenicity will be collected at baseline, Week 6 and when ALT is elevated or when there is a 50% drop in α-Gal A expression and/or prior to initiation of a corticosteroid treatment if possible.

w) Future research specimens include plasma and serum.

x) Subject must be fully vaccinated at least one month before infusion with ST-920. COVID-19 Assessments will be performed as outlined in Appendix 7.

y) Serum pregnancy test should be performed by the central laboratory at Screening. At other visits, a urine pregnancy test should be performed by the local laboratory or Investigator.

APPENDIX 2: ERT WITHDRAWAL SCHEDULE OF EVENTS

PROCEDURE*	ERT Withdrawal Visit (a)	ERT Withdrawal Monitoring Visits (+/- 2 days) (b)		ERT Withdrawal Follow-Up Visit (+/- 2 days) (c)
		Week 4	Week 8	Week 12
Physical Examination	X			X
Vital Signs (d)	X			X
Clinical Laboratory	X			X
Concomitant Medications	X	X	X	X
AE Assessment	X	X	X	X
ERT Administration Log		X	X	X
Liver Panel (e)	X	X	X	X
α-Gal A Testing (f)	X	X	X	X
Gb-3 Testing (f)	X	X	X	X
Lyso Gb-3 Testing (f)	X	X	X	X
eGFR	X	X	X	X
Urine pregnancy test	X	X	X	X
ERT Clinical Assessment				X

* Assessments associated with ERT withdrawal that are duplicated at regularly scheduled study visits may be waived if visits are combined (Appendix 1).

a) ERT Withdrawal visit may occur at any time after the Week 4 visit (refer to Section 3.6 for additional guidance).

b) ERT Withdrawal Monitoring visits will occur on Week 4 and Week 8 ± 2 days after the ERT withdrawal visit. ERT Withdrawal Monitoring visits have assessments that do not require evaluation at the clinical site and may therefore be conducted remotely. Assessments for AEs and concomitant medications may be conducted by study staff over the phone.

c) The ERT Withdrawal Follow-Up visit will occur at Week 12 ± 2 days after the ERT withdrawal visit but can occur earlier at the discretion of the Site Investigator, if clinically indicated. However, ERT may be re-initiated at any time based on clinical circumstances or at the judgment of the Investigator.

d) Vital signs include height, weight, systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature; refer to the Study Reference Manual.

e) Liver panel (including assessment of AST, ALT, GGT, total and direct bilirubin, ALP, LDH, albumin, and total protein levels) does not need to be drawn as a separate sample if Clinical Laboratory Tests are obtained at the same visit.

f) Subjects must be able to provide additional samples for α-Gal A, Gb3, and lyso-Gb3 testing.

APPENDIX 3: CORTICOSTEROID REGIMEN

Corticosteroids may be initiated in response to ALT elevations that meet the criteria listed below at the discretion of the Investigator in discussion with the Medical Monitor.

ALT Level	Action
ALT ≥ 2x baseline but < ULN	1. Repeat liver panel within 24 hours 2. Rule out alternative etiology for ALT elevation and discuss with Sangamo's Medical Monitor 3. If ALT is ≥ 2 x ALT baseline in 2 consecutive assessments, start treatment with corticosteroids in consultation with the study Medical Monitor Continue monitoring liver tests twice weekly until ALT trends toward normalization and weekly until returns to baseline value
ALT ≥ 2x baseline and > ULN	1. Rule out alternative etiology for ALT elevation and discuss with Sangamo's Medical Monitor Start treatment with corticosteroids in consultation with the study Medical Monitor Liver enzymes will continue to be assessed at least twice a week until normalization and then per protocol thereafter analyzed locally or centrally.

Start oral prednisone or other equipotent corticosteroid at 60 mg/day for 1 week continuing with the following tapering down schedule:

Week 1	60 mg/day
Week 2	40 mg/day
Week 3	30 mg/day
Week 4	30 mg/day
Week 5	20 mg/day
Week 6	10 mg/day
Week 7	5 mg/day

Continue monitoring ALT throughout treatment. If ALT increases while on corticosteroids, the dose of prednisone (or equipotent corticosteroid) may be adjusted to a maximum of 90 mg/day after consultation with the study Medical Monitor.

APPENDIX 4: INSTRUCTION FOR LIVER BIOPSY SAMPLE COLLECTION AND TISSUE PREPARATION

Any subject who has an elevated alpha-fetoprotein and MRI mass suspicious for HCC or greater than 2 cm will undergo liver biopsy. Histopathologic examination and genomic analysis will be performed to evaluate the origin and nature of the tumor.

Liver Biopsy Sample Collection and Tissue Preparation for Genomic Analysis

Details of the histopathological evaluation, including the weight of liver tissue obtained from each biopsy sample, will be summarized in a report and sent to the Sponsor.

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, the Sponsor, 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. The Sponsor has therefore assigned a Medical Monitor to this study. Their duties are to aid the Site Investigator and, at the same time, the Sponsor 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 the Sponsor 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 the Sponsor. 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 the Sponsor.

The Site Investigator understands and agrees that the Sponsor 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 the Sponsor 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 the Sponsor 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 the Sponsor, 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 the Sponsor for review at least 60 days prior to submission of such written materials for publication, or any proposed oral presentation. The Sponsor 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, the Sponsor shall have the right to require the Site Investigator to, and Site Investigator shall, remove specifically identified confidential information of the Sponsor (other than the data or results of the study) and/or delay the proposed publication for an additional 60 days to enable the Sponsor 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 the Sponsor, and the Site Investigator must acknowledge his/her responsibilities thereunder.

APPENDIX 7: COVID-19 GUIDANCE: SCREENING ASSESSMENTS AND REMOTE VISITS

Screening Assessments and Monitoring for COVID-19 infection

At every study visit the site staff will monitor the subjects for COVID-19 symptoms as per individual site's process.

If there is no site-specific process, the site staff will ask the following questions:

1. Are you experiencing any of the following symptoms?
    a. New or worsening cough - Y/N
    b. Fever or feeling feverish - Y/N
    c. Shortness of breath - Y/N
    d. Sore throat - Y/N
    e. Body and/or muscle aches - Y/N
    f. Nausea, vomiting, and/or diarrhea - Y/N
    g. Loss of smell, and/or taste - Y/N
    (Questions regarding additional symptoms will be asked as per the updated list from CDC and WHO)
2. In the last 14 days, did you have close contact with a suspected or laboratory-confirmed COVID-19 patient? Y/N/ Don't know

If site staff checks yes to any of the above questions, the Investigator will discuss with Sangamo Medical Monitor to perform PCR test and the next steps. Serology test may be done during the study as per Investigator's discretion to measure -for SARS-CoV-2 antibodies and check for past infection. For details, refer to the Laboratory Manual.

An oral and/or nasal swab test will be done twice prior to study drug dosing to check for current COVID-19 infection using Polymerase Chain Reaction (PCR). In the future if a COVID-19 diagnostic test with similar specificity and sensitivity to PCR become available it may be used after discussing with the medical monitor. The first test can be done 10-14 days prior to planned dosing and the second test should be done 2-3 days prior to planned dosing. For details, refer to the Laboratory Manual.

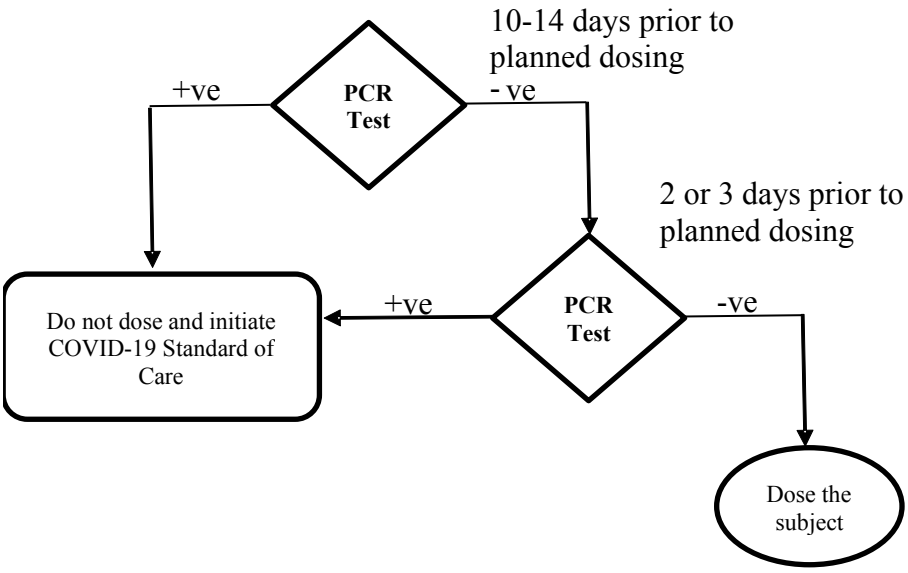

Figure 3: Schematic of COVID-19 Infection Testing Requirements

Subject Disposition in the Context of COVID-19

If a subject develops an active COVID-19 infection during the course of the study, the Investigator will work with the subject and the Sponsor Medical Monitor to determine the best course of action, delaying infusion until the COVID-19 infection has resolved. If a subject is withdrawn from the study because of COVID-19, the reason for early termination will be captured in the EDC system as such.

If the subject misses scheduled in-clinic visits due to COVID-19, an unscheduled visit will be conducted. At a minimum, clinical laboratory tests must be performed at the unscheduled visit. Wherever possible, subjects should not go more than 3 months or 2 consecutive scheduled visits without clinical laboratory tests being performed. For further information on remote visits, see Appendix 8.

For scenarios not delineated here or for further clarification, the Investigator should consult with the Sponsor Medical Monitor to determine the best course of action.

APPENDIX 8: REMOTE VISITS

Some visits to be conducted as remote visits consisting of a combination of telemedicine and/or home health visits at the subject's home, rather than requiring the subject to attend the clinical site for certain in-clinic visits. This is acceptable for certain visits according to the type of assessments required or under certain special circumstances, such as in response to COVID-19 (see Appendix 7).

A remote visit can only be conducted if the investigator and subject are in agreement, and there are no specific health concerns for the subject that require them to attend the clinical site. The Investigator should consult with the Sponsor Medical Monitor to determine the best course of action. If in-clinic visits are no longer possible, assessments categorised as in-clinic only activities will not be conducted.

Remote visits will be conducted by a Home Health Provider engaged by the Sponsor or CRO. The Home Health Provider will provide qualified and experienced research nurses who will be selected based on appropriate experience and location in relation to the clinical sites. The research nurses will undergo study-specific training and will be familiar with this clinical protocol as well as other relevant study documentation. The research nurses will be provided with study-specific manuals that include guidance on the visit schedule, individual assessments and standard process for conducting each visit.

The option of remote visits will be described to the subject during the consenting process and subjects will decide whether or not they consent to use this service.

For remote visits, some clinical laboratory assessments may be conducted by a central laboratory rather than at the local laboratory for each study site. Please refer to the Laboratory Manual for further details.