A MULTICENTER, OPEN-LABEL PHASE 2 EXTENSION TRIAL TO CHARACTERIZE THE LONG-TERM SAFETY AND TOLERABILITY OF SUBCUTANEOUS ELAMIPRETIDE IN SUBJECTS WITH GENETICALLY CONFIRMED PRIMARY MITOCHONDRIAL MYOPATHY (PMM)

NCT02976038

Final Approval Date: 29 January 2019

CLINICAL STUDY PROTOCOL

A MULTICENTER, OPEN-LABEL PHASE 2 EXTENSION TRIAL TO CHARACTERIZE THE LONG-TERM SAFETY AND TOLERABILITY OF SUBCUTANEOUS ELAMIPRETIDE IN SUBJECTS WITH GENETICALLY CONFIRMED PRIMARY MITOCHONDRIAL MYOPATHY (PMM)

Study Phase:	Phase 2
Study Number:	SPIMM-203
Document Version:	Version 3.0
Final Approval Date:	29 January 2019
Sponsor:	Stealth BioTherapeutics Inc. 275 Grove Street, Suite 3-107 Newton, MA 02466 Unites States of America
Sponsor Chief Clinical Development Officer:	Jim Carr, Pharm.D. Chief Clinical Development Officer 275 Grove Street 3-107, Newton, MA 02466, USA Jim.Carr@StealthBT.com +1 617-762-2503
Sponsor Medical Monitor:	Sandrin Bergheanu, M.D., Ph.D Medical Monitor 275 Grove Street 3-107, Newton, MA 02466, USA Sandrin.Bergheanu@StealthBT.com +1 617-762-2595 +31 (0) 641 476 460

PROTOCOL APPROVAL

Protocol Title:	A Multicenter, Open-Label Phase 2 Extension Trial to Characterize the Long-term Safety and Tolerability of Subcutaneous Elamipretide in Subjects with Genetically Confirmed Primary Mitochondrial Myopathy (PMM)
Protocol Number:	SPIMM-203
Protocol Date:	29 January 2019, Version 3.0

Jim Carr

Jim Carr, Pharm.D.
Chief Clinical Development Officer
Stealth BioTherapeutics Inc.

01/31/2019
Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure (IB) for elamipretide (MTP-131). I have read the SPIMM-203 protocol and agree to conduct the study as outlined. I confirm that I will conduct the study in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines. I will also ensure that sub-Investigator(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.
Name of Investigational Combination Product: Elamipretide delivery system
Name of Active Ingredient: Elamipretide (MTP-131)
Title of Study: A Multicenter, Open-Label Phase 2 Extension Trial to Characterize the Long-term Safety and Tolerability of Subcutaneous Elamipretide in Subjects with Genetically Confirmed Primary Mitochondrial Myopathy (PMM) (SPIMM-203)
Study Center(s): This study will be conducted in 4 centers in the United States (US)
Objectives: **Primary** • To assess the long-term safety and tolerability of single daily subcutaneous (SC) doses of 40 mg elamipretide administered with the elamipretide delivery system for up to 260 weeks **Secondary** • To obtain longitudinal efficacy data of single daily SC doses of 40 mg elamipretide administered with the elamipretide delivery system for up to 260 weeks on: o 6-Minute Walk Test (6MWT) o Patient Reported Outcomes (Neuro-QoL Fatigue questionnaire, Primary Mitochondrial Myopathy Symptom Assessment [PMMSA], Patient Global Assessment [PGA], EQ-5D-5L, Work Limitations Questionnaire [WLQ]) o Physician Global Assessment (PhGA)

Trial Design:
This open-label, non-comparative, extension trial will enroll subjects with genetically confirmed PMM who have completed the End-of-Study Visit in the SPIMM-201 and/or SPIMM-202 trial (if enrolled in both trials, the End-of-Study Visits in both trials must have been completed). Subjects who do not discontinue or withdraw from the trial will receive treatment with 40 mg SC elamipretide (study drug) administered with the elamipretide delivery system (elamipretide injection cartridge, the elamipretide pen injector and single-use needle) for the shortest of the following: 260 weeks; regulatory approval and commercial availability of the elamipretide delivery system in the subject's respective country; or termination of the clinical development for elamipretide in subjects with PMM. The Trial Schedule is presented in Attachment 1.

Screening Period: The Screening Period will begin with the signature of the informed consent form (ICF) for this trial and will last no longer than 28 days. During the Screening Period, subjects will undergo screening procedures as described in the Trial Schedule. For subjects enrolled in SPIMM-202, the Screening Period may not begin prior to the Week 12 Visit in the SPIMM-202 trial. Assessments completed as part of the Week 12 Visit in SPIMM-202 that are within the Screening Period may serve as Screening assessments and do not need to be reassessed. Inclusion and exclusion criteria will be assessed using Screening assessments. Subjects who complete Screening and meet all trial requirements, including all inclusion and none of the exclusion criteria, may enter the Treatment Period.

Treatment Period: The Treatment Period will begin on the day of the Baseline Visit, which is defined as Day 1. Subjects (and caregivers if needed) will be trained on the procedure for use of the elamipretide delivery system prior to first dose. An elamipretide delivery system training kit and checklist will be provided to the clinical site to assist in training. Study drug will be administered daily by the subject or trained caregiver in the abdomen, rotating around the four abdominal quadrants, or other appropriate location (after Investigator consultation with the Sponsor).

Assessments completed as part of the End-of-Study Visit in SPIMM-202 and are within 24 hours of the Baseline Visit may serve as Baseline assessments and do not need to be reassessed. Screening assessments that are within 24 hours of the Baseline Visit may also serve as Baseline assessments and do not need to be reassessed. Otherwise, Baseline assessments must be completed within 24 hours prior to receiving elamipretide. At the Baseline Visit, following completion of all Baseline procedures described in the Trial Schedule (except for the injection site reaction [ISR] assessment), subjects will be administered SC elamipretide at the trial center. Subjects (or trained caregivers) will administer elamipretide with the elamipretide delivery system on a daily basis at approximately the same time each day on all trial days (except for site visit days). Subjects will visit the trial site for the 3-Month Visit (Week 13), the 6-Month Visit (Week 26), and every 26 weeks afterward (additional 6- Month Visits) to administer study drug with the elamipretide delivery system, to complete assessments as described in the Trial Schedule, and to return all used trial supplies to the trial site.

Subjects will be scheduled to have Monthly Safety Visits completed by a visiting nurse (or designee) in between site visits until the Week 52 site visit. Monthly safety telephone calls will be completed in between site visits after the Week 52 site visit. The monthly safety telephone call script is provided in Attachment 4.

Follow-Up Period: The Follow-Up Period will begin after completion of End-of-Therapy Visit (Week 260) and will last for 2 weeks. During the Follow-Up Period, subjects will continue to follow all study requirements. At the end of the Follow-Up Period, subjects will return to the trial site for the End-of-Study/Early Discontinuation Visit for final safety and efficacy assessments and to return used and unused trial supplies and all other study instruments/materials to the trial site.
Number of Subjects (planned): Up to 36 subjects
Investigational Product, Dosage and Mode of Administration: Elamipretide injection will be supplied as a sterile 3.0 mL single-patient-use, multidose glass cartridge of sterile elamipretide injection solution (elamipretide HCl [80 mg/mL], phosphate buffer, and benzyl alcohol) for use with the elamipretide delivery system (elamipretide injection cartridge, the elamipretide pen injector, and needle) as described in the Pharmacy Manual and the Instructions for Use (IFU) pamphlet. The dose of elamipretide will be 40 mg administered as a once daily 0.5 mL SC injection with the elamipretide delivery system. Additional details regarding the investigational product (IP) will be provided in the Pharmacy Manual. Clinical site staff will train subjects (and caregivers if needed) and ensure understanding of proper SC injection technique and use of the elamipretide delivery system prior to first dose. An elamipretide delivery system training kit and checklist will be provided to the clinical site to assist in training. On days of clinical site visits, study drug will be administered at the clinical site by the trained caregiver or subject. On non-visit days, the subject (or trained caregiver) will administer study drug via daily SC injections in the abdomen, rotating around the four abdominal quadrants, or other appropriate location (after Investigator consultation with the Sponsor). The time of study drug administration should be approximately the same time each day (e.g., early morning, noon, or early afternoon). If a subject is concurrently receiving another SC therapy, unique locations for injections for the study drug, independent from the location of the concomitant therapy injections, should be used.
Reference Product: There is no reference product for this open-label non-comparative trial.

Inclusion Criteria:

A subject must meet ALL of the following inclusion criteria during the Screening Period:

1. Willing and able to provide a signed informed consent form (ICF) prior to participation in any trial-related procedures.
2. Investigator determines the subject can, and subject agrees to, adhere to the trial requirements for the length of the trial including self-administration (by subject or trained caregiver) of the study drug.
3. Subject completed the End-of-Study Visit in SPIMM-201 and/or SPIMM-202 (if enrolled in both trials, the End-of-Study Visits in both trials must have been completed).
4. Women of childbearing potential must agree to use 1 of the following methods of birth control from the date they sign the ICF through the End-of-Study Visit/ Early Discontinuation Visit:
    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).
5. Male subjects with female partners of child-bearing potential must be willing to use a highly effective method of contraception (see Section 9.3.11 for details) from the Screening Visit through the End-of-Study Visit/ Early Discontinuation Visit.

Exclusion Criteria:

A subject must NOT meet any of the following exclusion criteria during the Screening Period:

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 trial requirements.
2. Subject has received any investigational compound (excluding elamipretide) and/or has participated in another interventional clinical trial within 30 days prior to the SPIMM-203 Baseline Visit (excluding SPIMM-202) or is concurrently enrolled in any non-interventional research of any type judged to be scientifically or medically incompatible with the trial as deemed by the Investigator.
3. Subject experienced an adverse reaction attributed to study drug resulting in permanent discontinuation of study drug in the SPIMM-201 or SPIMM-202 trial.
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 SPIMM-203 Baseline Visit.

6. Subject has a history of clinically significant hypersensitivity or allergy to any of the excipients contained in the study drug.

Planned Trial Duration:
Screening Period: Up to 28 days
Treatment Period: Up to 260 weeks
Follow-Up Period: Up to 2 weeks

Criteria for Evaluation:

Safety Endpoints
Primary Safety Endpoint

- Number of subjects experiencing adverse events/adverse device effects (AEs/ADEs) (including Serious Adverse Events [SAEs]/Serious Adverse Device Effects [SADEs])

Secondary Safety Endpoint

- Changes in:
  - Vital Signs
  - Electrocardiograms (ECGs)
  - Clinical laboratory evaluations
  - Columbia Suicide Severity Rating Scale (C-SSRS)

Efficacy Endpoints
Primary Efficacy Endpoint

- Distance walked (meters) on the 6-minute walk test (6MWT)

Secondary Efficacy Endpoint

- Patient reported outcomes
  - Neuro-QoL Fatigue questionnaire
  - Primary Mitochondrial Myopathy Symptom Assessment (PMMSA)
  - Patient Global Assessments (PGA)
  - EQ-5D-5L
  - Work Limitations Questionnaire (WLQ)
- Physician Global Assessments (PhGA)

Statistical Methods:
Analysis Populations
Safety Population: All subjects who receive at least 1 dose of elamipretide.
Efficacy Evaluable Population: All subjects receiving at least one dose with any post-dose efficacy evaluations.
Safety Analyses
Safety analyses will include incidence of AEs/ADEs and SAEs/SADEs, deaths, premature discontinuation from the trial due to an AE/ADE (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 Efficacy Evaluable Population and will be largely descriptive in nature. 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. In both instances, data will be summarized over time. In addition, all trial data are to be displayed in the datalistings.
Additional details regarding analyses will be included in separate statistical analysis plan (SAP).
Subject disposition summaries will include the number of subjects enrolled and the numbers included in the Safety Population. The number and percentage of subjects who complete or discontinue from the trial 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.
Statistical analysis of this trial will be the responsibility of the Sponsor or its designee.

Sample Size:
This open-label extension trial will enroll up to 36 subjects with genetically confirmed PMM who have completed the End-of-Study Visit in the SPIMM-201 and/or SPIMM-202 trial (if enrolled in both trials, the End-of-Study Visits in both trials must have been completed) and who meet all eligibility criteria.

2. TABLE OF CONTENTS

3. ABBREVIATIONS AND DEFINITIONS

Term	Definition
6MWT	Six-Minute Walk Test
AE	Adverse Event
ADE	Adverse Device Effect
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the plasma concentration versus time curve
AUC0-last	Area under the plasma concentration vs time curve from time 0 to last available time point
AUC0-τ	Area under the plasma concentration vs time curve from time 0 to end of the dosing interval
BMI	Body Mass Index
CIOMS	Council for International Organizations of Medical Sciences
Cmax	Maximumplasma concentration
CFR	Code of Federal Regulations
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
ETC	Electron Transport Chain
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
IEC	Institutional Ethics Committee
IFU	Instructions for Use
IP	Investigational Product

Term	Definition
ISO	International Organization for Standardization
ISR	Injection Site Reaction
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MFD	Maximum feasible dose
mL	milliliter
MTP-131	SS-31, elamipretide, SBT-031, or Bendavia™
mtDNA	mitochondrial DNA
nDNA	nuclear DNA
PK	Pharmacokinetic(s)
PGA	Patient Global Assessment
PhGA	Physician Global Assessment
PMD	Primary MitochondrialDisease
PMM	Primary Mitochondrial Myopathy
PMMSA	Primary Mitochondrial Myopathy Symptom Assessment
PT	Preferred Term
QMS	Quality Management System
RA	Risk Assessment
SAE	Serious AdverseEvent
SADE	Serious Adverse Device Effect
SAP	Statistical AnalysisPlan
SC	Subcutaneous
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDD	Total Daily Dose
TEAE	Treatment-Emergent Adverse Event
TEADE	Treatment-Emergent Adverse Device Effect
UADE	Unanticipated Adverse Device Effect
WLQ	Work Limitations Questionnaire

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 guidelines, 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 elamipretide Investigator's Brochure (IB).

4.1. Primary Mitochondrial Myopathy (PMM)

Primary mitochondrial myopathy (PMM) are genetic disorders of the mitochondrial respiratory chain affecting predominantly, but not exclusively, skeletal muscle (Mancuso M, Hirano M., 2016). They are a group of conditions with genetic mutations in nuclear DNA (nDNA) and/or mitochondria DNA (mtDNA) causing oxidative phosphorylation abnormalities that result in clinical signs and symptoms. The electron transport chain (ETC) is responsible for respiration and oxidative phosphorylation resulting in the production of 90% of adenosine triphosphate (ATP) in the body, the primary energy source for cells. Of the >25,000 genes in the nDNA genome, approximately 300 have been directly implicated in encoding mitochondrial ETC proteins and another 400 in playing a role in mitochondrial function. In addition, the 37 genes in the mtDNA genome encode 13 proteins critical for oxidative phosphorylation (Niyazov D, et al., 2016; Lightowlers R, et al., 2015). PMM caused by nDNA mutations, are inherited through maternal and/or paternal germlines and affects all cells of the body as opposed to PMM caused by mtDNA mutations, which are maternally inherited and may not affect all cells. Each cell may contain a different percentage of wild type and mutant mtDNA, a concept known as heteroplasmy. When mutant heteroplasmy increases above a certain threshold, normal function of the cell may not be maintained leading to cell dysfunction and clinical pathology a concept known as the threshold effect. During embryogenesis, mutant mtDNA randomly segregates within developing tissue causing a segregation of the mutations in specific organs. This results in a wide variations in the phenotype of affected individuals (Niyazov D, et al., 2016).

The hallmark of PMMs is the heterogeneity of the clinical presentation with multiple organ system involvement and poor genotype-phenotype correlation. PMM have a wide range of onset from birth to late adulthood and highly variable symptoms, signs, severity, and prognosis. Historically, the different PMM subtypes were referred to by acronyms depicting the clinical presentation such as mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), Leber's hereditary optic neuropathy (LHON) or by physician named syndromes such as Kearns-Sayre (KSS). With the advent of genetic testing it became apparent that many of PMMs fall on the same spectrum with very variable phenotypic expressions making attempts to characterize genotype to phenotype correlations very challenging. Furthermore, current understanding of the natural history of PMM is limited (Schaefer A, et al., 2006). Although every organ system can be impaired in PMMs, organs with highest energy demand, such as skeletal muscle, heart, kidney, eye, and CNS are usually the first to be affected. Myopathy and exercise intolerance are prominent features in the adults and in some pediatric cases with Primary Mitochondrial Diseases (PMDs) causing signs and symptoms of fatigue (88%) and exercise intolerance (78% of the patients with PMD did not achieve internationally advised

levels of physical activity [10,000 steps per day]) (Gorman G, et al., 2015; Apabhai S, et al., 2011).

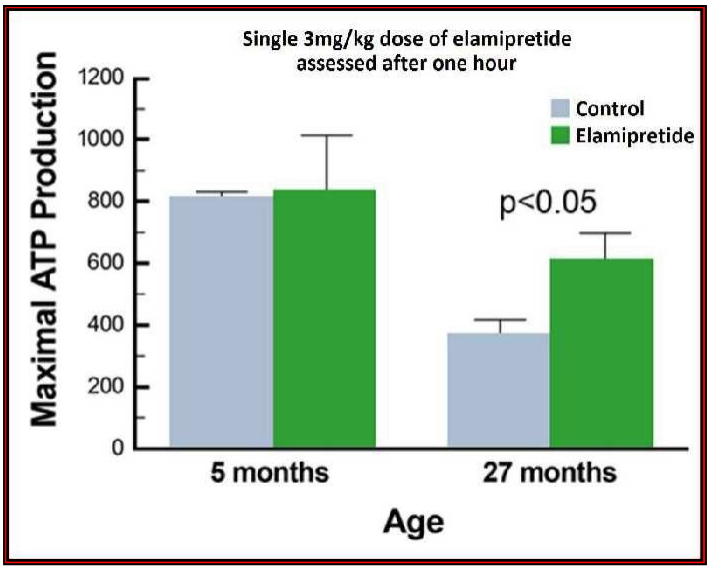
4.2. Elamipretide Risk/Benefit Assessment

4.2.1. Potential Benefits

4.2.1.1. Preclinical studies

Elamipretide has not been studied in any preclinical models specific to PMM. However, elamipretide has been shown to be effective in restoring ATP production in preclinical models of both skeletal and cardiac muscle dysfunction of aged mice (Siegel M, et al., 2013). In this study, skeletal muscle energetics were measured in vivo one hour after injection of either elamipretide or saline using a combination of optical and ^{31}P magnetic resonance spectroscopy in old and young mice (27 months and 5 months, respectively). ATP production in the old mice was found to increase and to be comparable to that in young mice one hour after a single treatment with elamipretide (Figure 1). These findings demonstrated a rapid reversal of age-related declines in resting and maximal mitochondrial ATP production, whereas, there was no observable effect on young, healthy muscle. In the same study, consistent results were observed after a week of dosing with elamipretide, with a favorable difference in the exercise tolerance of old mice, and again no significant effect was seen in young mice.

Figure 1: ATP Production in Young (5 month) and Old (27 month) Mice Following a Single Treatment with Elamipretide



Mean +/- SEM, n = 5 – 7 per group

Several reports demonstrate elamipretide's ability to prevent skeletal muscle atrophy. For example, in a rat model of muscle wasting, elamipretide reduced the loss of the diaphragm muscle function caused by 12 hours of mechanical ventilation (Powers S, et al., 2011). Similarly, elamipretide prevented casting-induced (i.e., immobilization) skeletal muscle atrophy via protecting mitochondrial function (Talbert E, et al., 2013).

Additionally, in a study using a mouse model, myopathy induced by the chemotherapeutic agent doxorubicin, which induced muscle atrophy, it was shown that elamipretide protected both skeletal and heart muscle atrophy via prevention of mitochondrial ROS dysfunction and myopathy production and is, therefore, suggesting its therapeutic potential in this setting of myopathy (Min K, et al., 2011).

4.2.1.2. Clinical Studies

The SPIMM-201 trial was a phase 1/2 multi-center, randomized, double-blind, placebo-controlled, multiple-ascending IV dose trial that enrolled subjects with genetically confirmed PMD with exercise intolerance and/or symptoms of myopathy, PMM. Three escalating IV doses (0.01, 0.10, and 0.25 mg/kg/hour) were studied in 3 sequential cohorts of 12 patients (one dose per cohort) and infused over 2 hours daily for 5 days. Within each cohort, 9 subjects were randomized to active drug and 3 subjects were randomized to placebo.

An improvement over baseline in the distance walked in the 6MWT on Day 5 was observed in subjects treated with 0.25 mg/kg/hr elamipretide compared to placebo in the pre-specified analysis, with a mean change in baseline of 65.4 m vs. 20.9 m (p=0.0528). In a post-hoc analysis with backward elimination ANCOVA, a nominally statistically significant improvement over baseline in the distance walked on Day 5 was observed in subjects treated with 0.25 mg/kg/hr elamipretide compared to placebo, with an adjusted mean change in baseline of 51.2 m vs 3.0 m (p = 0.0297). The ANCOVA model also suggests the extent of improvement was a function of the extent of diminished capacity at baseline, with greater improvement resulting for those with greater diminished capacity, in a dose-related manner.

4.2.2. Potential Risks

4.2.2.1. Nonclinical Study Safety Findings

The nonclinical testing of elamipretide encompasses a program of studies in pharmacology, metabolism, pharmacokinetics (PK), and toxicology.

Elamipretide was effective in multiple models of cardio-renal disease and skeletal muscle dysfunction and has been active across all species tested to date, including rat, guinea pig, rabbit, dog, sheep, and pig. The effective dose range was 0.05 to 0.5 mg/kg/day. Based on results from a battery of secondary and safety pharmacology studies, elamipretide is not expected to cause any adverse off-target pharmacodynamic effects at therapeutic concentrations.

The nonclinical GLP repeat-dose toxicity studies (IV and SC) in rats, rabbits and dogs indicated no elamipretide-related systemic toxicity even upon chronic administration. Elamipretide 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 were mediated by histaminergic-like reactions. Effects were associated with maximum elamipretide plasma concentration (C_{max}) and were rapidly reversible as plasma concentrations of elamipretide (and histamine) decreased. Dose administration was not associated with any adverse effects on cardiovascular, respiratory or central nervous system function; off-target non-adverse effects were limited to transient decrease of blood pressure and heart rate, consistent with histaminergic-like reactions. In all studies, the severity of the effects was proportional to C_{max} for elamipretide;

thus, the safety margin is estimated based on C_{max}, and not area under the plasma-concentration-time curve (AUC). 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 observed human exposures at clinical doses.

Intravenous administration of elamipretide to rats and dogs was well tolerated at the administration site. Local injection site reactions evident upon SC administration varied with species, dose and dose concentration.

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, embryo-fetal, or neonatal development.

Elamipretide is metabolized via sequential C-terminal degradation to the tripeptide M1 and the dipeptide M2. The apparent $t_{½}$ of M1 was comparable to that of elamipretide, whereas $t_{½}$ of M2 was longer than that of elamipretide. No sex difference was evident for either metabolite. The two metabolites were evaluated for systemic toxicity and in vivo genotoxicity. When tested directly, both M1 and M2 were negative for gene mutation and for receptor binding. Systemic exposure to the metabolites in rats and dogs was not related to any toxicity in acute, subchronic, or chronic studies. Neither M1 nor M2 metabolites showed biological activity when evaluated in an ex vivo guinea pig heart model. At a concentration of 1 μM, neither metabolite provided myocardial protection against ischemic reperfusion injury.

4.2.2.2. Human Safety

Parenteral administration of elamipretide was assessed following single and multiple IV and SC doses in approximately 200 healthy subjects in 11 completed clinical pharmacology studies. Single IV doses ranged from 0.005 mg/kg/hour to 0.25 mg/kg/hr, typically administered over 4 hours, while 0.25 mg/kg/hr administered over 1 hour daily for 7 days was the multiple-dose regimen studied. Single SC doses ranged from 2 mg to 80 mg administer as 0.5 or 1 mL injections, while multiple-dose regimen of 6 mg to 80 mg administered as 0.25, 0.5, or 1 mL injections daily for 7 days were studied.

No safety concerns have been identified with administration of IV or SC elamipretide for up to seven days in these studies. The only systemic AE reported in over 5% of subjects was headache (7.3%). Nausea and hyponatraemia were each reported in 3.0% of the subjects. All other events were reported with incidence of <2.0%. The majority of TEAEs were assessed by the investigator to be of mild severity, resolved without sequelae and did not require intervention. There were no significant findings for group mean clinical laboratory, vital sign, ECG, or physical examination parameters within or across trials.

The SC formulation of elamipretide has been studied in both single- and multiple-dose trials in healthy volunteers and patient populations. Generally, injection of SC elamipretide resulted in mild or moderate injection site reactions (ISRs), frequently characterized by erythema, induration, bruising, pruritus, pain, and/or urticaria. Injection site reactions were reported intermittently across dosing with elamipretide, with most subjects experiencing ISRs beginning upon first administration of elamipretide and continuing throughout treatment, with resolution of

the ISRs typically occurring the day of last elamipretide administration. The resolution of ISRs, however, has occurred as late as 14 days after the end of elamipretide treatment in one subject.

In subjects with renal impairment, exposure to elamipretide and both of its metabolites (M1 and M2), as measured by AUC, increased proportionally to the degree of renal impairment. However, there was no evidence of increased toxicity as a consequence of impaired renal function. Similarly, in the drug-drug interaction (DDI) studies carried out to date, co-administration of elamipretide with aspirin, with clopidogrel, or with unfractionated heparin (UFH) did not indicate a change in the nature, severity or frequency of AEs to the safety profile of either elamipretide or the comparator.

Elamipretide, administered by parenteral routes, was also assessed in completed studies in multiple patient populations including subjects with stable CHF, ACS subjects who were undergoing primary PCI and stenting for STEMI, subjects with AKI undergoing PTRA, subjects with genetically confirmed mitochondrial disease with signs and symptoms of mitochondrial myopathy and/or exercise intolerance, subjects over 60 years of age with evidence of skeletal muscle mitochondrial dysfunction, and an ongoing open-label study of in subjects with AMD. Single and multiple IV and SC doses of elamipretide were assessed with generally no notable differences between the elamipretide and placebo arms in the frequency or severity of AEs, except for ISRs with SC elamipretide administration. Additionally, eosinophilia was reported as an AE and laboratory data demonstrated elevations (>0.45 cells $x10^9$/L) in eosinophils beginning at approximately 28 days after initiation of elamipretide treatment in numerous subjects. These laboratory findings have not been reported to be associated with any systemic clinical manifestations of eosinophilia. To date, these elevations were demonstrated to have returned to within normal range or to baseline levels at the follow-up visits. There were no other identified safety concerns in these trials with respect to other clinical laboratory results, physical examinations, vital signs, ECG data between the elamipretide and placebo. In general, the safety profile of systemic elamipretide was consistent with the pre-existing, comorbid medical conditions.

Elamipretide has been studied in subjects with PMM. The SPIMM-201 trial was a phase 1/2 multi-center, randomized, double-blind, placebo-controlled, multiple-ascending IV dose trial that enrolled subjects with genetically confirmed PMM. Three escalating IV doses (0.01, 0.10, and 0.25 mg/kg/hour) were studied in 3 sequential cohorts of 12 patients (one dose per cohort) and infused over 2 hours daily for 5 days. Within each cohort, 9 subjects were randomized to active drug and 3 subjects were randomized to placebo. There were no deaths, SAEs or TEAEs resulting in withdrawal in this trial. Overall, there were no obvious differences in TEAEs, vital signs, lab values, ECG changes, or suicide assessments among the 4 treatment groups.

5. OBJECTIVES

5.1. Primary Objective

To assess the long-term safety and tolerability of single daily subcutaneous (SC) doses of 40 mg elamipretide administered with the elamipretide delivery system for up to 260 weeks

5.2. Secondary Objectives

- To obtain longitudinal efficacy data of single daily SC doses of 40 mg elamipretide administered with the elamipretide delivery system for up to 260 weeks on:
    - 6-Minute Walk Test (6MWT)
    - Patient Reported Outcomes (Neuro-QoL Fatigue questionnaire, Primary Mitochondrial Myopathy Symptom Assessment [PMMSA], Patient Global Assessment [PGA], EQ-5D-5L, Work Limitations Questionnaire [WLQ])
    - Physician Global Assessment (PhGA)

6. INVESTIGATIONAL PLAN

6.1. Study Design

This open-label, non-comparative, extension trial will enroll subjects with genetically confirmed PMM who have completed the End-of-Study Visit in the SPIMM-201 and/or SPIMM-202 trial (if enrolled in both trials, the End-of-Study Visits in both trials must have been completed). Subjects who do not discontinue or withdraw from the trial will receive treatment with 40 mg SC elamipretide (study drug) administered with the elamipretide delivery system (elamipretide injection cartridge, the elamipretide pen injector and single-use needle) for the shortest of the following: 260 weeks; regulatory approval and commercial availability of the elamipretide delivery system in the subject's respective country; or termination of the clinical development for elamipretide in subjects with PMM. The Trial Schedule is presented in Attachment 1.

Screening Period: The Screening Period will begin with the signature of the informed consent form (ICF) for this trial and will last no longer than 28 days. During the Screening Period, subjects will undergo screening procedures as described in the Trial Schedule. For subjects enrolled in SPIMM-202, the Screening Period may not begin prior to the Week 12 Visit in the SPIMM-202 trial. Assessments completed as part of the Week 12 Visit in SPIMM-202 that are within the Screening Period may serve as Screening assessments and do not need to be reassessed. Inclusion and exclusion criteria will be assessed using Screening assessments. Subjects who complete the Screening Period and meet all trial requirements, including all inclusion and none of the exclusion criteria, may enter the Treatment Period.

Treatment Period: The Treatment Period will begin on the day of the Baseline Visit, which is defined as Day 1. Subjects (and caregivers if needed) will be trained on the procedure for use of the elamipretide delivery system prior to first dose. An elamipretide delivery system training kit and checklist will be provided to the clinical site to assist in training. Study drug will be administered daily by the subject or trained caregiver in the abdomen, rotating around the four abdominal quadrants, or other appropriate location (after Investigator consultation with the Sponsor). Assessments completed as part of the End-of-Study Visit in SPIMM-202 and are within 24 hours of the Baseline Visit may serve as Baseline assessments and do not need to be reassessed. Screening assessments that are within 24 hours of the Baseline Visit may also serve as Baseline assessments and do not need to be reassessed. Otherwise, Baseline assessments must be completed within 24 hours prior to receiving elamipretide. At the Baseline Visit, following completion of all Baseline procedures described in the Trial Schedule (except for the injection site reaction [ISR] assessment), subjects will be administered SC elamipretide at the trial center. Subjects (or trained caregivers) will administer elamipretide with the elamipretide delivery system on a daily basis at approximately the same time each day on all trial days (except for site visit days). Subjects will visit the trial site for the 3-Month Visit (Week 13), the 6-Month Visit (Week 26), and every 26 weeks afterward (additional 6-Month Visits) to administer study drug with the elamipretide delivery system, to complete assessments as described in the Trial Schedule, and to return all used trial supplies to the trial site. Subjects will be scheduled to have Monthly Safety Visits completed by a visiting nurse (or designee) in between site visits until the Week 52 site visit. Monthly safety telephone calls will be completed in between site visits after the Week 52 site visit. The monthly safety telephone call script is provided in Attachment 4.

Follow-Up Period: The Follow-Up Period will begin after completion of End-of-Therapy Visit (Week 260) and will last for 2 weeks. During the Follow-Up Period, subjects will continue to follow all study requirements. At the end of the Follow-Up Period, subjects will return to the trial site for the End-of-Study/Early Discontinuation Visit for final safety and efficacy assessments and to return used and unused trial supplies and all other study instruments/materials to the trial site.

6.2. Study Schedule

Study procedures and their timing are summarized in the Trial Schedule (Attachment 1) and Study Schematic (Attachment 2).

6.2.1. Screening Visit/Period: Day -28 to Day -1

NOTE: Assessments completed as part of the Week 12 Visit in SPIMM-202 that are within the Screening Period may serve as Screening assessments and do not need to be reassessed.

- Review and sign the ICF
- Register subject for SPIMM-203 (subjects will be assigned the same subject number from the SPIMM-201 and/or SPIMM-202 trial)
- If not concurrently enrolled in SPIMM-202 during the Screening Period, update relevant medical history since the End-of-Study Visit in the SPIMM-201 and/or SPIMM-202 trial (as described in Section 6.3.1)
- If not concurrently enrolled in SPIMM-202 during the Screening Period, update concomitant medication/procedures (including supplements and vitamins) since the End-of-Study Visit in the SPIMM-201 and/or SPIMM-202 trial (as described in Section 6.3.1)
- Review all inclusion and exclusion criteria
- Complete a physical examination (as described in Section 6.3.1)
- Collect vital signs (as described in Section 6.3.2)
- Complete 12-lead resting ECG (as described in Section 6.3.3)
- Draw blood for clinical laboratory testing as outlined in Attachment 3
- Complete a serum pregnancy for women of child-bearing potential ONLY for subjects not concurrently enrolled in SPIMM-202 during the Screening Period
- Collect urine for clinical urinalysis as outlined in Attachment 3
- Complete the Columbia Suicide Severity Rating Scale (C-SSRS) "Baseline/Screening" or "Since Last Visit" as described in Section 6.3.5 and outlined in Attachment 10 and Attachment 11, respectively.

6.2.2. Treatment Period (260 weeks [± 14 days])

6.2.2.1. Baseline Visit (Day 1)

NOTE: Assessments completed as part of the End-of-Study Visit in SPIMM-202 and are within 24 hours of the Baseline Visit may serve as Baseline assessments and do not need to be

reassessed. Screening assessments that are within 24 hours of the Baseline Visit may also serve as Baseline assessments and do not need to be reassessed. Otherwise, Baseline assessments must be completed within 24 hours prior to receiving elamipretide. All study procedures must be completed prior to administering study drug. Study procedures should be completed in the order described below. The 6MWT should be completed after all other trial procedures except study drug administration and ISR assessment.

- Review all inclusion and exclusion criteria
- If not concurrently enrolled in SPIMM-202 during the Screening Period, update relevant medical history that occurred/changed during the Screening Period (as described in Section 6.3.1)
- If not concurrently enrolled in SPIMM-202 trial during the Screening Period, record AEs that occurred during the Screening Period (as described in Section 9.3.9)
- If not concurrently enrolled in SPIMM-202 during the Screening Period, update concomitant medication/procedures (including supplements and vitamins) that occurred/changed during the Screening Period (as described in Section 6.3.1)
- Complete a physical examination (as described in Section 6.3.1)
- Collect vital signs (as described in Section 6.3.2)
- Complete 12-lead resting ECG (as described in Section 6.3.3)
- Draw blood for clinical laboratory testing as outlined in Attachment 3
- Collect urine for clinical urinalysis testing as outlined in Attachment 3
- Complete a urine pregnancy for women of child-bearing potential. The urine pregnancy test during the End-of-Study Visit in SPIMM-202 is acceptable if within the Screening Period
- Complete the C-SSRS “Since Last Visit” (as described in Section 6.3.5 and outlined in Attachment 11)
- Complete the Neuro-QoL Fatigue questionnaire (as described in Section 6.3.6 and as outlined in Attachment 5)
- Complete the PMMSA (as described in Section 6.3.7 and as provided in Attachment 6)
- Complete the PGA (as described in Attachment 7)
- Complete the EQ-5D-5L (as described in Attachment 12)
- Complete the WLQ if the subject self-reports currently working (as described in Attachment 13)
- Complete the PhGA (as described in Attachment 8)
- Conduct the 6MWT (as described in Section 6.3.12 and as outlined in Attachment 9)
- Provide elamipretide delivery system supplies
- Train subject (and caregivers if needed) on the procedure for administration of study drug with the elamipretide delivery system

- Administer (by subject or trained caregiver) study drug with the elamipretide delivery system
- Assess for ISR 30 (± 5) minutes after study drug administration with the elamipretide delivery system (as described in Section 6.3.13)
- Remind women of childbearing potential and male subjects with female partners of child-bearing potential to use a highly effective method of contraception until 28 days after the last dose of study drug
- Document any AEs/ADEs that occurred during the Baseline Visit
- Schedule next site visit

6.2.2.2. Monthly Safety Visits (every 4 weeks [±7 days])

Monthly safety visits by a visiting nurse (or designee) should occur between site visits until the Week 52 site visit.

- Draw blood for clinical laboratory testing as outlined in Attachment 3.
- Remind subject (or trained caregiver) to administer study drug with the elamipretide delivery system daily
- Remind subject of proper elamipretide delivery system storage

6.2.2.3. 3-Month Visit (Week 13 ± 14 days); 6-Month Visits (Week 26 and every 26 weeks after ± 14 days); End-of-Therapy Visit (Week 260 ± 14 days)

NOTE: All study procedures must be completed prior to administering study drug. Study procedures should be completed in the order described below. The 6MWT should be completed after all other trial procedures except study drug administration and ISR assessment.

- Document concomitant medication/procedures (including supplements and vitamins) since the last site visit or monthly safety telephone call
- Document AEs/ADEs
- Complete a physical examination (as described in Section 6.3.1)
- Collect vital signs (as described in Section 6.3.2)
- Complete 12-lead resting ECG (as described in Section 6.3.3)
- Draw blood for clinical laboratory testing as outlined in Attachment 3
- Collect urine for clinical urinalysis testing as outlined in Attachment 3
- Complete the C-SSRS "Since Last Visit" (as described in Section 6.3.5 and outlined in Attachment 11)
- Complete the Neuro-QoL Fatigue questionnaire (as described in Section 6.3.6 and as outlined in Attachment 5)
- Complete the PMMSA (as described in Section 6.3.7 and as provided in Attachment 6)
- Complete the PGA (as described in Attachment 7)
- Complete the EQ-5D-5L (as described in Attachment 12)

- Complete the WLQ if the subject self-reports currently working (as described in Attachment 13)
- Complete the PhGA (as described in Attachment 8)
- Conduct the 6MWT (as described in Section 6.3.12 and as outlined in Attachment 9)
- Provide elamipretide delivery system supplies
- Train subject (and caregivers if needed) not previously trained on the procedure for administration of study drug with the elamipretide delivery system
- Administer (by subject or trained caregiver) study drug with the elamipretide delivery system
- Assess for ISR 30 (± 5) minutes after study drug administration with the elamipretide delivery system (as described in Section 6.3.13)
- Remind women of childbearing potential and male subjects with female partners of child-bearing potential to use a highly effective method of contraception until 28 days after the last dose of study drug
- Schedule next site visit

6.2.2.4. Monthly Safety Telephone Call (every 4 weeks [±7 days])

Monthly safety telephone calls will be completed in between site visits after the Week 52 site visit. Monthly safety telephone calls should follow the monthly telephone script provided in Attachment 4.

- Document concomitant medication/procedures (including supplements and vitamins) since the last site visit or monthly safety telephone call
- Document AEs/ADEs
- Remind subject (or trained caregiver) to administer study drug daily with the elamipretide delivery system and to reference the Information for Use (IFU) pamphlet for any issues

6.2.3. Follow-Up Period (14 days [+14 days])

6.2.3.1. End-of-Study Visit/ Early Discontinuation Visit (Week 262 +14 days)

NOTE: Study procedures should be completed in the order described below. The 6MWT should be completed after all other assessments.

- Document concomitant medication/procedures (including supplements and vitamins) since the last site visit or monthly safety telephone call
- Document AEs/ADEs
- Complete a physical examination (as described in Section 6.3.1)
- Collect vital signs (as described in Section 6.3.2)
- Complete 12-lead resting ECG (as described in Section 6.3.3)
- Draw blood for clinical laboratory testing as outlined in Attachment 3

- Collect urine for clinical urinalysis testing as outlined in Attachment 3
- Complete a urine pregnancy for women of child-bearing potential
- Complete the C-SSRS "Since Last Visit" (as described in Section 6.3.5 and outlined in Attachment 11)
- Complete the Neuro-QoL Fatigue questionnaire (as described in Section 6.3.6 and as outlined in Attachment 5)
- Complete the PMMSA (as described in Section 6.3.7 and as provided in Attachment 6)
- Complete the PGA (as described in Attachment 7)
- Complete the EQ-5D-5L (as described in Attachment 12)
- Complete the WLQ if the subject self-reports currently working (as described in Attachment 13)
- Complete the PhGA (as described in Attachment 8)
- Conduct the 6MWT (as described in Section 6.3.12 and as outlined in Attachment 9)
- If applicable, collect all trial supplies not previously returned

6.2.4. Unscheduled Visits

Unscheduled Visits occur outside of pre-specified site visits. If an Unscheduled Visit occurs, assessments to be completed are in the judgement of the Investigator. If other assessments are completed, study procedures should be completed in the order described below.

- Document concomitant medication/procedures (including supplements and vitamins) since the last site visit or monthly safety telephone call
- Document AEs/ADEs
- Complete a physical examination (as described in Section 6.3.1)
- Collect vital signs (as described in Section 6.3.2)
- Complete 12-lead resting ECG (as described in Section 6.3.3)
- Draw blood for clinical laboratory testing as outlined in Attachment 3
- Collect urine for clinical urinalysis testing as outlined in Attachment 3
- Complete a urine pregnancy for women of child-bearing potential
- Complete the C-SSRS "Since Last Visit" (as described in Section 6.3.5 and outlined in Attachment 11)
- Complete the Neuro-QoL Fatigue questionnaire (as described in Section 6.3.6 and as outlined in Attachment 5)
- Complete the PMMSA (as described in Section 6.3.7 and as provided in Attachment 6)
- Complete the PGA (as described in Attachment 7)
- Complete the EQ-5D-5L (as described in Attachment 12)
- Complete the WLQ if the subject self-reports currently working (as described in

Attachment 13)

- Complete the PhGA (as described in Attachment 8)
- Conduct the 6MWT (as described in Section 6.3.12 and as outlined in Attachment 9)
- Administer (by subject or trained caregiver) study drug with the elamipretide delivery system
- Assess for ISR 30 (± 5) minutes after study drug administration with the elamipretide delivery system (as described in Section 6.3.13)
- Remind women of childbearing potential and male subjects with female partners of child-bearing potential to use a highly effective method of contraception until 28 days after the last dose of study drug

6.3. Study Assessments

The following section describes study assessments occurring during the study. Study assessments and procedures are presented by study visit in Attachment 1.

6.3.1. Medical History and Physical Examination

For subjects not concurrently enrolled in SPIMM-202 during the Screening Period, at the Baseline Visit, new medical history (including concomitant medications/procedures) since the End-of-Study Visit in the SPIMM-201 and/or SPIMM-202 trial will be taken. Previous medical history (including concomitant medications/procedures do not need to be recorded and will be taken from the SPIMM-201 and/or SPIMM-202 trial.

At all site visits, a complete physical examination will be performed. This will include a full review of the following systems: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, extremities, and nervous system. Weight will also be collected.

6.3.2. 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.

6.3.3. Electrocardiograms (ECGs)

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

ECG intervals (PR, RR, QRS, QT), heart rate and ECG findings will be recorded for each subject. Based on signs or symptoms, additional 12-lead ECGs may be performed.

6.3.4. Clinical Laboratory Testing

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

6.3.4.1. Blood chemistries

Blood will be collected at all study center visits. Analysis will include testing for parameters included in Attachment 3. Blood chemistry lab parameters should also be collected approximately monthly at the Monthly Safety Visits by a visiting nurse (or designee) between site visits until the Week 52 site visit.

6.3.4.2. Hematology

Blood will be collected at all study center visits. Analysis will include testing for parameters included in Attachment 3. Hematology lab parameters should also be collected approximately monthly (approximately every 4 weeks) at the Monthly Safety Visits by a visiting nurse (or designee) between site visits until the Week 52 site visit.

6.3.4.3. Additional Laboratory Assessments

Blood will be collected at all study center visits. Analysis will include testing for parameters included in Attachment 3. Additional laboratory assessment parameters should also be collected approximately monthly (approximately every 4 weeks) at the Monthly Safety Visits by a visiting nurse (or designee) between site visits until the Week 52 site visit.

6.3.4.4. Urinalysis

Urine will be collected at all study center visits and will include testing for parameters included in Attachment 3.

6.3.4.5. Pregnancy tests

A serum pregnancy test is required for women of child-bearing potential at the Screening Visit for subjects not concurrently enrolled in SPIMM-202 during the Screening Period. Results of the Baseline Visit pre-dose urine pregnancy test (or urine pregnancy test during the End-of-Study Visit in SPIMM-202 if within the Screening Period) must be evaluated before enrollment to ensure eligibility. Urine pregnancy test will also be performed for women of childbearing potential at the End-of-Study/Early Discontinuation Visit.

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

At the Screening Visit, the C-SSRS "Since Last Visit" should be completed and recorded. If the subject did not enroll in SPIMM-202, the C-SSRS "Baseline/Screening" should be completed instead (Attachment 10). At all other clinical visits, the C-SSRS "Since Last Visit" will be completed and recorded for all subjects. The C-SSRS "Since Last Visit" is included in Attachment 11.

6.3.6. The Neuro-QoL Fatigue Questionnaire

At all study center visits, subjects will be instructed to complete the Neuro-QoL Fatigue questionnaire. The Neuro-QoL Fatigue questionnaire is in Attachment 5.

6.3.7. Primary Mitochondrial Myopathy Symptom Assessment (PMMSA)

At all study center visits, subjects will be instructed to complete the PMMSA. The PMMSA is in Attachment 6.

6.3.8. Patient Global Assessment (PGA)

The Investigator or designee should ask the subjects for their overall assessment of their PMM

symptoms. The PGA is provided in Attachment 7.

6.3.9. EQ-5D-5L

At all study center visits, subjects will be instructed to complete the EQ-5D-5L. The EQ-5D-5L is in Attachment 12.

6.3.10. Work Limitations Questionnaire (WLQ)

At all study center visits, subjects will be instructed to complete the WLQ if the subject self-reports currently working. The WLQ is in Attachment 13.

6.3.11. Physician Global Assessment (PhGA)

The Investigator or designee will provide an overall assessment of the subject's PMM symptoms. The PhGA is provided in Attachment 8. The same Investigator or designee should administer the PhGA at each visit for a particular subject.

6.3.12. 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 9. Study centers will be provided with a 6MWT Kit, as well as standardized training.

6.3.13. Injection Site Reaction (ISR) Assessment

A skin examination of the injection site (abdomen, rotating around the four abdominal quadrants, or other appropriate location [after Investigator consultation with the Sponsor]) will be performed by the Investigator (or designee) at all clinical site visits. The skin examination should occur at 30 (±5) minutes after study drug administration with the elamipretide delivery system. The presence and severity of pain, erythema, swelling, and pruritus at the injection site will be assessed. Scoring of erythema, swelling, pruritus and pain will be done using a 5-point scale using the "Table for Grading the Severity of Site Reactions to Injections" provided in Attachment 14:

- None = 0
- Mild = 1
- Moderate = 2
- Severe = 3
- Potentially life-threatening = 4

NOTE: Any ISR captured as part of this assessment should be reported as an AE/ADE, as per the judgement of the Investigator, according to guidelines detailed in Section 9.3.8.1.4. Any ISR that meets any of the criteria of a SAE/serious adverse device effect (SADE) (Section 9.3.7.) should be reported within 24 hours of the clinical site first becoming aware of the event (as outlined in Section 9.3.10).

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 should not be repeated, and subjects should not 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 ALL of the following inclusion criteria during the Screening Period:

1. Willing and able to provide a signed informed consent form (ICF) prior to participation in any trial-related procedures.
2. Investigator determines the subject can, and subject agrees to, adhere to the trial requirements for the length of the trial including self-administration (by subject or trained caregiver) of the study drug.
3. Subject completed the End-of-Study Visit in SPIMM-201 and/or SPIMM-202 (if enrolled in both trials, the End-of-Study Visits in both trials must have been completed).
4. Women of childbearing potential must agree to use 1 of the following methods of birth control from the date they sign the ICF through the End-of-Study Visit/ Early Discontinuation Visit:
    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).
5. Male subjects with female partners of child-bearing potential must be willing to use a highly effective method of contraception (see Section 9.3.11 for details) from the Screening Visit through the End-of-Study Visit/ Early Discontinuation Visit.

7.2. Exclusion Criteria

A subject must NOT meet any of the following exclusion criteria during the Screening Period:

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 trial requirements.
2. Subject has received any investigational compound (excluding elamipretide) and/or has participated in another interventional clinical trial within 30 days prior to the SPIMM-203 Baseline Visit (excluding SPIMM-202) or is concurrently enrolled in any non-interventional research of any type judged to be scientifically or medically incompatible with the trial as deemed by the Investigator.
3. Subject experienced an adverse reaction attributed to study drug resulting in permanent discontinuation of study drug in the SPIMM-201 or SPIMM-202 trial.
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 SPIMM-203 Baseline Visit.
6. Subject has a history of clinically significant hypersensitivity or allergy to any of the excipients contained in the study drug.

7.3. Prohibited Medications

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

The concurrent use of sacubitril (an antihypertensive drug used in combination with valsartan marketed under the brand name, Entresto®, in the US and EU) is prohibited, due to a lack of current information regarding possible drug interactions.

All medications, including over-the-counter treatments, vitamins, or supplements, are recommended to have been unchanged and constant for at least 1 month prior to the Baseline Visit. All concomitant medications/procedures 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 collected and should be recorded in the source data and the eCRF.

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 (AEs)/Adverse Device Effects (ADEs) to their decision to withdraw consent, and any AE/ADE 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/Adverse Device Effect
    - If the Investigator decides that the subject should be withdrawn because of an AE/ADE or a clinically significant laboratory value, the elamipretide delivery system is to be discontinued and appropriate measures are to be taken. The Sponsor or its designee is to be alerted immediately.
    - Known pregnancy or breastfeeding during the study therapy administration period. Study center personnel must report every pregnancy as soon as possible as described Section 9.3.11.

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

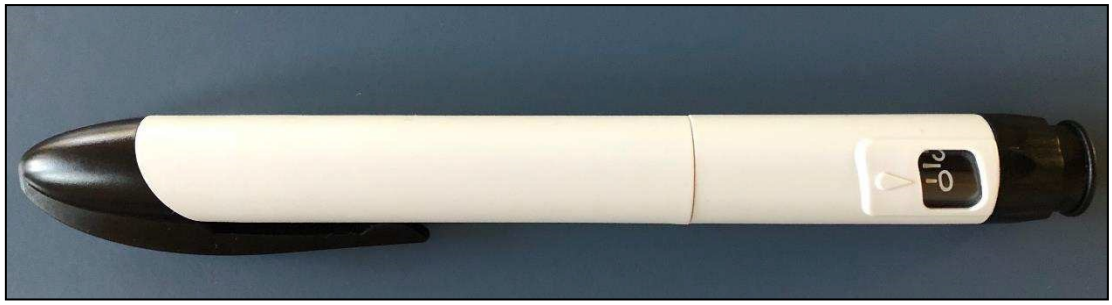
Up to 36 subjects will receive 40 mg elamipretide administered with the elamipretide delivery system as a single daily SC injection for the shortest of the following: 260 weeks; regulatory approval and commercial availability of the elamipretide delivery system in the subject's respective country; or termination of the clinical development for elamipretide.

Elamipretide injection will be supplied as a labeled sterile 3.0 mL single-patient-use, multidose glass cartridge (containing an elastomeric plunger and an elastomeric septum secured with a crimped aluminum cap) for use with the elamipretide delivery system. Each cartridge contains up to five (5) 40 mg doses (0.5 mL per injection of 80 mg/mL sterile elamipretide solution) per injection. Elamipretide solution is an aqueous sterile solution of 80 mg/mL elamipretide HCl formulated in sodium phosphate buffer and benzyl alcohol.

8.1.1. Elamipretide Pen Injector

The elamipretide pen injector was developed by Stealth BioTherapeutics exclusively for use with the elamipretide injection 3 mL cartridge.

Figure 2: Elamipretide Pen Injector



The elamipretide pen injector has a common classification of Piston Syringe Class II in accordance with 21 CFR 880.5860. The elamipretide delivery system is designated system A in accordance with ISO 11608-1:2014.

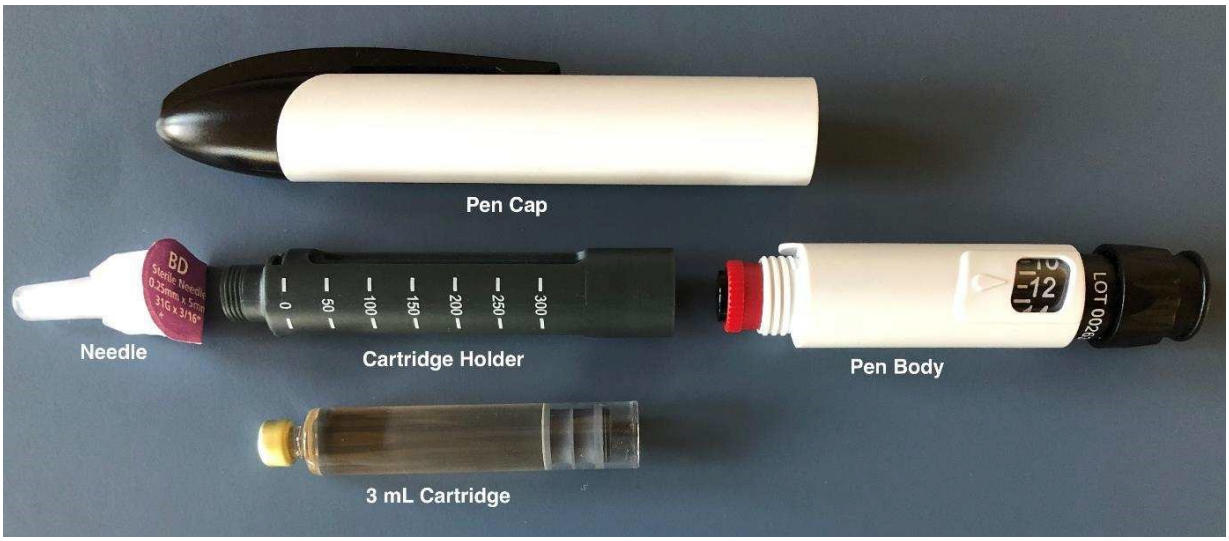
The elamipretide pen injector is designed, manufactured and controlled in accordance with 21CFR 820, ISO 13485 and ISO 14971, as appropriate. Specifically, the elamipretide pen injector is manually assembled, in a single-piece flow process (by a single operator), at the facilities of Haselmeier in accordance with cGMPs, ISO 13485, and Quality Management System (QMS).

8.1.2. Elamipretide Delivery System

The elamipretide pen injector along with the elamipretide injection cartridge and the pen needle constitute the elamipretide delivery system which will be used in SPIMM-203. The elamipretide delivery system is for personal use (single subject) for SC administration of a fixed dose (0.5 mL) of elamipretide injection. The needle provided should be used. The elamipretide delivery system is operated mechanically and contains no electronics. The elamipretide delivery system major components are depicted in Figure 3. The user will assemble and use the elamipretide

delivery system per the IFU that will be provided to each subject.

Figure 3: Elamipretide Delivery System (expanded view of major components)



The materials used in the elamipretide delivery system are standard materials for medical devices. Materials that may come in contact with the subject have been assessed for biocompatibility in accordance with ISO 10993-1; the elamipretide delivery system is biocompatible when used as intended. The manufacturer of the elamipretide pen injector (Haselmeier) had conducted a device design Risk Assessment (RA) for the elamipretide pen injector with an insulin cartridge and concluded that the elamipretide pen injector is safe for use. Stealth BioTherapeutics has conducted a design risk RA and a use-related RA for the elamipretide delivery system and concluded that the elamipretide delivery system is safe for use as intended.

Each subject or caregiver will be trained in the use of the elamipretide delivery system per the IFU prior to administration of the first dose. An elamipretide delivery system training kit and checklist will be provided to the clinical site to assist in training.

The subject (or trained caregiver) will administer study drug with the elamipretide delivery system via daily SC injections in the abdomen, rotating around the four abdominal quadrants, or other appropriate location (after Investigator consultation with the Sponsor). The time of study drug administration should be approximately the same time each day (e.g., early morning, noon, or early afternoon). If a subject is concurrently receiving another SC therapy, unique locations for injections for study drug, independent from the location of the concomitant therapy injections, should be used.

8.2. Materials and Supplies

The elamipretide single-patient-use, multidose glass cartridge of sterile elamipretide injection solution and delivery system will be dispensed and stored according to the Pharmacy Manual. The elamipretide multidose glass cartridges are to be stored refrigerated at 2 to 8°C (36 to 46°F) in a secure area until dispensed. Temperature records must be maintained and temperature excursions reported as soon as they are discovered. Short term excursions (less than 72 hours) in storage temperature up to room temperature (15 to 30°C or 59 to 86°F) during shipping, storage, handling, and patient transport may be acceptable and will not compromise the usability of the investigative product supply. The sponsor should be

notified in the case of an excursion. The single-patient-use, multidose cartridge, while in use in the elamipretide delivery system, should be stored at room temperature in the elamipretide pen injector for up to five (5) days.

The elamipretide pen injector should be stored at room temperature and not refrigerated, even when assembled and in-use with a multi-dose cartridge. The ancillary supplies (pen needles and alcohol wipes) may be stored at room temperature.

Additional information will be provided in the Pharmacy Manual. An IFU pamphlet will be provided to assist in training.

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 elamipretide injection cartridges and elamipretide pen injectors. These records should contain the dates, quantity, and the following:

- Received at study center,
- 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 elamipretide delivery system supplies following reconciliation of all elamipretide delivery system supplies.

8.4. Rationale for Selection of Doses in the Study

During the course of clinical development, multiple clinical pharmacology studies have been conducted to assess the safety, tolerability and PK of elamipretide and its metabolites. Two similarly designed trials (SPISC-101 and SPISC-102) have been conducted to evaluate the

safety, tolerability and PK of single (2-80 mg) and 7-day repeat-dose administration (6-80 mg) of ascending doses of elamipretide administered SC to healthy volunteers. In these studies, elamipretide was associated 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.

The systemic exposure (in terms of mean area under the plasma concentration vs time curve from time 0 to end of the dosing interval ($AUC_{0-\tau}$) 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.

An additional clinical pharmacology study (SPICP-101) demonstrates the effect of decreased renal function on plasma exposure and provides guidelines for use in patients with renal insufficiency in addition to providing a comparison of IV to SC PK. PK, safety and theoretical safety margins from toxicology studies support the use of SC elamipretide up to 40 mg/day in patients with creatinine clearance > 30 mL/min without the need for dose adjustment.

The SPIMM-201 study provides supporting information regarding safety and plasma exposure in

the PMM population following repeat-dose administration of elamipretide at 0.01, 0.1, 0.25 mg/kg/hr as a 2-hour IV infusion (Total Daily Dose [TDD] 0.02, 0.2, 0.5 mg/kg) for 5 days. Elamipretide demonstrated an acceptable safety and tolerability profile. The primary efficacy endpoint (distance walked on the 6MWT) appeared to improve with increasing doses and the highest level of functional improvement was observed at 0.25 mg/kg/day, a TDD of 0.5 mg/kg/day. PK data is presented in Table 1.

Table 1: SPIMM-201: Mean Steady-State PK Parameters* on Day 5 (males and females combined) Following Repeat Administration of elamipretide (MTP-131) at 0.01, 0.1 and 0.25 mg/kg/hr as a 2-hour IV infusion, Once Daily, for 5 Days

Dose	Mean Body Weight of Dose Group (kg)	Mean Total Daily Dose (TDD) (mg)	Analyte	C_{max} (ng/mL) [n]	$AUC_{0\text{-last}}$ (ng.h/mL) [n]
0.01 mg/kg/hr given as a 2hr IV infusion	70.6	1.412	MTP-131	35.8 [n=7]	140 [n=6]
			M1	15 [n=7]	111 [n=7]
			M2	2.6 [n=7]	44 [n=6]
0.1 mg/kg/hr given as a 2hr IV infusion	63.7	12.74	MTP-131	498 [n=9]	1,992 [n=5]
			M1	183 [n=9]	1,672 [n=5]
			M2	39.6 [n=9]	661 [n=8]
0.25 mg/kg/hr given as a 2hr IV infusion	59.2	29.6	MTP-131	1,050 [n=9]	4,050 [n=7]
			M1	285 [n=9]	2,190 [n=7]
			M2	68.8 [n=9]	1,169 [n=8]

*Calculations based on nominal time points.

Bioavailability for C_{max} and area under the plasma concentration vs time curve from time 0 to last available time point ($AUC_{0\text{-last}}$) following administration of a TDD of 40 mg elamipretide as a two hour, IV infusion and as a single SC injection can be estimated by applying a correction factor to the IV parameters to normalize TDD to 40 mg (assumes proportionality of relationship between dose levels and exposure parameters for elamipretide, M1 and M2, as previously described) and deriving percentage exposures (Table 2).

Table 2: SPIMM-201: Estimated Bioavailability of SC administration (40 mg as a 1 mL injection) versus Two Hour IV Infusion Following Repeat Administration of elamipretide (MTP-131)

						PK Parameters following 40mg		**Estimated Bioavailability**	
Dose	Mean TDD (mg)	Correction factor for 40 mg TDD	Analyte	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng.h/mL)	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (ng.h/mL)	**C_{max}**	**$AUC_{0\text{-last}}$**
0.25 mg/kg/hr given as a 2hr IV infusion	29.6	1.35	MTP-131	1,418	5,468	1,300	3,720	**92%**	**68%**
			M1	385	2,957	436	3,100	**113%**	**105%**
			M2	92.9	1,578	88.0	1,950	**95%**	**124%**

*Calculations based on nominal time points.

Despite bioavailability of 68% (by $AUC_{0\text{-last}}$) when comparing the SC injection to the two-hour IV infusion, exposure to elamipretide by 40 mg SC injection will remain similar to or greater than exposure demonstrated in the SPIMM-201 study in subjects weighing <80 kg therefore, treatment effect is not likely to be altered by the change in dose route.

To enable chronic dosing of elamipretide, chronic (26-weeks in rat, SPI-CIT-15-03; 39-weeks in dog, SPI-CIT-15-02) repeat-dose toxicology studies have been conducted to evaluate the systemic toxicity and local tolerability of elamipretide administered as SC injections, once daily. No systemic toxicity was apparent at any elamipretide dose tested and the predominant study findings were related to local injection site reactions and tolerability. Safety margin calculations for both non-clinical species, compared to the 40 mg/day (1 mL) SC dose in man are provided in Table 3.

Table 3: SPI-CIT-15-03, SPI-CIT-15-02: Key Summary Steady-state PK Parameters Days 182 (Rat) and 273 (Dog) at the NOAEL/MFD with Safety Margins vs. Human Exposure (SPISC-101, 40 mg/day)

					PK in Man Following 40mg SC		Safety Margin	
Study / NOAEL	**Species**	**Analyte**	**C_{max} (ng/mL)**	**$AUC_{0\text{-last}}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**$AUC_{0\text{-last}}$ (ng.h/mL)**	**By C_{max}**	**By AUC**
SPI-CIT-15-03 15 mg/kg/day	Rat	MTP-131	6,875	23,850	1,300	3,720	x5	x6
		M1	7,385	43,000	436	3,100	x17	x14
		M2	260	2,470	88.0	1,950	x3	x1.8
SPI-CIT-15-02 10 mg/kg/day	Dog	MTP-131	13,050	21,135	1,300	3,720	x10	x6
		M1	1,709	5,507	436	3,100	x4	x1.8
		M2	312	5,093	88.0	1,950	x4	x3

The data displayed demonstrate that exposure to elamipretide, M1 and M2 in the chronic toxicology studies are supportive of chronic dosing at 40 mg/day by SC injection, in human.

8.5. Treatment Compliance

During the treatment period, study drug will be administered daily by a trained caregiver or self-administration. Subjects will be asked about treatment compliance during the monthly safety telephone calls and site visits.

9. SAFETY AND EFFICACY EVALUATIONS AND APPROPRIATENESS OF MEASUREMENTS

Study procedures and their timing are summarized in Attachment 1.

9.1. Safety measures

9.1.1. Primary safety measure

- AEs/ADEs (including SAEs/SADEs)

9.1.2. Secondary safety measure

- Changes in:
  - Vital signs
  - ECGs
  - Clinical laboratory evaluations
  - Columbia Suicide Severity Rating Scale (C-SSRS)

9.2. Efficacy Measures

9.2.1. Primary efficacy measure

- Distance walked (meters) on the 6MWT

9.2.2. Secondary efficacy measure

- Patient reported outcomes
  - Neuro-QoL Fatigue questionnaire
  - Primary Mitochondrial Myopathy Symptom Assessment (PMMSA)
  - Patient Global Assessments (PGA)
  - EQ-5D-5L
  - Work Limitations Questionnaire (WLQ)
- Physician Global Assessments (PhGA)

9.3. Safety

9.3.1. Adverse Events (AEs)/Adverse Device Effects (ADEs)

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

Comprehensive assessment of AEs/ADEs experienced by the subject will be performed from the time of the subject's signature of informed consent, throughout the course of the trial, and until the conclusion of the clinical study's post treatment follow-up period.

Subjects must be seen by a physician or designee (an appropriately trained healthcare professional) at every study visit and the evaluation must be documented. Trial site personnel will report any AE/ADE, whether observed by the Investigator (or designee), or reported by the subject.

The Investigator is responsible for promptly documenting and reporting all AEs/ADEs observed during the study in the subject's eCRF and applicable forms.

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An ADE is an AE related to the use of an investigational medical device. This includes any event resulting from insufficient or inadequate instruction for use, deployment, installation, or operation, or any malfunction of the investigational medical device or any event resulting from user error or from intentional misuse of the investigational medical device.

Should the study drug be discontinued due to an AE/ADE deemed probably or possibly related to study drug/elamipretide delivery system (per Section 9.3.8.1.2), reinitiating (rechallange) of the study drug may be possible, after consultation with the Sponsor.

9.3.2. Pre-Treatment Events

Adverse Events that occur while the subject is concurrently enrolled in the SPIMM-202 trial and the SPIMM-203 Screening Period, will be collected in the SPIMM-202 trial eCRF and not as AEs in SPIMM-203 trial. Once the subject has completed the End-of-Study in the SPIMM-202 trial, AEs should be reported only in the SPIMM-203 eCRF.

For subjects not concurrently enrolled in SPIMM-202 trial during the SPIMM-203 Screening Period, untoward events and/or incidental diagnoses that occur prior to study drug administration will be assessed by the Investigator and recorded as either medical history or as an AE. If the event is assessed by the Investigator as related to a study procedure, related to the previous exposure to study drug, and/or meets seriousness criteria, it will be recorded as an AE on the AE eCRF, processed, and followed accordingly.

9.3.3. Baseline Medical Conditions

Baseline medical conditions, related or not related to the therapeutic area of interest/investigation, that worsen in severity or frequency during the study in a way that is not consistent with natural disease progression, in the opinion of the Investigator, should be recorded and reported as AEs/ADEs.

9.3.4. Medical and Surgical Procedures

Medical or surgical procedures scheduled prior to signing the ICF, but occurring during the study should not be captured as AEs. The condition leading to the procedure should be listed in the medical history and the procedure should be captured on the concurrent procedures page. Medical or surgical procedures not scheduled prior to signing the ICF should not be recorded as

AEs; the condition that led to the need to perform the medical or surgical procedure will be the AE/ADE and the procedure should be captured on the concurrent procedures pages.

9.3.5. Abnormal Laboratory and Other Abnormal Investigational Findings

Abnormal laboratory findings or other objective measurements, deemed clinically significant by the Investigator should be reported as an AE/ADE.

When reporting an abnormal laboratory finding as an AE/ADE, the description of the abnormality, rather than the abnormal value itself, should be recorded. A clinical diagnosis should be reported if the Investigator believes the finding is consistent with a disease process.

9.3.6. Symptomatic Overdose

In the event of an overdose of study medication, the Investigator should use clinical judgment in treating the signs and symptoms of the overdose. The signs and symptoms should be reported as AEs/ADEs. Overdoses must be reported immediately to the study Medical Monitor.

9.3.7. Serious Adverse Events (SAEs)/Serious Adverse Device Effect (SADEs)

A SAE/SADE is any AE/ADE that:

- Results in death.
- Is life-threatening. The term "life-threatening" refers to a situation 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/incapacity.
- Is a congenital anomaly/birth defect.
- Is a medically important event or reaction

A SADE is an ADE that might have led to the SADE, in a participant, user or other person if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. They are handled under the SAE reporting system.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Any non-serious AE/ADE that worsens and meets the criteria for an SAE/SADE should be reported as a new AE/ADE and as an SAE/SADE. The start date of the SAE should be the date the AE/ADE worsened to meet the criteria for a SAE/SADE.

The Investigator is expected to take all therapeutic measures necessary for resolution of the SAE/SADE. Any medications or procedures necessary for treatment of the SAE/SADE must be recorded on the appropriate screen(s) of the subject's eCRF.

As part of the routine medical monitoring, the medical monitor (or designee) will review all SAEs/SADEs reported in the SPIMM-203 trial, looking for any safety data trends or elamipretide delivery system related issues.

9.3.8. Recording of Adverse Events (AEs)/Adverse Device Effects (ADEs)

Complete and accurate data on all AEs/ADEs experienced for the duration of the reporting period (defined below) will be recorded on an ongoing basis on the Adverse Event Case Report Form (CRF). All SAEs/SADEs must be reported using the study specific SAE Report Form, in addition to the Adverse Event CRF.

It is important that each AE/ADE entry include a verbatim term along with, onset and resolution dates, severity, seriousness, relationship to the study drug/elamipretide delivery system, action taken with respect to the study drug/elamipretide delivery system, and its outcome.

Investigators should use the AE/ADE definitions provided in the above sections and should observe the following guidelines when completing the AE pages of the CRF:

- Whenever possible, recognized medical terms should be used to describe AEs/ADEs rather than colloquialisms (for example, ‘influenza’ rather than ‘flu’), and abbreviations should be avoided.
- Adverse events/ADEs should be described using a specific clinical diagnosis, if this is available, rather than a list of signs or symptoms (for example, ‘congestive heart failure’ rather than ‘dyspnea, rales and cyanosis’). However, signs/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/ADEs.

Provisional diagnosis (e.g. “suspected myocardial infarction”) is acceptable but should be followed up to a definite diagnosis if finally, available. Similarly, a fatal event with an unknown cause should be recorded as “Unknown”. Please note that death is an outcome, not an event. The cause of death should be reported as the event. If the cause is unknown, “death, cause unknown” or “sudden death” can be entered as the event. When identified, the cause of death should be entered as the event on a follow-up form, with supporting documentation if available (e.g., death certificate, autopsy report).

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE/ADE rather than the procedure itself.

9.3.8.1. Investigator Assessments

9.3.8.1.1. Severity/Intensity

Severity, which is a description of the intensity of manifestation of the AE/ADE, is distinct from the regulatory definition of seriousness The Investigator is required to grade the severity of each AE/ADE according to the following guidelines.

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

Mild: Associated with no limitation of usual activities or only slight discomfort; generally not requiring alteration or cessation of study drug administration; and/or not needing therapeutic intervention.

Moderate: Associated with limitation of usual activities or significant discomfort; generally requiring alteration or cessation of study drug administration; and/or requiring therapeutic intervention.

Severe: Associated with inability of patient to carry out usual activities or very marked discomfort; considered to be life-threatening; resulting in significant disability or incapacity; and requiring therapeutic intervention.

9.3.8.1.2. Relationship to the Study Drug/Elamipretide Delivery System

Investigators must systematically assess the causal relationship of AEs/ADEs to the study drug or elamipretide delivery system according to the following guidelines:

Probable: A causal relationship is clinically/biologically highly plausible, there is a plausible time sequence between onset of the AE/ADE and administration of the study drug/use of the elamipretide delivery system, the event is unlikely to be attributed to underlying/concurrent disease, other drugs, or other factors, 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/ADE and administration of the study drug/use of the elamipretide delivery system.

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

Unrelated: A causal relationship is clinically/biologically improbable, there is not a plausible time sequence between onset of the AE/ADE and administration of the study drug/use of the elamipretide delivery system, the event is likely to be attributed to underlying/concurrent disease, other drugs, or other factors, and there is no reasonable response on withdrawal.

9.3.8.1.3. Outcomeof AdverseEvent (AE)/Adverse Device Effect (ADE)

Investigators must follow all AEs/ADEs and SAEs/SADEs until the clinical study's post treatment follow-up period until resolution, stabilization, or withdrawal of consent. Resolution is defined as:

- Recovered/Resolved;
- Recovering/Resolving
- Not recovered/Not resolved
- Recovered/Resolved with sequelae;
- Fatal; or
- Unknown.

9.3.8.1.4. Investigator Injection Site Reaction (ISR) Assessment

Any ISR following SC administration, should be reported as an AE/ADE. To standardize the reporting of ISRs, the following guidance should be followed when reporting an ISR as an AE/ADE:

- The ISR should be assessed for severity using the "Table for Grading the Severity of Site Reactions to Injections" provided in Attachment 14.
- Any ISR that meets any of the criteria of a SAE/SADE (Section 9.3.7) should be reported within 24 hours of the clinical site first becoming aware of the event (as outlined in Section 9.3.10).
- The ISR should be reported as the characteristic of the ISR, rather than the general term of "Injection Site Reaction". For instance, erythema associated with an ISR should be reported as "injection site erythema" or "redness at injection site" rather than the broad term "injection site reaction".
- For ISRs which reoccur following a subsequent SC injection, only one event should be recorded on the eCRF, with the overall duration to include the start date of the first reported event and the end date of the last recurrent event. The severity grade should be the most severe of the recurrent event during this period.

The AEs/ADEs reported as a result of an ISR should be recorded on the subject's ISR AE/ADE eCRF. The Investigator is expected to use their clinical judgement regarding treatments for ISRs. Any medications or procedures necessary for treatment of the ISR signs and/or symptoms must be recorded on the subject's eCRF.

9.3.9. Adverse Event (AE)/Adverse Device Effect (ADE) Reporting Period

The AE/ADE reporting period begins when the subject signs the ICF and continues through the clinical study's post treatment follow-up period.

After study completion, all SAEs/SADEs with an ongoing/unknown outcome will be followed-up until resolution or stabilization. Additional information on SAEs/SADEs, obtained after database lock, will reside solely in the safety database.

Adverse Events that occur while the subject is concurrently enrolled in the SPIMM-202 trial and the SPIMM-203 Screening Period, will be collected in the SPIMM-202 trial eCRF and not as AEs in SPIMM-203 trial. Once the subject has completed the End-of-Study in the SPIMM-202 trial, AEs/ADEs should be reported only in the SPIMM-203 eCRF.

For subjects not concurrently enrolled in SPIMM-202 trial during the SPIMM-203 Screening Period, untoward events and/or incidental diagnoses that occur prior to study drug administration will be assessed by the Investigator and recorded as either medical history or as an AE. If the event is assessed by the Investigator as related to a study procedure, related to the previous exposure to study drug, and/or meets seriousness criteria, it will be recorded as an AE on the AE eCRF, processed, and followed accordingly. New protocol related AEs/ADEs (caused by any intervention required by the protocol) and updates on all AEs/ADEs 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/ADEs 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/SADEs and medically relevant ongoing/unknown outcome AEs/ADEs will be followed-up until resolution or stabilization by the Sponsors Pharmacovigilance department. Beyond this defined reporting period, any new SAE/SADE spontaneously reported to the Sponsor by the Investigator would be collected and processed. Additional information on SAE/SADE, obtained after database lock, will reside solely in the safety database.

Within the study, all subjects who took at least 1 dose of study drug, 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 Screen failure subjects, new AEs and updates must be recorded in the SPIMM-202 eCRFs until the date the subject was determined to be a screen failure. Beyond that date, only SAEs/SADEs and medically relevant AEs/ADEs will be followed-up by the Sponsor's Pharmacovigilance group and all data will be housed within the safety database.

9.3.10. Serious Adverse Event (SAE)/Serious Adverse Device Effect (SADE) Expedited Reporting

In the event of a SAE/SADE occurring during the reporting period, the Investigator must immediately (within 24 HOURS after becoming aware of the SAE/SADE) inform Sponsor as detailed in the Clinical Trial Pharmacovigilance Procedural Manual.

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

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

All SAE/SADE reports should be transmitted according to the safety management plan.

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

All SAE/SADE 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 medications/procedures 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 Management 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/ADE 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.

9.3.11. Pregnancy and Contraception

Any pregnancy in a female subject or female partner of a male subject during the course of the study and until the last follow-up visit must be reported on the Pregnancy Report Form (Part I) within 24 hours of learning of the pregnancy even if no AE/ADE has occurred. If the investigator suspects the pregnancy has resulted from an interaction of the study medication with contraceptives, then the pregnancy is considered as an AE; however, all pregnancies must be recorded in the AE page/section of the CRF.

The Pregnancy Report Form (Part I) must be transmitted according to the same process as described for SAE/SADE reporting in the Clinical Trial Pharmacovigilance Procedural Manual. Investigators must actively follow up, document, and report on the outcome of every pregnancy, even if the subject is withdrawn from the trial.

The Investigator must notify the Sponsor of the pregnancy outcome using the Pregnancy Report Form (Part II). In the event of the mother experiencing an abnormal outcome which meets of the criteria of an SAE/SADE, the SAE Report Form must be completed. In the event of the child/fetus experiencing an abnormal outcome the Parent-Child/Fetus Report form must be completed.

Any abnormal outcome must be reported in an expedited manner, while normal outcomes must be reported within 45 days from delivery.

9.3.12. 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 (and inform the Sponsor of) any applicable site-specific requirements related to the reporting of SAEs/SADEs involving his/her subjects to the Ethics Committee/Institutional Review Board (EC/IRB) that approved the trial.

In accordance with ICH GCP guidelines, the Sponsor will inform the Investigator of findings that could adversely affect the safety of subjects, impact the conduct of the trial, or alter the EC's/IRB's approval/favorable opinion to continue the trial. In particular, and in line with respective regulations, the Sponsor will inform the Investigator of AEs/ADEs that are both serious and unexpected and are considered to be related to the administered study drug or elamipretide delivery system ("suspected unexpected serious adverse reactions" or SUSARs or "unanticipated adverse device effects" or UADEs). The Investigator should place copies of these Safety reports in the Investigator Site File. National 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 Institutional Ethics Committee (IEC)/central IRB and will maintain records of these notifications. When direct reporting by the Sponsor is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety reports provided by the Sponsor and for filing copies of all related correspondence in the Investigator Site File.

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

9.4. 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 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 EDC 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 EDC 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, 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 and/or SPIMM-202 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.

Baseline is defined as the SPIMM-203 Baseline assessments.

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.

11.2.4.2. Analysis Populations

The Safety Population, will include all study subjects who receive at least 1 dose of study drug. The Efficacy Evaluable Population will include all subjects receiving at least one dose with any post-dose efficacy assessments.

11.2.5. Efficacy Analyses

For primary and secondary efficacy endpoints, trends over time in all continuous endpoints will be summarized using descriptive statistics (mean, median, standard deviation, minimum, maximum). Categorical variables will be described using frequencies and percentages.

Efficacy analyses will be conducted on the Efficacy Evaluable Population and will be largely descriptive in nature.

11.2.6. Safety Analyses

Safety data analysis will be conducted on all subjects in the Safety Population.

11.2.6.1. Adverse Events (AEs)/Adverse Device Effects (ADEs)

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

All reported AEs/ADEs will be listed, but only treatment-emergent adverse events (TEAEs)/Treatment-emergent adverse device effects (TEADEs) will be summarized.

The incidence of all TEAEs/TEADEs, drug relationship with TEAEs/TEADEs, and severity of TEAE/TEADEs 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. If a subject has the same AE/ADE 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 AE/ADE 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).

11.2.6.2. Deaths and Other Serious Adverse Events

Listings will be provided for the following:

- Deaths
- SAEs/SADEs
- AEs/ADEs leading to discontinuation of study drug/elamipretide delivery system

11.2.6.3. Clinical Laboratory Evaluations

Summary tables for laboratory parameters (including hematology, chemistry, additional laboratory assessments, 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. Shift tables for urinalysis will show the number of subjects who are normal/abnormal at baseline and normal/abnormal at the end of study.

11.2.6.4. Vital Signs

Vital signs data will be summarized by changes from baseline values 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.

11.2.6.5. Electrocardiogram (ECG)

Electrocardiogram data will be summarized by changes from baseline values 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, RR, QRS, and QT will also be listed.

11.2.6.6. 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 elamipretide with the elamipretide delivery system.

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

1. Apabhai S, Gorman GS, Sutton L, Elson JL, Plötz T, et al. Habitual Physical Activity in Mitochondrial Disease. 2011; 6(7): e22294. doi: 10.1371/journal.pone.0022294.
2. Gorman G, Schaefer AM, Ng Y, et al. Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. Annals of Neurology. 2015;77(5):753-759. doi:10.1002/ana.24362.
3. Lightowlers RN, Taylor RW, Turnbull DM. Mutations causing mitochondrial disease: What is new and what challenges remain?. Science. 2015;349(6255):1494-9.
4. Mancuso M, Hirano M. Physician Guide to Mitochondrial Myopathies. National Organization for Rare Disorders. 2016. Accessed on 28Jun2017. Accessible at: http://nordphysicianguides.org/mitochondrial-myopathies-mm/
5. Min K, Smuder AJ, Kwon OS, Kavazis AN, Szeto HH, Powers SK. Mitochondrial-targeted antioxidants protect skeletal muscle against immobilization-induced muscle atrophy. J Appl Physiol (1985). 2011 Nov;111(5):1459-66.
6. Niyazov D, M, Kahler S, G, Frye R, E, Primary Mitochondrial Disease and Secondary Mitochondrial Dysfunction: Importance of Distinction for Diagnosis and Treatment. Mol Syndromol 2016;7:122-137.
7. Powers SK, Hudson MB, Nelson WB, Talbert EE, Min K, Szeto HH, Kavazis AN, Smuder AJ. Mitochondria-targeted antioxidants protect against mechanical ventilation-induced diaphragm weakness. Crit Care Med. 2011 Jul;39(7):1749-59.
8. Schaefer AM, Phoenix C, Elson JL, McFarland R, Chinnery PF, Turnbull DM. Mitochondrial disease in adults: a scale to monitor progression and treatment. Neurology. 2006 Jun 27;66(12):1932-4.
9. Siegel MP, Kruse SE, Percival JM, Goh J, White CC, Hopkins HC, Kavanagh TJ, Szeto HH, Rabinovitch PS, Marcinek DJ. Mitochondrial targeted peptide rapidly improves mitochondrial energetics and skeletal muscle performance in aged mice. Aging Cell. 2013 Oct;12(5):763-771.
10. Talbert E, Smuder A, Min K, Kwon OS, Szeto HH, Powers SK. Immobilization-induced activation key proteolytic systems in skeletal muscles is prevented by a mitochondria-targeted antioxidant. J Appl Physiol. 115:529-538, 2013.

14. ATTACHMENTS

Attachment 1 Trial Schedule

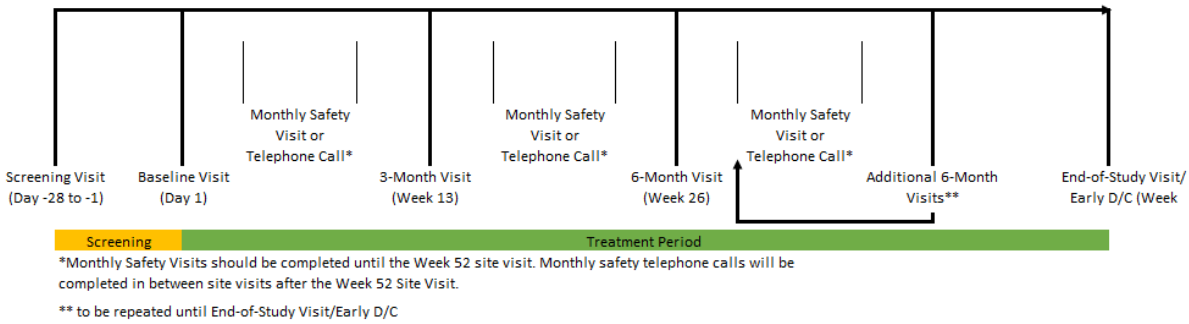
	Screening[a]	Baseline[b]	Treatment Period			Follow-Up Period	Unscheduled
Parameter	**(Day -28 to -1)**	**Baseline Visit (Day 1)**	**Monthly Safety Visits (±7 days)[c]**	**Monthly Safety Telephone Call (±7 days)[c]**	**3-Month Visit (Week 13 ±14 days); 6-Month Visits (Week 26 and every 26 weeks after ±14 days); End-of-Therapy Visit (Week 260 ±14 days)**	**End-of-Study Visit/Early Discontinuation Visit (Week 262 +14 days)**	**Unscheduled Visit[d]**
Informed Consent	X						
Subject Registration[e]	X						
Review of inclusion/exclusion criteria	X	X					
Demographics[f]							
Relevant Medical History[g]	X	X					
Concomitant Medication/Procedure Review[g]	X	X		X	X	X	X
Review AEs/ADEs[h]		X		X	X	X	X
Physical Exam[i]	X	X			X	X	X
Vital Signs[j]	X	X			X	X	X
12-Lead ECG[k]	X	X			X	X	X
Pregnancy Test[l]	X	X				X	X
Blood Chemistry, Hematology, and Additional Laboratory Assessments[m]	X	X	X		X	X	X
Urinalysis[m]	X	X			X	X	X
C-SSRS "Baseline/Screening"[n]	X						
C-SSRS "Since Last Visit"	X	X			X	X	X
Neuro-QoL Fatigue		X			X	X	X
PMMSA		X			X	X	X
Patient Global Assessment		X			X	X	X
EQ-5D-5L		X			X	X	X
WLQ[o]		X			X	X	X
Physician Global Assessment		X			X	X	X
Six Minute Walk Test[p]		X			X	X	X
Study Drug Administration[q]		X	X	X	X		X
ISR Assessment[r]		X			X		X

a. The ICF must be signed prior to any trial related procedures are performed. Subjects, who are <18 years of age, may be required by the trial center to have a

minor assent in addition to the ICF of the parent/guardian. Assessments completed as part of the End-of-Study Visit in the SPIMM-202 trial that are within the Screening Period can serve as Screening assessments and do not need to be reassessed. For subjects enrolled in SPIMM-202, the Screening Period may not begin prior to the Week 12 Visit in the SPIMM-202 trial.

b. Assessments completed as part of the End-of-Study Visit in SPIMM-202 and are within 24 hours of the Baseline Visit may serve as Baseline assessments and do not need to be reassessed. Screening assessments that are within 24 hours of the Baseline Visit may also serve as Baseline assessments and do not need to be reassessed. Otherwise, Baseline assessments must be completed within 24 hours prior to receiving elamipretide.
c. Subjects will be scheduled to have Monthly Safety Visits completed by a visiting nurse (or designee) in between site visits until the Week 52 site visit. Monthly safety telephone calls will be completed in between site visits after the Week 52 site visit. The monthly safety telephone call script isprovided in Attachment 4.
d. If an Unscheduled Visit occurs, assessments to be completed are in the judgement of the Investigator.
e. Subject will be assigned the same subject number from SPIMM-201 and/or SPIMM-202 trial.
f. Demographic data does not need to be recorded and will be taken from the SPIMM-201 and/or SPIMM-202 trial.
g. For subjects not concurrently enrolled in SPIMM-202 during the Screening Period, at the Baseline Visit, new medical history (including concomitant medications/procedures) since the End-of-Study Visit in the SPIMM-202 trial will be taken. Previous medical history (including concomitant medications/ procedures do not need to be recorded and will be taken from the SPIMM-202 trial
h. For subjects not concurrently enrolled in SPIMM-202 trial during the Screening Period, record any AEs that occurred during the Screening Period (as described in Section 9.3.9)
i. 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 will also be collected.
j. Vital signs will include HR, RR, and BP after sitting for 5 min, andtemperature.
k. All scheduled ECGs must be performed after the subject has rested quietly for at least 10 min in the supine position.
l. A serum pregnancy test is required at the Screening Visit if not concurrently enrolled in SPIMM-202 during the Screening Period. Results of the Baseline Visit pre-dose urine pregnancy test (or urine pregnancy test during the End-of-Study Visit in SPIMM-202 if within the Screening Period) must be evaluated before enrollment to ensure eligibility. Urine pregnancy test will also be performed for women of childbearing potential at the End-of-Study/ Early Discontinuation Visit.
m. See Attachment 3 for laboratory tests. Additional blood samples at the first 6-Month Visit will be collected and stored for assessing the immunogenicity potential of the study drug.
n. Only to be completed if subject did not enroll in SPIMM-202.
o. Only to be completed if the subject self-reports currently working.
p. The 6MWT should be performed after all other trial procedures except study drug administration and ISR assessment.
q. Subjects (and caregivers if needed) will be trained on the procedure for administration of study drug with the elamipretide delivery system (elamipretide injection, the elamipretide pen injector, and needle). On days of trial visits, the study drug administered with the elamipretide delivery system should be administered at the clinical site. At site visits where elamipretide is injected, administration should occur at the study center after completion of all procedures, except for the ISR assessment. Elamipretide administration on days of Monthly Safety Visits and monthly safety telephone calls will be completed by the subject (or trained caregiver).
r. The skin examination should occur at 30 (±5) minutes after study drug administration with the elamipretide delivery system. The presence and severity of pain, erythema, swelling, and pruritus at the injection site will be assessed. Scoring of erythema, swelling, pruritus and pain will be done using a 5-point scale using the “Table for Grading the Severity of Site Reactions to Injections” provided in Attachment 14.

Attachment 2 Trial Schematic



*Monthly Safety Visits should be completed until the Week 52 site visit. Monthly safety telephone calls will be completed in between site visits after the Week 52 Site Visit.

** to be repeated until End-of-Study Visit/Early D/C

Attachment 3 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	Venous lactate
	Additional Laboratory Assessments
	Interleukin-5 (IL-5)
	Immunoglobulin E (IgE)

Attachment 4 Monthly Safety Telephone Call Script

This page provides a sample script for the phone call that may occur approximately every 4 weeks after the patient is enrolled in SPIMM-203 to ensure the safe and compliant use of the elamipretide delivery system and to appropriately collect the safety events with use of the elamipretide delivery system.

The sample script below is provided to assist clinical sites with conducting monthly safety telephone calls. Additional questions are permitted to ensure completeness of answers.

During each monthly safety telephone call, the following script should be followed:

Script

Hello, my name is_____, and I'm calling from (name of facility and/or Investigator's name office). I am calling since it has been a month since we last spoke about your experience using elamipretide, the study drug in the SPIMM-203 trial you are involved in. May I ask you a few questions about your experience?

Have you or a trained caregiver been administering the study drug daily?

How many days since (our last telephone call or your last site visit) have you missed administering the study drug?

Do you have any questions/concerns regarding administering the study drug?

Have you experienced any worsening of your health or any new problems/conditions while on the study drug since (our last telephone call or your last site visit)?

Have you started or changed any medications since (our last telephone call or your last site visit)?

Could we schedule the next (telephone call or site visit)? (schedule telephone call or site visit)

Do you have any additional questions?

Thank you for speaking with me today. If you have any additional questions, please call me at (phone number) and/or to reference the Information for Use (IFU) pamphlet for the elamipretide delivery system for any issues.

Attachment 5 Neuro-QoL Fatigue Questionnaire

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 <u>starting</u> things because I was too tired……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG05	I had trouble <u>finishing</u> 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 6 Primary Mitochondrial Myopathy Symptom Assessment (PMMSA)

	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?	□	□	□	□

Attachment 7 Patient Global Assessment (PGA)

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 8 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 9 Six-Minute Walk Test (6MWT)

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. 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 10 Columbia-Suicide Severity Rating Scale (C-SSRS) "Baseline/Screening"

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

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 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.	**Lifetime: Time He/She Felt Most Suicidal**	**Past Months**
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 some intent to act on such thoughts, 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. Lifetime - ***Most Severe Ideation:*** ____ ***Type # (1-5)*** ____ ***Description of Ideation*** Past X Months - ***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 (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (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 (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop 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)*	**Lifetime**	**Past Years**
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. ***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_____?*** ***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** ☐ Total # of Attempts _____	**Yes** **No** Total # of Attempts
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐	**Yes** **No**
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. ***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:	**Yes** ☐ **No** ☐ Total # of interrupted _____	**Yes** **No** Total # of interrupted
Aborted 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. ***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:	**Yes** ☐ **No** ☐ Total # of aborted _____	**Yes** **No** Total # of aborted
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). ***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:	**Yes** ☐ **No** ☐	**Yes** **No**
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐	**Yes** **No**

Answer for Actual Attempts Only	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 reflexes intact; 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 11 Columbia-Suicide Severity Rating Scale (C-SSRS) "Since Last Visit"

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

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 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 some intent to act on such thoughts, 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
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(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
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop 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. ***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_____?*** ***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** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐
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. ***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:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted 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. ***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:	**Yes** ☐ **No** ☐ Total # of aborted _____
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). ***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:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	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 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* _____
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 12 EQ-5D-5L

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

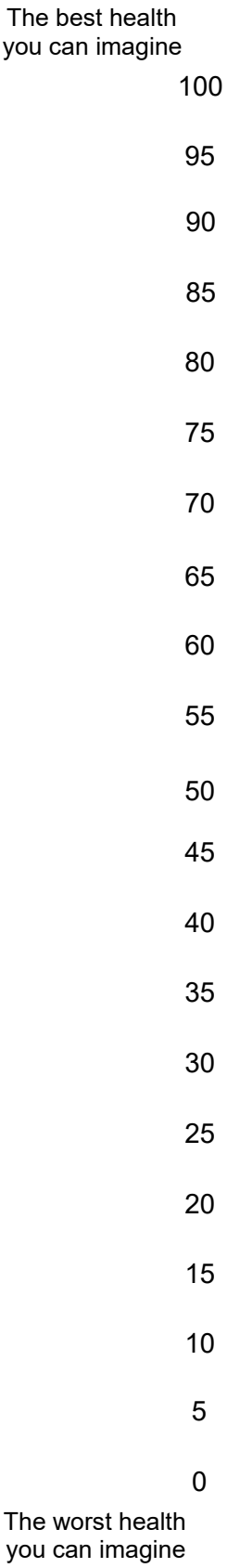
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = [ ]



Attachment 13 Work Limitations Questionnaire (WLQ)

CONFIDENTIAL

Work Limitations Questionnaire©

Self-Administered Long-Form

Fill in Today's Date

Month		Day		Year	

Instructions

Health problems can make it difficult for working people to perform certain parts of their jobs. We are interested in learning about how your health may have affected you at work during the past 2 weeks.

(1) The questions will ask you to think about your physical health or emotional problems. These refer to any ongoing or permanent medical conditions you may have and the effects of any treatments you are taking for these. Emotional problems may include feeling depressed or anxious.

(2) Most of the questions are multiple choice. They ask you to answer by placing a mark in a box.

For example:

How satisfied are you with each of the following . . .?

(Mark one box on each line a. and b.)

	Not At All Satisfied	Moderately Satisfied	Very Satisfied
a. Your local schools.	☐1	☐2	■3
b. Your local police department. . .	☐1	■2	☐3

These marks tell us you are very satisfied with your local schools and moderately satisfied with your local police department.

OPTIONAL PAGE

3. Before you begin answering any questions, we would like you to write some information on the calendar.

   - Find today's date. Mark that box.
   - Count back 2 weeks and mark that box too.

This 2-week period is the subject of most of the questions. Feel free to mark other important dates such as birthdays, family events, or work deadlines. Please use the calendar to help you answer correctly.

Insert calendar here.

Questions 1 through 5 ask about how your health has affected you at work during the past 2 weeks. Please answer these questions even if you missed some workdays.

- Mark the *"Does not apply to my job"* box only if the question describes something that is not part of your job.
- If you have more than one job, report on your **main** job only.

1. In the past 2 weeks, how much of the time did your physical health or emotional problems make it difficult for you to do the following?

(Mark one box on each line a. through e.)

	Difficult all of the time (100%)	**Difficult** most of the time	**Difficult** some of the time (about 50%)	**Difficult** a slight bit of the time	**Difficult** none of the time (0%)	Does not apply to my job
a. work the required number of hours	? 1	? 2	? 3	? 4	? 5	? 6
b. get going easily at the beginning of the workday	? 1	? 2	? 3	? 4	? 5	? 6
c. start on your job as soon as you arrived at work	? 1	? 2	? 3	? 4	? 5	? 6
d. do your work without stopping to take breaks or rests	? 1	? 2	? 3	? 4	? 5	? 6
e. stick to a routine or schedule	? 1	? 2	? 3	? 4	? 5	? 6

PLEASE READ CAREFULLY

These questions ask you to rate the amount of time you were able to handle certain parts of your job without difficulty.

2. a. In the past 2 weeks, how much of the time were you **able** to walk or move around different work locations (for example, go to meetings), without difficulty caused by physical health or emotional problems?

(Mark one box.)

Able all of the time (100%)	? 1
Able most of the time	? 2
Able some of the time (about 50%)	? 3
Able a slight bit of the time	? 4
Able none of the time (0%)	? 5
Does not apply to my job	? 6

b. In the past 2 weeks, how much of the time were you **able** to lift, carry, or move objects at work weighing more than 10 lbs., without difficulty caused by physical health or emotional problems?

(Mark one box.)

Able all of the time (100%)	? 1
Able most of the time	? 2
Able some of the time (about 50%)	? 3
Able a slight bit of the time	? 4
Able none of the time (0%)	? 5
Does not apply to my job	? 6

c. In the past 2 weeks, how much of the time were you **able** to sit, stand, or stay in one position for longer than 15 minutes while working, without difficulty caused by physical health or emotional problems?

(Mark one box.)

Able all of the time (100%)	? 1
Able most of the time	? 2
Able some of the time (about 50%)	? 3
Able a slight bit of the time	? 4
Able none of the time (0%)	? 5
Does not apply to my job	? 6

d. In the past 2 weeks, how much of the time were you **able** to repeat the same motions over and over again while working, without difficulty caused by physical health or emotional problems?

(Mark one box.)

Able all of the time (100%)	? 1
Able most of the time	? 2
Able some of the time (about 50%)	? 3
Able a slight bit of the time	? 4
Able none of the time (0%)	? 5
Does not apply to my job	? 6

e. In the past 2 weeks, how much of the time were you **able** to bend, twist, or reach while working, without difficulty caused by physical health or emotional problems?

(Mark one box.)

Able all of the time (100%)	? 1
Able most of the time	? 2
Able some of the time (about 50%)	? 3
Able a slight bit of the time	? 4
Able none of the time (0%)	? 5
Does not apply to my job	? 6

f. In the past 2 weeks, how much of the time were you **able** to use hand-held tools or equipment (e.g., a phone, pen, keyboard, computer mouse, drill, hairdryer, or sander), without difficulty caused by physical health or emotional problems?

(Mark one box.)

Able all of the time (100%)	? 1
Able most of the time	? 2
Able some of the time (about 50%)	? 3
Able a slight bit of the time	? 4
Able none of the time (0%)	? 5
Does not apply to my job	? 6

PLEASE READ CAREFULLY

These questions ask about difficulties you may have had at work.

3. In the <u>past 2 weeks</u>, how much of the time did your physical health or emotional problems make it difficult for you to do the following?

(Mark one box on each line a. through f.)

	Difficult all of the time (100%)	**Difficult** most of the time	**Difficult** some of the time (about 50%)	**Difficult** a slight bit of the time	**Difficult** none of the time (0%)	Does not apply to my job
a. keep your mind on your work	? 1	? 2	? 3	? 4	? 5	? 6
b. think clearly when working	? 1	? 2	? 3	? 4	? 5	? 6
c. do work carefully	? 1	? 2	? 3	? 4	? 5	? 6
d. concentrate on your work	? 1	? 2	? 3	? 4	? 5	? 6
e. work without losing your train of thought	? 1	? 2	? 3	? 4	? 5	? 6
f. easily read or use your eyes when working	? 1	? 2	? 3	? 4	? 5	? 6

The next questions ask about difficulties in relation to the people you came in contact with while working. These may include employers, supervisors, coworkers, clients, customers, or the public.

4. In the <u>past 2 weeks</u>, how much of the time did your physical health or emotional problems make it difficult for you to do the following?

(Mark one box on each line a. through c.)

	Difficult all of the time (100%)	**Difficult** most of the time	**Difficult** some of the time (about 50%)	**Difficult** a slight bit of the time	**Difficult** none of the time (0%)	Does not apply to my job
a. speak with people in-person, in meetings or on the phone	? 1	? 2	? 3	? 4	? 5	? 6
b. control your temper around people when working	? 1	? 2	? 3	? 4	? 5	? 6
c. help other people to get work done	? 1	? 2	? 3	? 4	? 5	? 6

These questions ask about how things went at work overall.

5. In the <u>past 2 weeks</u>, how much of the time did your physical health or emotional problems make it difficult for you to do the following?

(Mark one box on each line a. through e.)

	Difficult all of the time (100%)	**Difficult** most of the time	**Difficult** some of the time (about 50%)	**Difficult** a slight bit of the time	**Difficult** none of the time (0%)	Does not apply to my job
a. handle the workload	? 1	? 2	? 3	? 4	? 5	? 6
b. work fast enough	? 1	? 2	? 3	? 4	? 5	? 6
c. finish work on time	? 1	? 2	? 3	? 4	? 5	? 6
d. do your work without making mistakes	? 1	? 2	? 3	? 4	? 5	? 6
e. feel you've done what you are capable of doing	? 1	? 2	? 3	? 4	? 5	? 6

Attachment 14 Table for Grading the Severity of Injection Site Reactions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE- THREATENING
Injection Site Pain or Tenderness	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (eg, abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling	Same as for **Injection Site Erythema or Redness**	Same as for **Injection Site Erythema or Redness**	Same as for **Injection Site Erythema or Redness**	Same as for **Injection Site Erythema or Redness**
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

Adapted from Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014.

Signature Certificate

Document Reference: VMRKBNJ2HIBCGUBANGXN66

RightSignature
Easy Online Document Signing

Jim Carr
Party ID: 2H2HANIG4JD93NXRJ4SR98
IP Address: 50.203.117.38
VERIFIED EMAIL: jim.carr@stealthbt.com

Electronic Signature:

Jim Carr

Multi-Factor
Digital Fingerprint Checksum aa0f9b9d48495b0b1d9cd54cd33d791c053f1f03

Timestamp	Audit
2019-01-31 04:56:17 -0800	All parties have signed document. Signed copies sent to: John J. Jones, Jim Carr, and Quality Systems.
2019-01-31 04:56:17 -0800	Document signed by Jim Carr (jim.carr@stealthbt.com) with drawn signature. - 50.203.117.38
2019-01-31 04:55:52 -0800	Document viewed by Jim Carr (jim.carr@stealthbt.com). - 50.203.117.38
2019-01-30 14:11:06 -0800	Document created by Quality Systems (qualitysystems@stealthbt.com). - 96.230.125.25

This signature page provides a record of the online activity executing this contract.