Title: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Crossover Study to Evaluate the Safety, Tolerability, and Efficacy of Subcutaneous Injections of Elamipretide (MTP-131) in Subjects with Genetically Confirmed Mitochondrial Disease Previously Treated in the Stealth BioTherapeutics SPIMM-201 Study

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Document Date: 21 October 2016

CLINICAL STUDY PROTOCOL

A Phase 2 Randomized, Double-Blind, Placebo-Controlled Crossover Study to Evaluate the Safety, Tolerability, and Efficacy of Subcutaneous Injections of Elamipretide (MTP-131) in Subjects with Genetically Confirmed Mitochondrial Disease Previously Treated in the Stealth BioTherapeutics SPIMM-201 Study

Study Phase:	Phase 2
Study Number:	SPIMM-202
Document Version:	Version 5.0
Final Approval Date:	21 October 2016
Sponsor:	Stealth BioTherapeutics Inc. 275 Grove Street, Suite 3-107 Newton, MA 02466 Unites States of America
Sponsor Medical Monitor:	Doug Weaver, MD Chief Medical Officer 275 Grove Street 3-107, Newton, MA 02466 Doug.Weaver@stealthbt.com +1 313-806-4194

Confidentiality Statement

PROTOCOL APPROVAL

Protocol Title:	A Phase 2 Randomized, Double-Blind, Placebo-Controlled Crossover Study to Evaluate the Safety, Tolerability, and Efficacy of Subcutaneous Injections of Elamipretide (MTP-131) in Subjects with Genetically Confirmed Mitochondrial Disease Previously Treated in the Stealth BioTherapeutics SPIMM-201 Study
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[redacted]

10/22/2016

Doug Weaver, MD Date

Medical Monitor, Stealth BioTherapeutics

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for elamipretide (MTP-131). I have read the SPIMM-202 protocol and agree to conduct the study as outlined. I confirm that I will conduct the study in accordance with ICH GCP guidelines. I will also ensure that subInvestigator(s) and other relevant members of my staff have access to copies of this protocol, and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date (DD/MMM/YYYY)

1. SYNOPSIS

Name of Sponsor/Company: Stealth BioTherapeutics Inc.

Investigational Product: MTP-131 (elamipretide)

Title of Study: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Crossover Study to Evaluate the Safety, Tolerability, and Efficacy of Subcutaneous Injections of MTP-131 Elamipretide (MTP-131) in Subjects with Genetically Confirmed Mitochondrial Disease Previously Treated in the Stealth BioTherapeutics SPIMM-201 Study

Study Center(s): This study will be conducted in 4 centers in the United States (US)

Objectives:

Primary

- To evaluate the effect of single daily subcutaneous (SC) doses of elamipretide administered for 4 weeks on 6-minute walking distance (6MWD).

Secondary

- To evaluate the safety and tolerability of single daily SC doses of elamipretide administered for 4 weeks
- To evaluate the effects of single daily SC doses of elamipretide administered for 4 weeks on:
  - Accelerometry
  - Triple Timed Up and Go (3TUG) Test o Patient Reported Outcomes o Exploratory biomarkers
  - Physician Global Assessment (PhGA)

Study Design: This randomized, double-blind, placebo-controlled crossover study will enroll up to 36 subjects with genetically confirmed mitochondrial disease who have completed participation in the SPIMM-201 study. Subjects will have previously received 5 days of intravenous elamipretide (0.01, 0.10 or 0.25 mg/kg/hour infused for 2 hours) or placebo (randomized 3:1) in the SPIMM-201 study.
Subjects will be randomized (1:1) to one of two sequence groups: 4-weeks of treatment with 40 mg elamipretide administered once daily SC in Treatment Period 1 followed by 4-weeks of treatment with placebo administered once daily SC in Treatment Period 2 (separated by 4week washout period), or vice versa (Attachment 3).
Given the challenges of scheduling Visiting Nurses visits to subject's homes (e.g. remote geographic locations, subject scheduling conflicts, extreme weather or other natural disasters etc.), in consultation and agreement with the Sponsor and Investigator, Visiting Nurse visits may be postponed, changed or cancelled.
Screening: Screening will begin with the signature of the informed consent form (ICF) and will last at least 7 days and no more than 30 days. During Screening, subjects will undergo screening procedures as described in the Study Schedule (Attachment 1) and will be instructed to wear a wrist accelerometer daily (24 hours per day), wear a hip accelerometer

daily during waking hours (minimum of at least 7 consecutive days immediately prior to the Baseline Visit), and complete daily Mitochondrial Disease (MD) Symptom Assessments in an electronic or paper diary to characterize their baseline disease status. Subjects who complete Screening and continue to meet all study requirements, including all inclusion and none of the exclusion criteria, may enter Treatment Period 1.

Treatment Period 1: Treatment Period 1 will begin on the day of the Baseline Visit, which is defined as Study Day 1. At the Baseline Visit, following completion of all Baseline procedures described in the Study Schedule, subjects will be administered study drug SC at the study center. Subjects or caregivers will receive instructions on scheduling daily home (or other location) visits with the Visiting Nurse and will be assigned a Visiting Nurse who may administer (or observe) study drug subcutaneously on a daily basis for the first week of Treatment Period 1 and at least weekly thereafter. The Visiting Nurse visit on Day 2 is required, however, the Visiting Nurse Visits during Days 3-7 are not mandatory and the patient (or caregiver) and the Visiting Nurse should determine the frequency and necessity of these visits. Subjects (or caregivers) will be trained on the procedure for administration of study drug and will administer study drug on a daily basis (except for days corresponding to study center visits and potentially Visiting Nurse Visits) at approximately the same time each day. If, for any reason, a subject (or caregiver) is unable/unwilling to administer study drug, a Visiting Nurse may be provided for daily administration of study drug. The Visiting Nurse will also draw blood for safety labs at Week 1 and Week 2 Visits. The Visiting Nurse will administer (or observe) study drug at the Week 3 Visit and remind subjects to wear the hip accelerometer during waking hours for at least 7 consecutive days immediately prior to the Week 4 Visit. Subjects will continue to follow all study requirements, including completing daily MD Symptom Assessments and recording the location and time of the study drug administration in an electronic or paper diary as well as wearing the wrist accelerometer daily. Treatment Period 1 will conclude with a visit to the study center at the Week 4 Visit and subjects will return all used and unused vials to the study center at this visit.

Washout: Washout will begin on the day after the Week 4 Visit and will last for at least 4 weeks. The Visiting Nurse will visit at the Week 6 Visit to provide the subject with the Neuro-QoL Fatigue questionnaire to complete, and will collect the completed questionnaire. The Visiting Nurse will also draw blood for safety labs. The Visiting Nurse will ensure the subject is wearing a wrist accelerometer daily (24 hours per day), remind the subject to wear a hip accelerometer daily during waking hours (minimum of at least 7 consecutive days immediately prior to the Week 8 Visit), and complete daily MD Symptom Assessments in an electronic or paper diary.

Treatment Period 2: Treatment Period 2 will begin with a visit to the study center for the Week 8 Visit. Subjects will be administered study drug SC at the study center following completion of all baseline procedures described in the Study Schedule. A Visiting Nurse will administer (or observe) study drug on a weekly basis at home (or other location) and will draw blood for safety labs on Week 9 and Week 10, as described in the Study Schedule. Subjects (or caregivers) will administer study drug on a daily basis at approximately the same time each day (except for days corresponding to study center visits and potentially Visiting Nurse Visits). The Visiting Nurse will administer (or observe) study drug at the

Week 11 Visit and will remind subjects to wear the hip accelerometer during waking hours for at least 7 consecutive days immediately prior to the Week 12 Visit. Subjects will

continue to follow all study requirements, including completing daily MD Symptom Assessments and recording the location and time of the study drug administration in an electronic or paper diary as well as wearing the wrist accelerometer daily. Treatment Period 2 will conclude with a visit to the study center at the Week 12 Visit and subjects will return all used and unused vials to the study center at this visit. **Follow-Up:** Follow-Up will begin after completion of Treatment Period 2 and will last for 2 weeks. During follow-up, subjects will continue to follow all study requirements, including completing daily MD Symptom Assessments in an electronic or paper diary as well as wearing the wrist accelerometer daily. At the end of Follow-up, subjects will return to the study center for the End-of-Study/Early Discontinuation Visit for final safety and efficacy assessments and to return all remaining study equipment, as described in the Study Schedule.
Number of Subjects (planned): Up to 36 subjects
Investigational Product, Dosage and Mode of Administration: Elamipretide (MTP-131) will be supplied as 40 mg/1 mL of sterile solution for subcutaneous injection. The dose of elamipretide will be 40 mg administered as a once daily 1 mL SC injection. Study drug will be administered by either the study center clinical staff, a Visiting Nurse, caregiver or the subject via daily SC injection, preferably in the abdomen (rotating around the four abdominal quadrants), at approximately the same time each day.
Reference Product: Matching placebo will be administered subcutaneously according to the same schedule and conditions as elamipretide.
Inclusion Criteria: A subject must meet the following criteria prior at the Baseline Visit to be eligible for inclusion in the study: 1. Willing and able to provide signed informed consent form (ICF) prior to participation in any study-related procedures. 2. Subject completed participation in the SPIMM-201 study without a significant protocol deviation that would suggest the subject may not be able to complete all study requirements in the opinion of the Sponsor. 3. Subject must reside in North America for the duration of the study. 4. Subject agrees to adhere to the study requirements for the length of the trial. 5. Subject has not received study drug in the SPIMM-201 study within 3 weeks prior to Screening.

6. Women of childbearing potential must agree to use 1 of the following methods of birth control from the date they sign the ICF until two months after the last dose of study drug:
    a. Abstinence, when it is in line with the preferred and usual lifestyle of the subject. Subject agrees to use an acceptable method of contraception should they become sexually active.
    b. Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy (the vasectomy procedure must have been conducted at least 60 days prior to the Screening Visit or confirmed via sperm analysis).
    c. Barrier method (e.g., condom or occlusive cap) with spermicidal foam/gel/film/cream AND either hormonal contraception (oral, implanted, or injectable) or an intrauterine device or system.

    Note: Non-childbearing potential is defined as surgical sterilization (e.g., bilateral oophorectomy, hysterectomy, or tubal ligation) or postmenopausal (defined as permanent cessation of menstruation for at least 12 consecutive months prior to the Screening Visit).
7. Subject has been on stable medications (including over-the-counter treatments, vitamins, or supplements), or medications that will not impact the safety or efficacy endpoints of the trial, in the opinion of the Investigator for at least 1 month prior to the Baseline Visit.

Exclusion Criteria:

A subject who meets any of the following criteria at Screening will be excluded from the study:

1. Subject has any prior or current medical condition that, in the judgment of the Investigator, would prevent the subject from safely participating in and/or completing all study requirements (i.e. unstable angina or recent myocardial infarction).
2. Subject has received any investigational compound and/or has participated in another interventional clinical study within 30 days prior to the Baseline Visit or is concurrently enrolled in any non-interventional research of any type judged to be scientifically or medically incompatible with the study as deemed by the Investigator in consultation with the Sponsor.
3. Subject experienced an adverse reaction to study drug in the SPIMM-201 study that contraindicates further treatment with elamipretide in the opinion of the Investigator and/or Sponsor.
4. Female subjects who are pregnant, planning to become pregnant, or lactating.
5. Subject has undergone an in-patient hospitalization within the 1 month prior to the Screening Visit or is likely to need in-patient hospitalization or a surgical procedure during the course of the study
6. Subject has a creatinine clearance ≤30 mL/min as calculated by the Cockcroft Gault equation.
7. Subject has QTc elongation defined as a QTc >450 msec in male subjects and >480 msec in female subjects.
   Note: At the initial electrocardiogram (ECG), if QTc exceeds these parameters, the ECG may be repeated 2 more times, and the average of the 3 QTc values used to determine the subject's eligibility.
8. Subject has uncontrolled hypertension in the judgment of the Investigator (e.g. elevated above >160 mmHg systolic or >100 mmHg diastolic despite appropriate treatment on two consecutive readings).
9. Subject has a history of clinically significant hypersensitivity or allergy to any of the excipients contained in the study drug.
10. Subject has a history of active alcoholism or drug addiction during the year before the Screening Visit.
11. Subject is an Investigator/study center personnel or immediate family* of Investigator/study center personnel.
12. Subject is a Sponsor employee (permanent, temporary contract worker, or designee responsible for the conduct of the study) or immediate family* of a Sponsor employee.
    * Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted

Planned Study Duration:

Screening: 7-30 days
Treatment Period 1: 4 weeks
Washout: 4 weeks
Treatment Period 2: 4 weeks
Follow-up: 2 weeks

Criteria for Evaluation:
Primary Endpoint

- Distance walked (meters) on the 6-minute walk test (6MWT) **Secondary Endpoints**
- Adverse Events (AEs)
- Vital Signs
- ECGs
- Clinical laboratory evaluations
- Accelerometer counts
- Patient reported outcomes (Neuro-QoL Fatigue questionnaire, Mitochondrial Disease [MD] Symptom Assessment, and Patient Global Assessment [PGA]) □ 3TUG Test score
- Exploratory biomarkers
- Physician Global Assessment (PhGA)

Statistical Methods:
After all subjects complete the first treatment period, at the discretion of the Sponsor, the data from the first treatment period may be unblinded and an interim analysis may be

conducted.

Analysis Populations

All subjects who receive at least one dose of study drug will be included in both the Safety Population and in the Intention-to-Treat (ITT) Population.

Safety Analyses

Safety analyses will include incidence of AEs and SAEs, deaths, premature discontinuation from the study due to an AE (regardless of relationship to study drug), and change in ECG, clinical laboratory data, and vital signs.

Efficacy Analyses

Efficacy analyses will be conducted on the ITT population. In general, categorical variables will be summarized by the count (N) and percentage of subjects (%). Continuous variables will be summarized by the number of non-missing observations (N), mean, standard deviation, median, minimum, and maximum values. All study data are to be displayed in the data listings.

Additional details regarding analyses will be included in separate statistical analysis plan. Subject disposition summaries will include the number of subjects enrolled and the numbers included in the ITT populations. The number and percentage of subjects who complete or discontinue from the study will be summarized by reason for discontinuation. Subject's age, sex, weight, height, body mass index (BMI), and other demographic characteristics will be recorded and summarized. Medical history will be listed.

Sample Size:

Subject numbers (up to 36 subjects) are limited to those residing in North America having previously completed participation in the SPIMM-201 study and who meet all eligibility criteria.

2. TABLE OF CONTENTS

3. ABBREVIATIONS AND DEFINITIONS

Term	Definition
3TUG	Triple Timed Up and Go Test
6MWD	Six-minute walk distance
6MWT	Six-minute walk test
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the plasma concentration versus time curve

$AUC_{0-\tau}$	Area under the plasma concentration vs time curve from time 0 to end of the dosing interval
AUC_{0-inf}	Area under the plasma concentration curve from baseline to infinity
AUC_{0-24}	Area under the plasma concentration curve from baseline to 24 hours postdose
BMI	Body mass index
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum plasma concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic data capture
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	investigational medicinal product
IV	intravenous
ITT	intention-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MM	Mitochondrial myopathy
mL	milliliter
MTP-131	SS-31, elamipretide, or Bendavia™
Term	**Definition**
mtDNA	mitochondrial DNA
nDNA	nuclear DNA
PK	pharmacokinetic(s)
PGA	Patient Global Assessment
PhGA	Physician Global Assessment
PMD	Primary mitochondrial disease
PT	preferred term
SAE	serious adverse event
SAP	Statistical Analysis Plan

SC	subcutaneous
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

4. INTRODUCTION

This study will be conducted in strict accordance with the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, ICH GCP guideline, and all applicable laws and regulations. For detailed information on the study drug and the nonclinical and clinical studies conducted to date, please refer to the most recent edition of the MTP-131 Investigator's Brochure (IB).

4.1. Mitochondrial Myopathy

Mitochondrial Myopathy (MM) is a condition resulting from respiratory chain dysfunction in the mitochondria that, when involving of skeletal muscle, leads to muscle weakness and atrophy, and limited exercise capacity and tolerance. MM is a functional consequence of Primary Mitochondrial Disease (PMD) of either mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) origin. Normally, in response to exercise and physical activity, ventilation and cardiac output are increased resulting in the delivery of more oxygen to the muscle via the bloodstream. In MM, there is an exaggerated response to physical exercise because the increased oxygen available in the arterial bloodstream cannot be effectively utilized by the skeletal muscle. This results in limited exercise capacity and easy fatigability. The severity of MM is variable and frequently involves progressive reduction in exercise capacity that impacts the patient's ability to live a normal life. It is a rare condition for which there are no FDAapproved treatments (DiMauro et al. 2003, DiMauro & Schon 2003; Pfeffer and Chinnery 2013; Tarnopolsky 2004; Elson et al. 2013).

4.2. Elamipretide Risk/Benefit Assessment

4.2.1. Potential Benefits

MTP-131 has not been studied in any preclinical models specific to MM. However, MTP-131 has been shown to be effective in preclinical models in numerous disease states, including skeletal and cardiac muscle dysfunction, which are of relevance to MM. For example, MTP131 restored adenosine triphosphate (ATP) production in the skeletal muscle of aged mice. (Siegel et al. 2013) In this study, skeletal muscle energetics were measured in vivo one hour after injection of either MTP-131 or saline using a combination of optical and ^{31}P magnetic

resonance spectroscopy in old and young mice (27 months and 5 months, respectively [n=5-7 per group]). ATP production in old (27 months) mice was found to be comparable to that in young (5 months) mice one hour after a single treatment with MTP-131 (Figure 1). These results demonstrated a rapid reversal of age-related declines in resting and maximal mitochondrial ATP production, without any observable effect on young muscle. Consistent results were observed after 8 days of dosing with MTP-131, with a favorable difference in the exercise tolerance of old mice (n=7-8), and no significant effect in young mice (n=5) (Figure 2).

Figure 1 ATP Production (Mean ±SEM) in Young and Aged Mice Following a Single Treatment with MTP-131

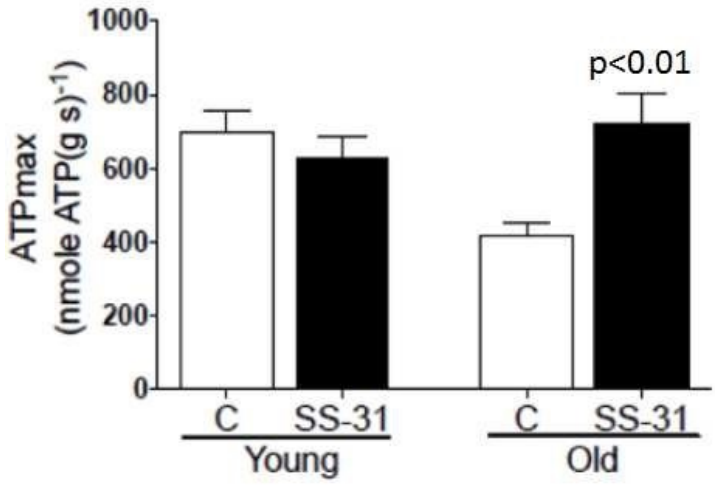
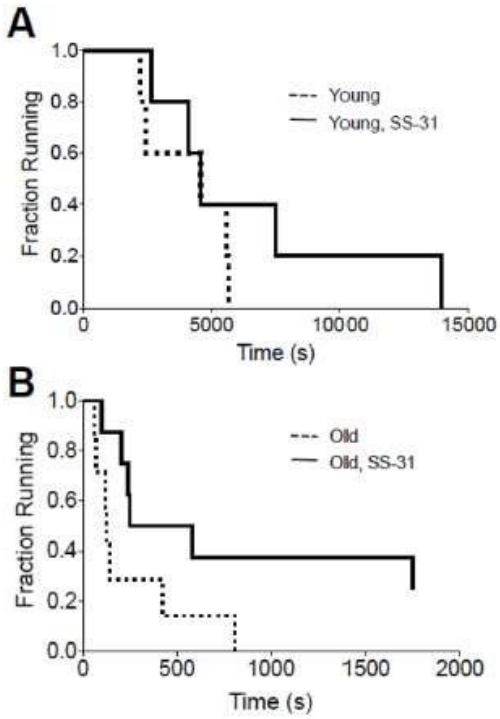


Figure 2 Exercise Tolerance in Young and Old Mice Following One Week of Treatment with MTP-131



Also, in a rat model of muscle wasting, MTP-131 reduced functional loss of the diaphragm muscles after animals were placed on a ventilator for 12 hours. (Powers et al. 2011) Similarly, MTP-131 prevented casting-induced skeletal muscle atrophy via protecting mitochondrial function. (Talbert et al. 2013)
In a study using a mouse model of immobilization induced skeletal muscle atrophy, it was shown that MTP-131 rescues skeletal muscle from disuse-induced atrophy via prevention of mitochondrial ROS production and is, therefore, suggestive of therapeutic potential in this clinical situation (Min et al. 2011).

4.2.2. Potential Risks

4.2.2.1. Safety findings – Nonclinical studies

Toxicology studies in rats and dogs showed that elamipretide has an acceptable profile that permits clinical investigations in humans for the proposed duration of the study.

In nonclinical safety studies in rats and dogs, no safety issues relevant to either IV infusion or SC administration at therapeutic doses were identified during the nonclinical evaluation of MTP-131. MTP-131 did not cause end-organ toxicity at any dosage tested in either rats or dogs. Systemic toxicity at high doses was manifested primarily by acute and transient clinical signs, which may have been mediated by histaminergic-like reactions. Effects were associated with maximum MTP-131 plasma concentration (C_{max}) and were rapidly reversible as plasma concentrations of MTP-131 and histamine decreased. Dose administration was not associated with any adverse effects on cardiovascular, respiratory or central nervous system function; offtarget non-adverse effects were limited to transient decrease of blood pressure and heart

rate, which is thought to be consistent with histaminergic-like reactions. In all studies, the severity of the effects was proportional to C_{max} for MTP-131; thus, the safety margin is estimated based on C_{max}, and not area under the plasma concentration-time curve (AUC). The plasma MTP-131 threshold concentration for clinically-relevant adverse effects appears to be ~20,000 ng/mL in both rats and dogs, which is more than 10-fold higher than the maximum anticipated human exposures in this trial.

Elamipretide was negative for genotoxicity in the full battery of tests and caused no significant hemolysis or inhibition of receptor binding. Elamipretide was not associated with adverse effects on fertility or embryo-fetal development.

No formal immunotoxicity studies have been performed. As a tetrapeptide the immunogenic potential of the drug is expected to be low.

4.2.2.2. Human safety

The safety profile of multiple SC doses of elamipretide has not yet been evaluated in MM patients. Though the trial is ongoing (and blinded), elamipretide doses up to 0.2 mg/kg administered IV over 2 hours were safe and well-tolerated in 24 patients with mitochondrial myopathy in the SPIMM-201 study. No SAEs or deaths have been recorded.

In 7 completed single-dose IV trials in healthy subjects, the most commonly reported treatment emergent adverse events (TEAEs) in subjects dosed with MTP 131 were headache, nausea, and hyponatremia. Across the 3 trials evaluating single IV doses of elamipretide in cardio-renal patient populations (i.e., chronic HF, acute kidney injury, and acute coronary syndrome), single IV doses of elamipretide were generally safe and well tolerated with no notable differences between the elamipretide and placebo treatment groups in the frequency or severity of adverse events.

Both single-dose SC administration and multiple-dose SC administration of elamipretide doses of up to 80 mg/day, for seven days, were well tolerated in healthy adult subjects. No deaths or drug-related SAEs occurred, and no subjects withdrew from the study for drug-related reasons. The most commonly reported TEAE in the elamipretide treatment group was injection site erythema with intercurrent mild pruritus and/or pain reported with similar frequency after single and multiple doses; injection site reactions generally resolved within 4 hours and were not associated with long-term effects in any subject.

4.2.3. Conclusions

In summary, based on the clinical and nonclinical study data, acceptable safety risks are expected for the proposed current study.

5. OBJECTIVES

5.1. Primary Objective

To evaluate the effect of single daily subcutaneous (SC) doses of elamipretide administered for 4 weeks on 6-minute walking distance (6MWD).

5.2. Secondary Objectives

- To evaluate the safety and tolerability of single daily SC doses of elamipretide administered for 4 weeks

- To evaluate the effects of single daily SC doses of elamipretide administered for 4 weeks on:
    - Accelerometry ○ Triple Timed Up and Go (3TUG) Test ○ Patient Reported Outcomes ○ Exploratory biomarkers
    - Physician Global Assessment (PhGA)

6. INVESTIGATIONAL PLAN

6.1. Study Design

This randomized, double-blind, placebo-controlled crossover study will enroll up to 36 subjects with genetically confirmed mitochondrial disease who have completed participation in the SPIMM-201 study. Subjects will have previously received 5 days of intravenous elamipretide (0.01, 0.10 or 0.25 mg/kg/hour infused for 2 hours) or placebo (randomized 3:1) in the SPIMM-201 study.

Subjects will be randomized (1:1) to one of two sequence groups: 4-weeks of treatment with 40 mg elamipretide administered once daily SC in Treatment Period 1 followed by 4-weeks of treatment with placebo administered once daily SC in Treatment Period 2 (separated by 4-week washout period), or vice versa (Attachment 3).

Given the challenges of scheduling Visiting Nurses visits to subject's homes (e.g. remote geographic locations, subject scheduling conflicts, extreme weather or other natural disasters etc.), in consultation and agreement with the Sponsor and Investigator, Visiting Nurse visits may be postponed, changed or cancelled.

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Treatment Period 1: Treatment Period 1 will begin on the day of the Baseline Visit, which is defined as Study Day 1. At the Baseline Visit, following completion of all Baseline procedures described in the Study Schedule, subjects will be administered study drug SC at the study center. Subjects or caregivers will receive instructions on scheduling daily home (or other location) visits with the Visiting Nurse and will be assigned a Visiting Nurse who may administer (or observe) study drug subcutaneously on a daily basis for the first week of Treatment Period 1 and at least weekly thereafter. The Visiting Nurse visit on Day 2 is required, however, the Visiting Nurse Visits during Days 3-7 are not mandatory and the patient (or caregiver) and the Visiting Nurse should determine the frequency and necessity of these visits. Subjects (or caregivers) will be trained on the procedure for administration of study drug and will administer study drug on a daily basis (except for days corresponding to study center visits and potentially Visiting Nurse Visits) at approximately the same time each day. If, for any reason, a subject (or caregiver) is unable/unwilling to administer study drug, a Visiting Nurse may be provided for daily administration of study drug. The Visiting Nurse will also draw blood for safety labs at Week 1 and Week 2 Visits. The Visiting Nurse will administer (or observe) study drug at the Week 3 Visit and remind subjects to wear the hip accelerometer during waking hours for at least 7 consecutive days immediately prior to the Week 4 Visit. Subjects will continue to follow all study requirements, including completing daily MD

Symptom Assessments and recording the location and time of the study drug administration in an electronic or paper diary as well as wearing the wrist accelerometer daily. Treatment Period 1 will conclude with a visit to the study center at the Week 4 Visit and subjects will return all used and unused vials to the study center at this visit.

Washout: Washout will begin on the day after the Week 4 Visit and will last for at least 4 weeks. The Visiting Nurse will visit at the Week 6 Visit to provide the subject with the Neuro-QoL Fatigue questionnaire to complete, and will collect the completed questionnaire. The Visiting Nurse will also draw blood for safety labs. The Visiting Nurse will ensure the subject is wearing a wrist accelerometer daily (24 hours per day), remind the subject to wear a hip accelerometer daily during waking hours (minimum of at least 7 consecutive days immediately prior to the Week 8 Visit), and complete daily MD Symptom Assessments in an electronic or paper diary.

Treatment Period 2: Treatment Period 2 will begin with a visit to the study center for the Week 8 Visit. Subjects will be administered study drug SC at the study center following completion of all baseline procedures described in the Study Schedule. A Visiting Nurse will administer (or observe) study drug on a weekly basis at home (or other location) and will draw blood for safety labs on Week 9 and Week 10, as described in the Study Schedule. Subjects (or caregivers) will administer study drug on a daily basis at approximately the same time each day (except for days corresponding to study center visits and potentially Visiting Nurse Visits). The Visiting Nurse will administer (or observe) study drug at the Week 11 Visit and will remind subjects to wear the hip accelerometer during waking hours for at least 7 consecutive days immediately prior to the Week 12 Visit. Subjects will continue to follow all study requirements, including completing daily MD Symptom Assessments and recording the location and time of the study drug administration in an electronic or paper diary as well as wearing the wrist accelerometer daily. Treatment Period 2 will conclude with a visit to the study center at the Week 12 Visit and subjects will return all used and unused vials to the study center at this visit.

Follow-Up: Follow-Up will begin after completion of Treatment Period 2 and will last for 2 weeks. During follow-up, subjects will continue to follow all study requirements, including completing daily MD Symptom Assessments in an electronic or paper diary as well as wearing the wrist accelerometer daily. At the end of Follow-up, subjects will return to the study center for the End-of-Study/Early Discontinuation Visit for final safety and efficacy assessments and to return all remaining study equipment, as described in the Study Schedule.

6.2. Discussion of Design and Control

This is a randomized, double-blind, placebo-controlled, multi-center two-period crossover study in subjects with genetically confirmed mitochondrial disease who completed participation in the SPIMM-201 study.

Up to thirty-six subjects will be randomized (1:1) to one of two sequence groups: 4-weeks of treatment with 40 mg elamipretide administered once daily SC in Treatment Period 1 followed by 4-weeks of treatment with placebo administered once daily subcutaneously in Treatment

Period 2 (separated by 4-week washout period), or vice versa. A four week washout was selected to considerably reduce the likelihood of a carryover effect based on the known

pharmacokinetics of elamipretide and anticipated turnover of mitochondria. The crossover design was selected because of the additional anticipated power due to subjects serving as their own control.

Blinded treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

6.3. Study Schedule

Study procedures and their timing are summarized in the Schedule of Clinical Assessments (Attachment 1), Schedule of Visiting Nurse Assessments (Attachment 2), and Study Schematic (Attachment 3). A list of all clinical laboratory tests to be performed is found in Attachment 4.

6.3.1. Screening: At least 7 days and no longer than 30 days

NOTE: When possible, all study procedures should be completed in the order described below:

- Review and sign the Informed Consent Form (ICF)
- Record demographics (age, gender, ethnicity, race)
- Update relevant medical history since participation in the SPIMM-201 study
- Document concomitant medication (including supplements and vitamins)
- Collect Vital signs (as described in Section 6.4.3)
- Complete 12-lead resting ECG (as described in Section 6.4.4)
- Draw blood for clinical laboratory testing as outlined in Attachment 4
- Collect urine for clinical urinalysis as outlined in Attachment 4
- Complete a serum pregnancy for women of child-bearing potential
- Review all inclusion and exclusion criteria
- Complete the Columbia Suicide Severity Rating Scale (C-SSRS) “Lifetime” (as described in Section 6.4.2 and outlined in Attachment 11)
- Complete a physical examination (as described in Section 6.4.1)
- Complete the Neuro-QoL Fatigue questionnaire (as described in Section 6.4.8 and as outlined in Attachment 6)
- Complete the Mitochondrial Disease (MD) Symptom Assessment (as described in Section 6.4.9 and as outlined in Attachment 7) and collect results in an electronic or paper diary. The MD Symptom Assessment should be completed daily during the study

(Baseline Visit to End-of-Study/Early Discontinuation Visit) in an electronic or paper diary.

- Train the subject on wrist and hip accelerometer; wrist and hip accelerometer are to be worn daily during Screening (hip accelerometer is to be worn at minimum during the 7 consecutive days immediately prior to the Baseline Visit). All efforts should be made to wear the wrist accelerometer on the same wrist throughout the entirety of the study.

Conduct the 6MWT (as described in Section 6.4.6 and as outlined in Attachment 5) Complete the 3TUG Test. The 3TUG Test should be started after completion of 6MWT and after at least 15 minutes rest (as described in Section 6.4.7 and as outlined in Attachment 8)

6.3.2. Treatment Period 1

6.3.2.1. Baseline Visit (Day 1)

NOTE: Subjects who have been deemed eligible during Screening Period will return for randomization and the following procedures will be performed. All study procedures must be completed prior to administering study drug. When possible, all study procedures should be completed in the order described below:

- Collect of medical history since the Screening Visit
- Document concomitant medication (including supplements and vitamins) Document AEs related to a study procedure and/or meet seriousness criteria that occurred since the signing of the informed consent form as Section 9.6.2.
- Collect Vital signs (as described in Section 6.4.3)
- Complete 12-lead resting ECG (as described in Section 6.4.4)
- Draw blood for clinical laboratory testing as outlined in Attachment 4
- Draw blood for exploratory biomarkers (as described in Section 6.4.11)
- Collect urine for clinical urinalysis as outlined in Attachment 4
- Complete a urine pregnancy for women of child-bearing potential
- Review all inclusion and exclusion criteria
- Complete a physical examination (as described in Section 6.4.1)
- Complete the C-SSRS “Since Last Visit” (as described in Section 6.4.2 and outlined in Attachment 12)
- Complete the Neuro-QoL Fatigue questionnaire (as described in Section 6.4.8 and as outlined in Attachment 6)
- Complete the Mitochondrial Disease (MD) Symptom Assessment (as described in Section 6.4.9 and as outlined in Attachment 7) and collect results in an electronic or paper diary. The MD Symptom Assessment should be completed daily during the study (Baseline Visit to End-of-Study/Early Discontinuation Visit) in an electronic or paper diary.

- Complete the Physician's Global Assessment (PhGA) (as described in Section 6.4.12 and as outlined in Attachment 9)
- Complete the Patient's Global Assessment (PGA) (as described in Section 6.4.13 and as outlined in Attachment 10)
- Conduct the 6MWT (as described in Section 6.4.6 and as outlined in Attachment 5) Complete the 3TUG Test. The 3TUG Test should be started after completion of 6MWT and after at least 15 minutes rest (as described in Section 6.4.7 and as outlined in Attachment 8)
- Sync wrist and hip accelerometers and confirm subject is wearing wrist accelerometer Inject study drug record the location and time of the study drug administration in an electronic or paper diary
- Schedule and discuss home (or other location) visit schedule by the Visiting Nurse

6.3.2.2. Visiting Nurse Visits: Days 2 – 7

A Visiting Nurse may administer (or observe) study drug at approximately the same time each day on Days 2 through Day 7 and will train subjects and/or caregivers on the storage and procedures for administration of study drug. The Visiting Nurse visit on Day 2 is required, however, the Visiting Nurse Visits during Days 3-7 are not mandatory and the patient (or caregiver) and the Visiting Nurse should determine the frequency and necessity of these visits. The Visiting Nurse will also confirm the subject is wearing his/her wrist accelerometer and ensure the accelerometer is charged. The Visiting Nurse should confirm the subject is also completing the MD Symptom Assessment and recording the study drug injection location and time in an electronic or paper diary. Refer to the Schedule of Visiting Nurse Assessments in Attachment 2.

6.3.2.3. Visiting Nurse Visits: Week 1 (Day 8 ± 1), Week 2 (Day 15 ± 2), and Week 3 (Day 22 ± 2)

A Visiting Nurse will administer (or observe) study drug and confirm both accelerometers are charged and ensure the subject is wearing wrist accelerometer. The Visiting Nurse will also ensure appropriate storage and use of the study drug at each Visit. At the Week 1 and Week 2 Visits, blood for clinical chemistry and clinical hematology will be collected. The Visiting Nurse should confirm the subject is also completing the MD Symptom Assessment and recording the study drug injection location and time in an electronic or paper diary. At the Week 3 Visit, the Visiting Nurse will instruct the subject to wear hip accelerometer for 7 consecutive days immediately prior to Week 4 Visit. Refer to the Schedule of Visiting Nurse Assessments in Attachment 2.

6.3.2.4. Week 4 (Day 29 + 6 days)

NOTE: Subjects will be instructed to wear the hip accelerometer for the 7 consecutive days immediately prior to the Week 4 Visit. Study drug administration should occur before all study procedures. When possible, all study procedures should be completed in the order described below:

The following evaluations will be performed:

- Inject study drug record the location and time of the study drug administration in an electronic or paper diary

  Document concomitant medication (including supplements and vitamins)

- Document AEs
- Complete a physical examination (as described in Section 6.4.1)
- Complete the C-SSRS "Since Last Visit" (as described in Section 6.4.2 and outlined in Attachment 12)
- Collect Vital signs (as described in Section 6.4.3)
- Complete 12-lead resting ECG (as described in Section 6.4.4)
- Draw blood for clinical laboratory testing as outlined in Attachment 4
- Draw blood for exploratory biomarkers (as described in Section 6.4.11)
- Collect urine for clinical urinalysis as outlined in Attachment 4
- Complete the Neuro-QoL Fatigue questionnaire (as described in Section 6.4.8 and as outlined in Attachment 6)
- Complete the Mitochondrial Disease (MD) Symptom Assessment (as described in Section 6.4.9 and as outlined in Attachment 7) and collect results in an electronic or paper diary. The MD Symptom Assessment should be completed daily during the study (Baseline Visit to End-of-Study/Early Discontinuation Visit) in an electronic or paper diary.
- Complete the Physician's Global Assessment (PhGA) (as described in Section 6.4.12 and as outlined in Attachment 9)
- Complete the Patient's Global Assessment (PGA) (as described in Section 6.4.13 and as outlined in Attachment 10)
- Conduct the 6MWT (as described in Section 6.4.6 and as outlined in Attachment 5) Complete the 3TUG Test. The 3TUG Test should be started after completion of 6MWT and after at least 15 minutes rest (as described in Section 6.4.7 and as outlined in Attachment 8)

- Sync wrist and hip accelerometers and confirm subject is wearing wrist accelerometer
- Collect all used and unused study drug vials from the subject

6.3.3. Washout

Washout will be at least 4 weeks in duration. If all used and unused study drug vials were not returned at the Week 4 Visit, the unscheduled Visiting Nurse Visit will be scheduled to collect all remaining vials (or other arrangements will be made to ship the remaining vials back to the site). The subject will be instructed to continue to wear an accelerometer on his/her wrist and will continue to complete the MD Symptom Assessment (as described in Section 6.4.9 and as outlined in Attachment 7) collect the results in an electronic or paper diary. The MD Symptom Assessment should be completed daily during Washout Period. The Visiting Nurse will visit at the Week 6 Visit to provide the subject with the Neuro-QoL Fatigue questionnaire to complete, and will collect the completed questionnaire. The Visiting Nurse will also draw blood for safety labs. The Visiting Nurse will ensure the subject is wearing a wrist accelerometer daily (24 hours per day), remind the subject to wear a hip accelerometer daily during waking hours (minimum of at least 7 consecutive days immediately prior to the Week 8 Visit).

6.3.4. Treatment Period 2

6.3.4.1. Week 8 (Day 57 + 5)

NOTE: All study procedures must be completed prior to administering study drug. When possible, all study procedures should be completed in the order described below:

- Document concomitant medication (including supplements and vitamins)
- Document AEs
- Complete a physical examination (as described in Section 6.4.1)
- Complete the C-SSRS “Since Last Visit” (as described in Section 6.4.2 and outlined in Attachment 12)
- Collect Vital signs (as described in Section 6.4.3)
- Complete 12-lead resting ECG (as described in Section 6.4.4)
- Draw blood for clinical laboratory testing as outlined in Attachment 4
- Draw blood for exploratory biomarkers (as described in Section 6.4.11)
- Collect urine for clinical urinalysis as outlined in Attachment 4
- Complete the Neuro-QoL Fatigue questionnaire (as described in Section 6.4.8 and as outlined in Attachment 6)

- Complete the Mitochondrial Disease (MD) Symptom Assessment (as described in Section 6.4.9 and as outlined in Attachment 7) and collect results in an electronic or paper diary. The MD Symptom Assessment should be completed daily during the study (Baseline Visit to End-of-Study/Early Discontinuation Visit) in an electronic or paper diary.
- Complete the Physician's Global Assessment (PhGA) (as described in Section 6.4.12 and as outlined in Attachment 9)
- Complete the Patient's Global Assessment (PGA) (as described in Section 6.4.13 and as outlined in Attachment 10)
- Conduct the 6MWT (as described in Section 6.4.6 and as outlined in Attachment 5)
- Complete the 3TUG Test. The 3TUG Test should be started after completion of 6MWT and after at least 15 minutes rest (as described in Section 6.4.7 and as outlined in Attachment 8)
- Sync wrist and hip accelerometers and confirm subject is wearing wrist accelerometer

  Inject study drug record the location and time of the study drug administration in an electronic or paper diary

6.3.4.2. Visiting Nurse Visits: Week 9 (Day 64 ± 2), Week 10 (Day 71 ± 2), Week 11 (Day 78 ± 2)

A Visiting Nurse will administer (or observe) study drug and confirm both accelerometers are charged and ensure the subject is wearing wrist accelerometer. The Visiting Nurse will also ensure appropriate storage and use of the study drug at each Visit. At the Week 9 and Week 10 Visits, blood for clinical chemistry and clinical hematology will be collected. The Visiting Nurse should confirm the subject is also completing the MD Symptom Assessment and recording the study drug injection location and time in an electronic or paper diary. At the Week 11 Visit, the Visiting Nurse will instruct the subject to wear hip accelerometer for 7 consecutive days immediately prior to Week 12 Visit. Refer to the Schedule of Visiting Nurse Assessments in Attachment 2.

6.3.4.3. Week 12 (Day 85 + 6)

NOTE: Subjects will be instructed to wear the hip accelerometer for the 7 consecutive days immediately prior to the Week 12 Visit. Study drug administration should occur before all study procedures. When possible, all study procedures should be completed in the order described below:

- Inject study drug record the location and time of the study drug administration in an electronic or paper diary
- Document concomitant medication (including supplements and vitamins)

- Document AEs
- Complete a physical examination (as described in Section 6.4.1)
- Complete the C-SSRS "Since Last Visit" (as described in Section 6.4.2 and outlined in Attachment 12)
- Collect Vital signs (as described in Section 6.4.3)
- Complete 12-lead resting ECG (as described in Section 6.4.4)
- Draw blood for clinical laboratory testing as outlined in Attachment 4
- Draw blood for exploratory biomarkers (as described in Section 6.4.11)
- Collect urine for clinical urinalysis as outlined in Attachment 4
- Complete the Neuro-QoL Fatigue questionnaire (as described in Section 6.4.8 and as outlined in Attachment 6)
- Complete the Mitochondrial Disease (MD) Symptom Assessment (as described in Section 6.4.9 and as outlined in Attachment 7) and collect results in an electronic or paper diary. The MD Symptom Assessment should be completed daily during the study (Baseline Visit to End-of-Study/Early Discontinuation Visit) in an electronic or paper diary.
- Complete the Physician's Global Assessment (PhGA) (as described in Section 6.4.12 and as outlined in Attachment 9)
- Complete the Patient's Global Assessment (PGA) (as described in Section 6.4.13 and as outlined in Attachment 10)
- Conduct the 6MWT (as described in Section 6.4.6 and as outlined in Attachment 5)
- Complete the 3TUG Test. The 3TUG Test should be started after completion of 6MWT and after at least 15 minutes rest (as described in Section 6.4.7 and as outlined in Attachment 8)
- Sync wrist and hip accelerometers and confirm subject is wearing wrist accelerometer
- Collect all used and unused study drug vials from the subject

6.3.5. Follow-up Period

Follow-Up will be approximately 2 weeks in duration. If all used and unused study drug vials were not returned at the Week 4 Visit, the unscheduled Visiting Nurse Visit will be scheduled to collect all remaining vials (or other arrangements will be made to ship the remaining vials back to the site). The subject will be instructed to continue to wear an accelerometer on his/her

wrist and will continue to complete the MD Symptom Assessment (as described in Section 6.4.9 and as outlined in Attachment 7) collect the results in an electronic or paper diary during the Follow-Up Period.

6.3.5.1. End-of-Study/Early Discontinuation Visit (Day 99 + 7 days /Early Discontinuation)

NOTE: When possible, all study procedures should be completed in the order described below:

- Document concomitant medication (including supplements and vitamins)
- Document AEs
- Complete a physical examination (as described in Section 6.4.1)
- Complete the C-SSRS "Since Last Visit" (as described in Section 6.4.2 and outlined in Attachment 12)
- Collect Vital signs (as described in Section 6.4.3)
- Complete 12-lead resting ECG (as described in Section 6.4.4)
- Draw blood for clinical laboratory testing as outlined in Attachment 4
- Draw blood for exploratory biomarkers (as described in Section 6.4.11)
- Collect urine for clinical urinalysis as outlined in Attachment 4
- Complete a urine pregnancy for women of child-bearing potential

  Complete the Neuro-QoL Fatigue questionnaire (as described in Section 6.4.8 and as outlined in Attachment 6)
- Complete the Mitochondrial Disease (MD) Symptom Assessment (as described in Section 6.4.9 and as outlined in Attachment 7) and collect results in an electronic or paper diary. The MD Symptom Assessment should be completed daily during the study (Baseline Visit to End-of-Study/Early Discontinuation Visit) in an electronic or paper diary.
- Complete the Physician's Global Assessment (PhGA) (as described in Section 6.4.12 and as outlined in Attachment 9)
- Complete the Patient's Global Assessment (PGA) (as described in Section 6.4.13 and as outlined in Attachment 10)
- Conduct the 6MWT (as described in Section 6.4.6 and as outlined in Attachment 5)
- Complete the 3TUG Test. The 3TUG Test should be started after completion of 6MWT and after at least 15 minutes rest (as described in Section 6.4.7 and as outlined in Attachment 8)

- Collect and sync the wrist and hip accelerometers.

6.4. Study Assessments

The following section describes study assessments occurring during the study. Study assessments and procedures are presented by study visit in Attachment 1. Details regarding clinical laboratory tests are found in Attachment 4.

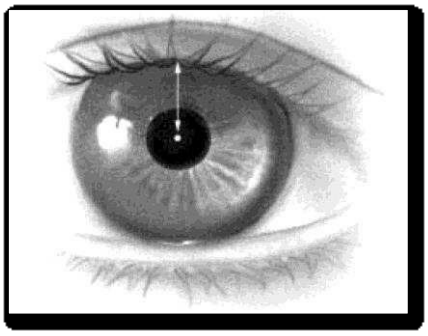
6.4.1. Medical History and Physical Examination

At the Screening Visit, a medical history (since participation in the SPIMM-201 study) will be taken, including measurement of height.

At the Baseline Visit, a review of the medical history (including concomitant medication and procedures) since the Screening visit will be taken.

At the Screening, Baseline, Week 4, Week 8, Week 12, and End-of-Study/Early Discontinuation Visits, a complete physical examination will be performed. This will include a full review of the following systems: general appearance, skin, head, eyes (only if ptosis is present [i.e. an upper marginal reflex distance below 2 mm or an asymmetry of more than 2 mm between the eyes] the marginal reflex distance should be measured and recorded for both eyes as shown below in Figure 3), ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, extremities, and nervous system. The Scale for the Assessment and Rating of Ataxia (SARA) (provided in Attachment 13) will be completed during every physical examination for all subjects. Height will only be measured at the Screening Visit. Weight should be taken during each physical examination.

Figure 3 Marginal Reflex Distance



6.4.2. Columbia Suicide Severity Rating Scale (C-SSRS)

At the Screening Visit, the C-SSRS "Lifetime Recent" will be recorded. The C-SSRS "Lifetime Recent" is included in Attachment 11. At all subsequent clinical visits, the C-SSRS "Since Last Visit" will be recorded. The C-SSRS "Since Last Visit" is included in Attachment 12.

6.4.3. Vital signs

During all study center visits, the vital signs measurements will include temperature, heart rate, respiration rate and blood pressure, recorded in the sitting position after at least 5 minutes rest. At the Baseline Visit these vital signs measurements will be performed as part of the study eligibility confirmation.

6.4.4. Electrocardiograms (ECGs)

A 12-lead ECG will be obtained after the subjects has rested quietly for 10 minutes in the supine position at all study center visits.

ECG intervals (PR, QRS, QT, QTc), heart rate and ECG findings will be recorded for each subject. Based on signs or symptoms, additional 12-lead ECGs may be performed. The QTc correction factor used to calculate the QTc value will be collected from each site.

6.4.5. Clinical Laboratory Testing

Sample collection, processing and handling details are provided in the Laboratory Manual.

6.4.5.1. Blood chemistries

Blood will be collected at all study center visits as well as Visiting Nurse visits on Week 1, Week 2, Week 6, Week 9, and Week 10. Analysis will include testing for parameters included in Attachment 4.

6.4.5.2. Hematology

Blood will be collected at all study center visits as well as Visiting Nurse visits on Week 1, Week 2, Week 6, Week 9, and Week 10. Analysis will include testing for parameters included in Attachment 4.

6.4.5.3. Urinalysis

Urine will be collected at all study center visits and will include testing for parameters included in Attachment 4.

6.4.5.4. Pregnancy tests

Women of child-bearing potential will have a serum pregnancy test performed at the Screening Visit. Women of child-bearing potential will have a urine pregnancy test at the Baseline Visit and the results of the Baseline Visit pre-dose pregnancy test must be evaluated before randomization to ensure eligibility. A urine pregnancy test will also be performed for women of childbearing potential at the End-of-Study/Early Discontinuation Visit.

6.4.6. 6-Minute Walk Test (6MWT)

At all study center visits, the distance walked (in meters) during the 6MWT will be recorded. The 6MWT instructions are provided in Attachment 5. Study centers will be provided with a 6 Minute Walk Test Kit (if needed), as well as standardized training.

6.4.7. Triple Timed Up and Go (3TUG) Test

At all study center visits, the time (in seconds) to complete the 3TUG Test will be recorded. The 3TUG Test instructions are provided in Attachment 8. The 3TUG Test should be performed after completion of the 6MWT and at least 15 minutes rest.

6.4.8. The Neuro-QoL Fatigue Questionnaire

At all study center visits, subjects will be instructed to complete the Neuro-QoL Fatigue questionnaire. The Neuro-QoL questionnaire should be completed prior to administration of study drug during Treatment Period 1 and Treatment Period 2. The Visiting Nurse will visit at the Week 6 Visit to provide the subject with the Neuro-QoL Fatigue questionnaire to complete, and will collect the completed questionnaire. The Neuro-QoL Fatigue questionnaire is in Attachment 6.

6.4.9. Mitochondrial Disease (MD) Symptom Assessment

Starting at the Screening Visit, subjects will be instructed to complete the Mitochondrial Disease (MD) Symptom Assessment daily for the duration of the study (Screening through End-of-Study/Early Discontinuation Visit). The MD Symptom Assessment will be completed and recorded in an electronic or paper diary. The MD Symptom Assessment is in Attachment 7.

6.4.10. Accelerometry

Starting at the Screening Visit, subjects will be provided with a wrist and hip accelerometer and instructions for use. Subjects will be instructed to wear the wrist accelerometer from the Screening Visit through the End-of-Study/Early Discontinuation Visit 24 hours per day. Subjects will be encouraged to wear the hip accelerometer during waking hours from the Screening Visit through the End-of-Study/Early Discontinuation Visit. All efforts should be made to wear the wrist accelerometer on the same wrist throughout the entirety of the study.

Subjects will be specifically instructed to wear the hip accelerometer during waking hours for a minimum of 7 consecutive days immediately prior to the Baseline, Week 4, Week 8, and Week 12 Visits. Subjects will return both the wrist and hip accelerometers by the completion of his/her participation in the study.

6.4.11. Exploratory biomarkers

Blood will be collected at the Baseline, Week 4, Week 8, Week 12, and End-of-Study/Early Discontinuation Visits for analysis of exploratory biomarkers as outlined in Attachment 4. Blood samples for analysis of exploratory biomarkers will be collected prior to study drug administration on the Baseline and Week 8 Visits. Additional blood samples at the Baseline of Treatment Period 1 and End-of-Study/Early Discontinuation Visits will be collected and stored for assessing the immunogenicity potential of the study drug.

6.4.12. Physician Global Assessment (PhGA)

The Investigator or designee will provide an overall assessment of the subject's mitochondrial disease symptoms at the Baseline, Week 4, Week 8, Week 12, and End-of-Study/Early Discontinuation Visits. The PhGA is provided in Attachment 9. The same Investigator or designee should administer the PhGA at each visit for a particular subject.

6.4.13. Patient Global Assessment (PGA)

The Investigator or designee should ask the subjects for their overall assessment of their mitochondrial disease symptoms at the Baseline, Week 4, Week 8, Week 12, and Endof-Study/Early Discontinuation Visits. The PGA is provided in Attachment 10.

7. STUDY POPULATION

The inclusion and exclusion criteria for participation in this study are provided below. All screening procedures must be completed during the Screening period, but may be performed on different days. Screening procedures cannot be repeated, and subjects cannot be re-screened without the Sponsor's approval. If a subject is re-screened, they will maintain their original screening number. Subjects may only be enrolled into the study one time.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

7.1. Inclusion Criteria

A subject must meet the following criteria prior at the Baseline Visit to be eligible for inclusion in the study:

1. Willing and able to provide signed informed consent form (ICF) prior to participation in any study-related procedures.
2. Subject completed participation in the SPIMM-201 study without a significant protocol deviation that would suggest the subject may not be able to complete all study requirements in the opinion of the Sponsor.
3. Subject must reside in North America for the duration of the study.
4. Subject agrees to adhere to the study requirements for the length of the trial.
5. Subject has not received study drug in the SPIMM-201 study within 3 weeks prior to Screening.

6. Women of childbearing potential must agree to use 1 of the following methods of birth control from the date they sign the ICF until two months after the last dose of study drug:
    a. Abstinence, when it is in line with the preferred and usual lifestyle of the subject. Subject agrees to use an acceptable method of contraception should they become sexually active.
    b. Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy (the vasectomy procedure must have been conducted at least 60 days prior to the Screening Visit or confirmed via sperm analysis).
    c. Barrier method (e.g., condom or occlusive cap) with spermicidal foam/gel/film/cream AND either hormonal contraception (oral, implanted, or injectable) or an intrauterine device or system.

    Note: Non-childbearing potential is defined as surgical sterilization (e.g., bilateral oophorectomy, hysterectomy, or tubal ligation) or postmenopausal (defined as permanent cessation of menstruation for at least 12 consecutive months prior to the Screening Visit).
7. Subject has been on stable medications (including over-the-counter treatments, vitamins, or supplements), or medications that will not impact the safety or efficacy endpoints of the trial, in the opinion of the Investigator for at least 1 month prior to the Baseline Visit.

7.2. Exclusion Criteria

A subject who meets any of the following criteria at Screening will be excluded from the study:

1. Subject has any prior or current medical condition that, in the judgment of the Investigator, would prevent the subject from safely participating in and/or completing all study requirements (i.e. unstable angina or recent myocardial infarction).
2. Subject has received any investigational compound and/or has participated in another interventional clinical study within 30 days prior to the Baseline Visit or is concurrently enrolled in any non-interventional research of any type judged to be scientifically or medically incompatible with the study as deemed by the Investigator in consultation with the Sponsor.
3. Subject experienced an adverse reaction to study drug in the SPIMM-201 study that contraindicates further treatment with elamipretide in the opinion of the Investigator and/or Sponsor.
4. Female subjects who are pregnant, planning to become pregnant, or lactating.
5. Subject has undergone an in-patient hospitalization within the 1 month prior to the Screening Visit or is likely to need in-patient hospitalization or a surgical procedure during the course of the study

6. Subject has a creatinine clearance ≤30 mL/min as calculated by the Cockcroft Gault equation.
7. Subject has QTc elongation defined as a QTc >450 msec in male subjects and >480 msec in female subjects.

   Note: At the initial ECG, if QTc exceeds these parameters, the ECG may be repeated 2 more times, and the average of the 3 QTc values used to determine the subject's eligibility.
8. Subject has uncontrolled hypertension in the judgment of the Investigator (e.g. elevated above >160 mmHg systolic or >100 mmHg diastolic despite appropriate treatment on two consecutive readings);
9. Subject has a history of clinically significant hypersensitivity or allergy to any of the excipients contained in the study drug.
10. Subject has a history of active alcoholism or drug addiction during the year beforethe Screening Visit.
11. Subject is an Investigator/study center personnel or immediate family* ofInvestigator/study center personnel.
12. Subject is a Sponsor employee (permanent, temporary contract worker, or designeeresponsible for the conduct of the study) or immediate family* of a Sponsor employee.
    * Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted

7.3. Prohibited Medications

The use of any other investigational drug except elamipretide is prohibited during the conduct of the current trial.

All medications, including over-the-counter treatments, vitamins, or supplements, must have been stable, or medications that will not impact the safety or efficacy endpoints of the trial, in the opinion of the Investigator for at least 1 month prior to the Baseline Visit. All concomitant medications will be recorded in the source data and the Electronic Case Report Form (eCRF). Changes in dosages of current medications (including over-the-counter vitamins or supplements) during the conduct of the study will be discouraged, unless required to treat an Adverse Event.

Subjects will be instructed to maintain their normal diet, daily caffeine and fiber intake throughout the study period.

7.4. Discontinuations

7.4.1. Discontinuation of Subjects

Subjects may be discontinued for the following reasons:

- Investigator Decision ○ The Investigator decides that the subject should be discontinued from the study for any reason.
- Subject Decision ○ The subject or the subject's designee, (e.g., parents or legal guardian), requests to be withdrawn from the study.
    - Subjects who withdraw should be explicitly asked about the contribution of possible adverse events to their decision to withdraw consent, and any adverse event information elicited should be documented.
    - Preferably the subject should withdraw consent in writing and, if the subject or the subject's representative refuses or is physically unavailable, the study center should document and sign the reason for the subject's failure to withdraw consent in writing.
    - The subject is lost to follow-up after a reasonable number of attempts to contact the subject (including documented phone calls and/or emails, and a certified letter) have been completed.
- Sponsor Decision ○ The Sponsor or its designee stops the study or stops the subject's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP guidelines.
- Adverse Event
    - If the Investigator decides that the subject should be withdrawn because of an AE or a clinically significant laboratory value, the investigational product is to be discontinued and appropriate measures are to be taken. The Sponsor or its designee is to be alerted immediately.

Any subject withdrawing from the study will be asked to complete the Early Discontinuation visit assessments (see Attachment 1).

7.4.2. Discontinuation of Study Center

Study center (research center) participation may be discontinued if the Sponsor or its designee, the Investigator, or the Ethics Committee (EC) of the study center judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP guidelines.

7.4.3. Discontinuation of the Study

The study will be discontinued if the Sponsor or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP guidelines.

8. TREATMENT

8.1. Treatments Administered

Up to 36 subjects will receive study drug administered as a single daily subcutaneous (SC) injection containing either 40 mg elamipretide or placebo for at least 28 consecutive days in Treatment Period 1 and at least 28 consecutive days in Treatment Period 2. Study drug will be administered daily to the subject, preferably in the abdomen (rotating around the four abdominal quadrants), by either the study center clinical staff, a Visiting Nurse, a caregiver, or the subject. Administration of study drug will occur at approximately the same time every day during each Treatment Period.

At the Baseline Visit, study drug will occur after completion of all baseline procedures (see Section 6.3.2.1). Study drug injection will occur at the study center at the Baseline Visit.

Subjects or caregivers will receive instruction on scheduling daily home (or other location) visits with the Visiting Nurse and will be assigned a Visiting Nurse who may administer (or observe) study drug subcutaneously on a daily basis for the first week of Treatment Period 1 and at least weekly thereafter. The Visiting Nurse visit on Day 2 is required, however, the Visiting Nurse Visits during Days 3-7 are not mandatory and the patient (or caregiver) and the Visiting Nurse should determine the frequency and necessity of these visits. Subjects (or caregivers) will be trained on the procedure for administration of study drug and will administer study drug on a daily basis (except for days corresponding to study center visits and potentially Visiting Nurse Visits) at approximately the same time each day.

Study drug injection will occur at the study center on Week 8 and subjects will be instructed to schedule weekly Visiting Nurse visits for the duration of Treatment Period 2.

If, for any reason, a subject (or caregiver) is unable/unwilling to administer study drug, a Visiting Nurse may be provided for daily administration of study drug.

8.2. Materials and Supplies

Study drug (elamipretide and placebo) will be dispensed, stored, and administered according to the Pharmacy Manual.

8.2.1. Elamipretide

Elamipretide (MTP-131) drug product will be provided as a sterile solution for administration by SC injection. Each single-use vial contains sufficient volume to extract one milliliter of drug product containing 40 mg elamipretide, as MTP-131 acetate, in an isotonic, unpreserved, clear, colorless solution.

8.2.2. Placebo

The placebo for this trial will be provided as a sterile solution in matching sterile glass vials and is composed of the excipients used to manufacture the investigational drug elamipretide without the active drug substance. The placebo will be handled and administered identically as active drug.

8.3. Treatment Logistics and Accountability

All drug accountability records must be kept current, and the Investigator must be able to account for all used and unused vials of study drug. These records should contain the dates, quantity, and study drug:

- Received at study center
- Administered to each subject,
- Dispensed to each subject,
- Returned from each subject, and
- Disposed of at the study center or returned to the Sponsor or designee

The clinical monitor responsible for the study center will provide written approval for the destruction or return of unused study drug vials following reconciliation of all clinical supplies.

8.4. Method of Assignment to Treatment and Randomization

At the Baseline Visit, after eligibility criteria have been confirmed, a treatment kit number will be assigned to each subject on the basis of a centralized computer-generated randomization schedule. Subjects will be randomized into 1 of 2 treatment sequences in a 1:1 fashion to receive either elamipretide 40 mg followed by placebo (after 4 week washout) or placebo followed by elamipretide 40 mg (after 4 week washout).

8.5. Rationale for Selection of Doses in the Study

The dose and route of administration (i.e., 40 mg in 1 mL via SC injection) for the current study has previously been tested in a clinical trial involving healthy subjects (SPISC-101). Five consecutive daily IV doses ranging from 0.02 mg/kg to 0.5 mg/kg administered over 2 hours have been tested in subjects with genetically confirmed mitochondrial disease (SPIMM201). The doses for the current study were chosen based on the systemic exposure profile, as well as the safety observed in previous clinical trials.

The plasma elamipretide threshold concentration for clinically-relevant adverse effects appears to be ~20,000 ng/mL in both rats and dogs, which is more than 10-fold higher than the maximum anticipated human exposures. In healthy human adults, systemic exposure (in terms of mean $AUC_{0-\tau}$ on Day 7) to elamipretide following repeat SC injection at 40 mg in 1 mL was 3,810 ng·h/mL, while mean C_{max} on Day 7 was 1,320 ng/mL. No accumulation of elamipretide was seen following repeat dosing for seven consecutive days. Neither metabolite of elamipretide (M1 and M2) is active or implicated in toxicology.

In a completed Phase 1 trial (SPISC-101), elamipretide given SC to healthy volunteers at doses up to 40 mg in 1 mL once daily for seven consecutive days was well tolerated, with no systemic safety issues. Local injection site reactions were limited to transient, local erythema and occasional pruritus, pain, or swelling, which resolved spontaneously, generally within 4 hours post-dose, without sequelae.

Elamipretide demonstrated an acceptable safety and tolerability profile with multiple IV infusions of up to 0.5 mg/kg administered over 2 hours in subjects with genetically confirmed mitochondrial disease in an ongoing Phase 1/2 trial (SPIMM-201).

8.5.1. Comparison of the PK and Metabolism of IV and SC Administration

MTP-131 given by SC injection demonstrates rapid absorption, with parent T_{max} occurring approximately 0.6 hours following administration. When administered by IV infusion, parent T_{max} is controlled by the duration of infusion, and occurs at the end of drug delivery (either 2 hours or 4 hours in studies completed to date) and a similar pattern is noted for the metabolites. As expected, from the point of T_{max}, MTP-131, M1 and M2 demonstrate similar elimination profiles following IV and SC administration, with $t_{½}$ for parent generally occurring between 2 and 3 hours post-dose completion. A strong correlation between C_{max} and AUC_{0-24} following repeat administration of MTP-131 at 20 mg by a 1 hour IV infusion and C_{max} and AUC_{0-24} following administration of MTP-131 at 20 mg by SC injection is evident (Table 1).

Table 1: Comparative Pharmacokinetics of MTP-131, M1 and M2 in Clinical Studies Following a 7-day Repeat Administration of MTP-131 at Approximately 20 mg/day by IV or SC Administration

Analyte	Route	Day of Dosing	ean* Pharmacokinetic Parameters			
			T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-24}[1] or $AUC_{0-\tau}$[2] (ng.hr/mL)	Accumulation Ratio[3]
MTP-131	SC	1	0.64	715	1990	
		7	0.63	663	1890	1.01
	IV	1	1	921	2409	
		7	1	938	2355	0.98
M1	SC	1	2.25	197	1330	
		7**	2.00	215	1420	1.13
	IV	1**	2	201	1662	
		7	2	201	1637	0.98

[1] AUC_{0-24} calculated for Day 1 values

[2] $AUC_{0-\tau}$ calculated for Day 7 values where τ =48hrs

[3] Accumulation ratio calculated as $AUC_{0-\tau\ (Day\ 7)}/AUC_{0-24(Day\ 1)}$

M2	SC	1	4.88	24.5	350	
		7	4.84	34.9	580	1.72
	IV	1	6	22.2	393	
		7	6	35.1	635	1.62

^SC dose = 20 mg (as 0.5 mL x 40 mg/mL); IV dose ~ 20 mg (as 0.25 mg/kg/hr X 1 h; assuming 80 kg body weight)

*SC Administration (Ref. SPISC-101) - mean values calculated from n=8, except as noted; IV administration (Ref. SPICP-101) – mean values calculated from n=6

** Mean values calculated from n=6

Table 2 describes the pharmacokinetic parameters generated following daily administration of elamipretide by subcutaneous injection at 40 mg/day.

Table 2: Pharmacokinetic Parameters on Days 1 and 7 Following Once Daily Administration of MTP-131 as a Subcutaneous Injection of 40 mg/day (as a 1 mL injection of 40 mg/mL)

		Mean* Pharmacokinetic Parameters (CV %)			
Analyte	**Day of Dosing**	**T_{max} (hr)**	**C_{max} (ng/mL)**	**AUC_{0-24}[1] or $AUC_{0-\tau}$[2] (ng.hr/mL)**	**t½ (hr)**
MTP-131	1	0.77 (22.0)	1210 (20.3)	3750 (11.8)	2.97 (11.4)
	7	0.66 (19.7)	1320 (21.0)	3810 (13.4)	3.36 (16.2)
M1	1	2.50 (21.4)	439 (23.1)	3160 (17.2)	3.20 (12.1)
	7	2.63 (34.9)	436 (15.3)	3200 (13.5)	3.97 (12.8)
M2	1	6.25 (32.8)	51.1 (16.2)	773 (17.5)	11.2 (13.4)
	7	5.00 (32.1)	88.8 (14.4)	1410 (16.5)	20.9 (20.5)

*Mean values calculated from n=8

[1] AUC_{0-24} calculated for Day 1 values

[2] $AUC_{0-\tau}$ calculated for Day 7 values where τ =48hrs

8.6. Continued Access to Investigational Medicinal Product

Study subjects will not have access to clinical trial medication following the conclusion of the study.

8.7. Blinding and Unblinding Procedures

The study personnel and subjects will be blinded to treatment until the database is locked. The Investigator will contact the Sponsor prior to unblinding any subject's treatment sequence unless in the instance of a medical emergency.

In case of an immediate medical emergency or if directed by the Sponsor, and only if the information is required by the Investigator to manage a subject's AE, is a subject's treatment assignment to be unblinded prematurely. In cases of medical emergency, the Investigator may unblind a subject's treatment assignment using the computerized system according to the instructions received. The Sponsor must be notified as soon as possible regarding the reason for unblinding.

Whenever the treatment assignment of an individual subject is unblinded, the individual who performed the unblinding, the date, time and reason for the unblinding must be logged in the computerized unblinding system (IWRS) and also included in source documentation. The name of the individual who broke the blind must be included in the study center's source documentation.

The Sponsor designated CRO will control and document, according to the appropriate Standard Operating Procedures, the disclosure of treatment assignments, and treatment identity. These procedures ensure that no blinded staff (CRO, study center, Sponsor) will have premature access to the subjects' treatment assignments.

At completion of Treatment Period 1 and at the discretion of the Sponsor, the data may be unblinded to inform Phase 3 planning. Designated Sponsor and CRO personnel will be documented and will not be involved in the conduct of the remainder of the study.

8.8. Treatment Compliance

During the treatment period, study drug will be administered by study center clinical staff, Visiting Nurse, caregiver, or subject. Injection times and locations will be recorded.

9. EFFICACY AND SAFETY EVALUATIONS AND APPROPRIATENESS OF MEASUREMENTS

Study procedures and their timing are summarized in Attachment 1, Attachment 2 and in Attachment 3.

9.1. Efficacy Measures

9.1.1. Primary efficacy measure

Distance walked (meters) during 6MWT.

9.1.2. Secondary efficacy measure

- Accelerometer counts
- Patient reported outcomes (Neuro-QoL Fatigue questionnaire, Mitochondrial Disease [MD] Symptom Assessment and Patient Global Assessment [PGA])
- 3TUG Test score
- Exploratory biomarkers
- Physician Global Assessment (PhGA)

9.1.3. Safety measures

The safety and tolerability end-points will be assessed by:

- AEs
- Vital signs
- ECGs
- Clinical laboratory evaluations

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting Sponsor or its 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 the appropriate medical care of subjects during the study.

The Investigator remains responsible for following, through an appropriate health care option, of AEs that are serious, considered related to the study treatment or the study, or that caused the subject to discontinue before completing the study. The subject should be followed until the event is resolved or explained.

The safety profile of elamipretide will be assessed through the recording, reporting, and analyzing of AEs, clinical evaluations, and laboratory tests.

Comprehensive assessment of any apparent toxicity experienced by study subjects will be performed throughout the course of the study, from the time of the subject's signature of

informed consent. Study center personnel will report any AE, whether observed by the Investigator or reported by the subject. The reporting period for AEs is described in Section 9.6.2.

9.1.4. Adverse Events

An AE is defined as any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory findings, or diseases that emerge or worsen relative to baseline during administration of an investigational medicinal product (IMP), regardless of causal relationship.

Adverse Events may include the following:

- Suspected adverse drug reactions: side effects known or suspected to be caused by the study drug.
- Other medical experiences, regardless of their relationship with the study drug, such as injury, surgery, accidents, extensions of symptoms or apparently unrelated illnesses, and significant abnormalities in clinical laboratory values, psychological testing, or physical examination findings.
- Events occurring as a result of protocol interventions (pre- or post-IMP administration)
- Reactions from study drug overdose, abuse, withdrawal, sensitivity, or toxicity. The Sponsor has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent.

9.2. Pre-Treatment Events

Untoward events and/or incidental diagnoses that occur prior to study drug administration are by definition, unrelated to the study drug. Pre-treatment events or incidental diagnoses will be recorded on the past medical history electronic case report form (eCRF). However, if a pretreatment event is assessed by the Investigator as related to a study procedure and/or meets seriousness criteria, it will be recorded as an AE on the AE eCRF, processed, and followed accordingly.

9.3. Baseline Medical Conditions

Those medical conditions related to the disease under study whose changes during the study are consistent with natural disease progression, or which are attributable to a lack of clinical efficacy of the study drug, are NOT considered as AEs and should not be recorded as such in the eCRF. These are handled in the efficacy assessments and should be documented on the medical history page of the eCRF.

Baseline medical conditions, not in the therapeutic area of interest/investigation, that worsen in severity or frequency during the study should be recorded and reported as AEs.

9.4. Abnormal Laboratory and Other Abnormal Investigational Findings

Abnormal laboratory findings and other objective measurements should NOT be routinely captured and reported as AEs. However, abnormal laboratory findings or other objective measurements should be reported on the AE pages of the eCRF that:

- meet the criteria for a SAE
- result in discontinuation of the IMP
- require medical intervention or
- are judged by the Investigator to be clinically significant changes from baseline

When reporting an abnormal laboratory finding on the AE pages of the eCRF, if available, a clinical diagnosis should be recorded rather than the abnormal value itself (for example, "anemia" rather than "decreased red blood cell count" or "hemoglobin = 10.5 g/dL".

9.5. Serious Adverse Events

A serious adverse event (SAE) is any AE from this study that:

- Results in death. In case of a death, the cause of death is used as the AE term, and the fatality is considered as the OUTCOME.
- Is life-threatening. The term "life-threatening" refers to a SAE 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 cause death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is otherwise considered medically important.

Important medical events may be considered as SAEs when, based upon medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via an IMP is also considered an SAE and all such cases should be reported in an expedited manner as described in Section 9.7.

9.5.1. Events that Do Not Meet the Definition of a Serious Adverse Event

Elective hospitalizations to simplify study treatment or study procedures (e.g., an overnight stay) are not considered as SAEs. However, all events leading to unplanned hospitalizations (not documented prior to ICF signing) or unplanned prolongation of an elective hospitalization (e.g., undesirable effects of any administered treatment) must be documented and reported as SAEs.

9.6. Recording of Adverse Events

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be recorded on an ongoing basis in the appropriate section of the electronic Case Report Form (eCRF). Among these AEs, all serious AEs must be additionally documented and reported using the study specific SAE Report Form.

It is important that each AE report include a description of the event along with the duration (onset and resolution dates), severity, relationship to study drug, potential causal factors, treatment given or other action taken (including dose modification or discontinuation of the IMP), and the outcome.

As the quality and precision of acquired AE data are critical, Investigators should use the AE definitions provided and should observe the following guidelines when completing the AE pages of the eCRF:

- Whenever possible, recognized medical terms should be used to describe AEs rather than lay terms (for example, “influenza” rather than “flu”), and abbreviations should be avoided.
- Adverse events should be described using a specific clinical diagnosis, if available, rather than a list of signs or symptoms (for example, “congestive heart failure” rather than “dyspnea, rales, and cyanosis”). However, signs and symptoms that are not associated with an identified disease or syndrome, or for which an overall diagnosis is not yet available, should be reported as individual AEs.
- Provisional diagnoses (e.g., “suspected myocardial infarction”) are acceptable, but should be followed up with a definitive diagnosis if later available. Similarly, a fatal event with an unknown cause should be recorded as “death of unknown cause.”
- In cases of surgical or diagnostic procedures, the condition or illness leading to the procedure is considered the AE rather than the procedure itself.

Adverse events occurring secondary to other events (e.g., sequelae or complications) should be identified by the primary cause. A primary AE, if clearly identifiable, generally represents the most accurate clinical term to record in the eCRF.

9.6.1. Investigator Assessments

9.6.1.1. Severity/Intensity

Investigators must assess the severity/intensity of AEs according to the following qualitative toxicity scale:

Mild: The subject is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate: The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe: Significant impairment of functioning: the subject is unable to carry out usual activities.

9.6.1.2. Relationship to the Investigational Medicinal Product (IMP)

Investigators must systematically assess the causal relationship of AEs to the study drug using the following definitions (the decisive factor being the temporal relationship between the AE and administration of the study drug):

Probable: A causal relationship is clinically/biologically highly plausible, there is a plausible time sequence between onset of the AE and administration of the study drug, and there is a reasonable response on withdrawal.

Possible: A causal relationship is clinically/biologically plausible and there is a plausible time sequence between onset of the AE and administration of the study drug.

Unlikely: A causal relationship is improbable and another documented cause of the AE is most plausible.

Unrelated: A causal relationship can be excluded and another documented cause of the AE is most plausible.

9.6.2. Adverse Event Reporting Period

The AE reporting period begins when the subject signs the ICF and continues through the clinical study's post treatment follow-up period, defined as 14 days after last administration of study drug.

Note that AEs that occur between the time subject signs the ICF and the time the subject is dosed with study drug will be summarized in the medical history eCRF and not as an AE unless the event meets the definition of an SAE or is related to a study procedure. New protocol related AEs (caused by any intervention required by the protocol) and updates on all AEs ongoing or with an unknown outcome must be recorded until the last subject visit required by the protocol. A last batch of queries will be sent after last study visit if remaining ongoing/unknown outcomes of reported AEs are pending. After the last batch of queries with all collected data have been fully processed, CRFs and database will no longer be updated.

However, SAEs and medically relevant ongoing/unknown outcome AEs will be followed-up until resolution or stabilization by the Sponsors Pharmacovigilance department. Beyond this defined reporting period, any new SAE spontaneously reported to the Sponsor by the Investigator would be collected and processed. Additional information on SAE, obtained after database lock, will reside solely in the safety database.

Within the study, all subjects who took at least 1 dose of IMP, whether they completed the treatment period or not, should enter the 14-day period as defined above.

If a subject is documented as lost-to follow-up, ongoing/unknown outcome AEs will not be followed-up.

For screening failure subjects, new AEs and updates must be recorded in the CRFs until the date the subject was determined to be a screen failure. Beyond that date, only SAEs and medically relevant AEs will be followed-up by the Sponsor's Pharmacovigilance group and all data will be housed within the safety database.

9.7. Serious Adverse Event Expedited Reporting

In the event an SAE occurs during the reporting period, the Investigator must immediately (within a maximum of 24 hours after becoming aware of the event) inform the Sponsor as detailed in the Clinical Trial Pharmacovigilance Procedural Manual.

For any SAE, the following minimum information is required as initial notification:

- Investigator/Reporter with full contact information
- Subject identification details (study number, study center number, subject number)
- Study drug administration details (dose and dates)
- Event verbatim terms, a brief description of signs/symptoms/diagnosis and the date of onset
- Seriousness criteria(ion) met
- Relationship of the event to the study drug (e.g., the causality according to the Investigator)

Reporting procedures and timelines are the same for any new follow-up information on a previously reported SAE.

All SAE reports must be completed as described in the eCRF completion guidelines and submitted through the Electronic Data Capture (EDC) system of the clinical database. Other relevant information from the clinical database (including demographic data, medical history, concomitant drug and study drug dosing information) will automatically be sent via the EDC system when the SAE form is submitted.

The names, addresses, telephone and fax numbers for SAE back-up reporting (paper), are included in the Safety Reporting Plan.

The Investigator/Reporter must respond to any request for follow-up information (e.g., additional information, outcome and final evaluation, specific records where needed) or to any question the Sponsor may have on the AE within the same timelines as described for initial reports. This is necessary to permit a prompt assessment of the event by the Sponsor and (as applicable) to allow the Company to meet strict regulatory timelines associated with expedited safety reporting obligations.

9.7.1. Pregnancy and Contraception

Any pregnancies must be reported to the Investigator in the two months after the last dose of study drug. In addition, women of childbearing potential must agree to use 1 of the following methods of birth control from the date they sign the ICF until two months after the last dose of study drug:

a) Abstinence, when it is in line with the preferred and usual lifestyle of the subject. Subject agrees to use an acceptable method of contraception should they become sexually active.

b) Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy (the vasectomy procedure must have been conducted at least 60 days prior to the Screening Visit or confirmed via sperm analysis).

c) Barrier method (e.g., condom or occlusive cap) with spermicidal foam/gel/film/cream AND either hormonal contraception (oral, implanted, or injectable) or an intrauterine device or system.

Non-childbearing potential is defined as surgical sterilization (e.g., bilateral oophorectomy, hysterectomy, or tubal ligation) or postmenopausal (defined as permanent cessation of menstruation for at least 12 consecutive months prior to the Screening Visit).

For male subjects with female partners of child-bearing potential, highly effective methods of contraception must be adhered to prior to entry into the study and for at least 2 months after last dose of study drug. Highly effective methods of contraception is defined as the usage by the female partner of any form of hormonal contraception or intra-uterine device (which should be established prior to the start of the study) plus usage by one of the partners of an additional spermicide-containing barrier method of contraception. Male subjects with pregnant partners must use a condom with spermicide from the start of treatment until at least 2 months after the last dose of study drug. Sperm or egg donation by subjects is not permitted from the start of treatment until 2 months after the study drug was administered.

Only pregnancies considered by the Investigator as related to study treatment (e.g., resulting from an interaction between study drug and a contraceptive drug) are considered AEs unto themselves. However, all pregnancies with an estimated conception date that occurred during the AE reporting period, as defined in Section 9.6.2, must be recorded in the AE section of the eCRF. For this study, this applies to pregnancies in female subjects and in female partners of male subjects.

The Investigator must notify the Sponsor in an expedited manner of any pregnancy using the

Pregnancy Form and the back-up reporting procedure as described in the Clinical Trial Pharmacovigilance Procedural Manual. Investigators must actively follow up, document, and report on the outcome of all pregnancies.

The Investigator must notify the Sponsor of these outcomes using Section II of the Pregnancy Form and submit the information using the back-up reporting procedure. Any abnormal outcome must be reported in an expedited manner as described in Section 9.7, while normal outcomes must be reported within 45 days from delivery.

In the case of an abnormal outcome, whereby the mother sustains an event, the SAE Report Form is required and will be submitted as described above.

9.7.2. Responsibilities to Regulatory Authorities, Investigators and Ethics Committees

The Sponsor will send appropriate safety notifications to regulatory authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs involving subjects to the EC that approved the study.

In accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) GCP guidelines, the Sponsor will inform the Investigator of findings that could adversely affect the safety of subjects, impact the conduct of the study, or alter the EC's approval/favorable opinion to continue the study. In particular, and in line with respective regulations, the Sponsor will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product (SUSARs). The Investigator should place copies of the safety reports in the Investigator site file. Country-specific regulations with regard to safety report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor will provide appropriate safety reports directly to the concerned lead IEC and will maintain records of these notifications. When direct reporting by the Sponsor is not clearly defined by country- or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC of any safety reports provided by the Sponsor and or filing copies of all related correspondence in the site file.

For studies covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs will be carried out in accordance with that directive and with related guidances.

9.8. Appropriateness of Measurements

The measures used to assess safety in this study are consistent with those widely used and generally recognized as reliable, accurate, and relevant.

10. DATA QUALITY ASSURANCE

To ensure accurate, complete, and reliable data, the Sponsor or its representatives will do the following:

- Provide instructional material to the study centers, as appropriate
- Sponsor start-up training to instruct the Investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- Make periodic visits to the study center
- Be available for consultation and stay in contact with the study center personnel by mail, telephone, and/or fax
- Review and evaluate eCRF data and use standard computer edits to detect errors in data collection
- Conduct a quality review of the database

In addition, the Sponsor or its representatives will periodically check a sample of the subject data recorded against source documents at the study center. The study may be audited by the Sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the Investigator will keep records of laboratory tests, clinical notes, and subject medical records in the subject files as original source documents for the study. If requested, the Investigator will provide the Sponsor, applicable regulatory agencies, and applicable ECs with direct access to original source documents.

10.1. Data Capture System

An electronic data capture system will be used in this study. The study center will maintain a separate source for the data entered by the study center into the Sponsor-provided electronic data capture system.

Case report form data will be encoded and stored in a clinical study database. Data managed by a central vendor, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system.

Any data for which paper documentation provided by the subject will serve, as a source document will be identified and documented by each study center in that center's study file. Paper documentation provided by the subject may include, for example, a paper diary to collect subject reported outcome measures (e.g., a rating scale), a daily dosing schedule, or an event diary.

11. SAMPLE SIZE AND STATISTICAL METHODS

11.1. Determination of Sample Size

Subject numbers (up to 36 subjects) are limited to those having previously participated in the SPIMM-201 study, who meet all eligibility criteria.

11.2. Statistical and Analytical Plans

11.2.1. General Considerations

All study data are to be displayed in the data listings.

Statistical analysis of this study will be the responsibility of the Sponsor or its designee.

Additional details regarding analyses will be included in separate statistical analysis plan (SAP).

11.2.2. Subject Disposition

All subjects who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

11.2.3. Subject Characteristics

Subject's age, sex, weight, height, body mass index (BMI), and other demographic characteristics will be recorded and summarized.

Medical history will be listed.

11.2.4. Endpoints and Methodology

11.2.4.1. General Considerations

Data will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minima, and maxima) for continuous variables and using frequencies and percentages for discrete variables. Data will be presented by treatment group as appropriate, where treatment is defined fore subjects within a specific period. Formal statistical tests (where performed) will be 2-sided and teste active vs. placebo at the alpha=0.05 level of significance.

11.2.4.2. Analysis Populations

Up to thirty-six subjects will be randomized and will receive either elamipretide or placebo (in the first treatment period, followed by the alternative treatment in the second treatment period) according to the randomly assigned treatment sequence.

Statistical analysis will be performed in the following populations:

Intention-to-Treat (ITT) Population – Includes all study subjects who receive at least 1 dose of study drug, according to the assigned treatment in a given period.

Safety Population – Includes all study subjects who receive at least 1 dose of study drug according to treatment received within a period.

The details of all analyses will be described in the Statistical Analysis Plan to be finalized before unblinding.

11.2.5. Efficacy Analyses

For primary and secondary efficacy endpoints, the change from baseline in all continuous endpoints will be summarized using descriptive statistics (mean, median, standard deviation, minimum, maximum) by treatment group. Categorical variables will be described using frequencies and percentages by treatment group.

Efficacy analyses will be conducted on the ITT population. All test of treatment effects will be conducted at a 2-sided alpha level of 0.05.

Analyses will be conducted utilizing a mixed model repeated measures (MMRM) approach. No adjustments to alpha-levels will be made for secondary endpoints. Details of the model will be specified in the Statistical Analysis Plan.

11.2.6. Interim Analysis

When all subjects have had opportunity to complete the first treatment period, an interim analysis may be conducted at the discretion of the sponsor. The purpose of the interim analysis will be for the planning of future studies. The study will not be stopped at the interim to claim benefit.

11.2.7. Safety Analyses

Safety data analysis will be conducted on all subjects in the Safety Population with treatment group determined by treatment received in a particular period (i.e., subjects dosing in both periods will be counted in both treatment groups).

11.2.7.1. Adverse Events

The number and percentage of subjects experiencing 1 or more AEs will be summarized by treatment group, relationship to study drug, and severity. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology. AEs will be summarized by system organ class (SOC), preferred term (PT), and treatment group.

All reported AEs will be listed, but only treatment-emergent adverse events (TEAEs) will be summarized.

The incidence of all TEAEs, drug relationship with TEAEs, and severity of TEAE will be summarized. In the summary tables, subjects may be counted under multiple SOCs and PTs, but for each SOC and PT, subjects are only counted once (within a treatment group). If a subject has the same AE on multiple occasions (with a treatment period), the highest severity

(severe > moderate > mild) or drug relationship (probable > possibly related > unlikely related > unrelated) recorded for the event will be presented. If severity is missing, subjects will be included as missing (for severity). If drug relationship is missing, subjects will be included in related tables (e.g., considered related).

11.2.7.2. Deaths and Other Serious Adverse Events

Listings will be provided for the following:

- Deaths
- SAEs
- AEs leading to discontinuation of study drug

11.2.7.3. Clinical Laboratory Evaluations

Summary tables for laboratory parameters (including hematology, chemistry, and urinalysis) will include descriptive statistics of change relative to baseline where appropriate, and data listings of clinically significant abnormalities.

Subjects with laboratory data outside the normal range will be listed with abnormal values flagged.

Shift tables (e.g., tables that show the number of subjects who are low, normal, or high at baseline versus each post-baseline scheduled assessment) will be produced.

The number and percentage of subjects with urinalysis results outside the normal range will be presented by endpoint and visit for each treatment group. Shift tables for urinalysis will show the number of subjects who are normal/abnormal at baseline and normal/abnormal at the end of study.

11.2.7.4. Vital Signs

Vital signs data will be summarized by changes from baseline values at each treatment group using descriptive statistics.

Shift tables for heart rate and blood pressure (e.g., tables that show the number of subjects who are low, normal, or high at baseline versus each post-baseline scheduled assessment) will be produced.

11.2.7.5. Electrocardiogram

ECG data will be summarized by changes from baseline values at each treatment group using descriptive statistics.

Electrocardiogram results (normal versus abnormal) and an assessment of the clinical significance of any abnormalities (in the opinion of the Investigator) will be listed for individual subjects. Intervals of PR, QRS, QT, and QTc will also be listed.

11.2.7.6. Other Safety Parameters

Any other safety data captured on the eCRF will be listed.

12. INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

12.1. Informed Consent

The Investigator is responsible for ensuring that the subject understands the potential risks and benefits of participating in the study, including answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject willingness to continue his or her participation in the study.

The ICF will be used to explain the potential risks and benefits of study participation to the subject in simple terms before the subject is entered into the study, and to document that the subject is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The Investigator is responsible for ensuring that informed consent is given by each subject or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.

As used in this protocol, the term "informed consent" includes all consent and assent given by subject or their legal representatives.

12.2. Ethical Review

The Sponsor or its representatives must approve all ICFs before they are used at investigative study center. All ICFs must be compliant with the ICH guideline on GCP.

Documentation of EC approval of the protocol and the ICF must be provided to the Sponsor before the study may begin at the investigative study center. The EC will review the protocol as required.

The study center's EC should be provided with the following:

- The current IB and updates during the course of the study
- ICF
- Relevant curricula vitae

12.3. Regulatory Considerations

This study will be conducted in accordance with:

1) Consensus ethics principles derived from international ethics guidelines, including the CIOMS International Ethical Guidelines
2) The ICH GCP Guideline [E6]

3) Applicable laws and regulations

The Investigator or designee will promptly submit the protocol to applicable EC(s). Some of the obligations of the Sponsor may be assigned to a third party organization.

An identification code assigned to each subject will be used in lieu of the subject's name to protect the subject's identity when reporting AEs and/or other study-related data.

12.3.1. Protocol Approval

The Sponsor's responsible medical officer will approve the protocol, confirming that, to the best of their knowledge, the protocol accurately describes the planned design and conduct of the study.

12.3.2. Final Report Approval

The Sponsor's responsible medical officer will approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

12.3.3. Study Monitoring

The Investigators and institution(s) will permit study-related monitoring of the CRF data by Stealth BioTherapeutics Inc., or their assignee by providing direct access to source data and/or documents. The study monitor will verify the eCRFs 100% against the source documentation. Deviations from the protocol with regard to subject enrollment or study conduct will also be noted in the source documentation, in the eCRF and a complementary database. A Sponsor representative will visit the study center to initiate the study, prior to the first treatment of the first subject, and at agreed times throughout the study, including at the end of the study. Drug dispensing and clinical drug supply records will be 100% verified at the study center by the study monitor. It is understood that all subject specific information is confidential and no documentation that can link study information to the specific subject will be collected or retained by the Sponsor.

12.3.4. Retention of Records

All study related material including source documents, eCRFs, Central Authority, and EC correspondence and analyses and any other documentation required by applicable laws and regulations will be maintained for 15 years after completion of the study or notification from the Sponsor that the data can be destroyed, whichever comes first.

12.3.5. Disclosure of Information

Information concerning the investigational medication and patent application processes, scientific data or other pertinent information is confidential and remains the property of Stealth BioTherapeutics Inc. The Investigator may use this information for the purposes of the study only. It is understood by the Investigator that Stealth BioTherapeutics Inc., will use information developed in this clinical study in connection with the development of the investigational medication and therefore may disclose it as required to other clinical

Investigators and to regulatory agencies. In order to allow the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

The Investigator may not submit for publication or presentation the results of this study without first receiving written authorization from Stealth BioTherapeutics Inc. Stealth BioTherapeutics Inc., agrees that before it publishes any results of the study, it shall provide the Investigator with at least 30 days for review of the pre-publication manuscript prior to the submission of the manuscript to the publisher.

13. REFERENCES

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14. ATTACHMENTS

Attachment 1 Schedule of Assessments (Study Center Visits)

	Screening	Treatment Period 1		Washout	Treatment Period 2		Follow-Up/Early Discontinuation
	Visit 1 (Screening Visit)	Visit 2 (Baseline)	Visit 3 (Week 4)		Visit 4 (Week 8)	Visit 5 (Week 12)	Visit 6 (End-of-Study/Early Discontinuation Visit)
Parameter	**< -30 Day ≥ -7**	**Day 1**	**Day 29 (+6)**		**Day 57 (+5)**	**Day 85 (+6)**	**Day 99 (+7)**
Informed Consent[a]	X						
Demographics	X						
Review of Inclusion/Exclusion Criteria	X	X					
Medical and Surgical History	X	X (update)					
Concomitant Medication Review	X	X	X		X	X	X
Review AEs		X	X		X	X	X
Physical Examination[b]	X	X	X		X	X	X
C-SSRS "Lifetime Recent"	X						
C-SSRS "Since Last Visit"		X	X		X	X	X
Vital Signs[c]	X	X	X		X	X	X
12-Lead ECG[d]	X	X	X		X	X	X
Clinical Chemistry & Hematology[e]	X	X	X		X	X	X
Clinical Urinalysis	X	X	X		X	X	X
Exploratory Biomarkers[f]		X	X		X	X	X
Pregnancy Test[g]	X	X					X
Hip & Wrist Accelerometer Sync		X	X		X	X	X
Hip Activity Monitoring[h]	Days -7 to -1		Days 22-28	Days 51-57		Days 79-86	
Wrist Activity Monitoring[h]	X----------Daily----------X						

Neuro-QoL Fatigue Questionnaire	X	X	X		X	X	X
MD Symptom Assessment[i]	X----------Daily----------X						
	Screening	**Treatment Period 1**		**Washout**	**Treatment Period 2**		**Follow-Up/Early Discontinuation**
	Visit 1 (Screening Visit)	**Visit 2 (Baseline)**	**Visit 3 (Week 4)**		**Visit 4 (Week 8)**	**Visit 5 (Week 12)**	**Visit 6 (End-of-Study/Early Discontinuation Visit)**
Parameter	**< -30 Day ≥ -7**	**Day 1**	**Day 29 (+6)**		**Day 57 (+5)**	**Day 85 (+6)**	**Day 99 (+7)**
PhGA		X	X		X	X	X
PGA		X	X		X	X	X
Six Minute Walk Test[j]	X	X	X		X	X	X
3TUG Test[j,k]	X	X	X		X	X	X
Study Drug Administration[l]		X-----Daily------ X			X-----Daily-----X		

a. The ICF must be signed prior to any study related procedures are performed. Subjects, who are <18 years of age, may be required by the study center to have a minor assent in addition to the ICF of the parent/guardian.

b. Height will only be measured at the Screening Visit, and used in the study to calculate BMI. Physical examination will include: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, extremities, and nervous system. Weight should be taken during each physical examination. c. Vital signs will include HR, RR, and BP after sitting for 5 min, and temperature.

d. All scheduled ECGs must be performed after the subject has rested quietly for at least 10 min in the supine position.

e. See Attachment 4 for clinical laboratory tests. The Visiting Nurse will collect blood for clinical chemistry and clinical hematology during his/her Week 1, Week 2, Week 6, Week 9, and Week 10 Visits.

f. Blood will be collected for the analysis of biomarkers as specified in the lab manual. Blood samples will be collected prior to study drug administration on the Baseline and Week 8 Visits. Additional blood samples at the Baseline of Treatment Period 1 and End-of-Study/ Early Discontinuation Visits will be collected and stored for assessing the immunogenicity potential of the study drug.

g. Serum pregnancy test will be done for women of childbearing potential at screening. Results of the Baseline Visit pre-dose urine pregnancy test must be evaluated before randomization to ensure eligibility. Urine Pregnancy test will also be performed for women of childbearing potential at the End-of-Study/Early Discontinuation Visit.

h. Subjects will wear an activity monitor on their wrist daily (from the Screening Visit to the End-of-Study/Early Discontinuation Visit). All efforts should be made to wear the wrist accelerometer on the same wrist throughout the entirety of the study. In addition, subjects will wear an activity monitor on their belt for a minimum of 7 consecutive days immediately prior to the Baseline, Week 4, Week 8, and Week 12 Visits.

i. On a daily basis during the study (from the Screening Visit to the End-of-Study/Early Discontinuation Visit), subjects will use an electronic or paper diary to complete the MD Symptom Assessment questionnaire (Attachment 7).

j. The 6MWT (Attachment 5) and 3TUG Test (Attachment 8) should be performed after all other study procedures (except for study drug administration at the Baseline and Week 8 Visits).

k. The 3TUG Test (Attachment 8) should be performed after the 6MWT and after at least 15 minutes rest.

l. On days of study visits, study drug will be administered by study center clinical staff. At Baseline and Week 8 Visit, study drug administration will occur after the completion of all Visit procedures. At the Week 4 and Week 12 Visits, study drug administration should occur prior to all other study procedures. During the first week of Treatment Period 1, study drug may be administered (or observed) by a Visiting Nurse and subsequently the Visiting Nurse will administer (or observe) study drug on a weekly basis, while subjects (or caregivers) will self-administer on all other days of Treatment Period 1. During Treatment Period 2, a Visiting Nurse will administer (or observe) study drug on a weekly basis, while subjects (or caregivers) will self-administer on all other days of Treatment Period 2. The location (preferably in the abdomen [rotating around the four abdominal quadrants]) and time of the study drug administration (at approximately the same time each day) will be recorded in an electronic or paper diary.

Attachment 2 Schedule of Visiting Nurse Assessments

	Treatment Period 1				Washout	Treatment Period 2		
		Week 1	Week 2	Week 3	Week 6	Week 9	Week 10	Week 11
Parameter	**Days 2-7[a]**	**Day 8 ± 1**	**Day 15 ± 2**	**Day 22 ± 2**	**Day 43 ± 2**	**Day 64 ± 2**	**Day 71 ± 2**	**Day 78 ± 2**
Confirm Study Drug Storage Conditions								
Study Drug Administration[b]	X	X	X	X		X	X	X
Clinical Chemistry & Hematology[c]		X	X		X	X	X	
Review wrist activity monitoring[d]	X	X	X	X	X	X	X	X
Remind hip activity monitoring[e]				X	X			X
Review Study drug compliance[f]		X	X	X		X	X	X
Review completion of daily MD Symptom Assessment	X	X	X	X	X	X	X	X
Neuro-QoL questionnaire					X			

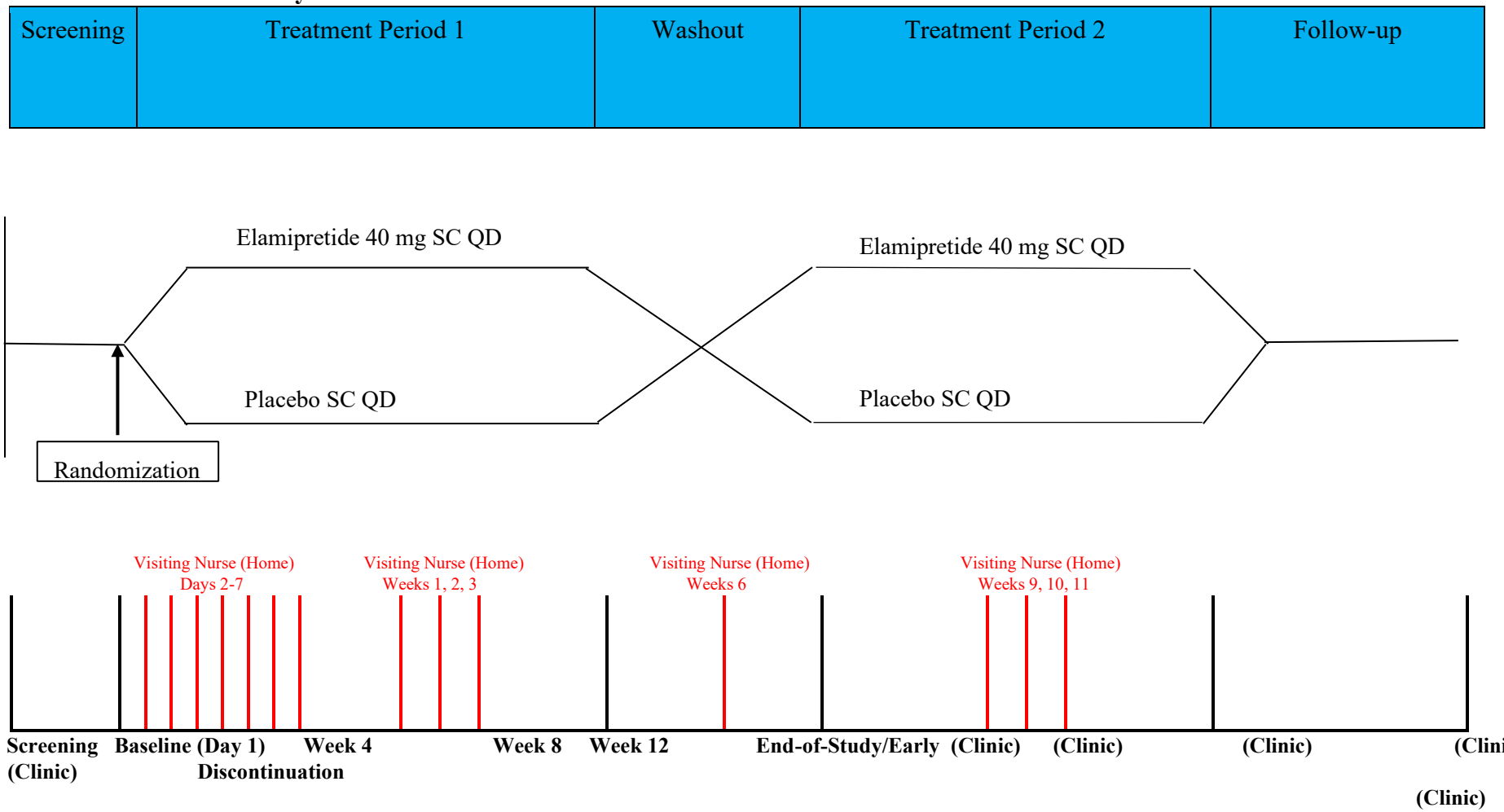
a. The Visiting Nurse visit on Day 2 is required, however, the Visiting Nurse Visits during Days 3-7 are not mandatory and the patient (or caregiver) and the Visiting Nurse should determine the frequency and necessity of these visits.

b. During the first week of Treatment Period 1, study drug may be administered by a Visiting Nurse and subsequently the Visiting Nurse will administer (or observe) study drug on a weekly basis, while subjects (or caregivers) will administer on all other days of Treatment Period 1. During Treatment Period 2, a Visiting Nurse will administer (or observe) study drug on a weekly basis, while subjects (or caregivers) will self-administer on all other days of Treatment Period 2. If, for any reason, a subject (or caregiver) is unable/unwilling to administer study drug, a Visiting Nurse may be provided for daily administration of study drug. c. See Attachment 4 for clinical laboratory tests.

d. Subjects will be asked to wear an activity monitor on their wrist daily (from the Screening Visit to the End-of-Study/Early Discontinuation Visit) 24 hours per day. All efforts should be made to wear the wrist accelerometer on the same wrist throughout the entirety of the study. The Visiting Nurse will remind the subject to wear the wrist activity monitor 24 hours per day and will remind the subject to charge the monitor.

e. Subjects will be encouraged to wear an activity monitor on their belt daily during waking hours and at minimum, must wear the hip activity monitor for 7 consecutive days immediately prior to the Baseline, Week 4, Week 8, and Week 12 Visits. The Visiting Nurse will ensure the hip accelerometers are changed and remind subjects at the Week 3, Week 6, and Week 11 Visits to wear the hip accelerometer for the a minimum of 7 consecutive days immediately prior to the Week 4, Week 8, and Week 12 Visits, respectively.
f. The Visiting Nurse will assess compliance with study drug administration and may re-train the subject or caregiver on proper administration technique, as appropriate.
g. On a daily basis during the study (from the Screening Visit to the End-of-Study/Early Discontinuation Visit), subjects will use an electronic or paper diary to complete the MD Symptom Assessment (Attachment 7).

Attachment 3 Study Schematic



Attachment 4 Clinical Laboratory Tests

Clinical Hematology:	**Clinical Chemistry:**
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Total bilirubin
Leukocytes (WBC)	Direct bilirubin
Neutrophils, segmented	Alkaline phosphatase (ALK-P)
Lymphocytes	Alanine aminotransferase (ALT)
Monocytes	Aspartate aminotransferase (AST)
Eosinophils	Blood urea nitrogen (BUN)
Basophils	gamma-glutamyl transpeptidase (GGTP)
Platelets	Creatine kinase (CK)
	Creatinine
Urinalysis:	Calcium
Specific gravity	Glucose (non-fasting)
pH	Albumin
Protein	Chloride
Glucose	Triglycerides
Ketones	LDL
Blood	HDL
Leukocyte esterase	
	Exploratory Biomarkers
	GDF-15
	FGF-21
	Glutathione

Attachment 5 Six Minute Walk Test

Six-Minute Walk Test

PURPOSE AND SCOPE

This document serves as a guideline for the 6-minute walk test (6 MWT) for the study. It outlines the set-up, patient preparation, step-by step procedures, and safety measures.

REQUIRED EQUIPMENT

1. Countdown timer (or stopwatch)
2. Mechanical lap counter
3. Two small cones to mark the turnaround points
4. A chair that can be easily moved along the walking course
5. Worksheets on a clipboard
6. A source of oxygen
7. Sphygmomanometer
8. Telephone
9. Automated electronic defibrillator
10. Bean bag

SET-UP

- The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The walking course must be 30 m in length. A 100-ft hallway which is equivalent to 30 meters is, desirable. The length of the corridor should be marked every 3 m. The turnaround points should be marked with a cone (such as an orange traffic cone). A starting line, which marks the beginning and end of each 60-m lap, should be marked on the floor using brightly colored tape.

- The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate.

- A “warm-up” period before the test should not be performed.

SAFETY ISSUES

1. Testing should be performed in a location where rapid appropriate response to an emergency is possible.

2. Available supplies must include oxygen, sub lingual nitroglycerine, aspirin, albuterol MDI. A telephone and other means should be in place to enable a call for help.

3. The technician should be certified in cardiopulmonary resuscitation with a minimum of basic life support by an AHA approved CPR course or local country equivalent. ACLS certification is desirable.

4. Physicians are not required to be present during all tests, and may be present depending on physician's judgment.

5. If a patient is on chronic oxygen therapy, oxygen should be given at their standard rate or as directed by a physician or protocol.

PATIENT PREPARATION

1. Comfortable clothing should be worn.
2. Patients should not have nail polish.
3. Appropriate shoes for walking should be worn.
4. Patients should use their usual walking aids during the test (cane, walker, etc.).
5. Patients usual medical regimen should be continued.
6. A light meal is acceptable before early morning or early afternoon tests.
7. Patients should not have exercised vigorously within 2 hours of beginning the test.

SUPPLEMENTAL OXGEN

1. If oxygen supplemental is needed during the walks and serial tests are planned (after an intervention other than oxygen therapy), then during all walks by that patient oxygen should be delivered in the same way with the same flow.

2. If the flow must be increased during subsequent visits due to worsening gas exchange, this should be noted on the worksheet and considered during interpretation of the change noted in documentation.

3. The type of oxygen delivery device should also be noted on the report. For instance, the patient carried liquid oxygen or received oxygen via an oxygen tank. It is not recommended that the patient pushes or pulls the oxygen tank themselves, nor should the technician walk close to the patient to pull or push the oxygen tank, as that may result in them "pacing" the patient and influencing the distance walked. If technician is walking with the oxygen tank, an extension tubing of at least 10 feet should be used (document that the oxygen delivery is stable) so that the technician is not close to the patient. Pulsed oxygen delivery is not recommended for this study; all oxygen delivery should be continuous.

4. Measurements of the pulse and SpO_2 should be made after waiting at 10 minutes after any change in oxygen delivery.

RECOMMENDATIONS

- All testing should be performed about the same time of day to minimize intraday variability.

- It is preferred that the same technician perform the test for each patient.

PRE-TEST

1. Record start time. Provide a paper copy of the Borg scale to the patient. Have the patient stand and rate their baseline dyspnea and over fatigue by circling the most appropriate number on the Borg scale.

2. Measure baseline blood pressure, respiratory rate and oxygen saturation (SpO_2). Check pulse rate from the oximeter. Complete the first portion of the 6MWT worksheet.

3. Set the lap counter to zero and the timer to 6 minutes. Assemble all necessary equipment (lap counter, timer, clip- board, Borg Scale, worksheet) and move to the starting point.

4. Instruct the patient as follows **using the exact script provided**:

- The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

- You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

- Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

- "Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.

- Start now or whenever you are ready."

5. Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start
the timer.

7. Do not talk to anyone other than the patient during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the patient returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the patient see you do it. Exaggerate the click using body language, like using a stop-watch at a race.

- After the **first minute**, tell the patient the following (in even tones): "You are doing well. You have 5 minutes to go."

- When the timer shows **4 minutes remaining**, tell the patient the following: "Keep up the good work. You have 4 minutes to go."

- When the timer shows **3 minutes remaining**, tell the patient the following: “You are doing well. You are halfway done.”

- When the timer shows **2 minutes remaining**, tell the patient the following: “Keep up the good work. You have only 2 minutes left.”

- When the timer shows only **1 minute remaining**, tell the patients: “You are doing well. You have only 1 minute to go.”

- Do not use other words of encouragement (or body language to speed up).

- If the patient stops walking during the test and needs a rest, say this: “You can lean against the wall if you would like; then continue walking whenever you feel able.” **Do not stop the timer**. If the patient stops before the 6 minutes are up and refuses to continue (or you decide

that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

- When the timer is **15 seconds from completion**, say this: “In a moment I’m going to tell you to stop. When I do, just stop right where you are and I will come to you.”

- When the **timer rings (or buzzes),** say this**: “Stop!”** Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

8. Note the distance walked.

9. Reasons for stopping the 6MWT immediately:

   - Chest Pain
   - Intolerable dyspnea
   - Leg cramps, staggering
   - Diaphoresis, pale or ashen appearance
   - There are no specific limits of oxygen saturation or heart rate that automatically mandate cessation of the test; the Tester is to observe the patient throughout the walk for clinical signs of severe desaturation or tachycardia.
   - Tester’s judgment that it is unsafe to continue, if there is doubt whether a test should be stopped early because of patient symptoms, it is better to err on the side of safety and stop the test early.

○ Have a chair available near the course for the patient to sit in and recover. ○ If a severe prolonged desaturation occurs, consult with the supervising physician as needed and treat the patient as needed, e.g., provide supplemental oxygen.

Post-Test:

1. Record stop time. Immediately upon stopping, provide a paper copy of the Borg scale for patient to complete. Have the patient circle the most appropriate number on the scale for the post walk Borg dyspnea and fatigue levels and ask this: "How did you feel during the test? What if anything kept you from walking further?
2. Measure blood pressure and respiratory rate. Complete the second portion of the

6MWT worksheet.

3. Measure SpO_2 and check for at least 20 seconds. Record and check pulse rate from the oximeter. Oxygen should be administered as appropriate.
4. It is not necessary to report all the reasons for stopping the 6MWT as adverse events, medical judgment should be employed for making this determination.

5

5. Record the number of laps from the counter (or tick marks on the worksheet).

6. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.

7. Congratulate the patient on good effort and offer a drink of water.

THE BORG SCALE

0 Nothing at all
0.5 Very, very slight (just noticeable)
1 Very slight
2 Slight (light)
3 Moderate
4 Somewhat severe
5 Severe (heavy)
6

7 Very severe
8
9
10 Very, very severe (maximal)

At the beginning of the 6-Minute exercise, the patient will be given a paper copy of the Borg scale with the following instructions given in the writing at the time the scale is administered. **"Please grade your level of shortness of breath using this scale."** Then ask this: **"Please grade your level of fatigue using this scale."**

After the post-test recovery period, remind the patient of the breathing number that they chose before the exercise and ask the patient to grade their breathing level again. Then ask the patient to grade their level of fatigue, after reminding them their grade before the exercise.

Six-Minute Walk Test Worksheet

Patient ID#: _____ Visit Name: _____ Date: _____

☐Not Done If 6 MWT not done, mark applicable box: Specify: _____

Supplemental oxygen during the test: ☐ Yes ☐ No If yes, specify O_2 flow: _____ L/min Type: _____

	Pre-walk	Post-walk
Time	___:___	___:___
Blood Pressure	_____	_____
Heart Rate	_____	_____
Respiratory Rate	_____	_____
SpO_2	_____ %	_____%
Dyspnea (Borg Scale)	_____	_____
Fatigue (Borg Scale)	_____	_____

Stopped during the test? ☐ Yes ☐ No If yes, mark applicable box: ☐ Diaphoresis ☐ Angina ☐ Light headedness

☐ Leg cramps ☐ Intolerable dyspnea ☐ Mental confusion/headache ☐ Other (specify): _____

Number of laps: _____ (x 60 meters) + final partial lap: _____ meters = Total distance walked in 6 minutes: _____ meters

Tech Comments:

Name and signature of technician: _____ Date: _____

Attachment 6 Neuro-QoL Item Bank v1.0 - Fatigue

Fatigue

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Rarely	Sometimes	Often	Always
NQFTG13	I felt exhausted……...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG11	I felt that I had no energy……...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG15	I felt fatigued……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG06	I was too tired to do my household chores.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG07	I was too tired to leave the house……...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG10	I was frustrated by being too tired to do the things I wanted to do……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG14	I felt tired……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG02	I had to limit my social activity because I was tired…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG01	I needed help doing my usual activities because of my fatigue…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

NQFTG03	I needed to sleep during the day…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG04	I had trouble starting things because I was too tired……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG05	I had trouble finishing things because I was too tired……...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG08	I was too tired to take a short walk…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG09	I was too tired to eat…….....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG12	I was so tired that I needed to rest during the day……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG16	I felt weak all over……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	In the past 7 days…	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
NQFTG17	I needed help doing my usual activities because of weakness……...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG18	I had to limit my social activity because I was physically weak……...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

NQFTG20	I had to force myself to get up and do things because I was physically too weak..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Attachment 7 Mitochondrial Disease (MD) Symptom Assessment

	Not at all	Mild	Moderate	Severe
1. During the past 24 hours, how severe was your worst feeling of tiredness at rest?	☐	☐	☐	☐
2. During the past 24 hours, how severe was your worst feeling of tiredness during activities?	☐	☐	☐	☐
3. During the past 24 hours, how severe was your worst feeling of muscle weakness at rest?	☐	☐	☐	☐
4. During the past 24 hours, how severe was your worst feeling of muscle weakness during activities?	☐	☐	☐	☐
5. During the past 24 hours, how severe were your worst balance problems?	☐	☐	☐	☐
6. During the past 24 hours, how severe were your worst vision problems?	☐	☐	☐	☐
7. During the past 24 hours, how severe was your worst abdominal discomfort (feeling nauseous, bloated, or in pain)?	☐	☐	☐	☐
8. During the past 24 hours, how severe was your worst muscle pain?	☐	☐	☐	☐
9. During the past 24 hours, how severe was your worst numbness?	☐	☐	☐	☐
10. During the past 24 hours, how severe was your worst headache?	☐	☐	☐	☐

At Screening Visit Only:

Of the symptoms included in the list below, which do you consider to be your most bothersome symptom? Please select only one response from the options listed below.

- Tiredness at rest
- Tiredness during activities
- Muscle weakness at rest
- Muscle weakness during activities
- Balance problems
- Vision problems
- Abdominal discomfort (feeling nauseous, bloated, or in pain)
- Muscle pain
- Numbness
- Headache

Attachment 8 Triple Timed Up and Go (3TUG) Test

The 3TUG Test is a modification of the Timed Up and Go Test. The 3TUG Test is the Timed Up and Go Test repeated 3 times without pause.

Equipment: A stopwatch

Directions: Patients wear their regular footwear and can use a walking aid if needed. Begin by having the patient sit back in a standard arm chair and identify a line 3 meters or 10 feet away on the floor.

Instructions to the patient:
When I say **"Go,"** I want you to:

1. Stand up from the chair
2. Walk to the line on the floor at your normal pace
3. Turn
4. Walk back to the chair at your normal pace
5. Sit down again
6. Repeat this for a total of 3 times without pause

On the word "Go" begin timing.

Record the time it takes the subject to complete the 3TUG Test (Steps 1-6 above), without stopping the timer until the 3TUG Test is complete.

Record time: _____ seconds

Attachment 9 Physician Global Assessment (PhGA)

Make an estimate of the overall health status of the examinee based on your findings from the physician's examination, regardless of the completeness of the examination.

1. Excellent
2. Very Good
3. Good
4. Fair

5. Poor

Attachment 10 Patient Global Assessment

The patient global assessment should be completed by the Investigator asking the patient:

In general, would you say your health is…

1. Excellent
2. Very Good
3. Good
4. Fair
5. Poor

Attachment 11 Columbia-Suicide Severity Rating Scale (C-SSRS) "Lifetime Recent"

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Lifetime Recent - Clinical

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION		
*Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If t*he answer to *question 2 is "yes"*, ask questi*ons 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.*	**Lifetime: Time He/She Felt Most Suicidal**	**Past 1 month**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. **Have you wished you were dead or wished you could go to sleep and not wake up?** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. **Have you actually had any thoughts of killing yourself?** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where* or how I would actually do *it*...and I would never go through with it.*"* **Have you been thinking about how you might do this?** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to *"I have the* thoughts but I definitely *will not do anything about them."* **Have you had these thoughts and had some intention of acting on them?** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. **Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. <u>Lifetime</u> - **Most Severe Ideation:** _____ _____ **Type # (1-5)** **Description of Ideation** <u>Recent</u> **- Most Severe Ideation:** _____ _____ **Type # (1-5)** **Description of Ideation**	Most Severe	Most Severe
Frequency **How many times have you had these thoughts?** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration **When you have the thoughts how long do they last?** (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time	____	____
Controllability **Could/can you stop thinking about killing yourself or wanting to die if you want to?** (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (0) Does not attempt to control thoughts	____	____
Deterrents **Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?** (1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped you (0) Does not apply	____	____
Reasons for Ideation What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you w*ere feeling (in other words you couldn't go on living with this pain or how you were* feeling) or was it to get attention, revenge or a reaction from others? Or both? (1) Completely to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on (2) Mostly to get attention, revenge or a reaction from others living with the pain or how you were feeling) (3) Equally to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on and to end/stop the pain living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOR (Check all that apply, so long as these are separate events; must ask about all types)	**Lifetime**	**Past 3 months**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, as a result of act. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is **any** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. **There does not have to be any injury or harm**, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Have you made a suicide attempt?	Total # of Attempts	Total # of Attempts
Have you done anything to harm yourself?		
Have you done anything dangerous where you could have died?		
What did you do?		
Did you_____ as a way to end your life?		
Did you want to die (even a little) when you_____?		
Were you trying to end your life when you _____?		
Or Did you think it was possible you could have died from_____?		
Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** **No**	**Yes** **No**
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	☐ ☐	☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (if not for that, actual attempt would have occurred). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything? If yes, describe:	Total # of interrupted	Total # of interrupted
Aborted or Self-Interrupted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any selfdestructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything? If yes, describe:	Total # of aborted or self-interrupted	Total # of aborted or self-interrupted
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)? If yes, describe:	Total # of preparatory acts	Total # of preparatory acts

	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:

Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g., comatose with reflexesintact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; medical hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	Enter Code _____	Enter Code _____	Enter Code _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	Enter Code _____	Enter Code _____	Enter Code _____

Attachment 12 Columbia-Suicide Severity Rating Scale (C-SSRS) "Since Last Visit"

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit - Clinical

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

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SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is *"yes", complete "Intensity of Ideation" section below.*	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. **Have you wished you were dead or wished you could go to sleep and not wake up?** If yes, describe:	**Yes** **No** ☐ ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. **Have you actually had any thoughts of killing yourself?** If yes, describe:	**Yes** **No** ☐ ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an* overdose but I never made a specific plan as to when, where *or how I would actually do it…*and I would never go through with it.*"* **Have you been thinking about how you might do this?** If yes, describe:	**Yes** **No** ☐ ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to *"I have the thoughts but I* definitely will not do anything about them.*"* **Have you had these thoughts and had some intention of acting on them?** If yes, describe:	**Yes** **No** ☐ ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. **Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?** If yes, describe:	**Yes** **No** ☐ ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). **Most Severe Ideation:** _____ _____ **Type # (1-5)** **Description of Ideation**	Most Severe
Frequency **How many times have you had these thoughts?** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration **When you have the thoughts, how long do they last?** (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time	____
Controllability **Could/can you stop thinking about killing yourself or wan** **to?** (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (0) Does not attempt to control thoughts	____
Deterrents **Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?** (1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped you (0) Does not apply	____

Reasons for Ideation What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way *you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention*, revenge or a reaction from others? Or both?

(1) Completely to get attention, revenge or a reaction from others

(2) Mostly to get attention, revenge or a reaction from others

(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain

(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)

(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply

____

SUICIDAL BEHAVIOR

(Check all that apply, so long as these are separate events; must ask about all types)

Since Last Visit

Actual Attempt:

A potentially self-injurious act committed with at least some wish to die, as a result of act. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is **any** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. **There does not have to be any injury or harm**, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.

Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.

Yes No ☐

☐

Have you made a suicide attempt?

Have you done anything to harm yourself?

Have you done anything dangerous where you could have died?

- **What did you do?**
- **Did you_____ as a way to end your life?**
- **Did you want to die (even a little) when you_____?**
- **Were you trying to end your life when you _____?**
- **Or did you think it was possible you could have died from_____?**

Total # of Attempts

_____

Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent) If yes, describe:

Yes No

Has subject engaged in Non-Suicidal Self-Injurious Behavior?

☐ ☐

Interrupted Attempt:

When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (if not for that, actual attempt would have occurred). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.

Yes No ☐

☐

Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?

If yes, describe:

Total # of interrupted

_____

Aborted or Self-Interrupted Attempt:

When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.

Yes No ☐

☐

Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?

If yes, describe:

Total # of aborted or self-interrupted

_____

Preparatory Acts or Behavior:

Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).

Yes No ☐

☐

Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?

If yes, describe:

Total # of preparatory acts

_____

Suicide: Death by suicide occurred since last assessment.	**Yes** **No** ☐ ☐
	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burnsless than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; medical hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body;extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	Enter Code _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	Enter Code _____

Attachment 13 Scale for the Assessment and Rating of Ataxia

Rater: _____date: _____patient:_____

Scale for the assessment and rating of ataxia (SARA)

1) Gait		2) Stance	
Proband is asked (1) to walk at a safe distance parallel to a wall including a half-turn (turn around to face the opposite direction of gait) and (2) to walk in tandem (heels to toes) without support. **0 Normal, no difficulties in walking, turning and walking tandem (up to one misstep allowed)** **1 Slight difficulties, only visible when walking 10 consecutive steps in tandem** **2 Clearly abnormal, tandem walking >10 steps not possible** **3 Considerable staggering, difficulties in half-turn, but without support** **4 Marked staggering, intermittent support of the wall required** **5 Severe staggering, permanent support of one stick or light support by one arm required** **6 Walking > 10 m only with strong support (two special sticks or stroller or accompanying person)** **7 Walking < 10 m only with strong support (two special sticks or stroller or accompanying person)** **8 Unable to walk, even supported**		Proband is asked to stand (1) in natural position, (2) with feet together in parallel (big toes touching each other) and (3) in tandem (both feet on one line, no space between heel and toe). Proband does not wear shoes, eyes are open. For each condition, three trials are allowed. Best trial is rated. **0 Normal, able to stand in tandem for > 10 s** **1 Able to stand with feet together without sway, but not in tandem for > 10s** **2 Able to stand with feet together for > 10 s, but only with sway** **3 Able to stand for > 10 s without support in natural position, but not with feet together** **4 Able to stand for >10 s in natural position only with intermittent support** **5 Able to stand >10 s in natural position only with constant support of one arm** **6 Unable to stand for >10 s even with constant support of one arm**	
Score		**Score**	

3) Sitting		4) Speech disturbance	
Proband is asked to sit on an examination bed without support of feet, eyes open and arms outstretched to the front. **0 Normal, no difficulties sitting >10 sec** **1 Slight difficulties, intermittent sway** **2 Constant sway, but able to sit > 10 s without support** **3 Able to sit for > 10 s only with intermittent support** **4 Unable to sit for >10 s without continuous support**		Speech is assessed during normal conversation. **0 Normal** **1 Suggestion of speech disturbance** **2 Impaired speech, but easy to understand** **3 Occasional words difficult to understand** **4 Many words difficult to understand** **5 Only single words understandable** **6 Speech unintelligible / anarthria**	
Score		**Score**	

Rater: _____date: _____patient:_____

5) Finger chase			6) Nose-finger test		
Rated separately for each side Proband sits comfortably. If necessary, support of feet and trunk is allowed. Examiner sits in front of proband and performs 5 consecutive sudden and fast pointing movements in unpredictable directions in a frontal plane, at about 50 % of proband´s reach. Movements have an amplitude of 30 cm and a frequency of 1 movement every 2 s. Proband is asked to follow the movements with his index finger, as fast and precisely as possible. Average performance of last 3 movements is rated. **0 No dysmetria** **1 Dysmetria, under/ overshooting target <5 cm** **2 Dysmetria, under/ overshooting target < 15 cm** **3 Dysmetria, under/ overshooting target > 15 cm** **4 Unable to perform 5 pointing movements**			**Rated separately for each side** Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to point repeatedly with his index finger from his nose to examiner's finger which is in front of the proband at about 90 % of proband's reach. Movements are performed at moderate speed. Average performance of movements is rated according to the amplitude of the kinetic tremor. **0 No tremor** **1 Tremor with an amplitude < 2 cm** **2 Tremor with an amplitude < 5 cm 3 Tremor with an amplitude > 5 cm** **4 Unable to perform 5 pointing movements**		
Score	**R**ight	**L**eft	**Score**	**R**ight	**L**eft
mean of both sides (R+L)/2			mean of both sides (R+L)/2		

7) Fast alternating hand movements

Rated separately for each side

Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to perform 10 cycles of repetitive alternation of pro- and supinations of the hand on his/her thigh as fast and as precise as possible. Movement is demonstrated by examiner at a speed of approx. 10 cycles within 7 s. Exact times for movement execution have to be taken.

0 Normal, no irregularities (performs <10s)

1 Slightly irregular (performs <10s)

2 Clearly irregular, single movements difficult to distinguish or relevant interruptions, but performs <10s

3 Very irregular, single movements difficult to distinguish or relevant interruptions, performs >10s

4 Unable to complete 10 cycles

8) Heel-shin slide

Rated separately for each side

Proband lies on examination bed, without sight of his legs. Proband is asked to lift one leg, point with the heel to the opposite knee, slide down along the shin to the ankle, and lay the leg back on the examination bed. The task is performed 3 times. Slide-down movements should be performed within 1 s. If proband slides down without contact to shin in all three trials, rate 4.

0 Normal

1 Slightly abnormal, contact to shin maintained 2 Clearly abnormal, goes off shin up to 3 times during 3 cycles

3 Severely abnormal, goes off shin 4 or more times during 3 cycles

4 Unable to perform the task

Score	**R**ight	**L**eft	**Score**	**R**ight	**L**eft
mean of both sides (R+L)/2			mean of both sides (R+L) / 2		

2

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