A Pilot Investigator Initiated Study to Evaluate the Safety, Tolerability and Efficacy of Elamipretide in the Treatment of Advanced Symptoms of Friedreich Ataxia (FRDA)

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Short Title: FRDA Investigator Initiated Study (IIS) with Elamipretide

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Principal Investigator (PI)/IND Sponsor: Dr. David Lynch, The Children's Hospital of Philadelphia (CHOP)

Research Sponsor: Friedreich Ataxia Research Alliance (FARA)

Industry Sponsor: Stealth Biotherapeutics, Inc. (SBT)

PROTOCOL SYNOPSIS

Protocol Title: A Pilot Investigator Initiated Study to Evaluate the Safety, Tolerability and Efficacy of Elamipretide in the Treatment of Advanced Symptoms of Friedreich Ataxia	
Protocol Number: SPIFA-101	**Phase**: Phase I/II
Test Drug: ELAMIPRETIDE	**Indication**: Friedreich Ataxia (FRDA)
Number and Country of Study Sites: 1 study center in the United States.	

Objectives:

Primary Study Objective

To evaluate the safety, tolerability, and activity of ELAMIPRETIDE in treating vision loss in Friedreich Ataxia (FRDA).

Primary Efficacy Objective.

To evaluate the effect of high dose (40-60mg) vs low dose (20-30mg) ELAMIPRETIDE on high contrast visual acuity in FRDA compared to baseline at 52 weeks with the option to extend for an additional 52 weeks if there are objective signs of clinical improvement on primary or secondary endpoints. The interim analysis will be based on data from a 36-week visit. For subjects worse than 20/800 at study start, they will be followed using low vision alternatives only.

Secondary Efficacy Objectives

To evaluate the effect of high dose ELAMIPRETIDE at 52 weeks compared to low dose, on

- Low contrast vision
- Low luminescence visual acuity
- Ocular Coherence Tomography (retinal ganglion cell loss)
- Visual Function Questionnaire (patient reported outcome measure)
- Cardiac strain defined as $\varepsilon = (L-L_0)/L_0$ in each dimension (Echo only)
- Cardiac fibrosis, as measured by T1 mapping (CMR only)
- Stroke volume, cardiac

Study Design:

This is an, single site study examining the safety and efficacy of high dose vs low dose-ELAMIPRETIDE in the treatment of advanced stage FRDA symptoms, specifically vision loss and cardiac disease in adults and older children. Subjects who have genetically confirmed FRDA with onset before age 18, with vision loss (VA worse than 20/40) at the time of study initiation or an ejection fraction (EF) less than 50% with visual acuity worse than 20/20 at the time of study initiation are eligible. All subjects who choose to participate will receive high dose vs low dose-ELAMIPRETIDE and then be followed for 52 weeks. All subjects in this study will return at 16 weeks, 36 weeks, and 52 weeks for evaluation. An interim analysis on the safety and efficacy data from the 36-week visit will be conducted when the final subject reaches 36 weeks and used to make a determination on continuing the study for an additional 52 weeks beyond the week 52 visit (the next scheduled visit after 36 weeks).

Details of study activities are provided in the *Schedule of Assessments*.

Subject Population:

Subjects with genetically confirmed FRDA and VA worse than 20/40 (binocular) or an EF of less than 50% with visual acuity worse than 20/20. There will be up to 30 subjects enrolled (consented), for a total of 16 evaluable subjects on study drug.

For subjects qualifying by vision dysfunction, most subjects will have high contrast visual acuities of 20/50 to 20/800. The others will have VA worse than 20/800 but will have at least equal to hand motion vision. These subjects will be followed using the low vision alternatives to high contrast VA.

For subjects enrolled based on cardiac dysfunction, EF at most recent echocardiogram (within 1 year) must be less than 50%, and they must have a visual acuity worse than 20/20.

Inclusion Criteria:

Eligible subjects must meet **all** of the following criteria:

1. Genetically confirmed FRDA (point mutations or deletions allowed).
2. Age $\geq$16 years.
3. Disease onset before 18 years of age.
4. If female, the subject is not pregnant or lactating or intending to become pregnant before, during, or within 30 days after the last dose of study drug. Female subjects of child-bearing potential must have a negative serum pregnancy test result at Screening, a negative urine pregnancy test result at Baseline.
5. All subjects must agree to use a reliable method of contraception throughout the study and for 30 days after the last dose of study drug. Male subjects should not father a baby during the study or for at least 30 days after the last dose of study drug.
6. All concomitant medications (including over-the-counter medications), vitamins, and supplements must be at stable doses for 30 days prior to study entry and kept stable throughout the study to the best of their ability.
7. Visual acuity (VA) worse than 20/40 (binocular) on the basis of FRDA. Must not be correctable by refraction, or subjects must have sufficient physical exam findings of optic neuropathy (funduscopic, visual fields, or retinal ganglion cell loss) to justify the primary diagnosis of FRDA related optic neuropathy

Or

8. EF less than 50% at last evaluation (within 1 year before screening), with a history consistent with cardiomyopathy from FRDA, and VA 20/25-20/40.

Exclusion Criteria:

Eligible subject must meet **none** of the following criteria:

1. Any unstable illness that in the investigator's opinion precludes participation in the study.
2. Use of any investigational product within 30 days prior to Screening.
3. A history of substance abuse.
4. Diagnosis of active HIV or Hepatitis B or C infection.
5. Presence of severe renal disease (eGFR <30 mL/min) or hepatic disease (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] >2x the upper limit of normal) as evidenced by laboratory results at Screening.
6. Clinically significant abnormal white blood cell count (ANC <1500), hemoglobin (< 9.0 gm/dL), or platelet count (100 K or >500 K) as evidenced by laboratory test results at Screening.
7. Any other active cause of optic neuropathy (Vitamin B12 deficiency, Vitamin E deficiency, etc.) or cardiac disease

8. EF less than 35% at last echocardiographic evaluation
9. Uncontrolled arrhythmia
10. Current use of any systemic chronic immunosuppressive drugs
11. Current use of Metformin

Dose Regimen/Route of Administration:

Subjects will receive daily subcutaneous (SC) dosing of ELAMIPRETIDE (40-60 MG or 20-30 mg)

Dosage Form and Strength Formulation:

80 mg/mL sterile solution of SC ELAMIPRETIDE will be used in this study.

Duration of Treatment and Follow-Up:

The planned treatment duration is 52 weeks (1 year) with the option to extend for an additional 52 weeks (2 years).

Criteria for Evaluation:

Safety Assessments

- Adverse event (AE) and serious adverse event (SAE) monitoring, concomitant medication monitoring, and physical examinations throughout the study.
- Vital signs, clinical safety laboratory evaluations (complete blood count, chemistry, PK, and urinalysis), and pregnancy testing (if applicable) at all on-treatment clinic visits.
- Electrocardiogram (ECG) at Screening, Baseline/Day 1, with additional ECGs at 16 week, 36 weeks, 52 weeks, and 104 weeks.

Efficacy Assessments

- High contrast visual acuity (primary outcome) or low vision alternative*
- Low contrast visual acuity
- Low luminescence visual acuity
- Optical coherence tomography (OCT) of the retina
- Visual Function Questionnaire (VFQ)
- Cardiac MRI (CMR) or Echocardiogram (Echo)** only Baseline, 36 weeks, and 104 weeks (final efficacy assessment)

Additional Efficacy Assessments

- Modified Friedreich Ataxia Rating Scale (mFARS) Neurological Exam
- FRDA Activities of Daily Living (FA-ADL)
- FRDA Functional Disability Scale
- Redenlab Speech Assessments
- Patient Global Impression of Change (PGIC)
- Clinician Global Impression of Change (CGIC)

All done at Baseline, 16 weeks, 36 weeks, 52 weeks and 104 weeks, (Except OCT, CMR, Echo, FRDA-ADL, mFARS, PGIC and CGIC at Baseline, 36 weeks and 52 or 104 weeks)

**Low vision alternative will include quantitative testing of hand motions and count fingers assessments based on available references*

***Echo's will be offered as an alternative for subjects who are not cardiac MRI compatible, as well as for scheduling conflicts when the cardiac MRI is not available.*

Statistical Analyses:

Safety Endpoints,

Adverse event and concomitant medication data will be summarized. Clinical laboratory safety data, vital sign data, and ECG interval data will be summarized with descriptive statistics for Baseline, post-dose, and change from Baseline to post-dose values.

Efficacy Endpoints

For visual function, the primary efficacy endpoint is the observed change from Baseline to Week 104 in high contrast visual acuity as compared to baseline.

Individuals with worse than 20/800 vision at baseline will be analyzed as a separate group, using recovery of light perception, hand motions, or recovery to 20/800 vision (lowest line on ETDRS charts). (Early treatment in Diabetic retinopathy study)

Secondary Efficacy Endpoints

Comparison between Baseline and Week 52 in

- Low contrast vision scores
- Retinal nerve fiber layer on OCT
- VFQ
- CMR –fibrosis by T1 mapping (CMR only)
- Ejection fraction
- Stroke volume
- Strain (Echo only)

Sample Size Estimate:

At least 8 subjects with VA 20/40-20/800 inclusive on both sides

At most 8 subjects with VA worse than 20/800.

At least 3 subjects with EF <50%

SCHEDULE OF ASSESSMENTS

Study Phase	Screening	Baseline										
Visit #	-1	0	1	2	3	4	5	6	6	7	8	9
Study Days (± visit window)	-60 to 0 days	Day 0	Day 7 ± 7	Day 28 ±14	Day 112±14	Day 252±14	Day 364±14	Day 476±14	Day 476±14	Day 616±14	Day 728±14	Day 756±14
Study Week	-8-0	0	1	4	16	36	52	68	68	88	104	108
Type of Visit	In person	In person	Remote	Remote	In person	In person	In person	Optional In person	Remote	Remote	In person	Remote
Expected Volume of Blood Collected	10 mL	8 mL			8 mL	8 mL	8 mL				8 mL	
Informed Consent	X											
Review of Inclusion/Exclusion Criteria	X	X										
Demographics, Medical History, Genetic Confirmation; Randomization	X											
Physical Examination	X	X			X	X	X	X			X	
Vital Signs: BP, HR, Temp, RR	X	X			X	X	X	X			X	
Weight, Height, BMI	X	X			X	X	X	X			X	
Prior/Concomitant Medications	X	X			X	X	X	X			X	
Clinical Laboratory Evaluation (CBC, CMP, GGT, LDH, CPK, Mag, Phos)[2]	X	X			X	X	X				X	

Pregnancy Test (Serum/Urine)	X	X			X	X	X	X			X	
HIV, Hepatitis B/C Testing	X											
Plasma for Biomarkers (Serum Ferritin[3], Krebs cycle enzymes[4]), Storage for future use		X									X	
Binocular VA[5]	X	X			X	X	X	X			X	
OCT[6]	X	X				X	X	X			X	
Electrocardiogram[16] (ECG)	X	X			X	X	X				X	
Echocardiogram[16] (Echo)	X	X				X					X	
CMR[1]		X				X					X	
Low Contrast VA[7]	X	X			X	X	X	X			X	
Low Luminescence VA[8]	X	X			X	X	X	X			X	
VFQ[9]	X	X			X	X	X	X			X	
Vision App[10]		X	X	X	X	X	X	X	X	X	X	X
Functional Disability Scale[11]	X	X				X	X	X			X	
Redenlab Speech Test[12]	X	X			X	X	X				X	
Activities of Daily Living[13]	X	X				X	X	X			X	
Exit Interview						X						

CGIC/PGIC[14]	X*	X*				X	X	X			X	
mFARS Exam[15]	X	X				X	X	X			X	
Dispense Study Drug		X			X	X	X	X				
Drug Compliance					X	X	X	X			X	
Dispense Subject Diary		X			X	X	X	X				
Collect, Review, Return Subject Diary					X	X	X	X			X	
AE/SAE Assessment (phone calls between visits as needed)			X	X	X	X	X	X	X	X	X	X
End Treatment							X				X	

Footnotes

1. CMR: Cardiac Magnetic Resonance Imaging
2. Clinical Labs: CBC – Complete Blood Count, CMP – Complete Metabolic Panel; GGT – Gamma-Glutamyl Transferase; LDH – Lactate Dehydrogenase; CPK – Creatine Phosphokinase; Mag – Magnesium; Phos – Phosphorus
3. Ferritin: Serves as an FRDA biomarker as frataxin deficiency decreases ferritin levels
4. Krebs Cycle Enzymes: Performed by western blot of blood
5. Binocular Visual Acuity: Performed with both eyes open and represents a real-world visual assessment using ETDRS High Contrast letter charts.
6. OCT: Optical coherence tomography measures the thickness of the retina including the ganglion cell layer
7. Low Contrast Visual Acuity: Performed with both eyes open using Sloan low contrast letter charts. It represents a real-world visual assessment.
8. Low Luminance Vision: Performed with both eyes open and represent a real-world visual assessment. Used ETDRS High Contrast letter charts and a neutral filter over the light source
9. VFQ: Visual function questionnaire 25 is a NIH created measure for assessing visual quality of life.
10. Vision App: This is the eye handbook app which is used to assess vision remotely.
11. Functional Disability Scale: Is a measure of gait and disability used in assessment of ataxias
12. RedenLab Speech: Measured by a computer driven test of sentence repetitions.
13. ADL: The activities of daily living scale is an FRDA directed questionnaire addressing 9 types of activities in FRDA.
14. Exit Interview: Questionnaire to measure subject's feedback about the study drug.
15. CGIC/PGIC: At Screening/Baseline (*), clinicians and patients will complete a questionnaire to assess the severity of their illness, as well as their most bothersome symptom of the disease. After Screening, all follow-ups will require a simple one-question assessment for clinicians and patients to assess the overall change since starting study drug regarding benefit or worsening over time.
16. mFARS: This is an FRDA directed quantified neurological exam used as an outcome measure in FRDA subjects with up to moderate disease.
17. Cardiac MRI or Echo: Subjects will complete either the Cardiac MRI or an Echo, not both procedures. Once they are assigned to a specific group (based on MRI compatibility and/or scheduling conflicts) at the Baseline Visit, they will continue in that group for the remainder of the trial.

Abbreviations

AE	Adverse Event
BMI	Body Mass Index
CBC	Complete Blood Count
CGIC	Clinical Global Impression of Change
CHOP	Children's Hospital of Philadelphia
CMP	Comprehensive Metabolic Panel
CMR	Cardiac Magnetic Resonance Imaging
CPK	Creatine Phosphokinase
CRF	Case Report Form
ECG	Electrocardiogram
Echo	Echocardiograph
eGFR	Estimated Glomerular Filtration Rate
FA-ADL	Activities of Daily Living Scale for Friedreich Ataxia
FARA	Friedreich Ataxia Research Alliance
FARS	Friedreich Ataxia Rating Scales
FRDA	Friedreich Ataxia
FXN	Frataxin Gene
GGT	Gamma-Glutamyl Transferase
HIV	Human Immunodeficiency Virus
IVSTd	Interventricular Septal Thickness in Diastole
LDH	Lactate Dehydrogenase
LVH	Left Ventricular Hypertrophy
LVIDd	Left Ventricular Internal Diameter in Diastole
LVIDs	Left Ventricular Internal Diameter in Systole
LVOT	Left Ventricular Outflow Tract
mFARS	Modified Friedreich Ataxia Rating Scales
OCT	Optical Coherence Tomography
OTC	Over the Counter
PGIC	Patient Global Impression of Change
PK	Pharmacokinetic
PWTd	Posterior Wall Thickness in Diastole
RNA	Ribonucleic Acid
RVWTd	Right Ventricular Wall Thickness in Diastole
SBT	Stealth Biotherapeutics, Inc.
SC	Subcutaneous
SS31	Another name for Elamipretide
VA	Visual Acuity
VFQ	Visual Function Questionnaire

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1. Background Information and Rationale

1.1 Introduction

FRDA is a progressive neurodegenerative disorder with a prevalence of about 1 in 50,000 persons in the United States (1). Patients present with difficulty walking, loss of coordination, and dysarthria. Degeneration of the dorsal root ganglion neurons, their axons in the dorsal columns, and the dorsal spinocerebellar pathways gives rise to loss of proprioception and ataxia. A few other nuclei (including the dentate nucleus of the cerebellum) within the central nervous system (CNS) are affected and contribute to the ataxia. Additional clinical manifestations include cardiomyopathy, diabetes, scoliosis, optic neuropathy and sensorineural hearing loss, and as people approach later stages of the disease the cardiac and neuro-ophthalmological features of the disease become dominating (2-3). Indeed, cardiac disease is the major cause of early death in FRDA and over time at least 20% of people with FRDA become legally blind. These later stage patients would be greatly improved in quality of life by treatment targeted to these aspects of FRDA.

The abnormal gene in FRDA and its product (frataxin) provide insight into pathophysiological mechanisms in this disease (1). An expanded GAA triplet repeat is found in both alleles of the *FXN* gene in 98% of people with FRDA. This repeat is located within an intron, decreasing RNA transcription and levels of frataxin protein. Frataxin is targeted to the mitochondrion, where it modulates synthesis and repair of mitochondrial iron-sulfur clusters. This may initiate or propagate free radical reactions leading to cell death, consistent with mitochondrial dysfunction as a pathophysiological mechanism in FRDA. These observations suggest possible therapies for slowing the progression of FRDA, such as administration of antioxidants or other approaches that augment mitochondrial function.

1.2 Name and Description of Investigational Product

ELAMIPRETIDE (SS-31) is a tetra peptide with limited blood brain barrier penetration being developed for use in a variety of mitochondrial disorders, including FRDA, mitochondrial myopathy and Barth syndrome. It is believed to stabilize cardiolipin in the mitochondrial membrane, leading to improved mitochondrial function and decreased levels of toxic reactive oxygen species production, In animal and cellular models, ELAMIPRETIDE has reversed mitochondrial fragmentation and markers of disease in models of mitochondrial cardiomyopathies, FRDA, Barth syndrome and other disorders (4-6).

1.3 Findings from Clinical Trials and Experience

1.3.1 Clinical Experience in Adults and Children

In clinical trials in multiple mitochondrial disorders, ELAMIPRETIDE has been well tolerated and shows preliminary evidence of benefit. In a trial in primary mitochondrial myopathy, individuals treated with ELAMIPRETIDE at high dose subcutaneously walked farther in a 6 minute walk than those given placebo ($p = 0.053$). The increase in distance walked was also dose dependent ($p = 0.014$). No differences were observed in other efficacy and safety endpoints. The most common adverse events were headache and dizziness (17% and 8% of participants), but Placebo and treated individuals were not significantly different on adverse events. There were no serious adverse events. In a second study with intravenous ELAMIPRETIDE, the drug improved echocardiographic markers of heart failure during drug infusion. No serious adverse events were

noted. In a more recent study in Barth syndrome, subcutaneous ELAMIPRETIDE (40 mg) improved six minute walk scores. There were no serious adverse events. Interestingly benefit began to accrue after 6 months of treatment.

1.4 Selection of Drugs and Dosages

Elamipretide is available in a variety of forms: IV, SQ, and Ophthalmic. The subcutaneous form is being used as it gives high tissue levels to the heart and to the retina (higher to the retina than the ophthalmic form). The subcutaneous form has been used previously in mitochondrial myopathy and other diseases similar to FRDA, with a reasonable safety pattern.

1.5 Relevant Literature and Data

At present, the rationale for the use of ELAMIPRETIDE reflects its relative value in mitochondrial disorders, and *in vitro* data showing its ability to raise frataxin levels modestly and to reverse biomarkers of disease in FRDA. While there have been no direct trials in FRDA, but there is substantial biochemical evidence (Johnson et al., submitted). This is coupled with the lack of therapeutic alternatives for severely affected patients and the relative safety pattern of ELAMIPRETIDE. Present adverse events from ELAMIPRETIDE have been modest and based on its small size (4 amino acids) is not thought to be immunogenic.

In this trial, the present study will use clinical measures (visual acuity, neurological measures) and their surrogates (Cardiac MRI, optical coherence tomography) that are validated in FRDA. In addition, results can be placed in the context of existing FRDA natural history studies and other placebo-controlled trials from the past 5 years to better validate results and to assess their reproducibility for measuring clinical outcomes in the FRDA population (7-10). Dr. Lynch and colleagues at CHOP and the University of Pennsylvania have performed most of the studies on loss of vision in FRDA and are particularly adept at following its course as they have for > 20 years.

1.6 Compliance Statement

This study will be conducted in full accordance with all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, 21 CFR Parts 50, 54, 56, 312, 314 and 812 and the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonization (ICH). All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with The Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2. Study Objectives

The overall objective of this study is to explore whether treatment of late stage FRDA subjects (with visual and cardiac dysfunction) with ELAMIPRETIDE is safe, well-tolerated and of potential clinical benefit.

2.1 Primary Objective (or Aim)

The primary objective of this study is to investigate whether treatment with high dose vs low dose- ELAMIPRETIDE has an impact on visual outcomes over a period of 104 weeks starting at baseline. The primary endpoint will be the change in visual acuity.

2.2 Secondary Objectives (or Aim)

The secondary objectives are:

- To assess the effect of high dose vs low dose- ELAMIPRETIDE on visual function (apart from high contrast acuity)
- To assess the effect of high dose vs low dose- ELAMIPRETIDE on cardiac function in FRDA using, cardiac magnetic resonance imaging (CMR) and echocardiogram
- To assess the effect of high dose vs low dose- ELAMIPRETIDE on activities of daily living (ADL).
- To assess the effect of high dose vs low dose- ELAMIPRETIDE on neurological abilities (using the mFARS).
- To measure the effect of high dose vs low dose- ELAMIPRETIDE on frataxin levels in whole blood as well as biomarkers of FRDA (Ferritin-a marker of NRF2 activity that is decreased in FRDA)
- To assess safety and tolerability of high dose vs low dose- ELAMIPRETIDE in patients with FRDA.

3. Investigational Plan

3.1 General Schema of Study Design

This is an open label study in which potential subjects will be screened first to assess eligibility, after which they will be treated with high dose vs low dose- ELAMIPRETIDE for up to 52 weeks, with an optional extension up to 104 weeks. We expect that all subjects will initially be enrolled over a 10-week period.

3.1.1 Screening Phase

Adults and children with FRDA will be recruited using the PI's clinical practice, the Friedreich Ataxia Research Alliance patient registry, and general in/exclusion criteria. Potential suitable candidates for the trial will contact the Investigator or his staff, receive a short overview of the study and, if interested, will be invited to attend a screening visit. Prior to any assessments being made the subject/parents will be fully briefed on the particulars of the study and will receive an informed consent form. Only after informed consent (or parent/guardian consent and child assent for pediatric patients) has been obtained will the screening assessments be performed.

3.1.2 Study Treatment Phase (Start of the Study Intervention)

If the subject is eligible for the study following screening procedures and is willing to participate in the study, he/she will proceed to the treatment phase. The screening and baseline assessment and initiation of ELAMIPRETIDE treatment can be completed on the same day or the subject can have the baseline/initiation of treatment visit within 60 days of the screening visit.

The subjects will be randomized to high dose or low dose study drug, by the REDCap Data Base Program. The subject will then receive an initial dose of high dose vs low dose- ELAMIPRETIDE at baseline/initiation. This will be continued for the duration of the study. Subjects will receive instruction in subcutaneous injection prior to initial administration (this has been used previously with this population).

After 36 weeks of treatment by all subjects, data will be prepared for analysis. If the data reveal no evidence of benefit, then the study will be discontinued at the next planned evaluation (week 52) and all subjects will proceed to close out visits at week 52. If the data show some evidence of benefit or stabilization (see interim analysis below), then the subject will continue on active drug until week 104.

3.1.3 Follow-up Phase

After 52 or 104 weeks of treatment, the subject will discontinue ELAMIPRETIDE. A final follow-up visit will occur at week 56 or week 108 by phone, during which adverse and serious adverse events will be reevaluated.

3.2 Allocation to Treatment Groups and Blinding

This is a 2-dose study. Subjects will receive the high dose vs low dose- in an unblinded fashion, as they will be aware of the volume they are receiving.

3.3 Study Duration, Enrollment and Number of Sites

3.3.1 Duration of Study Participation

Unless dose limiting toxicity occurs, the study duration per subject will be at least 364 days and up to 756 days (± 7 days), including follow-up. This includes a potential 60-day window between the screening and baseline/initiation of treatment visits, 364 days or 728 days of open-label treatment from baseline to the 52- or 104-week follow-up visit, and 28 more days for the final follow-up visit at week 108. If screening and baseline visits are performed on the same day, study participation will last 756 ± 7 days.

3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at one site, the Children's Hospital of Philadelphia (CHOP). The data will be stored and managed securely at CHOP.

Recruitment will stop when approximately 16 subjects are enrolled and found to be eligible for the study based on results from the screening visit. It is expected that approximately 30 subjects may be screened to produce 16 evaluable subjects.

3.4 Study Population

3.4.1 Inclusion Criteria

Eligible subjects must meet **all** of the following criteria:

1. Genetically confirmed FRDA (point mutations or deletions allowed).
2. Age ≥ 16 years.
3. Disease onset before 18 years of age.
4. If female, the subject is not pregnant or lactating or intending to become pregnant before, during, or within 30 days after the last dose of study drug. Female subjects of childbearing

potential must have a negative serum pregnancy test result at Screening, a negative urine pregnancy test result at Baseline.

5. All subjects must agree to use a reliable method of contraception throughout the study and for 30 days after the last dose of study drug. Male subjects should not father a baby during the study or for at least 30 days after the last dose of study drug.
6. All concomitant medications (including over-the-counter medications), vitamins, and supplements must be at stable doses for 30 days prior to study entry and kept stable throughout the study to the best of their ability.
7. Visual acuity (VA) worse than 20/40 (binocular) on the basis of FRDA. Must not be correctable by refraction, or subjects must have sufficient physical exam findings of optic neuropathy (funduscopic, visual fields, or retinal ganglion cell loss) to justify the primary diagnosis of FRDA related optic neuropathy

   Or
8. EF less than 50% at last evaluation, with a history consistent with cardiomyopathy from FRDA, and VA 20/25-20/40.

3.4.2 Exclusion Criteria

1. Any unstable illness that in the investigator's opinion precludes participation in the study.
2. Use of any investigational product within 30 days prior to Screening.
3. A history of substance abuse.
4. Presence of severe renal disease (eGFR <30 mL/min or hepatic disease (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] >2x the upper limit of normal) as evidenced by laboratory results at Screening.
5. Complete blood count with absolute neutrophil count (ANC <1500), hemoglobin (<9.0 gm/dL), or platelet count (<100 K or >500 K), as evidenced by laboratory test results at Screening.
6. Any other active cause of optic neuropathy (Vitamin B12 deficiency, Vitamin E deficiency, etc.) or cardiac disease
7. EF less than 35% at last evaluation
8. Uncontrolled arrhythmia
9. Presence of active HIV or hepatitis B or C infection
10. Current use of any systemic chronic immunosuppressive drugs
11. Current use of Metformin

Subjects that do not meet all of the enrollment criteria may not be enrolled, though laboratory values may be repeated once. Any violations of these criteria must be reported in accordance with IRB policies and procedures.

4. Study Procedures

4.1 Screening Visit (Visit -1; Day -60 to 0)

Screening evaluations will be performed either on the same day or within a 60-day period prior to baseline and initiation of treatment with ELAMIPRETIDE (Visit 0). The Investigator or staff will inform each prospective subject of the nature of the study, explain the potential risks, and obtain written informed consent from the subject (for pediatric subjects, parent/guardian informed

consent and subject assent) prior to performing any study-related procedures and prior to the administration of study drug. Screening evaluations will consist of the following:

1. Review of inclusion/exclusion criteria, informed consent and assent obtained
2. Demographics and medical history (including documentation of genetic testing)
3. Physical examination
4. Serum pregnancy test (applicable to women of childbearing potential; must have a negative pregnancy test)
5. Review of 12-lead electrocardiogram (ECG) and echocardiogram (ECHO) within previous 12 months; if a result is not available, the respective procedure will need to be performed at screening; if the most recent ECG or ECHO for the subject is dated more than 12 months before screening and shows a clinically relevant abnormality, that procedure will need to be performed at screening.
6. Vital signs (blood pressure, heart rate, temperature)
7. Height, weight, and BMI
8. Clinical global impression scale
9. Assessment of concomitant medications (including medication history)

The results of the screening evaluation must meet the full inclusion/exclusion criteria for the subject to continue in the study and begin treatment with study medication.

4.2 Study Treatment Phase

If all eligibility criteria are met, the subject can complete the Baseline Visit on the same day as the Screening Visit. If the subject is eligible for the study following all screening procedures and is willing to participate in the study, the subject will return within 0-60 days for the baseline assessment and initiation of high dose vs low dose- ELAMIPRETIDE treatment. Due the COVID 19 pandemic, extended windows (+/- 14 days) will be allowed to facilitate safe travel, and should safe travel become impossible, telemedicine visits will be performed to capture as much data as possible. The following procedures will be performed at each visit (see Table 1):

4.2.1 Visit 0 (Day 0) – Baseline and Initiation of Treatment

1. Review Inclusion/Exclusion Criteria
2. Physical examination
3. Vital signs (blood pressure, heart rate, respiratory rate and temperature)
4. Height, weight, BMI
5. Assessment of concomitant medications
6. Binocular Vision
7. Low contrast vision
8. Low luminance vision
9. Optical coherence tomography
10. ECG

11. Cardiac MRI or Echo
12. FARS neurological exam and functional staging
13. Clinical laboratory tests including CBC and CMP, plus biomarker sample collection
14. Pregnancy Testing (if applicable)
15. Redenlab speech measures
16. Questionnaires – ADL, VFQ, CGI and PGI scales
17. Eye Handbook cell phone based vision app, Visual acuity and low contrast charts
18. Randomize to high dose vs low dose
19. Dispense study medication and subject diary

4.2.2 Visit 1 (Day 7 +/- 7 days) (Remote)

1. Assessment of concomitant medications
2. Assessment of AEs and SAEs
3. Eye handbook cell phone based vision app, Visual acuity and low contrast charts

4.2.3 Visit 2 (Day 28 +/- 14 days) (Remote)

1. Assessment of concomitant medications
2. Assessment of AEs and SAEs
3. Eye handbook cell phone based vision app, Visual acuity and low contrast charts

4.2.4 Visit 3 (Day 112 +/- 14 days)

1. Physical examination
2. Vital signs (blood pressure, heart rate, respiratory rate and temperature)
3. Height, weight, BMI
4. Assessment of concomitant medications
5. Binocular Vision
6. Low contrast vision
7. Low luminance vision
8. ECG
9. Clinical laboratory tests include CBC and CMP
10. Pregnancy Testing (if applicable)
11. Redenlab speech measures
12. Questionnaires – VFQ
13. Eye handbook cell phone based vision App, Visual acuity and low contrast charts
14. Dispense study medication and new subject diary
15. Study Drug Compliance and subject diary review
16. Assessment of AEs and SAEs

4.2.5 Visit 4 (Day 252 +/- 14 days)

1. Physical examination
2. Vital signs (blood pressure, heart rate, respiratory rate and temperature)
3. Height, weight, BMI
4. Assessment of concomitant medications
5. Binocular Vision
6. Low contrast vision
7. Low luminance vision
8. Optical coherence tomography
9. ECG
10. Cardiac MRI or Echo
11. FARS neurological exam and functional staging
12. Clinical laboratory tests include CBC and CMP
13. Pregnancy Testing (if applicable)
14. Redenlab speech measures
15. Questionnaires – ADL, VFQ, CGIC and PGIC scales, Exit Interview
16. Eye handbook cell phone based vision App, Visual acuity and low contrast charts
17. Dispense study medication and new subject diary
18. Study Drug Compliance and subject diary review
19. Assessment of AEs and SAEs

4.2.6 Visit 5 (Day 364 +/- 14 days)

1. Physical examination
2. Vital signs (blood pressure, heart rate, respiratory rate and temperature)
3. Height, weight, BMI
4. Assessment of concomitant medications
5. Binocular Vision
6. Low contrast vision
7. Low luminance vision
8. Optical coherence tomography
9. ECG
10. FARS neurological exam and functional staging
11. Clinical laboratory tests include CBC and CMP
12. Pregnancy Testing (if applicable)
13. Redenlab speech measures

14. Questionnaires – ADL, VFQ, CGIC and PGIC scales
15. Eye handbook cell phone based vision App, Visual acuity and low contrast charts
16. Dispense study medication and new subject diary
17. Study Drug Compliance and subject diary review
18. Assessment of AEs and SAEs
19. End of Treatment

4.2.7 Visit 6 (Day 476 +/- 14 days) (Optional In person or Remote)

Optional In Person Visit

1. Physical examination
2. Vital signs (blood pressure, heart rate, respiratory rate, and temperature)
3. Height, Weight, BMI
4. Assessment of concomitant medications
5. Binocular Vision
6. Low contrast vision
7. Low luminance vision
8. Optical coherence tomography
9. FARS neurological exam and functional staging
10. Pregnancy Testing (if applicable)
11. Questionnaires – ADL, VFQ, CGIC and PGIC scales
12. Eye handbook cell phone based vision App, Visual acuity and low contrast charts
13. Dispense Study Medication and new Subject Diary
14. Study Drug Compliance and Subject Diary Review
15. Assessment of AEs and SAEs

Remote Visit

1. Assessment of concomitant medications
2. Assessment of AEs and SAEs
3. Eye handbook cell phone based vision App, Visual acuity and low contrast charts

4.2.8 Visit 7 (Day 616 +/- 14 days) (Remote)

1. Assessment of concomitant medications
2. Assessment of AEs and SAEs
3. Eye handbook cell phone based vision App, Visual acuity and low contrast charts

4.2.9 Visit 8 (Day 728 +/- 14 days), Close-Out Visit

1. Physical examination

2. Vital signs (blood pressure, heart rate, respiratory rate and temperature)
3. Height, weight, BMI
4. Assessment of concomitant medications
5. Binocular Vision
6. Low contrast vision
7. Low luminance vision
8. Optical coherence tomography
9. ECG
10. Cardiac MRI or Echo
11. FARS neurological exam and functional staging
12. Clinical laboratory tests include CBC and CMP, plus biomarker sample collection
13. Pregnancy Testing (if applicable)
14. Redenlab speech measures
15. Questionnaires – ADL, VFQ, CGIC and PGIC scales
16. Eye handbook cell phone based vision App, Visual acuity and low contrast charts
17. Study Drug Compliance and subject diary review
18. Assessment of AEs and SAEs
19. End of Treatment

4.3 Follow-Up Phase

4.3.1 Visit 9 (Day 756 +/- 14 days), Remote Close-Out Visit

1. Eye handbook cell phone based vision App, Visual acuity and low contrast charts
2. Assessment of AEs and SAEs

4.4 Unscheduled Visits

If unexpected symptoms arise, the subject may be scheduled for an unscheduled visit. Any clinical tests and procedures deemed sufficiently valuable by the investigator for the safety and care of the subject may occur during the visit. Such procedures may include the following activities:

1. Physical exam including weight
2. Vital signs (blood pressure, heart rate, and temperature)
3. 12-lead ECG and ECHO
4. Assessment of concomitant medications
5. FARS/neurological exam
6. Clinical laboratory test

7. ADL scale
8. Assess study medication compliance
9. Assessment of AEs and SAEs
10. Low contrast vision
11. Optical coherence tomography
12. Eye handbook cell phone based vision App, Visual acuity and low contrast charts

4.5 Concomitant Medication

Any medication taken by a subject prior to and during the course of the study and the reason for use of the medication will be recorded on the case report form (CRF). During screening, each subject will be instructed to report the use of any medication to the Investigator. Subjects will also be instructed about the importance of not taking any medication other than acetaminophen throughout the study (including over-the-counter [OTC] medications) without first consulting the Principal Investigator.

4.6 Subject Completion/Withdrawal

Subjects may withdraw or be withdrawn from the study at any time for reasons including the following:

- At their own request or at the request of their legally authorized representative (consent withdrawn);
- Use of any investigational drug other than the study medication;
- If, in the Investigator's opinion, continuation in the study would be detrimental to the subject's well-being (i.e. adverse or serious adverse events, undercurrent illnesses, onset of a clinically significant medical condition, pregnancy)

In all cases, the reason for withdrawal will be recorded in the case report form (CRF). If the reason is not known, the subject must be followed to establish whether the reason was due to an adverse or serious adverse event (AE or SAE), and, if so, this must be reported in accordance with the procedures in Section 9.

All Visit 5 (Day 364) evaluations must be performed on all subjects at the time of early withdrawal. These subjects must also complete follow-up visits (at 28 days after termination of study medication).

The Investigator will make every effort to contact subjects lost to follow-up.

Subjects who have an ongoing AE or SAE at the time of study completion will be followed until the event resolves, or until the Investigator believes that further follow-up is not medically necessary.

5. Study Evaluations and Measurements

5.1 Screening and General Monitoring Evaluations

5.1.1 Medical History, FRDA Medical History, Demographics and Randomization

At the screening visit the following information will be collected:

- Date of birth, age, gender, and race
- Confirmation of genetic diagnosis, performed in an accredited clinical lab: A copy of the genetic testing reports confirming a diagnosis of Friedreich ataxia will be requested by the study staff and will be provided by study subjects at the time of screening.
- Medical history related to FRDA will include age of symptoms onset, first symptom, age of diagnosis, ambulation history (age when assistive devices required, current device), history of cardiac disease, diabetes, hearing problems, vision problems, and scoliosis
- Medical history and a review of systems of other medical conditions related to Dermatological, Hepatobiliary, Neurologic (other than disease under study), Ophthalmological, Renal, Psychiatric, ENT, Gynecological/Urologic, Allergy/ Immunologic, Pulmonary, Musculoskeletal, Cardiovascular Metabolic/Endocrine, Gastrointestinal, or Hemato/Lymphatic
- Prior and concomitant medications will be collected at Screening and every visit and recorded onto medication log.
- A standard 12-lead ECG and ECHO will be performed at screening if a previous study has not been performed or is not available for review within a period of twelve months prior to the screening date.
    - Data captured from the ECG: date procedure performed, heart rate, PR interval, QRS duration, QT interval, QTC, if voltage criteria for LVH is met, presence and type of arrhythmia (if applicable) and interpretation and comments.
    - Data captured from the ECHO: date procedure performed, PWTd, IVSTd, LVIDd, LVIDs, presence/absence of LVH, presence/absence of dilation LV, presence/absence LVOT obstruction, RVWTd, Ejection Fraction, atrial regurgitation (none, mild, moderate, severe), mitral regurgitation (none, mild, moderate, severe), tricuspid regurgitation (none, mild, moderate, severe), LVOT peak velocity, mitral inflow E/A ratio (ratio of the early (E) to late (A) ventricular filing velocities), tissue doppler (normal or abnormal), interpretation and comments (1).
- Additionally, all adult subjects enrolled in the Echocardiogram subgroup will have their Echo performed by the CHOP CPHS Cardiology Core. Once their procedure is completed a de-identified copy of their images from the study are uploaded onto a secure CHOP share drive. Those reports are then uploaded into PennBox for the Penn CHPS Echo team, Dr. Bonnie Ky, to read/interpret, as the CHOP CHPS Cardiology Core is unable to read/interpret adult subjects. The Penn CHPS Echo team will email a de-identified report back to the CHOP team. This report will be confirmed and signed by Dr. Lynch, Study PI, and uploaded into EPIC under Media to ensure we are compliant with all CHOP policies.

Randomization: If subject meets eligibility criteria, randomization to high dose or low dose will be done by the REDCap Data Base Program.

5.1.2 Physical Examination

Complete physical exams will be conducted (excluding genital/rectal exam) at Screening, Baseline (Day 0), and visits 3, 4, 5, 8 (Day112, 252, 364, 728). The physical examination will consist of an examination of the following: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, and extremities. Brief physical exams will be conducted during unscheduled visits

5.1.3 Vital Signs, Height, Weight, and BMI

Vital sign measurements (pulse rate, blood pressure, and temperature) will be obtained in the sitting position (after the subject has been sitting for 5 minutes) at each visit.

Weight (kg) and height (cm) will be assessed in ordinary indoor clothing (i.e., street clothes, scrubs, etc.) with shoes off, and will be recorded at every visit. Body mass index will be calculated for these visits as well and is defined as the subject's weight in kilograms divided by the square of the subject's height in meters (kg/m^2).

If clinically significant findings, as determined by the Investigator, are recorded for a particular symptom, sign or abnormal measurement, these measurements will be repeated at medically appropriate intervals until the value returns to an acceptable range, a specific diagnosis is established, or the condition is otherwise explained.

5.1.4 Clinical Laboratory Evaluations

A total of no more than approximately 25 mL of blood will be collected per subject per study visit according to the study visit schedule. For each study subject, no more than 3mL/kg will be drawn in an 8-week period, and no more that 2mL/kg will be drawn at any single visit. Subjects will have approximately 5 mL of blood drawn per in person visit in this study for the following hematology and chemistry assessments listed below. Subjects will have up to an additional 8 mL of blood drawn per visit in this study for the research assessments of frataxin protein.

Hematology, and chemistry, testing will be performed at the outpatient laboratory at CHOP. The following hematology and chemistry variables will be collected at various times throughout the study (as detailed in Schedule of Activities) to assess safety.

- Hematology:

  Erythrocytes: red blood cell (RBC) count, hematocrit, hemoglobin, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), red cell distribution width (RDW), and reticulocyte count;

  Leukocytes: white blood cell count and differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils) reported as absolute values.

- Serum Chemistry:

  Liver: ALP, ALT (serum glutamic-pyruvic transaminase [SGPT]), AST (serum glutamic-oxaloacetic transaminase [SGOT]), bilirubin (total, direct, and indirect), gamma-glutamyl transferase (GGT), and lactic dehydrogenase (LDH); Renal: blood urea nitrogen (BUN), creatinine, and uric acid;

  Electrolytes: sodium, potassium, chloride, and carbon dioxide (CO_2 as bicarbonate);

General: Creatine phosphokinase (CPK), CK with reflex testing for isozymes if elevated, albumin, calcium, magnesium, phosphate, protein (total).

5.2 Efficacy Evaluations

These are the measures that will be used to assess the efficacy of the study intervention.

5.2.1 Primary Outcome Measure

The primary outcome measure will be the high contrast letter acuity. The result will be defined by the number of letters seen, with 7 letters more than baseline defined as a significant improvement. For individuals unable to see any letters at baseline, a significant improvement will be defined as being able to see 3 of 5 letters on the final line at the final examination

5.2.2 Secondary and Exploratory Outcome Measures

Secondary outcome measures will include the low luminance vision, color vision, ejection fraction, stroke volume and late gadolinium enhancement by cardiac MRI, mFARS scores, ADL and CGI scales

- Friedreich Ataxia Rating Scale (FARS): The FARS exam is a composite measure consisting of scores obtained from a standard neurological examination for FRDA and a number of timed tests as described previously. The summary value mFARS is calculated by omitting the bulbar peripheral nerve components
- Activities of Daily Living (ADL): The ADL questionnaire is a nine item instrument that focuses on physical activities.
- Patient Global Impression and Clinical Global Impression scales: The PGI rating scale is used to measure patient's observation of benefits and side effects from treatment. The CGI rating scale is used to measure symptom severity, improvement, and treatment efficacy based on the patient's own assessment (PGI) and the clinician's assessment (CGI). Severity and improvement are evaluated using a 7-point scale measuring patient status at present relative to baseline. Efficacy is evaluated on a 4-point scale with an additional scale measuring severity of side effects from treatment.
- Vision tests: Low luminance visions, Eye handbook cell phone based vision App, Visual acuity and low contrast charts. Each of these is a standard vision test in which a subject reads an eye chart under conditions of low contrast, low luminance (using a neutral filter placed in a light box and high contrast letter charts), or on a near card displayed by cellphone app. For the Eye Handbook app, it is expected that caregiver aid will be needed to facilitate testing in more severely affected individuals. The summary measure for each is the number of letters read.
- VFQ – This is a 25 item patient reported outcome on visual symptomatology. The summary measure is the total score.
- Optical Coherence Tomography- This is a clinically used technique to measure thickness of the retina. The summary measure is the retina thickness.
- Magnetic Resonance Imaging (MRI)/Echocardiogram: Cardiac MR imaging with gadolinium enhancement will measure stroke volume, strain and fibrosis (when available). Cardiac strain, defined as $\varepsilon = (L-L_0)/L_0$ In all dimensions, is measured by speckle tracking on echocardiographic studies . This parameter is abnormal in patients with FRDA.

- Serum Ferritin (biomarker of iron stores and NRF2 activity, which are depleted in FRDA)
- RedenLab Speech measures- This test provides a series of phrases and words provided through earphones and a computer that are recited by the subject. The speech produced is interpreted by a computer created paradigm and scored
- Exit Interview – A questionnaire to gauge the subject's feedback on the study drug and interest in continuing on drug.

5.3 Safety Evaluation

Safety will be evaluated by history updates, physical examinations, vital signs assessments, and routine clinical laboratory tests (including blood chemistry and hematology).

- Results from recent CBC and Chemistry Panel (if done within six months of screening visit). (See 5.1.4 for list of specific values collected). If CBC and blood chemistry have not been performed within six months of screening visit, this will be done at the CHOP outpatient laboratory at the screening visit.

If done within twelve months of screening date, records from all relevant clinical laboratory analyses will be requested from study subjects at the time of screening visits.

6. Statistical Considerations

6.1 Primary Endpoint

The change in visual acuity from baseline visit to 104-week follow-up visit.

6.2 Secondary Endpoints

The change in neurological outcomes and quality of life assessments including low contrast visual acuity

- Low luminescence visual acuity
- Optical coherence tomography of the retina
- Visual Function Questionnaire
- Cardiac MRI (Stroke volume and degree of late gadolinium enhancement)
- Echo (Strain, ejection fraction, stroke volume)
- Modified Friedreich Ataxia Rating Scale neurological exam
- FRDA Activities of Daily Living
- FRDA Functional Disability Scale
- Redenlab speech assessments
- Patient Global Impression of Change (PGIC)
- Clinician Global Impression of Change (CGIC)
- Eye handbook vision App

7. Statistical Methods

7.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender).

7.2 Efficacy Analysis

The primary analysis will be based on an intention to treat approach and will include all subjects who have baseline values at Visit 0.

The primary efficacy endpoint will be the change in visual acuity from baseline visit to the 104-week follow-up visit. It will be analyzed as the number of subjects with a significant improvement in vision compared to published natural history data. Comparisons will be made between the high dose vs low dose- groups.

Secondary endpoints will include changes to visual, neurological, and cardiac measure outcomes compared with baseline. Comparisons will be made between the high dose vs low dose- groups.

Exploratory endpoints include frataxin protein levels in whole blood from baseline visit to the 104-week follow-up visit. Comparisons will be made between the high dose vs low dose- groups.

For secondary outcomes, Data will be inspected for evidence of normality; if the data follow a normal distribution (skewness values less than 1), then paired t-tests will be used to compare baseline and treated outcome scores. If the data are not parametric, then appropriate non-parametric tests will be used.

7.3 Safety Analysis

All subjects entered into the study at Visit 0 will be included in the safety analysis. The frequencies of AEs by type, body system, severity and relationship to study drug will be summarized. SAEs (if any) will be described in detail. If necessary, an unscheduled visit will be arranged for the investigator to perform any clinical examinations and tests for the safety of the subject.

AE incidence will be summarized along with the corresponding exact binomial 95% two-sided confidence intervals. Comparisons will be made between the high dose vs low dose- groups

7.4 Sample Size and Power

In the absence of data on expected effect size, the analysis will be primarily exploratory in this investigator-initiated trial. Based on previous experience in FRDA, including with individuals of this age group, it is expected that a minimum of 16 subjects will be sufficient to identify a meaningful change in significant visual recovery in single patients (7 letters, return to chart) in a comparisons between the high dose vs low dose- groups. It is expected that no patients will improve to this degree in the absence of therapy. A successful result to the study will be defined by 50% of subjects improving by this degree.

7.5 Interim Analysis (separate safety and efficacy)

The safety monitor will review data at 50% enrollment for safety analysis.

Separately, after the 36-week visit, the statistician will analyze the data to establish whether any of the following criteria are met.

1. Significant improvement in vision for at least 3 of the subjects from baseline. A significant improvement will be defined for this analysis as an improvement of at least 3 letters on high contrast acuity, or a return of an individual to 20/800 (lowest line) for those unable to see the 20/800 line at baseline.
2. Improvement of the mean high contrast vision by 2 letters more in the high dose vs the low dose group.
3. Improvement of ejection fraction by at least 5 % in at least 3 of the subjects.
4. Improvement of the mean stroke volume by 5% across all subjects more in the high dose vs the low dose group.

Each of these individual criteria is chose based on the minimum amount to represent a biological change based on the day-to-day variability of the disorder. If any of these criteria are met, then the study will be continued. If none of these criteria are met, then the study may be discontinued.

8. Study Medication

8.1 Description

ELAMIPRETIDE (also known as MTP-131 and SS-31) is an aromatic-cationic tetrapeptide that readily penetrates cell membranes and transiently localizes to the inner mitochondrial membrane.

ELAMIPRETIDE 80mg/ml for injection is currently supplied as a ready-to-use sterile aqueous injection in an isotonic, colorless to yellow solution in a single-patient-use multi-dose glass vial for use with syringe and needle.

For detailed information on the proposed mechanism of action, results of the nonclinical and clinical studies conducted to date, and the risks and potential benefits of treatment with ELAMIPRETIDE, please refer to the most recent edition of the ELAMIPRETIDE Investigator's Brochure (IB).

8.2 Packaging/Labeling/Dosing

SBT will supply Investigational Medicinal Product (IMP), ELAMIPRETIDE for this study. For this study, ELAMIPRETIDE will be provided as a sterile solution for administration via subcutaneous (SC) injection. Each multi-dose for single patient use vial of drug product contains at least 3.75 mL of 80 mg/mL Elamipretide HCl, in an isotonic, colorless to yellow solution. Each vial will have a small amount of overfill to ensure extraction of all doses.

ELAMIPRETIDE must be stored according to the label conditions: Store at 2-8° C. Do not freeze.

Packaging and labeling as well as detailed instructions for the preparation, handling, and storage of the ELAMIPRETIDE drug product will depend on the individual patient's administration plan and will be provided to the PI /SPONSOR in the Pharmacy Manual.

Detailed instructions on how to order ELAMIPRETIDE drug product will be provided to the PI/SPONSOR upon study approval from the CHOP IRB.

PI/SPONSOR and or site staff will train the subjects (and/or caregivers) and ensure understanding of proper SC injection technique on Day 1 of drug treatment. Syringes will be standard clinically available insulin syringes with which most subjects and their families are familiar. Should it be necessary, subjects and caregivers will be trained in subcutaneous injection techniques at the Connelly Center at CHOP. This approach has been successful in previous clinical trials in FRDA of gamma interferon. On non-visit days, the subject (or trained caregiver) will administer the IMP via daily SC injections in the abdomen or thighs, rotating around the four abdominal quadrant and thigh, per the Instructions for Use (IFU). IMP administration should be at the same time each day (e.g., early morning, noon, or early afternoon).

The PI/SPONSOR is responsible for IMP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Drug preparation, accountability and storage will be performed in accordance with CHOP Investigational Drug Service (IDS) policies and procedures.

At this time only English language labels for ELAMIPRETIDE packaging will be supplied.

ELAMIPRETIDE Injection Solution – Composition

Component	Concentration	Function
ELAMIPRETIDE	80 mg/mL	Drug substance
Benzyl Alcohol	20 mg/mL	Preservative
Sodium Phosphate Monobasic, Monohydrate	4.14 mg/mL	Stabilizer/tonicity adjustment
Hydrochloric acid or sodium hydroxide	q.s. to pH 5.8	pH adjustment
Water for Injection	q.s. to 1.0 mL	Diluent

8.3 Dosing Schedule

The starting dose of ELAMIPRETIDE will be weight-based and may be adjusted based on renal function.

Weight Range (kg)	Daily Dose	Dosing Volume (mL)
20-60	40 mg SC daily (High Dose)	0.5
>60	60 mg SC daily (High Dose)	0.75
20-60	20 mg SC daily (Low Dose)	0.25
>60	30 mg SC daily (Low Dose)	0.38

*If the daily dose is further adjusted, the dosing volume should be rounded to the nearest hundredth of a mL

Additionally, the dose of ELAMIPRETIDE should be adjusted based on renal function (as assessed per local methods). All enrolled subjects will have eGFR> 30 mL/min, such that no dose adjustment will be needed unless change in renal function is observed.

While all previous clinical trials conducted with Elamipretide have utilized a 40 mg dose, further characterization of the exposure-response relationship suggests that the dose has not been optimized. Population PK modelling of data from the SPIMM-301 trial in primary mitochondrial myopathy found that there was a statistically significant relationship between plasma exposure (AUC0-24) and change in distance walked on the 6MWT ($p = 0.0262$) at a 40mg dose, suggesting that the exposure response curve has not been saturated. Additionally, across all development programs, there has been no exposure-safety relationship identified with Elamipretide. Besides injections site reactions (ISRs), the safety profile of Elamipretide has been comparable to placebo, with no differences noted based on varying systemic exposure. While this exposure-response relationship in this patient population may be slightly different from that observed in the PMM population, given the safety profile of Elamipretide, a dose to 60 mg was selected for this study to maximize the chance for a response. The 40 mg dose utilized in earlier clinical trials also represented a practical dose ceiling, as there were limitations in the dose volume for SC injection. The current formulation of Elamipretide is more concentrated and will support use of doses above 40mg.

For subjects who do not tolerate the dosing schedule, dose adjustments (temporary or permanent) and interruptions will be permitted. To improve long-term disease control and tolerability, dose reductions are allowed. The dose of ELAMIPRETIDE may be reduced or the frequency of administration may be reduced. Patients whose doses are reduced under this schema should have appropriate monitoring so that dose may be re-escalated to their initial dose if evidence of disease progression occurs. If dosing is modified, it will be initially halved by decreasing the injection volume by half.

As mentioned previously, there has been no exposure-safety relationship identified with Elamipretide. Besides injections site reactions (ISRs), the safety profile of Elamipretide has been comparable to placebo, with no differences noted based on varying systemic exposure. Additionally, the safety data across programs suggests that the severity of ISRs is comparable across all dose levels studied. The mechanism of ISRs is believed to be histamine release from mast cells, which occurs when Elamipretide is present in high concentrations in SC tissue. This is believed to be a threshold effect, as ISRs are seen at doses lower than 40mg, but do not change in characterization or severity at higher doses. Therefore, uniform dose modifications on the basis of ISRs or other safety parameters are not warranted. ISR tolerability and severity can certainly vary by patient, therefore dose modification or interruption should be considered on a case by case basis as necessary.

Regarding dose adjustments for renal function, the active moiety, Elamipretide, has a similar PK profile in patients with a normal GFR compared to patients with a GFR 30 mL/min. The accumulation ratio of Elamipretide in patients with moderate renal impairment at steady state is 1.08, indicating minimal accumulation following daily dosing. This similarity in the PK profile of Elamipretide across varying degrees of renal impairment is because Elamipretide is metabolized

rapidly via C-terminal degradation in plasma to the metabolites M1 and M2. Unlike Elamipretide, the PK profiles of the pharmacologically and toxicologically inactive metabolites M1 and M2 are more susceptible to changes in renal function. The M2 metabolite has an accumulation ratio of 3.61 at steady state in patients with moderate renal impairment, indicating accumulation upon daily dosing. The exclusion of patients with a GFR ≤ 30 mL/min reflects the loss of nonclinical safety margins for the M2 metabolite specifically, due to reduced renal elimination and accumulation in severe renal impairment. Because the active moiety is less influenced by changes in renal function, renal dose adjustments are not required. The PK profile of Elamipretide is anticipated to be comparable for all patients with a GFR >30 mL/min.

Should it be necessary to account for dosing modifications needed based on GFR, the Schwartz equation for GFR will be used.

eGFR =0.413 x (height/Scr) if height is expressed in centimeters.

8.4 Treatment Compliance and Adherence

Qualified members of the study staff will dispense study medication to subjects. Subjects will be given an IFU provided by SBT (see attachment to IRB application).

At the initiation of treatment visit, the PI/SPONSOR on the appropriate handling and administration of study medication will give subjects detailed instructions. Study staff will also educate study subjects and care givers on possible side effects and on appropriately logging symptoms, reactions, and dose administration dates and times on the subject diaries.

8.5 Drug Accountability

Adequate records of study drug receipt, dispensation, and disposition will be maintained in accordance with CHOP IDS policies and procedures. On an ongoing basis throughout the study, participants will be instructed to return unused supplies to the site for drug accountability purposes and to assess overall compliance. Drug compliance will be noted in study staff records. At study completion, final drug disposition will be performed in accordance with IDS policies and procedures.

9. Safety Management

9.1 Clinical Adverse Events

Clinical adverse and serious adverse events (AEs and SAEs) will be monitored throughout the study. SAE reporting will be limited to those SAEs that are possibly, probably or definitely related to the drug. Certain specific situations will provide criteria for discontinuing the study or a participant.

1. If 4 subjects have adverse events of grade 3 or higher using the following grading scale. Grade 1 Adverse event: adverse event released to study drug not requiring treatment; Grade 2: adverse event related to study drug requiring treatment; Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL; Grade 4 Life-threatening consequences; urgent intervention indicated.

2. For individual subjects, if any subject experiences a worsening in function more than 2x the expected rate of progression on either of the major outcomes (high contrast visual acuity and ejection fraction), they will be withdrawn. This corresponds to a worsening from baseline of 15 letters on VA or a worsening of EF of >10%.
3. Individual Subject Stopping Rule: Subjects will be withdrawn if they develop a severe skin reaction from the drug injections that is not sufficiently relieved by over-the-counter products (topical antihistamines, topical steroids).

9.2 Adverse Event Reporting

Unanticipated problems related to the research involving risks to subjects or others that occur during the course of this study (including SAEs) will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

The Investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's CRF and applicable forms. PI/SPONSOR is responsible for monitoring the safety of subjects who have entered this study and for alerting SBT/or its Pharmacovigilance (PV) designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject. The Investigator is responsible for facilitating the appropriate medical care.

9.3 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a subject who has received an intervention (drug, biologic, or other intervention). The occurrence does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

All AEs (including serious AEs) will be noted in the study records and on the case report form with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event.

9.4 Definition of a Serious Adverse Event (SAE)

An SAE is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death,
- A life-threatening event (at risk of death at the time of the event),
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant disability/incapacity, or
- A congenital anomaly/birth defect in the offspring of a subject.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug event when, based upon appropriate

medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A distinction should be drawn between serious and severe AEs. A severe AE is a major event of its type. A severe AE does not necessarily need to be considered serious. For example, nausea, which persists for several hours, may be considered severe nausea, but would not be an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

9.4.1 Relationship of SAE to Study Drug

The relationship of each SAE to the study intervention should be characterized using one of the following terms in accordance with CHOP IRB Guidelines: definitely, probably, possibly, unlikely or unrelated.

9.5 IRB Notification of SAEs and Other Unanticipated Problems

The Investigator will promptly notify the IRB of all on-site unanticipated, serious Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed using the eIRB system and in accordance with the timeline below. External SAEs that are both unexpected and related to the study intervention will be reported promptly after the investigator receives the report.

Type of Unanticipated Problem	Initial Notification (Phone, Email, Fax)	Written Report
Internal (on-site) SAEs Death or Life Threatening	24 hours	Within 2 calendar days
Internal (on-site) SAEs All other SAEs	7 days	Within 7 business days
Unanticipated Problems Related to Research	7 days	Within 7 business days
All other AEs	N/A	Brief Summary of important AEs may be reported at time of continuing review

9.5.1 Follow-Up Report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

9.6 Investigator Reporting of a Serious Adverse Event to Stealth

Details regarding the serious adverse event will also be entered into the eCRFs and into the subject's paper CRFs. The PI/SPONSOR will review and report adverse events to the Monitor as they are received. The significant adverse events (SAEs) will be further reviewed within 1-2 weeks and AEs will be reviewed by the medical monitor. An assessment of the risk benefit ratio will be discussed and reported. In parallel, SAEs will be reported to SBT.

9.7 Sponsor Reporting to the FDA

Sponsor will notify FDA in a written IND Safety Report suspected AEs with the use of the study drug deemed to be both serious and in which there is reasonable possibility that the study drug caused the AE. Non-serious adverse events will be reported in the FDA Annual Report.

9.8 Medical Emergencies

In medical emergencies, the investigator should use medical judgment and remove the subject from the immediate hazard. The sponsor, monitor and the IRB must be notified regarding the type of emergency and course of action taken and the procedures for SAE reporting must be followed.

10. Study Administration

10.1 Treatment Assignment Methods

10.1.1 Randomization

This is a randomized study of high vs low dose. Subjects will be randomized using the REDCap Data Base Program at the time of baseline visit. There will be no stratifications in the randomization process.

10.1.2 Blinding

Neither the subjects nor the Investigator will be blinded. The key will be maintained in the REDCap database.

10.2 Data Collection and Management

Clinical research coordinators in Dr. Lynch's lab are responsible for data input, management, storage, and security. All data will be entered into a secure REDCap database from which analysis can be performed.

10.3 Quality Control

The data collection process entails site staff completing source worksheets on paper for the initial capture of research data during subject encounters. The source worksheets are exact replicas of the case report forms and can be printed on demand. Site staff input the information on the case report forms into the password-protected study database in REDCap. The staff enters data by first creating a subject identification (using the three-digit identification number given to the subject at screening) or by updating a subject's data by entering the data collected into the web-based electronic data capture application. During data entry, checks are performed routinely to immediately flag problematic data (e.g., missing, out of range, inconsistent) allowing for the study staff to immediately correct the data.

Once the data are entered into the data spreadsheet, they are immediately stored on the CHOP server where they are accessible for review by study staff. In addition to the data spreadsheet, study staff will maintain a log of any corrections to the spreadsheet including the change in data values, the location of the change, the reason for it and the name of the staff member who changed the data. An original version of the spreadsheet (containing the originally entered data) will be retained.

This cycle of data entry, review, query identification and resolution, and correction occurs over the course of the study period until all subjects have completed the study. Once the last subject has completed the study, the database should have few, if any, remaining queries or corrections pending, allowing for very rapid database closure.

Once the study staff, and PI/SPONSOR confirm that all queries have been resolved and the database has been deemed “clean,” the database is officially locked. All permissions to make changes (append, delete, modify or update) will be granted on a case-by-case basis by the study PI.

10.3.1 Database Security

Since the study is taking place at a single site and will involve data collection on 16 subjects, CHOP will be able to maintain all data on-site in the form of a REDCap database, in a manner that is consistent with rules and regulations. The spreadsheet will be protected, encrypted, and backed up on the CHOP server. The data spreadsheet will not contain identifying information about the subjects; a document associating study ID numbers and individual names will be saved and protected separately. Study staff will maintain integrity, confidentiality and security of subject information. All personnel who work with the data are trained in the use of the database and sign confidentiality agreements. Access to the database will only be possible for study staff with access to the CHOP intranet server. The server is password-protected and securely monitored with virus protection software full-time and is updated regularly with the latest virus detection strings. All study staff have individual, password-protected accounts, and passwords must be changed on a regular basis.

10.4 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy and that the Investigator and other site personnel will not use such data and records for any purpose other than conducting the study. A limited dataset with no identifiers or PHI will be provided to SBT.

Subject names will not be included in the data spreadsheet containing research data collected in the context of the study. Only the subject number and subject initials will be recorded in CRFs, and if the subject name appears on any other document (e.g., pathologist report), the identifier will be removed before a copy is supplied to SBT. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be told that representatives of SBT, IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The Investigator and study staff will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified. This master list will be saved to the Investigator’s research shared drive, which will only be assessable by the PI and his study staff.

De-identified echo images will be shared with the Penn CHPS Echo team for the reading/ interpretation of adult echocardiograms. Data will be sent to Penn via a secure PennBox website in which only de-identified images will be uploaded. And then a report from Penn to CHOP will be sent via email (again, only de-identified data). The report will then be uploaded into EPIC via the Media tab for all subjects.

Blood samples that are sent out to other laboratories (Ian Blair's team) for analysis will be labeled with the subject's study ID number, subject's initials, and date of sample collection only.

No identifiable data will be used for future studies without first obtaining IRB approval or determination of exemption. The investigator will obtain a data use agreement between the provider (the PI) of the data and any recipient researchers (including others at CHOP) before sharing a limited dataset (PHI limited to dates and zip codes).

11. Regulatory and Ethical Considerations

11.1 Data and Safety Monitoring Plan

The Principal Investigator will be responsible for monitoring safety and reporting AEs and SAEs. In addition, an independent medical monitor will be identified.

11.1.1 Medical Monitor Responsibilities

The medical monitor is responsible for ensuring that study subjects are not exposed to unnecessary and unreasonable risks. The medical monitor will be an MD from the FRDA field; this person will be supported by a site monitor to collect information and by the study coordinator. This will include assessment of causality of adverse events and relative safety signals. The medical monitor is also responsible for monitoring the trial for adherence to the highest scientific and ethical standards. These standards include but are not limited to the following areas: monitoring subject recruitment and retention; protocol compliance; data quality control; reviewing the data; tracking and trending adverse events; data completeness and probability of success in a timely fashion. These events will be collected by the site monitor and the study coordinator and reported to the Medical monitor for assessment.

11.1.2 Reporting of Adverse Events to the Monitor

The PI/SPONSOR will review and report drug related adverse events to the Monitor as they are received. The significant adverse events (SAEs) will be reported within 2-3 days and reviewed as soon as possible. An assessment of the risk benefit ratio will be discussed and reported.

Before initiation of the clinical investigation, the sponsor-investigators will arrange a pretrial monitoring visit with the Office of Research Compliance (ORC) to confirm clinical trial readiness. After enrolling and starting administration of the investigational agent to the first subject, the sponsor-investigators will contact ORC to arrange a monitoring visit. Thereafter, ORC will monitor the study at least annually.

11.1.3 Communication/Recommendation from the Monitor

At the end of each evaluation, the Monitor will provide a verbal report to the Principal Investigator and selected study team members indicating areas of concern regarding performance and safety. Within one week of the meeting, the monitor will provide a written summary of the monitor's recommendations to the Principal Investigator. The monitor will recommend whether the study should be continued or whether the study should be terminated, temporarily suspended, or amended, as appropriate, based on whether the trial: 1) has answered the primary outcomes question; 2) will not be able to reach a firm conclusion; 3) is not conducted according to high scientific or ethical standards; 4) poses an unreasonable and unnecessary risk to study subjects.

11.2 Risk Assessment

The study medication is currently under investigation in a variety of metabolic and neurological disorders. In studies of the drug in humans, adverse events have been few and generally minor.

Participants will be monitored carefully throughout the course of this trial. Safety will be evaluated by history updates, physical examinations, vital signs assessments, routine clinical laboratory tests, and adverse event assessments. In addition, study staff will conduct several phone calls throughout the study as needed to evaluate AEs and SAEs. With this plan, the chance of significant side effects going undetected should be markedly reduced.

The specific known risks of Elamipretide have included Induration of injection sites resulted in nearly 10% study withdrawal in those participants receiving ≥8 days of s.c. study drug. Local reactions for ≥8 days s.c. included erythema, swelling, induration, mass, pain, pruritus, urticaria. Systemic effects included headache and dizziness.

Gadolinium enhancement for the cardiac MRI is of greater than minimal risk. Contrast agents can cause allergic reactions and kidney damage. Allergic reactions can include mild itching associated with hives and can be as serious life-threatening emergency from difficulties breathing. If this occurs, it is treatable.

The risks of other study procedures are generally small. Clinical outcome measures (vision measures, ataxia scales) and questionnaires are non-invasive and are very similar to standard clinical evaluation. The risks to all aspects of these assessments are minimal and include fatigue from study assessment.

A standard venous blood draw is of minimal risk. There is a risk of pain at the insertion of the needle that is only for a short time. There are low risks of fainting and infection. A trained phlebotomist will perform all venipunctures. All precautions will be taken to reduce the risks. The study subject will collect urine in a cup, without catheterizations.

The risks with the sample collection and analysis are directly related to confidentiality. All samples will be coded using labels containing only a study subject ID, initials, and date of sample collection. Laboratory personnel handling the study samples and performing the analyses will not have access to subject personal identifiers. When any data is published all identifiers will be removed. When data or resources are shared with collaborators no personal identifiers will be shared.

11.2.1 Potential Benefits of Trial Participation

The benefit to the subject as a result of the study is unknown. Subjects may benefit by finding some improvement in their condition while on the study drug. All subjects would be on active study medication rather than placebo and thus all participants would have the potential to notice some benefit in symptoms. This initial trial targets an advanced population for which the need for therapy is immediate.

In addition, there are no effective and/or approved treatments available for Friedreich ataxia. As ELAMIPRETIDE has the potential for benefit, this research provides the prospect for benefit to patients with FRDA worldwide. It also represents the prospect of indirect benefit by contributing to generalizable knowledge about FRDA, for which there is very limited therapeutic options.

11.2.2 Risk-Benefit Assessment

There are no approved treatments for Friedreich ataxia currently, and the participants in this study are not candidates for enrollment in any other intervention study. Other potential alternatives include no treatment or use of non-prescription antioxidants, whose clinical benefit have been shown to be minimal.

ELAMIPRETIDE has shown preliminary benefit in related mitochondrial disorders, and minimal evidence of major adverse events linked to drug.

The risks are greater than minimal in this study, but there is a potential for benefit due to a possible improvement in neurological features of FRDA and the untreatable nature of FRDA. The risk/benefit ratio is therefore low.

11.3 Recruitment Strategy

Study staff will develop a one-page flyer with basic inclusion and exclusion criteria for the study, along with contact information for potential subjects and their parents to use to find out more information about the study. The flyer will be distributed by email to all eligible subjects and parents of pediatric subjects who are followed in the CHOP Friedreich ataxia program (with the distribution list blinded to recipients). In addition, this study will be listed on www.ClinicalTrials.gov along with contact information for study staff and all basic information about this trial.

Potential subjects followed by Dr. Lynch for clinical care of their Friedreich ataxia may be notified of the study during their scheduled clinic visit once the trial is open to enrollment of subjects. They may speak with Dr. Lynch or one of his study staff about the study in more detail, and potentially enroll in this study at that time, with the explicit understanding that their decision to enroll or not enroll in the study will not impact any element of their clinical care. No record of the discussion regarding their potential enrollment in the study will be made in the clinical note.

Subjects may call The Children's Hospital of Philadelphia to enroll once the study opens for enrollment and is officially announced by the Children's Hospital of Philadelphia and FARA. During the initial telephone call, study staff will perform a screening questionnaire to determine basic eligibility after obtaining verbal consent for this screening. If the potential subject meets basic in/exclusion criteria, he/she will be invited to The Children's Hospital of Philadelphia for a screening visit, which will include all study activities outlined above. These activities will not be performed until informed consent and assent have been obtained.

The enrollment goal for this study is 16 participants. They will complete all study activities on an outpatient basis at CHOP.

11.4 Informed Consent/Assent and HIPAA Authorization

Potential participants or parents/guardians of potential pediatric subjects will be pre-screened by telephone and will therefore give verbal consent to disclose the information requested in the questionnaire. HIPAA authorization to conduct the pre-screening questionnaire via telephone will also be obtained verbally. Study staff will perform a screening questionnaire to determine basic eligibility only after obtaining verbal consent for this screening.

At the time of the screening visit, subjects and/or parent/guardian will meet with a study coordinator and/or the PI/SPONSOR in a private room to review the consent form in detail and will have an opportunity to have all questions answered by study staff. The Principal Investigator or a study physician will be present to answer questions and address concerns. They will be

reminded that participation is voluntary and their care at CHOP will not be affected by their decision to participate. They will sign the informed consent and included assent section if they would like to participate. As all study staff are experienced in clinical research, they will present the study in a professional, unbiased manner to the parents/guardians and the potential participants. Parents/guardians and potential participants will be given as much time as they need, up to a few weeks, to decide if they wish to participate. They will be reminded that participation is voluntary and that their medical care will not be affected by their decision to participate or not. HIPAA authorization will be noted on the informed consent form.

Study procedures will not be initiated until informed consent form is reviewed with the potential subject, and fully signed by study team and study subject.

Additionally, the option for remote consent via RedCap will be available to subjects. This alternative option will help reduce the length of the Screening Visit as fatigue is a key symptom of FRDA. It will also serve as an easier process for signing the consent form as many of the potential subjects in this trial may have limited use of their upper extremities and may have difficulty holding a pen to sign. To conduct the remote consent process, a copy of the informed consent form will be sent to the subject via email prior to a schedule consent phone call. The consenting process will be conducted over the phone with the study subject (and parent/legal guardian if the subject is under 18) when they are able to read through the consent form during the discussion. The RedCap e-Consent form will allow for the subject (and parent/legal guardian if the subject is under 18) to sign and date the consent form electronically. A copy of the signed consent form will automatically be emailed to the subject once they have completed the consent process.

11.5 Alteration of HIPAA Authorization

This research study presents greater than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. HIPAA authorization will be collected on the main study consent form at the time of the screening visit before any study activities are performed.

However, pre-screening questionnaires will be administered via telephone to determine which potential subjects are potentially eligible for the study based on a general review of medical history. For this procedure, verbal consent will be obtained from parents/guardians via telephone, before the questionnaire is administered, along with verbal HIPAA authorization.

11.6 Payment to Subjects/Families

Subjects will not be paid directly if they are under age 18. Pediatric subjects will not directly receive payments, reimbursements, or gifts.

Adult subjects and parents/guardians of pediatric subjects will receive up to $1,000 per study visit as reimbursement for travel and hotel expenses.. This would be a total of 6 visits to The Children's Hospital of Philadelphia, including the separate screening visit. If the screening activities were performed the same day as baseline activities, this would be a total of 5 visits to The Children's Hospital of Philadelphia. These reimbursements will be sent to the subject or the subjects’ parents/guardians in the form of checks from The Children’s Hospital of Philadelphia within 8 weeks of study visits. In order to be reimbursed, patients will be required to provide documentation of expenses associated with the research visit, including travel, meals, hotel stay,

and co-pays and other bills for procedures that are completed as both research and as standard of care. The subjects will need to complete a Form W-9 or have one on record at CHOP.

Participants will not receive financial rewards or inducements. There is also no cost to participation in the study. Participants who receive clinical care from the investigator or The Children's Hospital of Philadelphia will be responsible for those charges, as they are separate from the study.

12. Publication

The identity of all subjects will be withheld from any publication, abstract, lecture or other oral presentation that derives from this investigation. Publications will state that the study had the approval of the Institutional Review Board at The Children's Hospital of Philadelphia.

It is expected that the Principal Investigator will submit the data for a publication when the study is complete and has been evaluated.

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