Title: A Phase 3 Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Daily Subcutaneous Injections of Elamipretide in Subjects with Primary Mitochondrial Myopathy Followed by an Open-Label Treatment Extension

NCT: NCT03323749

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CLINICAL TRIAL PROTOCOL

A Phase 3 Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Daily Subcutaneous Injections of Elamipretide in Subjects with Primary Mitochondrial Myopathy Followed by an Open-Label Treatment Extension

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PROTOCOL APPROVAL

Protocol Title:	A Phase 3 Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Daily Subcutaneous Injections of Elamipretide in Subjects with Primary Mitochondrial Myopathy Followed by an Open-Label Treatment Extension
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Jim Carr

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

06/15/2018

Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for elamipretide (MTP-131). I have read the SPIMM-301 protocol and agree to conduct the trial as outlined. I confirm that I will conduct the trial in accordance with ICH 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 Trial: A Phase 3 Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Daily Subcutaneous Injections of Elamipretide in Subjects with Primary Mitochondrial Myopathy Followed by an Open-Label Treatment Extension

Trial site(s): Multicenter (North America and Europe); approximately 27 sites

Phase of development: 3

Objectives: This trial is designed with 2 parts, SPIMM-301 (PART 1) and SPIMM-301 OLE (PART 2). The objectives of each part are consistent with the trial design.

- PART 1 is a 24-week, randomized, double-blind, parallel-group, placebo-controlled assessment of the efficacy and safety of single daily subcutaneous (SC) doses of 40 mg elamipretide (vs placebo) administered with the elamipretide delivery system as a treatment for subjects with primary mitochondrial myopathy (PMM).
- PART 2 is an up to 144-week, open-label assessment of the long-term safety and tolerability of single daily SC doses of 40 mg elamipretide administered with the elamipretide delivery system in subjects with PMM.

PART 1 objectives are:

Primary

- To evaluate the effect of single daily SC doses of 40 mg elamipretide administered with the elamipretide delivery system for 24 weeks on the:
  - Distance Walked on the 6-Minute Walk Test (6MWT)
  - Total Fatigue on the Primary Mitochondrial Myopathy Symptom Assessment© (PMMSA)

Secondary

- To evaluate the effect of single daily SC doses of 40 mg elamipretide administered with the elamipretide delivery system for 24 weeks as measured by changes in the:
  - Fatigue During Activities on the PMMSA
  - Neuro-QoL Short Form Fatigue
  - Most bothersome symptom on the PMMSA
  - Neuro-QoL Fatigue activities of daily living (specific items from the Neuro-QoL Item Bank).
- To evaluate the safety and tolerability of single daily SC doses of 40 mg elamipretide administered with the elamipretide delivery system for 24 weeks

Exploratory

- To evaluate the effect of single daily SC doses of 40 mg elamipretide administered with the elamipretide delivery system for 24 weeks as measured by changes in the:
  - Individual symptoms on the PMMSA
  - Alternate version of the PMMSA Total Fatigue Score
  - Individual items of the Neuro-QoL Fatigue
  - EQ-5D-5L
  - Patient Global Impression (PGI) Scales
  - Clinician Global Impression (CGI) Scales

Pharmacokinetic (PK)

- To evaluate the PK of elamipretide

PART 2 objectives are:

- To assess the long-term safety and tolerability of single daily SC doses of 40 mg elamipretide administered with the elamipretide delivery system for up to 144 weeks

Methodology:

This randomized, double-blind, parallel-group, placebo-controlled trial will enroll approximately 202 subjects who have PMM. There are 2 parts to this trial.

- PART 1 is a 24-week, randomized, double-blind, parallel-group, placebo-controlled assessment of the efficacy and safety of single daily SC doses of 40 mg elamipretide (vs placebo) administered with the elamipretide delivery system as a treatment for subjects with PMM. Subjects will be randomized (in a ratio of 1:1) to one of two groups:
  - 24 weeks of single daily SC doses of 40 mg elamipretide or
  - 24 weeks of single daily SC doses of placebo.
- PART 2 is an up to 144-week, open-label assessment of the long-term safety and tolerability of single daily SC doses of 40 mg elamipretide administered with the elamipretide delivery system in subjects with PMM. Subjects who continue into PART 2 will receive treatment with 40 mg SC elamipretide administered with the elamipretide delivery system for up to 144 weeks. Thus, treatment during PART 2 will be as follows:
  - Subjects who are originally randomized to elamipretide during PART 1 (double-blind treatment) will continue receiving elamipretide during PART 2.
  - Subjects who are originally randomized to placebo during PART 1 (double-blind treatment) will switch to treatment with elamipretide during PART 2.

Note that the duration of PART 2 treatment for each subject will be the shortest of the following:

- 144 weeks
- Regulatory approval and commercial availability of the elamipretide delivery system in the subject's respective country

- Termination of the clinical development for elamipretide in subjects with PMM.

PART 1

Screening Period: Screening will begin with the subject's signature of the informed consent form (ICF) and will last a minimum of 7 days to a maximum of 28 days. Subjects not previously enrolled in SPIMM-300, however, may have a longer screening period for review by the Adjudication Committee to determine their eligibility for study enrollment. Subjects will undergo Screening procedures as described in the PART 1 Schedule of Assessments (Appendix 1) and will be trained and instructed to complete the PMMSA daily during the Screening Period, in an electronic or paper diary, in order to characterize their baseline disease status and to assess compliance. Subjects who complete Screening and continue to meet all trial requirements, including all Inclusion Criteria and none of the Exclusion Criteria, may be randomized (stratified by the subclassification of the genetic abnormality determined to be the primary cause of the subject's PMM [DiMauro 2003] as determined by the Adjudication Committee) and enter the Treatment Period.

Treatment Period: The Treatment Period will begin on the day of the Baseline Visit, which is defined as Day 1, and lasts for 24 weeks. Subjects (and caregivers if needed) will be trained on the procedure for administration of the elamipretide delivery system (the investigational medicinal product [IMP] [elamipretide or placebo], the elamipretide pen injector, and needle) and recording of the location (injection in the abdomen, rotating around the four abdominal quadrants, or other appropriate location [after Investigator consultation with the Sponsor]) and time (at approximately the same time each day [e.g., early morning, noon, or early afternoon]) of the IMP administration daily in the electronic or paper diary. An elamipretide delivery system training kit and checklist will be provided to the clinical site to assist in training. At the Baseline Visit, following completion of all Baseline procedures described in the PART 1 Schedule of Assessments, subjects or trained caregivers will administer IMP at the clinical site. On non-visit days, subjects (or trained caregivers) will administer the IMP daily during the Treatment Period. The subject will return to the clinical site for the Week 4, Week 12, and Week 24 Visits for assessments, to administer the IMP (subject or trained caregiver), and to return all used IMP supplies. During the Treatment Period, subjects will continue to follow all trial requirements, including recording the location and time of the IMP administration daily and completing the PMMSA daily. The Treatment Period will conclude with a visit to the clinical site at the Week 24 Visit when subjects will return all trial-related supplies.

At the Week 24 Visit, if the subject confirms they are willing and able to continue to adhere to trial requirements and the Investigator determines the subject meets the Continuation Criteria the subject may continue into Part 2. If the subject continues into PART 2, the subject will continue (or start, for subjects treated with placebo in PART 1) elamipretide therapy the day of the Week 24 Visit (using the PART 2 supply of IMP) and continue trial activities as described in the PART 2 Schedule of Assessments (Appendix 2). Subjects who will not continue into PART 2 will not be administered IMP and will enter the PART 1 Follow-Up Period.

For all subjects, it is the intent that subjects who discontinue IMP (at any time) for any reason will continue to be followed for all protocol-planned trial visits through the completion of the PART 1 Treatment Period, and will have all endpoints (including efficacy) collected accordingly. In the interest of the subject, subjects who withdraw consent or are withdrawn from the trial by the investigator should be encouraged to complete an Early Discontinuation Visit as soon as possible and an effort should be made to complete and report the observations as thoroughly as possible up to the date of withdrawal.

PART 1 Follow-Up Period (for subjects not continuing into PART 2): The PART 1 Follow-Up Period will begin after completion of the Week 24 Visit and will last for 4 weeks. Subjects will return to the

clinical site for the PART 1 End-of-Trial Visit for final safety assessments, as described in the PART 1 Schedule of Assessments, and return all remaining trial-related supplies not previously returned.

PART 2

While there is no screening period for PART 2, subjects continuing into PART 2 must meet the PART 2 Continuation Criteria. Subjects who decide not to continue in the PART 2 at the PART 1 Week 24 Visit are not eligible to participate in PART 2.

Treatment Period: The Treatment Period will begin on the day of the PART 1 Week 24 Visit (at the administration of IMP) using the PART 2 supply of IMP. Subjects (or trained caregivers) will administer the IMP daily during the Treatment Period. The subject will return to the clinical site for the Week 28, Week 36, and Week 48 Visits for assessments, to administer the IMP (subject or trained caregiver), and to return all used IMP supplies. Additional visits will occur every 24 weeks for the remainder of the Treatment Period, with phone calls to the subject every 12 weeks between clinical site visits. During the Treatment Period, subjects will continue to follow all trial requirements.

In the interest of the subject, subjects who withdraw consent or are withdrawn from the trial by the investigator should be encouraged to complete an Early Discontinuation Visit as soon as possible and an effort should be made to complete and report the observations as thoroughly as possible up to the date of withdrawal.

PART 2 Follow-Up Period: The PART 2 Follow-Up Period will begin after completion of the Week 168 Visit and will last for 4 weeks. Subjects will continue to follow all trial requirements. Subjects will return to the clinical site for the PART 2 End-of-Trial Visit for final safety assessments, as described in the PART 2 Schedule of Assessments, and return all remaining trial-related supplies not previously returned.

Number of subjects (planned): Approximately 202 subjects will be randomized.

SPIMM-301 Eligibility Criteria

A subject must meet all of the following Inclusion Criteria at the Baseline Visit to be eligible for inclusion in the SPIMM-301 trial:

1. Willing and able to provide a signed informed consent form (ICF) prior to participation in any trial-related procedures.
2. Agrees and is able to adhere to the trial requirements for the length of the trial, including the use of the elamipretide delivery system.
3. Subject is ≥16 and ≤80 years of age. In Germany, subjects must be ≥18 years of age.
4. Enrolled (signed ICF) in SPIMM-300 or have prior approval from the Sponsor to enroll without SPIMM-300 participation.
5. Diagnosed with PMM in the opinion of the Investigator, consisting of:
    a. Molecular genetic abnormality of the mitochondrial respiratory chain, and
    b. Subject reported symptoms (i.e., exercise intolerance, fatigue, muscle weakness) or physical examination findings of myopathy that are the predominant symptoms of the subject's mitochondrial respiratory chain disorder.
6. The subject's molecular genetic abnormality is consistent with PMM as confirmed by the Adjudication Committee.
7. Women of childbearing potential must agree to use 1 of the following methods of birth control from the date they sign the ICF until 28 days after the last dose of IMP:

a. Abstinence, when it is in line with the preferred and usual lifestyle of the subject. Subject agrees to use a highly effective method of contraception should they become sexually active.
b. Relationships with male partners who have been surgically sterilized by vasectomy (the vasectomy procedure must have been conducted at least 60 days prior to the Screening Visit).
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).

8. Male subjects with female partners of child-bearing potential must be willing to use a highly effective method of contraception from the date they sign the ICF until 28 days after the last dose of IMP.

A subject CANNOT meet any of the following Exclusion Criteria at the SPIMM-301 Baseline Visit to be eligible for inclusion in the trial:

1. Subject has myopathic signs and/or symptoms due to a neuropathic process (i.e. cerebellar dysfunctions and peripheral neuropathies) or a gait problem that would interfere with the 6MWT, in the opinion of the Investigator.
2. Female subjects who are pregnant, planning to become pregnant, or breastfeeding/lactating.
3. Walks < 100 meters or > 450 meters during the 6MWT at either the Screening Visit OR Baseline Visit.
4. At the Baseline Visit, the estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2, using the Screening Visit value with the Modification of Diet in Renal Disease (MDRD) Study equation.
5. Subject has undergone an in-patient hospitalization within the 30 days prior to the Baseline Visit or has a planned hospitalization or a surgical procedure during the trial.
6. Subject has clinically significant respiratory disease and/or cardiac disease (medical history or current clinical findings), in the opinion of the Investigator, or prior interventional cardiac procedure (e.g., cardiac catheterization, angioplasty/percutaneous coronary intervention, balloon valvuloplasty, etc.) within 3 months of the Baseline Visit.
7. Subject has a pacemaker, implantable cardioverter-defibrillator, or cardiac resynchronization therapy device OR QTc elongation (using the correction factor utilized at the clinical site) defined as a QTc >450 msec in male subjects and >480 msec in female subjects.

   Note: At the initial electrocardiogram (ECG), if QTc exceeds these parameters, the ECG may be repeated 2 more times (during the same visit), and the average of the 3 QTc values used to determine the subject's eligibility.
8. ECG evidence of acute ischemia, atrial fibrillation, or active conduction system abnormalities with the exception of any of the following:
   a. First degree AV-block

b. Second degree AV-block Type 1 (Mobitz Type 1 / Wenckebach type)
c. Right bundle branch block

9. Subject has severe vision impairment that, in the opinion of the Investigator, may interfere with their ability to complete all trial requirements
10. Subject has a seizure disorder that, in the opinion of the Investigator, may interfere with their ability to complete all trial requirements.
11. Active malignancy or any other cancer from which the subject has been disease-free for < 2 years.
12. Subject has a solid organ transplant and/or is currently receiving treatment with therapy for immunosuppression, in the opinion of the Investigator.
13. Subject has been previously diagnosed with human immunodeficiency virus (HIV), hepatitis B, or hepatitis C infection.
14. Subject has a history of a systemic eosinophilic illness and/or an eosinophil count >1,000 cells $x10^6$/L at the Screening Visit.
15. Subject is currently participating or has participated in an interventional clinical trial (i.e., investigational product or device, stem cell therapy, gene therapy) within 30 days of the Baseline Visit; or is currently enrolled in a non-interventional clinical trial (except for SPIMM-300) at the Baseline Visit which, in the opinion of the Investigator, may be potentially confounding to the results of the current trial (e.g. exercise therapy trial).
16. Subject has previously received elamipretide (MTP-131), for any reason.
17. Subject has a history of active substance abuse during the year before the Baseline Visit, in the opinion of the Investigator.
18. 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.

PART 2 Continuation Criteria

A subject must meet all of the following PART 2 Continuation Criteria at the Week 24 Visit in PART 1 to be eligible for PART 2:

1. Subjects must continue to be able and willing to adhere to the trial requirements.
2. Subject is appropriate to continue in PART 2 (i.e. subject was compliant in PART 1), in the opinion of the Investigator.
3. Subject has not had a serious adverse event (SAE)/serious adverse device effect (SADE) attributed to the elamipretide delivery system.
4. Subject has not permanently discontinued the elamipretide delivery system.

Investigational product, dosage and mode of administration:

Elamipretide injection will be supplied as a sterile 3.0 mL multidose glass cartridge containing 2.5 mL of elamipretide solution (elamipretide HCl [80 mg/mL], phosphate buffer, and benzyl alcohol) for use with the elamipretide delivery system (the investigational medicinal product [IMP] [elamipretide

or placebo], the elamipretide pen injector, and needle) as described in the Pharmacy Manual and 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.

Clinical site staff will train subjects (and caregivers if needed) and ensure understanding of proper SC injection technique on Day 1 and use of the elamipretide delivery system. An elamipretide delivery system training kit and checklist will be provided to the clinical site to assist in training. On Day 1 (and subsequent clinical site visits), IMP will be administered at the clinical site by the subject or trained caregiver. On non-visit days, the subject (or trained caregiver) will administer the IMP 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 the IMP 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 IMP, independent from the location of the concomitant therapy injections, should be used.

Reference therapy, dosage and mode of administration:

The placebo for this trial will be composed of sodium chloride, phosphate buffer, and benzyl alcohol similar to excipients used to manufacture the investigational drug but without the active drug substance. The placebo will be handled and administered identically to active drug.

Duration of Trial: Up to 176 weeks

This trial is designed with 2 parts, PART 1 and PART 2.

PART 1: Up to 32 weeks

- Screening Period: 7 to 28 days
- Treatment Period: 24 weeks
- PART 1 Follow-Up Period: 4 weeks (for subjects not continuing into PART 2). Subjects continuing into PART 2 will not participate in the PART 1 Follow-Up Period.

PART 2: Up to 148 weeks

- Treatment Period: Up to 144 weeks
- PART 2 Follow-Up Period: 4 weeks

Criteria for evaluation:

Efficacy:

Efficacy will only be assessed for PART 1.

Primary Endpoints

- Distance walked (meters) during the 6MWT
- Total Fatigue score on the PMMSA

Secondary Endpoints

- Fatigue During Activities score on the PMMSA
- Neuro-QoL Fatigue Short Form score
- Most bothersome symptom score on the PMMSA
- Neuro-QoL Fatigue activities of daily living (specific items from the Neuro-QoL Item Bank)

Exploratory Endpoints

- Individual symptom scores on the PMMSA
- Alternate version of the PMMSA Total Fatigue Score
- Individual item scores on the Neuro-QoL Fatigue
- EQ-5D-5L scores
- Patient Global Impression (PGI) Scales
  - PGI of Symptom scores
  - PGI of Change scores
- Clinician Global Impression (CGI) Scales
  - CGI of Symptom scores
  - CGI of Change scores

Pharmacokinetic (PK) Endpoints

- PK parameters

Safety

For both PART 1 and PART 2, safety will be assessed through collection of the following data:

- Adverse Events (AEs)/Adverse Device Effects (ADEs)
- Vital Signs
- Electrocardiograms (ECGs)
- Clinical laboratory evaluations
- Columbia-Suicide Severity Rating Scale (C-SSRS)

Statistical methods:

Sample Size:

A sample size of 202 subjects (101 per treatment arm) provides 90% power to detect a 30-meter difference between treatment groups in the 6MWT and also 90% power to detect a one unit difference in the PMMSA Total Fatigue Score, assuming standard deviations of 60 meters for 6MWT and 2 units for the PMMSA Total Fatigue Score, at an alpha-level of 0.025. The two-sided alpha-level of 0.025 is to account for a possible multiplicity adjustment for the primary endpoint family.

General Considerations

Data will be tabulated (by treatment group) using descriptive statistics (number of subjects, mean, median, standard deviation, minima, and maxima) for continuous variables and using frequencies and percentages for discrete variables. Inferential statistics will be presented where specified. A comprehensive statistical analysis plan (SAP) will be written and approved prior to database lock. This SAP will detail how missing values are to be handled, windows for trial visits, and how other analysis considerations will be addressed.

Statistical tests (where performed) will be 2-sided at the alpha=0.05 level of significance, except as noted to adjust for multiplicity.

Analysis Populations

Statistical analysis will be performed in the following populations:

- Safety Population – Includes all trial subjects who receive at least 1 dose of IMP. Subjects will be analyzed according to the actual treatment they receive.
- Intent-to-Treat (ITT) Population – Includes all trial subjects who receive at least one dose of IMP. Subjects will be analyzed according to the treatment group they were randomized to and generally included in efficacy analyses for which post-baseline data are available.
- Per-Protocol (PP) Population – Includes all ITT subjects without major protocol violations/deviations. The list of major protocol violations/deviations will be identified and specified in the SAP prior to final database lock for the trial that would lead to exclusion for the PP analysis.
- Pharmacokinetic (PK) Population – Includes all trial subjects who have at least one PK sample taken during their participation.

Disposition of Subjects

Subject disposition (including the number and percent of subjects who are randomized, who receive randomized treatment, who are included in each analysis population, who prematurely discontinue and reasons for discontinuation, and who complete the trial) will be tabulated by treatment group. The number and percentage of subjects by exposure duration will be tabulated.

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

Efficacy

The distance walked (meters) during the 6MWT and Total Fatigue score on the PMMSA constitute the family of primary endpoints. Efficacy analyses will be conducted on the ITT population.

Analyses of continuous endpoints will be conducted utilizing a mixed model repeated measures (MMRM) approach, with fixed effects for treatment, visit, the treatment-by-visit interaction, and subject as a random effect. The outcome is the change from baseline to each on-treatment time point. The baseline value and a baseline by visit interaction for the endpoint will be included as covariates. The primary time point is at Week 24; however, all protocol-scheduled time points will be included in the model. The exact details of the model, including variance-covariance structure and denominator degrees of freedom will be specified in the SAP.

The secondary endpoints are:

- Fatigue During Activities score on the PMMSA
- Neuro-QoL Fatigue Short Form score
- Most bothersome symptom score on the PMMSA
- Neuro-QoL Fatigue activities of daily living (specific items from the Neuro-QoL Item Bank)

These endpoints will be assessed in a similar manner as the primary efficacy endpoints.

There will be a number of exploratory endpoints investigated; these will be assessed in a similar manner as the primary efficacy endpoints.

A family-wise alpha level of 0.05 will be maintained for the primary endpoint family, using Hochberg's procedure at the primary time point of 24 weeks. If both primary endpoints are significantly different from placebo at the 0.05 (two-sided) level of significance (in favor of treatment), then both will be considered statistically significant. Otherwise the endpoint with the smaller p-value of the two will be considered statistically significant, if statistically significant at the 0.025 (two-sided) level of significance.

Select secondary and exploratory endpoints will be alpha-level protected in a hierarchical fashion, conditional upon the statistical significance of both endpoints in the primary endpoint family. Additional details will be specified in the SAP.

Safety Analyses

Safety data analysis will be conducted for the Safety Population.

All AEs/ADEs will be coded to system organ class (SOC) and preferred term (PT) using the latest Medical Dictionary for Regulatory Activities coding dictionary. All reported AEs/ADEs will be listed, but only treatment-emergent AEs (TEAEs)/Treatment-Emergent ADEs (TEADEs) will be summarized.

The incidence of all TEAEs/TEADEs, drug relationship with TEAEs/TEADEs, and severity of TEAEs/TEADEs will be summarized by treatment group. In the summary tables, subjects may be counted under multiple SOCs and PTs, but for each SOC and PT, subjects are only counted once for each treatment group. If a subject has the same AE/ADE on multiple occasions, the highest severity (severe > moderate > mild) or drug relationship (probable > possibly related > unlikely related > unrelated) recorded for the event will be presented. If severity is missing, subjects will be included as missing (for severity). If drug relationship is missing, subjects will be included in related tables (i.e., considered related). Summary tables will be organized by SOC, then PT.

Local tolerability (pain/tenderness, erythema, induration/swelling, and pruritus) of the injection site will be evaluated as an AE and summarized.

Summary tables for laboratory parameters (including clinical hematology and chemistry laboratory parameters, 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 parameter and visit for each treatment group. Shift tables for urinalysis will show the number of subjects who are normal/abnormal at baseline and normal/abnormal at the end of trial.

Vital signs and ECG data will be summarized similarly as clinical laboratory outcomes.

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3. ABBREVIATIONS AND DEFINITIONS

Term	Definition
6MWT	6-Minute Walk Test
ADE	Adverse device effect
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the plasma concentration versus time curve
$AUC_{0-\tau}$	Area under the plasma concentration vs time curve from time 0 to end of the dosing interval
AUC_{0-inf}	Area under the plasma concentration curve from baseline to infinity
AUC_{0-24}	Area under the plasma concentration curve from baseline to 24 hours postdose
BMI	Body mass index
CIOMS	Council for International Organizations of Medical Sciences
CGI	Clinician Global Impression Scales
C_{max}	Maximum plasma concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
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
IFU	Instructions for Use
IMM	Inner mitochondrial membrane
IMP	Investigational medicinal product
ISR	Injection site reaction
IV	Intravenous
ITT	Intention-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MFD	Maximum feasible dose
mL	Milliliter
MTP-131	Elamipretide, SS-31, SBT-031, or Bendavia™
mtDNA	Mitochondrial DNA
nDNA	Nuclear DNA
PK	Pharmacokinetic(s)
PGI	Patient Global Impression Scales
PMMSA	Primary Mitochondrial Myopathy Symptom Assessment
PT	Preferred term

Term	Definition
RA	Risk assessment
ROS	Reactive oxygen species
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SMP	Safety Management Plan
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TEADE	Treatment-emergent adverse device effect
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

4. INTRODUCTION

This pivotal trial will be conducted in strict accordance with the current versions of the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, ICH GCP guidelines, the Declaration of Helsinki, and all applicable laws and regulations. For detailed information on the elamipretide delivery system 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)

4.1.1. Background

The National Organization for Rare Disorders (NORD) Physician Guide to Mitochondrial Myopathies describes PMM as genetic disorders of the mitochondrial respiratory chain affecting predominantly, but not exclusively, skeletal muscle (Mancuso 2016). In PMM, there is an exaggerated response to physical exercise due to skeletal muscle respiratory chain dysfunction. The increased oxygen available during physical activity in the arterial bloodstream cannot be effectively utilized in PMM subjects by the skeletal muscle cells and as a result leads to debilitating muscle weakness, muscle atrophy, limited exercise capacity, and symptoms of fatigue. The severity of PMM is variable but the progressive reduction in muscle strength and exercise capacity eventually significantly compromises the ability to perform activities of daily living (DiMauro 2004; Pfeffer 2013; Tarnopolsky 2004).

4.1.2. Etiology

Mitochondria are cellular organelles with an inner and an outer membrane and a matrix containing mitochondrial DNA (mtDNA). Mitochondria host multiple metabolic pathways required for normal cellular function. Mitochondrial function is under the dual control of genes within mtDNA as well as within nuclear DNA (nDNA). PMM is caused by mutations in nDNA and/or mtDNA which result in electron transport chain (ETC) dysfunction and a corresponding reduction in oxidative phosphorylation and production of ATP (Chinnery 2014; DiMauro 2003). Mutations causing PMM are subclassified as follows (DiMauro 2003):

- Disorders involving mtDNA mutations that impair mitochondrial protein synthesis in toto
- Disorders involving mtDNA mutations that affect the subunits of the respiratory chain
- Disorders involving nDNA mutations in genes encoding subunits or ancillary proteins of the respiratory chain
- Disorders involving nDNA mutations causing defects of intergenomic signaling
- Disorders involving nDNA mutations causing defects of mitochondrial protein importation
- Disorders involving nDNA mutations causing alterations of the lipid milieu of the inner mitochondrial membrane

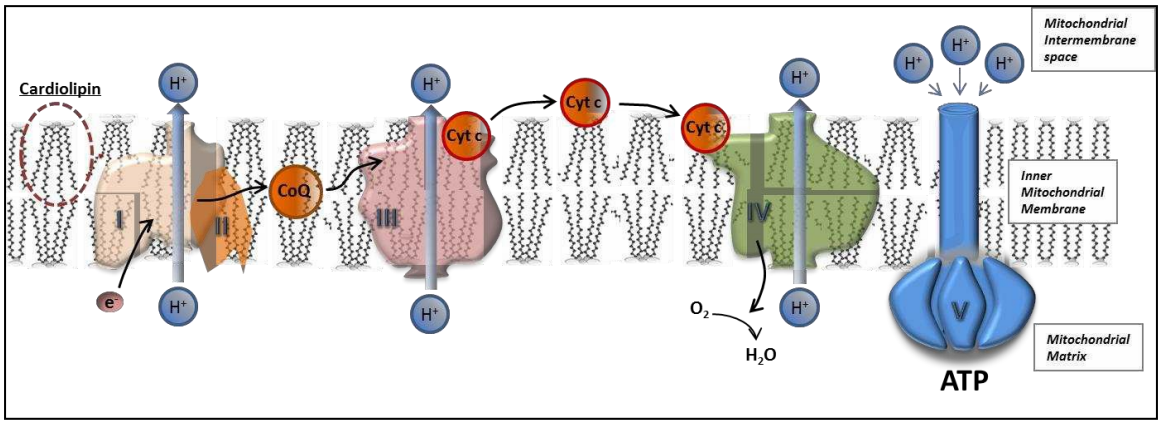
- Disorders involving nDNA mutations causing alterations of mitochondrial motility or fission

4.1.3. Pathophysiology

As noted above, PMM entails genetic disorders of the mitochondrial respiratory chain. The mitochondrial respiratory chain is located within the curves, or cristae, of the inner mitochondrial membrane (IMM), which are also the site for the highly-specialized proteins that form the complexes of the ETC. The curved architecture of the cristae helps keep the ETC complexes in close association with one another, increasing the efficiency of ATP production and minimizing electron leak. This curvature is attributed to cardiolipin, a conically-shaped phospholipid found only in the IMM. Cardiolipin also facilitates the tight association of individual ETC complexes into super-complexes which enhance respiratory chain efficiency.

Mitochondrial respiration, or oxidative phosphorylation, occurs via the complexes of the ETC, which is composed of four multi-subunit protein aggregates (Complexes I-IV) embedded in the IMM (Figure 1). These complexes, along with Complex V, are involved in the energetic processes of mitochondria. Energy extracted from dietary intake is converted into reducing equivalents (e.g., nicotinamide adenine dinucleotide [NADH]) that donate electrons to Complex I (NADH dehydrogenase). The energy released by the shuttling of these high-energy electrons along the ETC allows protons to be pumped from the matrix compartment of the mitochondrion into the intermembrane space. Two additional carriers comprise the ETC, Coenzyme Q_{10} (Co Q_{10}) and cytochrome c (Cyt c), each play critical roles in the efficient transfer of electrons through these successive oxidation-reduction reactions. The protons pumped into the mitochondrial intermembrane space are then used by Complex V (ATP synthase) to catalyze the conversion of adenosine diphosphate (ADP) and inorganic phosphate to ATP.

Figure 1: Oxidative Phosphorylation

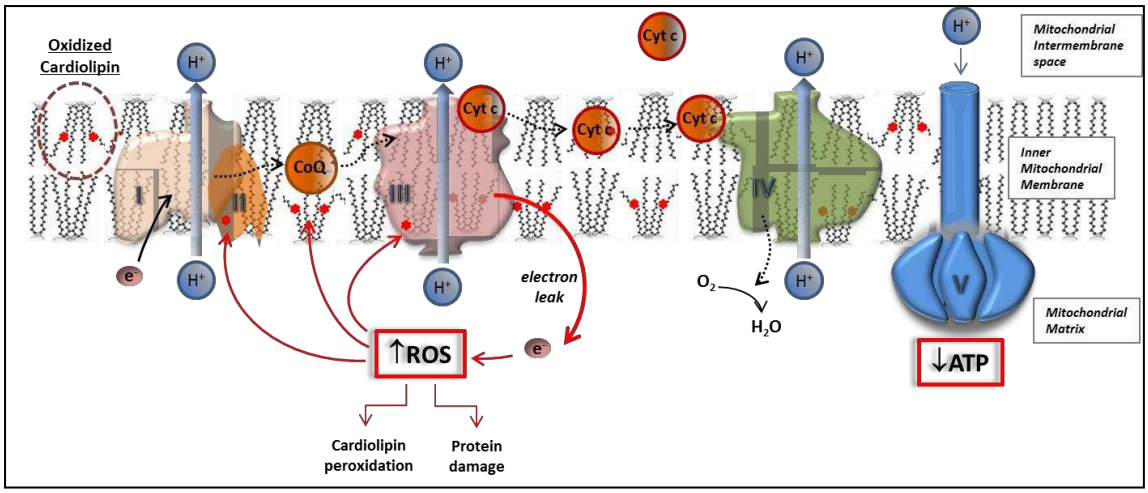


ATP=adenosine triphosphate; CoQ=coenzyme Q10; Cyt C=cytochrome C;
Reference: Adapted with permission from: Brown DA, Sabbah HN, Shaikh SR. Mitochondrial inner membrane lipids and proteins as targets for decreasing cardiac ischemia/reperfusion injury. Pharmacol Ther.2013 Dec;140(3):258-266.

Under normal metabolic conditions, most electrons flow down the ETC, ultimately reacting with oxygen at Complex IV to form water. However, in PMM, mtDNA and/or nDNA mutations result in respiratory chain dysfunction. This dysfunction results in the "leak" or escape of electrons prematurely from the ETC, creating reactive oxygen species (ROS) such as superoxide radical

(O_2^-), and hydrogen peroxide (H_2O_2) (Figure 2). As the name suggests, ROS are highly reactive, and attack mitochondrial components, especially membrane lipids such as cardiolipin. This causes altered cardiolipin structure which in turn disrupts IMM structure, leading to a relaxation of cristae curvature and a drifting apart of ETC complexes. This further reduces ETC efficiency and increases electron leakage, perpetuating a 'vicious cycle' entailing increased ROS production, increased oxidative stress, and further reductions in ATP generation. This "vicious cycle" leads to mitochondrial, cellular, and organ dysfunction typical of that seen in subjects with mitochondrial disease.

Figure 2: Creation of Reactive Oxygen Species (ROS)



ATP=adenosine triphosphate; CoQ=coenzyme Q10; Cyt C=cytochrome C; ROS=reactive oxygen species
Reference: Adapted with permission from: Brown DA, Sabbah HN, Shaikh SR. Mitochondrial inner membrane lipids and proteins as targets for decreasing cardiac ischemia/reperfusion injury. Pharmacol Ther.2013 Dec;140(3):258-266.

4.1.4. Clinical Presentation

Exercise-induced symptoms are common in PMM, in which mitochondrial dysfunction in skeletal muscle mitochondria leads to reduced energy production, increased lactate production and phosphocreatine (PCr) depletion (Mancuso 2016). Other skeletal muscle related manifestations of PMM are myalgia, muscle wasting, muscle cramps, recurrent rhabdomyolysis, progressive external ophthalmoplegia, and ptosis. Some subjects with PMM present with only skeletal muscle myopathy, while others present with other organ dysfunction, but in both conditions, the skeletal muscle myopathy is the predominant clinical manifestation of the disease.

4.1.5. Prevalence

PMM is a phenotype of Primary Mitochondrial Disease (PMD), a larger heterogeneous group of mitochondrial disorders with variable phenotypic expression. There has been no formal characterization of the prevalence in the United States of either PMM or PMD. However, PMD has been estimated to affect approximately 1 in 4,300-8,000 persons with varying degrees of disability (Gorman 2015; Ng 2016; Chinnery 2014). The most specific estimates of clinically affected and genetically confirmed adults (>16 years old) with PMD were reported by Newcastle University as recently as May 2015 based on a cohort of adult PMD subjects in North East

England from 1990 to 2011 (Gorman 2015). This study concluded that PMD affects at least 1 in 5,000 of the general population, with mtDNA mutations accounting for about three quarters (76.8%), and nDNA mutations accounting for about one quarter (23.2%) of the clinically affected adults with PMD. Since subjects diagnosed with PMM are a subset of PMD subjects, their prevalence can be estimated to be less than that of the larger PMD subject population.

4.1.6. Burden of Disease

PMM can result in significant deterioration of subject quality of life as routine activities of daily living (such as climbing stairs, grocery shopping, vacuuming, walking, or carrying out normal job functions) are limited by skeletal muscle weakness, poor endurance and easy fatigability. Loss of muscle mass and fixed weakness may also cause additional functional limitations (Taivassalo 2003; Taivassalo 2004). Patients with PMM face an inescapable range of daily challenges related to their disease including not being able to sustain muscle contraction, inability to take things from a high shelf, inability to go up and down stairs, feeling fatigued immediately upon waking in the morning, being bedbound, etc. This chronic disability can lead to depression and the inability to gain meaningful employment. On the more severe end, PMM can impact muscles that support breathing, cause weakness and wasting in muscles of the face and neck leading to difficulty with swallowing and slurred speech, vision loss and severe gastrointestinal dysfunction.

PMM is a life-long debilitating disease in which subjects suffer a myriad of incapacitating symptoms which directly affect quality of life, with no available therapies to significantly improve the most prominent symptoms of muscle weakness, exercise intolerance and fatigue.

4.1.7. Treatment

There are currently no approved treatments for PMM.

4.2. Pharmacologic Basis for Elamipretide as a Potential Treatment for Primary Mitochondrial Myopathy (PMM)

PMM is caused by genetic mutations in nDNA and/or mtDNA causing oxidative phosphorylation abnormalities which result in clinical signs and symptoms. This dysfunction results in a reduction in ATP and an increase in ROS production. This increase in ROS may reach a threshold and, due to cardiolipin peroxidation and ensuing degradation of IMM structure, trigger additional increased ROS generation by the ETC, an effect termed “ROS-induced ROS release (RIRR)” (Zorov 2000; Zorov 2006). These effects constitute a positive feedback mechanism for enhanced ROS production leading to additional significant mitochondrial structural abnormalities, dysfunction and cellular injury. At a certain level of mitochondrial dysfunction (decreased ATP and increased ROS production), subjects experience signs and symptoms of their disease.

As noted above, ROS attack and denature a number of components within the mitochondria, including the protein components of the ETC, membrane lipids (particularly cardiolipin), and mtDNA. In particular, the peroxidation or denaturing of cardiolipin has been associated with abnormal morphology of the inner mitochondrial membrane (IMM), reduced association of the ETC complexes within the IMM, a decline in ETC activity (ATP production), and the release of cytochrome c which initiates apoptotic signaling (Fry 1981; Chicco 2007).

Elamipretide improves mitochondrial function by restoring the physical and biochemical properties of the IMM through its association with cardiolipin. Stealth BT has demonstrated that treatment of cells or isolated organs undergoing oxidative stress with elamipretide can maintain the normal morphology of the IMM and the association of the ETC complexes within the IMM. Elamipretide normalizes IMM structure, which is important to keep the ETC complexes in optimal proximity to one another, and enhances interaction and association of the ETC complexes ("super-complex association") to increase respiratory function, increase ATP production, and decrease ROS generation. Various studies have shown an ensuing improvement in various downstream consequences of mitochondrial dysfunction following treatment with elamipretide, including reduced fibrosis, inflammation, and cell death.

4.3. Elamipretide Risk/Benefit Assessment

The Investigator's Brochure describes in detail the risks and potential benefits of treatment with elamipretide and should be referenced by the Investigator. A brief overview of risks and benefits is provided in the following sections.

4.3.1. Clinical Efficacy in Studies in Primary Mitochondrial Myopathy (PMM)

4.3.1.1. SPIMM-201

The SPIMM-201 trial was a phase 1/2 multi-center, randomized, double-blind, placebo-controlled, multiple ascending IV dose trial that enrolled subjects ≥16 and ≤65 years with PMM. Three escalating doses (0.01, 0.10, and 0.25 mg/kg/hour infused for 2 hours) were studied (one dose per cohort) and infused daily for 5 days. The primary efficacy endpoint was distance walked during the 6-Minute Walk Test (6MWT) after 5 days of treatment.

Five days of daily IV elamipretide was well tolerated with no increase in adverse events (AEs) or laboratory abnormalities compared to placebo. The most common TEAE overall was headache in 6 (16.7%) subjects, followed by dizziness in 3 (8.3%) subjects. There were no treatment-related TEAEs that were severe in intensity. Adverse event severity and/or frequency did not increase with dose.

The primary efficacy measure of interest was the change from Baseline in distance walked (meters) on the 6MWT. In addition to the 6MWT, the efficacy of elamipretide was explored using Cardiopulmonary Exercise Testing (CPET) parameters, subject reported outcomes (Newcastle Mitochondrial Disease Adult Scale [NMDAS] and a Daily Symptom Questionnaire [DSQ]), and plasma and urinary biomarkers.

The highest dose of elamipretide, 0.25 mg/kg/hr, was associated with a 44.1-meter improvement in distance walked on the 6MWT over placebo (p=0.0528) at Day 5 (Table 1). Further, there was a significant linear dose response for the 6MWT at Day 5, showing increasing benefit as the dose of elamipretide increases (p=0.014). There were no meaningful changes observed for other exploratory efficacy measures.

Table 1: Summary of Change from Baseline on Days 5 and 7 in Distance Walked (meters) on 6MWT (Trial SPIMM-201)

	Elamipretide			Placebo (N = 9)
	0.01 mg/kg/hr (N = 9)	0.10 mg/kg/hr (N = 9)	0.25 mg/kg/hr (N = 9)	
Baseline Mean (SD)[2]	363.9 (143.15)	421.9 (66.85)	360.2 (100.99)	369.8 (96.82)
Change on Day 5[1] Mean (SD)	14.2 (49.40)	34.3 (43.46)	65.4 (45.71)	20.9 (45.18)
LS Mean	13.5	36.5	64.5	20.4
LSM Diff[2] (90% CI)[3]	-7.0 (-44.1, 30.1)	16.1 (-21.6, 53.8)	44.1 (7.0, 81.2)	
p-value[3]	0.7523	0.4746	0.0528	
Change on Day 7[1] Mean (SD)	31.8 (41.10)	35.1 (56.56)	63.6 (63.30)	39.4 (60.74)
LS Mean	30.3	39.5	61.7	38.5
LSM Diff[2] (90% CI)[3]	-8.3 (-53.0, 36.5)	1.0 (-44.5, 46.4)	23.1 (-21.6, 67.9)	
p-value[3]	0.7561	0.9718	0.3872	

Abbreviations: 6MWT = 6-Minute Walk Test; CI = Confidence interval; LS = Least squares; LSM Diff = Least Squares Mean Difference; SD = Standard deviation.

1. Change from Baseline = value at Visit – value at Baseline Visit.
2. LSM Difference is elamipretide dose (0.01, 0.10, or 0.25 mg/kg/hr) minus placebo.
3. P-value and 90% CI of the difference are based on the ANCOVA model which included treatment as a factor and Baseline measure as a covariate.

4.3.1.2. SPIMM-202

SPIMM-202 was a phase 2, randomized, double-blind, placebo-controlled, multi-center two-period crossover trial which enrolled 30 of the 36 subjects who completed participation in the SPIMM-201 trial. Subjects were randomized (1:1) to one of two treatment sequences:

- Sequence 1: Period 1, 4 weeks of treatment with 40 mg subcutaneous (SC) elamipretide administered once daily, followed by a 4-week washout, and then, in Period 2, 4 weeks of treatment with SC placebo administered once daily.
- Sequence 2: Period 1, 4 weeks of treatment with SC placebo administered once daily, followed by a 4-week washout, and then, in Period 2, 4 weeks of treatment with 40 mg SC elamipretide administered once daily.

The primary objective of the trial was to evaluate the effect of 4 weeks of SC elamipretide administered once daily on the distance walked during the 6MWT. Secondary objectives were to evaluate the safety and tolerability (AEs, vital signs, ECGs, clinical laboratory evaluations) as well as additional efficacy assessments (described below) of 4 weeks of elamipretide administration.

Table 2 demonstrates that treatment with elamipretide 40 mg resulted in a 19.8-meter improvement in the 6MWT distance over treatment with placebo (p=0.0833).

Table 2: Summary of Change from Baseline to Day 28 in Distance Walked (meters) on 6MWT (Trial SPIMM-202)

Visit	Elamipretide 40 mg (n=29)	Placebo (n=30)
End of Treatment		
Mean (SD)	394.1 (134.16)	378.2 (125.10)
LS Mean	398.3 (LSM)	378.5 (LSM)
LSM Diff[1] (95% CI)	19.8 (-2.8, 42.5)	
p-value[2]	0.0833	

Abbreviations: 6MWT = 6-Minute Walk Test; CI = Confidence interval; LS = Least squares; LSM Diff = Least Squares Mean Difference; SD = Standard deviation.

1. LSM Difference is elamipretide minus placebo.
2. p-value and 95% CI of the difference are based on the mixed model which includes treatment, sequence and period as mixed effects and subjects nested within sequence as a random effect.

A pre-specified subgroup analysis revealed that subjects walking less than 450 meters (n=22) (more impaired) at baseline improved more on elamipretide (24.3 meters compared to placebo) than subjects walking more than 450 meters (n=8) (less impaired) at baseline (8.6 meters compared to placebo), a finding consistent with results from a post-hoc analysis of the SPIMM-201 trial.

The Primary Mitochondrial Myopathy Disease Symptom Assessment (the PMMSA, formerly the Mitochondrial Disease Symptom Assessment), a novel, daily patient-reported outcome (PRO) measure developed and validated by Stealth BT in accordance with FDA standards to assess key symptoms of PMM, was utilized to better understand the patients' perspective and disease experience during the trial. The PMMSA assesses 10 symptoms experienced by patients with PMM on a 4-point scale. Stealth BT analyzed the results using pre-specified fatigue subscales focusing on the myopathic symptoms most commonly associated with PMM, namely, tiredness at rest, tiredness during activities, muscle weakness at rest, and muscle weakness during activities (Total Fatigue Score) as well as tiredness during activities and muscle weakness during activities (Total Fatigue During Activities Score). The PMMSA Total Fatigue Score has been shown to be reliable and valid based on the meaningful correlations with the patient global assessment and physician global assessment as well as performance measures in both cross-sectional and longitudinal analyses. The score is also strongly associated with the Neuro-QoL Fatigue Short Form ($r=0.79$, $p<0.001$), which provides compelling evidence that it is measuring similar domains. Based on the anchor- and distribution-based responder definition analyses for the PMMSA Total Fatigue Score, an approximate 1.6-point change from baseline (approximately 14% on the scale) signifies a potentially clinically meaningful improvement.

While on elamipretide, subjects reported less Total Fatigue every week, culminating in a clinically meaningful 1.7-point reduction in symptom severity at the end of the treatment period compared to placebo (2.2 point [19%] reduction from baseline) ($p=0.0006$). Conversely, while on placebo, subject-reported Total Fatigue did not change by more than 0.1 points during the treatment period. Similarly, while on elamipretide, subjects reported less Total Fatigue During Activities every week, culminating in a 0.8-point reduction in symptom severity at the end of the treatment period ($p=0.0018$). Conversely, while on placebo, subject-reported Total Fatigue During Activities score did not change by more than 0.2 points during the treatment period.

Table 3 provides a summary of the change by trial week in the PMMSA fatigue scores.

Table 3: Summary of Change from Baseline by Week in PMMSA Fatigue Scores (Trial SPIMM-202)

Endpoint	Visit[1]	LSMean Elamipretide (n=30)	LSMean Placebo (n=30)	LSMean Difference (ELAM – Placebo) (95% CI)	p-value[2]
Total Fatigue	Pre-dose	11.3	11.2	0.1 (-0.9, 1.0)	0.8491
	Week 1	10.0	10.8	-0.8 (-1.4, -0.3)	0.0062
	Week 2	9.9	10.7	-0.9 (-1.6, -0.1)	0.0283
	Week 3	9.3	10.8	-1.4 (-2.3, -0.6)	0.0023
	Week 4	9.1	10.8	-1.7 (-2.6, -0.8)	0.0006
	Two Weeks Post-Treatment	10.4	10.9	-0.4 (-1.1, 0.3)	0.2247
Total Fatigue During Activities	Pre-dose	5.9	6.0	-0.1 (-0.6, 0.4)	0.6790
	Week 1	5.2	5.7	-0.4 (-0.7, -0.1)	0.0085
	Week 2	5.2	5.5	-0.4 (-0.8, 0.0)	0.0557
	Week 3	4.9	5.6	-0.7 (-1.2, -0.3)	0.0028
	Week 4	4.8	5.8	-0.8 (-1.2, -0.3)	0.0018
	Two Weeks Post-Treatment	5.4	5.7	-0.2 (-0.5, 0.1)	0.1013

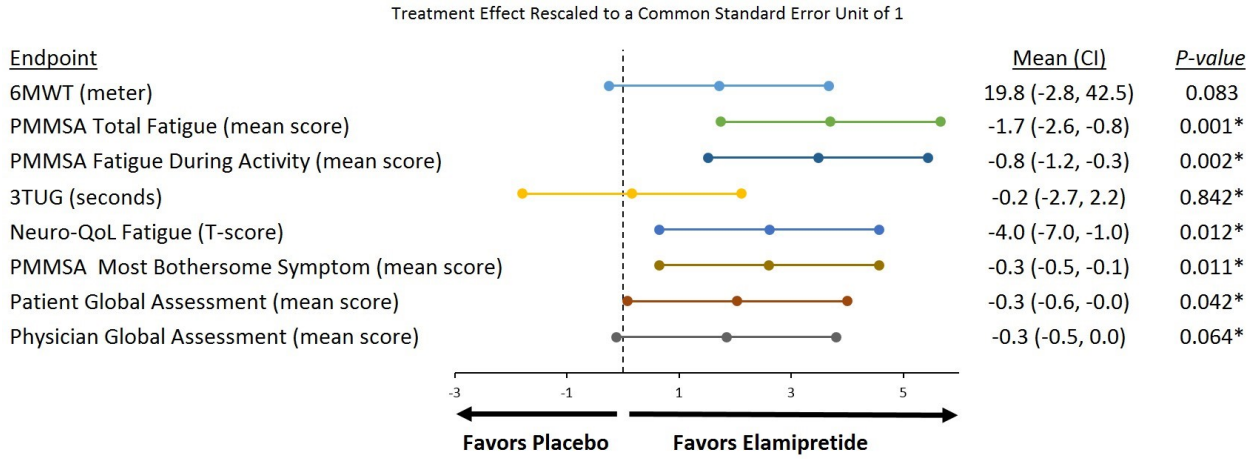
Abbreviations: 6MWT = 6-Minute Walk Test; CI = Confidence interval; LS = Least squares; LSM Diff = Least Squares Mean Difference; SD = Standard deviation.

1. Predose, Weeks 1, 2, 3, 4, and End of Treatment Period: for Period 1 and Period 2 based on the weekly average of the last 7 days of visit.
2. p-value and 95% CI of the difference are based on the mixed model which includes treatment, period, and sequence as fixed effects and subjects nested within sequence as a random effect. Weekly score calculated as the average of the daily scores over a week. If 4 or more daily scores are missing, the weekly score is set to missing.

Subjects also completed the Neuro-QoL Fatigue Short Form at baseline and at the end of each treatment period. The results suggested a reduction in reported fatigue and quality-of-life items during elamipretide treatment, with a 4-point T-score reduction relative to placebo (p=0.0115). In addition, the first time subjects completed the PMMSA, they were asked to identify which of the 10 items on the PMMSA was the “most bothersome” symptom of their disease. This individualized secondary endpoint compared the change in severity of the selected symptom when the subject was treated with elamipretide vs. placebo. In this individualized approach, all subjects had a “symptom change” endpoint, but the individual symptoms were different across subjects. By focusing on the most severe symptoms for each subject, there is inherent clinical relevance in the individualized symptom endpoint. The results demonstrated an improvement in the subjects' “most bothersome” symptom culminating in a 0.3-point difference between treatment intervals (p=0.0111).

Figure 3 below depicts the several efficacy variables in SPIMM-202.

Figure 3: SPIMM-202 Summary of Treatment Effect (Analysis Population – Intention-to-Treat [ITT]



*nominal *P-value*

4.3.2. Summary of Safety

4.3.2.1. 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 mouse, 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.

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 are 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 or embryo-fetal development. Similarly, elamipretide did not have any adverse effects on post-natal 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. In addition, in silico analysis for genotoxic structural alerts was conducted on new impurities introduced in the modified manufacturing process for elamipretide HCl. This analysis confirmed the absence of structural alerts for genotoxicity. When tested directly, both M1 and M2 were negative for gene mutation, for receptor binding, and rat mast cell degranulation. 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.

4.3.2.2. Clinical Trial Safety Findings

Parenteral administration of elamipretide was assessed following single and multiple IV and SC administrations. Dose levels studied ranged from approximately 0.7 mg/day to 300 mg/day. There were no apparent differences between the safety profiles of IV or SC elamipretide dosing routes except for injection site reactions which were widely reported in subjects receiving SC elamipretide.

Differences (≥ 2% difference) in systemic treatment-emergent adverse events (TEAEs) reported in elamipretide- and placebo-treated subjects, summarized by dosing duration is displayed in Table 4.

Table 4: Summary of Systemic TEAEs Reported in Greater Frequency (≥ 2% difference) in Elamipretide-treated Subjects Compared to Placebo-Treated Subjects

	Elamipretide	Placebo
Single Dose		
Headache	4.5%	2.3%
Repeat dose ≤ 8 days		
Dizziness	2.2%	0.0%
Repeat dose > 8 days (TEAEs > 5%)		
Increased eosinophils/eosinophilia	48.6%	0.0%
Upper respiratory tract infection	15.7%	0.0%
Increased blood immunoglobulin E	10.0%	0.0%
Dizziness	8.6%	1.4%
Headache	8.6%	2.9%
Urinary tract infection	7.1%	0.0%
Viral gastroenteritis	5.7%	0.0%

Analysis of eosinophils in longer-term dosing regimens was characterized by eosinophil counts above the upper limit of normal (nominally 0.4 $x10^9$/L), up to a maximum count of approximately 2.0 $x10^9$/L. There have been no clinical signs and symptoms associated with elevated eosinophils. Further, the increase in eosinophils was not related to changes in other white cells and total white cell counts have not significantly increased. No subject has been

withdrawn from treatment due to increased eosinophil counts. In general, the eosinophil counts appear to decrease to within normal limits with longer duration of elamipretide administration and return to pre-treatment levels after the end of elamipretide treatment. While TEAEs of respiratory tract and other infections have been reported at greater frequency than in placebo subjects, there is no evidence that these TEAEs are related to the increase in eosinophil counts. To further explore and characterize these findings of increased eosinophil counts, several studies have incorporated collection of Immunoglobulin E (IgE) values. Adverse events of blood Immunoglobulin E increased have been recorded, but no clear temporal relationship with an elevation in eosinophil counts has been established. Similar to the increase in eosinophils, there have been no clinical signs and symptoms associated with elevated IgE values.

In SPICP-103, high dose IV infusions (56 – 140 mg/day) of elamipretide were administered daily for five days in healthy subjects. Four subjects reported events of paraesthesia or oral paraesthesia. These events generally occurred immediately after the end of the drug infusion, at the T_{max} of elamipretide. Three of these AEs occurred in the 140-mg cohort, and 1 occurred in the 112-mg cohort and where C_{max} was approximately 4-fold higher than that expected with the 40-mg dose level selected for the Phase 3 clinical studies. All were reported to be mild in severity, resolved within 2 hours of symptom onset, and were not associated with hypersensitivity reactions.

Injection site reactions were reported in the majority of subjects (>90%) receiving elamipretide by SC injection in any study. Detailed characterization of the injection site reactions occurring in single dose SC clinical trials demonstrates that mild erythema, swelling and pruritus are the most commonly reported signs and symptoms and that pain and bruising may also be experienced. Generally, the injection site reactions resolved within 4 hours of elamipretide administration. In the longer-term studies reporting of injection site reaction commonly included the signs and symptoms previously mentioned as well as injection site induration, urticaria, haemorrhage and mass. In most subjects, the tolerability of the injection site reactions was not problematic and did not require treatment however, some subjects have been treated with topical and systemic antihistamines and/or topical corticosteroids in order to manage the impact of the signs and symptoms. In clinical trials > 8 days in duration, 4 subjects (5.7%) have discontinued study drug treatment due to injection site reactions and 2 additional subjects (2.9%) have had study drug interrupted due to injection site reaction.

All additional assessments of safety (including vital signs and laboratory, ECG and physical examination findings) across all clinical studies have been unremarkable.

In subjects with renal impairment who received elamipretide, exposure, as measured by AUC, to elamipretide and both of its metabolites (M1 and M2) 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 DDI studies carried out to date, co-administration of elamipretide with aspirin, with clopidogrel, or with UFH did not indicate a change in the nature, severity or frequency of AEs to the safety profile of either elamipretide or the comparator.

Across all studies, with either IV and SC formulation, there have been no reports of pregnancy, exposure during lactation, overdoses, or abuse or misuse.

4.3.2.2.1. Clinical Safety in Primary Mitochondrial Myopathy (PMM)

4.3.2.2.1.1. SPIMM-201

The SPIMM-201 trial was a phase 1/2 multi-center, randomized, double-blind, placebo-controlled, multiple ascending IV dose trial that enrolled subjects ≥16 and ≤65 years with PMM. Three escalating doses (0.01, 0.10, and 0.25 mg/kg/hour infused for 2 hours) were studied (one dose per cohort) and infused daily for 5 days. The trial enrolled three cohorts of 12 subjects. Within each cohort, 9 subjects were randomized to active drug and 3 subjects were randomized to placebo. Prior to each dose escalation, the safety and tolerability data from the previous cohort was reviewed. No dose-limiting safety concerns were identified and 36 subjects were enrolled.

Five days of daily IV elamipretide was well tolerated. Overall, at least one TEAE was reported by two-thirds of subjects. There were no deaths, serious AEs (SAEs), or TEAEs resulting in withdrawal in this trial. System Organ Classes (SOCs) with the most TEAEs were nervous system disorders (27.8%) and gastrointestinal disorders (16.7%). The most common TEAE overall was headache in 6 (16.7%) subjects, followed by dizziness in 3 subjects. There were no treatment-related TEAEs that were severe in intensity.

4.3.2.2.1.2. SPIMM-202

The SPIMM-202 trial was a randomized, double-blind, placebo-controlled, multi-center two period crossover trial which enrolled 30 of the 36 subjects who completed participation in the SPIMM-201 trial (all subjects residing in North America [35] were given the opportunity to participate). Subjects were randomized (1:1) to one of two sequence groups: 4 weeks of treatment with 40 mg SC elamipretide or placebo administered once daily in Treatment Period 1, followed by 4 weeks of treatment with the opposite treatment assignment once daily in Treatment Period 2, separated by 4-week washout period.

Twenty-eight days of daily SC elamipretide was generally well tolerated. Overall, at least one TEAE was reported by all (100%) subjects during elamipretide treatment and half (50%) of subjects while on placebo. Injection site reactions were experienced by 80.0% subjects during the elamipretide treatment period, frequently characterized by erythema (57%), pruritus (47%), pain (20%), urticaria (20%), and irritation (10%). There were no deaths or SAEs. One subject withdrew from the trial due to moderate injection site pain while on elamipretide treatment.

The only common systemic TEAE (>10%) reported during elamipretide treatment was dizziness (10%). Besides dizziness, all other TEAEs were reported with similar frequency and severity in subjects receiving elamipretide when compared to placebo.

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 (20.0%). These laboratory findings were neither reported to be associated with any clinical manifestations nor resulted in any reported TEAEs. In general, these elevations were demonstrated to have returned to within normal range or to baseline levels at the follow-up visit two weeks after the end of elamipretide treatment. There were no other identified safety concerns in this trial with respect to other clinical laboratory results, physical examinations, vital signs, ECG data or suicide assessments between the elamipretide and placebo treated periods.

4.4. Discussion of Trial Design and Control

SPIMM-301 is a randomized, double-blind, parallel-group, placebo-controlled assessment of efficacy and safety in subjects with PMM. Subjects will be randomized (1:1) to one of two groups: 24 weeks of single daily SC doses of 40 mg elamipretide administered with the elamipretide delivery system or 24 weeks of single daily SC doses of placebo. Blinded treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

PART 2 is an open-label, non-controlled treatment in which all subjects will receive elamipretide treatment for up to 144 weeks. This treatment period will allow for assessment of longer-term safety and tolerability in the target population, as well as allow for detection of less-frequent AEs/Adverse Device Effects (ADEs).

The Trial Schematics are presented in Appendix 3.

4.5. Rationale for Selection of Doses in the Trial

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. The clinical development objective of these studies was to determine the most appropriate dose and regimen for SPIMM-301. Using safety and efficacy outcomes from SPIMM-201 and SPIMM-202 to determine dose-response and chronic nonclinical exposure data to determine exposure margins, a dose of 40 mg of SC elamipretide administered daily was deduced to be the most appropriate dose to maximize desirable effects and minimize undesirable effects.

The SPIMM-201 trial (all subjects GFR > 60 mL/min) provided supporting information regarding safety and plasma exposure in the PMM population following repeat-dose administration of elamipretide at 0.01, 0.1, and 0.25 mg/kg/hr as a 2-hour IV infusion (Total Daily Dose [TDD] 0.02, 0.2, and 0.5 mg/kg) for 5 days. Elamipretide demonstrated an acceptable safety and tolerability profile. The highest dose of elamipretide, 0.25 mg/kg/hr. a TDD of 0.5 mg/kg/day, was associated with a 44.1-meter improvement in distance walked on the 6MWT over placebo (p=0.0528) at Day 5. Further, there was a significant linear dose response for the 6MWT at Day 5, showing increasing benefit as the dose of elamipretide increases (p=0.014). PK data from the SPIMM-201 trial in PMM subjects is presented in Table 5.

Table 5: 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 (Trial SPIMM-201)

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]	1992 [n=5]
			M1	183 [n=9]	1672 [n=5]
			M2	39.6 [n=9]	661 [n=8]

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]
0.25 mg/kg/hr given as a 2hr IV infusion	59.2	29.6	MTP-131	1050 [n=9]	4050 [n=7]
			M1	285 [n=9]	2190 [n=7]
			M2	68.8 [n=9]	1169 [n=8]

*Calculations based on nominal time points.

In normal renal function (GFR > 90 mL/min), the systemic exposure (in terms of mean $AUC_{0\text{-}\tau}$ 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.

Bioavailability for C_{max} and $AUC_{0\text{-last}}$ 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 6).

Table 6: Estimated Bioavailability of SC Administration (40 mg as a 1 mL injection) Versus Two Hour IV Infusion Following Repeat Administration of Elamipretide (MTP-131) (Trial SPIMM-201)

						PK Parameters following 40mg SC		**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	1418	5468	1,300	3,720	**92%**	**68%**
			M1	385	2957	436	3,100	**113%**	**105%**
			M2	92.9	1578	88.0	1,950	**95%**	**124%**

*Calculations based on nominal time points.

With a 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 be similar to exposure demonstrated in the 0.25 mg/kg/hr given as a 2hr IV infusion dose group in the SPIMM-201 trial in subjects weighing <80 kg therefore, it was hypothesized that treatment effect would not be altered by the change in dose route. This hypothesis was demonstrated in a further efficacy and safety trial in patients with PMM receiving 40 mg SC elamipretide (or placebo) once daily for 28 days (SPIMM-202).

In SPIMM-202, the primary efficacy results demonstrated that treatment with elamipretide 40 mg resulted in a 19.8-meter improvement in the 6MWT distance over treatment with placebo (p=0.0833). Additionally, besides injections site reactions (ISRs), the safety profile was comparable to placebo.

Chronic (26-weeks in rat, Study SPI-CIT-15-03; 39-weeks in dog, Study 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 (up to the maximum feasible dose due to local tolerability) and the predominant trial findings were related to local ISRs and tolerability. Safety margin calculations for both nonclinical species, compared to the 40 mg/day (1 mL) SC dose in man are provided in Table 7.

Table 7: Key Summary Steady-State PK Parameters Days 182 (Rat) and 273 (Dog) at the NOAEL/MFD with Safety Margins Versus. Human Exposure (SPISC-101, 40 mg/day) (Study SPI-CIT-15-03 and Study SPI-CIT-15-02)

					PK in Man Following 40mg SC		Safety Margin	
Trial / 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	6875	23,850	1,300	3,720	x5	x6
		M1	7385	43,000	436	3,100	x17	x14
		M2	260	2470	88.0	1,950	x3	x1.8
SPI-CIT-15-02 10 mg/kg/day	Dog	MTP-131	13050	21135	1,300	3,720	x10	x6
		M1	1709	5507	436	3,100	x4	x1.8
		M2	312	5093	88.0	1,950	x4	x3

The data displayed demonstrate that exposure to elamipretide, M1 and M2 in the chronic toxicity studies are supportive of chronic dosing at 40 mg/day by SC injection, in human, assuming an average body weight of approximately 75 kg and normal renal function (GFR > 90 mL/min).

To ensure inclusion of subjects representative of the PMM patient population, the impact of renal impairment on elamipretide, M1, and M2 was evaluated. Parent and metabolite exposure data from the chronic SC toxicity studies of elamipretide in rat and dog, extrapolated to predict exposure ($AUC_{0\text{-}24}$) in subjects with varying degrees of renal impairment following a SC dose of elamipretide at 40 mg/day, demonstrate that nonclinical exposure to M2 is adequate to support the chronic SC administration of elamipretide at 40 mg/day in subjects with GFR ≥ 30 mL/min. This assessment in based on metabolite exposure in one nonclinical species which is equal to, or greater than, the predicted exposure in subjects with reduced renal function.

The efficacy and safety data presented from subjects with PMM (SPIMM-201 and SPIMM-202) support 40 mg SC elamipretide as the appropriate dose to maximize the desirable effects without additional undesirable effects. The nonclinical exposure to metabolite M2 limits the study of higher doses of SC elamipretide, if we intend to be most inclusive of subjects (GFR ≥30 mL/min) with PMM.

5. TRIAL OBJECTIVES

This trial is designed with 2 parts, SPIMM-301 (PART 1) and SPIMM-301 OLE (PART 2). The objectives of each part are consistent with the trial design.

- PART 1 is a 24-week, randomized, double-blind, parallel-group, placebo-controlled assessment of the efficacy and safety of single daily SC doses of 40 mg elamipretide (vs placebo) administered with the elamipretide delivery system as a treatment for subjects with PMM.
- PART 2 is an up to 144-week, open-label assessment of the long-term safety and tolerability of single daily SC doses of 40 mg elamipretide administered with the elamipretide delivery system in subjects with PMM.

5.1. PART 1 Objectives

5.1.1. Primary Objective

The primary objective of PART 1 is to evaluate the effect of single daily SC doses of 40 mg elamipretide administered with the elamipretide delivery system for 24 weeks on the:

- Distance Walked on the 6MWT
- Total Fatigue on the Primary Mitochondrial Myopathy Symptom Assessment© (PMMSA)

5.1.2. Secondary Objectives

Secondary objectives of PART 1 are:

- To evaluate the effect of single daily SC doses of 40 mg elamipretide administered with the elamipretide delivery system for 24 weeks as measured by changes in the:
  - Fatigue During Activities on the PMMSA
  - Neuro-QoL Short Form Fatigue
  - Most bothersome symptom on the PMMSA
  - Neuro-QoL Fatigue activities of daily living (specific items from the Neuro-QoL Item Bank)
- To evaluate the safety and tolerability of single daily SC doses of 40 mg elamipretide administered with the elamipretide delivery system for 24 weeks.

5.1.3. Exploratory Objectives

Exploratory objectives of PART 1 are to evaluate the effect of single daily SC doses of 40 mg elamipretide administered with the elamipretide delivery system for 24 weeks as measured by changes in the:

- Individual symptoms on the PMMSA
- Alternate version of the PMMSA Total Fatigue Score

- Individual items on the Neuro-QoL Fatigue
- EQ-5D-5L
- Patient Global Impression (PGI) Scales
- Clinician Global Impression (CGI) Scales

5.1.4. Pharmacokinetics (PK)

- The PK of elamipretide

5.2. PART 2 Objective

The PART 2 objective is to assess the long-term safety and tolerability of single daily SC doses of 40 mg elamipretide administered with the elamipretide delivery system for up to 144 weeks.

6. INVESTIGATIONAL PLAN

6.1. SPIMM-301 Overall Trial Design

This randomized, double-blind, parallel-group, placebo-controlled trial will enroll approximately 202 subjects who have PMM. There are 2 parts to this trial.

- PART 1 is a 24-week, randomized, double-blind, parallel-group, placebo-controlled assessment of the efficacy and safety of single daily SC doses of 40 mg elamipretide (vs placebo) administered with the elamipretide delivery system as a treatment for subjects with PMM. Subjects will be randomized (in a ratio of 1:1) to one of two groups:
  - 24 weeks of single daily SC doses of 40 mg elamipretide or
  - 24 weeks of single daily SC doses of placebo.
- PART 2 is an up to 144-week, open-label assessment of the long-term safety and tolerability of single daily SC doses of 40 mg elamipretide administered with the elamipretide delivery system in subjects with PMM. Subjects who continue into PART 2 will receive treatment with 40 mg SC elamipretide administered with the elamipretide delivery system for up to 144 weeks. Thus, treatment during PART 2 will be as follows:
  - Subjects who are originally randomized to elamipretide during PART 1 (double-blind treatment) will continue receiving elamipretide during PART 2.
  - Subjects who are originally randomized to placebo during PART 1 (double-blind treatment) will switch to treatment with elamipretide during PART 2.

Note that the duration of PART 2 treatment for each subject will be the shortest of the following:

- 144 weeks
- Regulatory approval and commercial availability of the elamipretide delivery system in the subject's respective country
- Termination of the clinical development for elamipretide in subjects with PMM.

6.1.1. PART 1

6.1.1.1. PART 1 Screening Period

Screening will begin with the subject's signature of the informed consent form (ICF) and will last a minimum of 7 days to a maximum of 28 days. Subjects not previously enrolled in SPIMM-300, however, may have a longer screening period for review by the Adjudication Committee to determine their eligibility for study enrollment. Subjects will undergo Screening procedures as described in the PART 1 Schedule of Assessments (Appendix 1) and will be trained and instructed to complete the PMMSA daily during the Screening Period, in an electronic or paper diary, in order to characterize their baseline disease status and to assess compliance. Subjects who complete Screening and continue to meet all trial requirements, including all Inclusion Criteria and none of the Exclusion Criteria, may be randomized (stratified by the

subclassification of the genetic abnormality determined to be the primary cause of the subject's PMM [DiMauro 2003] as determined by the Adjudication Committee) and enter the Treatment Period.

6.1.1.2. PART 1 Treatment Period

The Treatment Period will begin on the day of the Baseline Visit, which is defined as Day 1, and lasts for 24 weeks. Subjects (and caregivers if needed) will be trained on the procedure for administration of the elamipretide delivery system (the investigational medicinal product [IMP] [elamipretide or placebo], the elamipretide pen injector, and needle), and recording of the location (injection in the abdomen, rotating around the four abdominal quadrants, or other appropriate location [after Investigator consultation with the Sponsor]) and time (at approximately the same time each day [e.g., early morning, noon, or early afternoon]) of the IMP administration daily in the electronic or paper diary. An elamipretide delivery system training kit and checklist will be provided to the clinical site to assist in training. At the Baseline Visit, following completion of all Baseline procedures described in the PART 1 Schedule of Assessments, subjects or trained caregivers will administer IMP at the clinical site. On non-visit days, subjects (or trained caregivers) will administer the IMP daily during the Treatment Period. The subject will return to the clinical site for the Week 4, Week 12, and Week 24 Visits for assessments, to administer the IMP (subject or trained caregiver), and to return all used IMP supplies. During the Treatment Period, subjects will continue to follow all trial requirements, including recording the location and time of the IMP administration daily and completing the PMMSA daily. The Treatment Period will conclude with a visit to the clinical site at the Week 24 Visit when subjects will return all trial-related supplies.

At the Week 24 Visit, if the subject confirms they are willing and able to continue to adhere to trial requirements and the Investigator determines the subject meets the Continuation Criteria the subject may continue into Part 2. If the subject continues into PART 2, the subject will continue (or start, for subjects treated with placebo in PART 1) elamipretide therapy the day of the Week 24 Visit (using the PART 2 supply of IMP) and continue trial activities as described in the PART 2 Schedule of Assessments (Appendix 2). Subjects who will not continue into PART 2 will not be administered IMP and will enter the PART 1 Follow-Up Period.

For all subjects, it is the intent that subjects who discontinue IMP (at any time) for any reason will continue to be followed for all protocol-planned trial visits through the completion of the PART 1 Treatment Period, and will have all endpoints (including efficacy) collected accordingly. In the interest of the subject, subjects who withdraw consent or are withdrawn from the trial by the investigator should be encouraged to complete an Early Discontinuation Visit as soon as possible and an effort should be made to complete and report the observations as thoroughly as possible up to the date of withdrawal.

6.1.1.3. PART 1 Follow-Up Period (for subjects not continuing into PART 2)

The PART 1 Follow-Up Period will begin after completion of the Week 24 Visit and will last for 4 weeks. Subjects will return to the clinical site for the PART 1 End-of-Trial Visit for final safety assessments, as described in the PART 1 Schedule of Assessments, and return all remaining trial-related supplies not previously returned.

6.1.2. PART 2

6.1.2.1. PART 2 Treatment Period

The Treatment Period will begin on the day of the PART 1 Week 24 Visit (at the administration of IMP) using the PART 2 supply of IMP. Subjects (or trained caregivers) will administer the IMP daily during the Treatment Period. The subject will return to the clinical site for the Week 28, Week 36, and Week 48 Visits for assessments, to administer the IMP (subject or trained caregiver), and to return all used IMP supplies. Additional visits will occur every 24 weeks for the remainder of the Treatment Period, with phone calls to the subject every 12 weeks between clinical site visits. During the Treatment Period, subjects will continue to follow all trial requirements.

In the interest of the subject, subjects who withdraw consent or are withdrawn from the trial by the investigator should be encouraged to complete an Early Discontinuation Visit as soon as possible and an effort should be made to complete and report the observations as thoroughly as possible up to the date of withdrawal.

6.1.2.2. PART 2 Follow-Up Period

The PART 2 Follow-Up Period will begin after completion of the Week 168 Visit and will last for 4 weeks. Subjects will continue to follow all trial requirements. Subjects will return to the clinical site for the PART 2 End-of-Trial Visit for final safety assessments, as described in the PART 2 Schedule of Assessments, and return all remaining trial-related supplies not previously returned.

6.2. Schedule of Visit Assessments

The Schedule of Assessments is described first for PART 1, which includes an up-to 4-week screening period, a 24-week double-blind treatment period, and a 4-week post-treatment follow-up period for subjects not continuing to PART 2. The Schedule of Assessments for PART 2 is then described, and includes an up-to 144 week PART 2 Treatment Period and a 4-week post-treatment follow-up period.

6.2.1. PART 1

Trial procedures and their timing are summarized in the PART 1 Schedule of Assessments (Appendix 1) and Trial Schematic (Appendix 3). All clinical site visits should occur at approximately (±2 hours) the same time during the day and subjects should have at least 1 hour of fasting (e.g., no large meals) prior to the 6MWT. Trial Days are relative to the Baseline Visit, and thus Day 1 is the first day of treatment with double-blind IMP, while Day -1 is the day immediately prior.

6.2.1.1. Screening Visit/Period: Day -28 to Day -1 (minimum of 7 days)

NOTE: The PMMSA at the Screening Visit should be the last trial assessment completed. The 6MWT at the Screening Visit should be completed prior to the PMMSA.

- Review and sign the Informed Consent Form (ICF).
- Record demographics (age, gender, ethnicity, race).

- Review all Inclusion and Exclusion Criteria.
- Record medical/surgical history and from subjects not previously enrolled in SPIMM-300, including previous genetic testing results (as described in Section 6.3.1). NOTE: genetic testing will not be provided as part of the SPIMM-301 trial.
- Record concomitant medication (including supplements and vitamins) (as described in Section 6.3.1).
- During the screening period, assess for any pre-treatment event and record as medical history or AE (as described in Sections 9.3).
- Complete a physical examination (as described in Section 6.3.2).
- Collect vital signs (as described in Section 6.3.4).
- Complete 12-lead resting ECG (as described in Section 6.3.5).
- Complete the Columbia Suicide Severity Rating Scale (C-SSRS) "Baseline/Screening" (as described in Section 6.3.3 and provided in Appendix 5).
- Draw blood and collect urine for clinical laboratory testing and urinalysis as outlined in Appendix 4 (and as described in Section 6.3.6).
- Complete serum pregnancy test (only for women of childbearing potential).
- Provide subject with the electronic or paper diary and train subject on the procedure to complete the PMMSA. Complete the PMMSA (as described in Section 6.3.8 and as outlined in Appendix 8) and collect results in the electronic or paper diary. The PMMSA should be completed daily during the Screening Period.
- Complete the Neuro-QoL Fatigue (as described in Section 6.3.9 and as provided in Appendix 9).
- Complete the EQ-5D-5L (as described in Section 6.3.10 and as provided in Appendix 10).
- Complete the Patient Global Impression (PGI) Scales (as described in Section 6.3.11 and as provided in Appendix 11).
- Complete the Clinician Global Impression (CGI) Scales (as described in Section 6.3.12 and as provided in Appendix 12).
- Conduct the 6MWT (as described in Section 6.3.13 and as outlined in Appendix 13).

6.2.1.2. Baseline Visit (Day 1)

NOTE: Subjects who have been deemed eligible during Screening Period will return for randomization and the following procedures will be performed. **The 6MWT must be completed after all other trial assessments.** On days of trial visits, the IMP should be administered at the clinic. At Baseline Visit, the IMP administration will occur after the completion of all Visit procedures.

- Review all Inclusion Criteria and Exclusion Criteria.

- Assess AEs/ADEs related to a trial procedure and/or meet seriousness criteria that occurred since the signing of the informed consent form as Section 9.9.2.
- Update medical/surgical history during the Screening Period (as described in Section 6.3.1).
- Update concomitant medication/procedures (including supplements and vitamins) during the Screening Period (as described in Section 6.3.1).
- Complete a physical examination (as described in Section 6.3.2).
- Collect vital signs (as described in Section 6.3.4).
- Complete 12-lead resting ECG (as described in Section 6.3.5).
- Complete the C-SSRS "Since Last Visit" (as described in Section 6.3.3 and provided in Appendix 6).
- Draw blood and collect urine for clinical laboratory testing and urinalysis as outlined in Appendix 4 (and as described in Section 6.3.6). An additional blood sample will be collected and stored for assessing the immunogenicity potential of the IMP.
- Complete urine pregnancy test (only for women of childbearing potential).
- Complete the PMMSA (as described in Section 6.3.8 and as outlined in Appendix 8) and collect results in the electronic or paper diary. The PMMSA should be completed daily during the Treatment Period.
- Complete the Neuro-QoL Fatigue (as described in Section 6.3.9 and as provided in Appendix 9).
- Complete the EQ-5D-5L (as described in Section 6.3.10 and as provided in Appendix 10).
- Complete the Patient Global Impression (PGI) Scales (as described in Section 6.3.11 and as provided in Appendix 11).
- Complete the Clinician Global Impression (CGI) Scales (as described in Section 6.3.12 and as provided in Appendix 12).
- Conduct the 6MWT (as described in Section 6.3.13 and as outlined in Appendix 13).

If the subject meets all SPIMM-301 eligibility criteria and has completed all baseline assessments, the subject may be randomized (as described in Section 8.5). Following randomization:

- Provide elamipretide delivery system supplies.
- Train subject (and caregivers if needed) on the procedure for administration of the elamipretide delivery system, and recording of the location (injection in the abdomen, rotating around the four abdominal quadrants, or other appropriate location [after Investigator consultation with the Sponsor]) and time (at approximately the same time each day [e.g., early morning, noon, or early afternoon]) of the IMP administration in the electronic or paper diary.

- Administer (by subject or trained caregiver) IMP with the elamipretide delivery system, recording the location, date, and time of the IMP administration in the electronic or paper diary.
- Assess for ISR 30 (±5) minutes after the IMP administration with the elamipretide delivery system (as described in Section 6.3.15).

6.2.1.3. Double-Blind Treatment Period

- Complete the PMMSA (as described in Section 6.3.8 and as outlined in Appendix 13) daily during Treatment Period.
- Subjects (or trained caregivers) will administer IMP with the elamipretide delivery system, recording the location, date, and time of the IMP administration in the electronic or paper diary.

6.2.1.4. Week 4 (Day 29 ±2), Week 12 (Day 85 ±4), and Week 24 (Day 169 +14 days) Visits

NOTE: The 6MWT must be completed after all other trial assessments. On days of trial visits, the IMP should be administered at the clinical site. At the Week 4, Week 12, and Week 24 Visits, the IMP administration should occur after all other trial procedures. At the Week 24 Visit, IMP administration will only occur if the subject is continuing to PART 2 of the SPIMM-301 trial.

- Collect all used IMP supplies (Week 4 and Week 12 Visits) and all trial-related supplies in addition to all elamipretide delivery system supplies (Week 24 Visit) and assess compliance.
- Provide new IMP supplies (Week 4 and Week 12). At the Week 24 Visit, if the subject is continuing to PART 2, provide new elamipretide delivery system supplies.
- Update concomitant medication/procedures (including supplements and vitamins) during the Treatment Period (as described in Section 6.3.1).
- Assess AEs/ADEs.
- Complete a physical examination (as described in Section 6.3.2).
- Collect vital signs (as described in Section 6.3.4).
- Complete 12-lead resting ECG (as described in Section 6.3.5).
- Complete the C-SSRS "Since Last Visit" (as described in Section 6.3.3 and provided in Appendix 6).
- Draw blood and collect urine for clinical laboratory testing and urinalysis as outlined in Appendix 4 (and as described in Section 6.3.6). At the Week 24 Visit, an additional blood sample will be collected and stored for assessing the immunogenicity potential of the IMP.
- Draw blood for PK testing as described in Section 6.3.14:
  - Week 4: 1 hour post dose (± 10 min)

  - Week 12: 30 min, 2 hours, and 4 hours post dose (± 10 min)
  - Week 24: pre-dose (-10 min)

- Complete the PMMSA (as described in Section 6.3.8 and as outlined in Appendix 8) and collect results in the electronic or paper diary. The PMMSA should be completed daily during the Treatment Period.
- Complete the Neuro-QoL Fatigue (as described in Section 6.3.9 and as provided in Appendix 9).
- Complete the EQ-5D-5L (as described in Section 6.3.10 and as provided in Appendix 10).
- Complete the Patient Global Impression (PGI) Scales (as described in Section 6.3.11 and as provided in Appendix 11).
- Complete the Clinician Global Impression (CGI) Scales (as described in Section 6.3.12 and as provided in Appendix 12).
- Conduct the 6MWT (as described in Section 6.3.13 and as outlined in Appendix 13).
- Administer (by subject or trained caregiver) IMP with the elamipretide delivery system, recording the location, date, and time of the IMP administration in the electronic or paper diary. This is not performed at Week 24 Visit unless the subject is continuing into PART 2. If the subject continues into PART 2, the subject will continue (or start, for subjects treated with placebo in PART 1) elamipretide therapy the day of the Week 24 Visit (using the PART 2 supply of IMP).

  Note: Administration of PART 2 IMP at the Week 24 Visit is the start of PART 2 Treatment Period.
- Assess for ISR 30 (±5) minutes after the IMP administration with the elamipretide delivery system (as described in Section 6.3.15). This is not performed at Week 24 Visit unless the subject is continuing into PART 2.
- 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 IMP (Week 24 Visit).
- Review all PART 2 Continuation Criteria (Week 24 Visit).
- Schedule next center visit:
  - Post-treatment follow-up visit for subjects not continuing into PART 2.
  - Week 28 visit for subjects continuing into PART 2.

6.2.1.5. PART 1 Post-Treatment Follow-Up Period (4 weeks [+7 days])

At the Week 24 Visit, the subject and the Investigator will determine whether the subject will continue into PART 2 (confirming the subject meeting the Continuation Criteria). Subjects who will not continue into PART 2 will complete the PART 1 Follow-Up Period and PART 1 End-of-Trial Visit.

For subjects not continuing into PART 2, the PART 1 Follow-Up Period will begin after completion of the Week 24 Visit and will last for 4 weeks. Subjects will return to the clinical site for the PART 1 End-of-Trial Visit for final safety assessments, as described in the PART 1 Schedule of Assessments, and return all remaining trial-related supplies not previously returned.

6.2.1.5.1. PART 1 End-of-Trial Visit (for subjects not continuing into PART 2) (Day 197 + 7 days)/Early Discontinuation Visit

- Collect all remaining trial-related supplies
- Document concomitant medication (including supplements and vitamins).
- Assess AEs/ADEs.
- Complete a physical examination (as described in Section 6.3.2).
- Collect vital signs (as described in Section 6.3.4).
- Complete 12-lead resting ECG (as described in Section 6.3.5).
- Complete the C-SSRS "Since Last Visit" (as described in Section 6.3.3 and provided in Appendix 6).
- Draw blood and collect urine for clinical laboratory testing and urinalysis as outlined in Appendix 4 (and as described in Section 6.3.6). At the Early Discontinuation Visit (if applicable), an additional blood sample will be collected and stored for assessing the immunogenicity potential of the IMP.
- Complete urine pregnancy test (only for women of childbearing potential).
- If applicable, collect all trial-related supplies not previously returned.
- If an Early Discontinuation Visit, 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 IMP.

6.2.2. PART 2

Trial procedures and their timing for PART 2 are summarized in the PART 2 Schedule of Assessments (Appendix 2) and Trial Schematic (Appendix 3). While there is no screening period for PART 2, subjects continuing into PART 2 must meet the PART 2 Continuation Criteria. Subjects who decide not to continue in the PART 2 at the PART 1 Week 24 Visit are not eligible to participate in PART 2.

Note: Administration of PART 2 IMP at the Week 24 Visit in PART 1 is the start of PART 2 Treatment Period.

During PART 2, an up-to 144-week Treatment Period is followed by a 4-week post-treatment Follow-Up Period and PART 2 End-of-Trial Visit that will close out each subject's participation in the trial. Trial weeks will be relative to the start of treatment in PART 1.

6.2.2.1. PART 2 Treatment Period

The treatment period during PART 2 will include both clinical site visits and phone calls from the site.

6.2.2.1.1. Clinical Site Visits: Week 28 (± 1 week), 36, 48, 72, 96, 120, 144, and 168 (± 2 weeks for each visit)

At all clinical site visits during the PART 2 Treatment Period visits, subjects will return used IMP supplies. At the Week 168 visit, subjects will return all trial-related supplies. On days of trial visits, the IMP should be administered with the elamipretide delivery system at the clinical site.

- Collect all used IMP supplies (all trial-related supplies at Week 168) and assess compliance. Collect the elamipretide pen injector at the Week 72 and 120 Visits.
- Provide new IMP supplies (except at the Week 168 visit) and a new elamipretide pen injector at the Week 72 and 120 Visits.
- Update concomitant medication/procedures (including supplements and vitamins) during the Treatment Period (as described in Section 6.3.1).
- Assess AEs/ADEs.
- Complete a physical examination (as described in Section 6.3.2).
- Collect vital signs (as described in Section 6.3.4).
- Complete 12-lead resting ECG (as described in Section 6.3.5).
- Complete the C-SSRS "Since Last Visit" (as described in Section 6.3.3 and provided in Appendix 6).
- Draw blood and collect urine for clinical laboratory testing and urinalysis as outlined in Appendix 4 (and as described in Section 6.3.6).
- Administer IMP with the elamipretide delivery system (except at the Week 168 Visit).
- Assess for ISR 30 (±5) minutes after the IMP administration with the elamipretide delivery system (as described in Section 6.3.15) (except at the Week 168 Visit).
- 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 IMP (Week 168 Visit).

6.2.2.1.2. Phone Calls: Weeks 60, 84, 108, 132, 156 (± 2 weeks for each)

A phone call from the site will be made to the subject to assess AEs/ADEs and concomitant medications (see Appendix 7 for a sample of the telephone script to use).

6.2.2.2. PART 2 Post-Treatment Follow-Up Period (4 weeks [+7 days])

The PART 2 Follow-Up Period will begin after completion of the Week 168 Visit and will last for 4 weeks. Subjects will continue to follow all trial requirements. Subjects will return to the

clinical site for the PART 2 End-of-Trial Visit for final safety assessments, as described in the PART 2 Schedule of Assessments, and return all remaining trial-related supplies not previously returned.

6.2.2.2.1. PART 2 End-of-Trial Visit (Week 172 + 7 days)/Early Discontinuation Visit

- Document concomitant medication (including supplements and vitamins).
- Assess AEs/ADEs.
- Complete a physical examination (as described in Section 6.3.2).
- Collect vital signs (as described in Section 6.3.4).
- Complete 12-lead resting ECG (as described in Section 6.3.5).
- Complete the C-SSRS "Since Last Visit" (as described in Section 6.3.3 and provided in Appendix 6).
- Draw blood and collect urine for clinical laboratory testing and urinalysis as outlined in Appendix 4 (as described in Section 6.3.6). At the Early Discontinuation Visit (if applicable), an additional blood sample will be collected and stored for assessing the immunogenicity potential of the IMP.
- Complete urine pregnancy test (only for women of childbearing potential).
- If applicable, collect all trial-related supplies not previously returned.
- If an Early Discontinuation Visit, 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 IMP.

6.3. Description of Trial Procedures

The following sections describe trial procedures occurring during the trial. Trial procedures and their timing are summarized in the Schedules of Assessments (for PART 1, Appendix 1, and for PART 2, Appendix 2).

6.3.1. Medical/Surgical History and Concomitant Medications/Procedures

Medical history and any concomitant medications will be recorded during the Screening Visit. At the Baseline Visit, a review of any additional medical history and/or new concomitant medication/procedures that occurred during the Screening Period will be completed. Concomitant medications/procedures should be updated and recorded at each clinical site visit. Subjects not previously enrolled in SPIMM-300 must have previous genetic testing information available, which will be reviewed by an Adjudication Committee, to determine eligibility for study enrollment. NOTE: genetic testing will not be provided as part of the SPIMM-301 trial.

6.3.2. Physical Examination

During all clinical site visits, a complete physical examination will be performed. The physical examination 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, nervous system, and weight. Height will only be measured at the Screening Visit.

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

At the Screening Visit, the C-SSRS "Baseline/Screening" will be completed and recorded. The C-SSRS "Baseline/Screening" is included in Appendix 5. At all other clinical site visits, the C-SSRS "Since Last Visit" will be recorded. The C-SSRS "Since Last Visit" is included in Appendix 6. Subjects who score positive on any C-SSRS will have appropriate referrals made either for a mental health evaluation or to the emergency room if necessary, in the opinion of the Investigator.

6.3.4. Vital Signs

During all clinical site 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 of rest.

6.3.5. Electrocardiograms (ECGs)

A 12-lead ECG will be obtained after the subject has rested quietly for 5 minutes in the supine position at all clinical site 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. The QT interval will be corrected programmatically in the clinical database.

6.3.6. Clinical Laboratory Testing

Sample collection, processing, and handling details are provided in the Laboratory Manual. Blood and urine will be drawn and collected at clinical site visits. Analysis will include testing for parameters included in Appendix 4. Additional blood samples at the Baseline, Week 24 Visit, and Early Discontinuation Visit (if applicable) will be collected and stored for assessing the immunogenicity potential of the IMP.

6.3.7. Pregnancy Tests

Women of child-bearing potential will have a serum pregnancy test performed at the Screening Visit. Women of child-bearing potential will have a urine pregnancy test at the Baseline Visit and the results of the Baseline Visit pre-dose pregnancy test must be evaluated before randomization to ensure eligibility. A urine pregnancy test will also be performed for women of childbearing potential at the PART 1 or PART 2 End-of-Trial or Early Discontinuation Visit.

6.3.8. Primary Mitochondrial Myopathy Symptom Assessment (PMMSA)

The Primary Mitochondrial Myopathy Symptom Assessment© (PMMSA) [2018] Stealth BioTherapeutics Inc. is a novel, daily patient-reported outcome measure, used to better understand the subject's perspective and disease experience during the trial. The PMMSA assesses 10 symptoms experienced by subjects with PMM, each on a 4-point scale. The Total Fatigue score comprises a subset of symptoms (including tiredness and muscle weakness). Each question in the PMMSA has 4 response options: 1=Not at all, 2=Mild, 3=Moderate, and 4=Severe. A daily total score will be calculated based on the daily average score of the questions

answered multiplied by the number of questions for the Total Fatigue score. PMMSA data for a minimum of 4 of the 7 days before Baseline and before each visit are necessary to calculate the PMMSA Total Fatigue Score.

During PART 1, starting at the Screening Visit, subjects will be instructed to complete the PMMSA daily during the Screening and Treatment Periods. At the Screening Visit, subjects will be provided with the electronic or paper diary and trained on the procedure to complete the PMMSA daily in the diary. At the Screening Visit, subjects will also identify which of the symptoms on the PMMSA is their most bothersome symptom of their PMM. The PMMSA is in Appendix 8.

6.3.9. The Neuro-QoL Fatigue

At all clinical site visits, subjects will be instructed to complete the Neuro-QoL Fatigue. The Neuro-QoL Fatigue is in Appendix 9.

6.3.10. EQ-5D-5L

At all clinical site visits, subjects will be instructed to complete the EQ-5D-5L. The EQ-5D-5L questionnaire is in Appendix 10.

6.3.11. Patient Global Impression (PGI) Scales

The PGI Scales will be completed to assess their overall assessment of their symptoms related to their diagnosis of PMM. The PGI Scales are provided in Appendix 11.

6.3.12. Clinician Global Impression (CGI) Scales

The Investigator (or designee) will provide an overall assessment of the subject's symptoms related to their diagnosis of PMM at all clinical site visits. The CGI Scales are provided in Appendix 12.

6.3.13. 6-Minute Walk Test (6MWT)

At all clinical site visits, the distance walked (in meters) during the 6MWT will be recorded. The 6MWT instructions are provided in Appendix 13.

Sites will be trained by CPC Clinical Research on the conduct of the 6MWT. CPC Clinical Research will develop trial specific material, train clinical sites, and ensure consistency and accuracy of conduct and data from the 6MWT across multiple sites. In order to obtain evaluable data on the 6MWT, the conduct of the 6MWT must be standardized across all participating sites. CPC Clinical Research will conduct a Site Endpoint Evaluation Visit (SEEV) which will include:

- Training each individual expected to conduct the 6MWT during the trial. Training will include education on the 6MWT, passing a brief quiz, and performing a mock test with the SEEV specialist. This must occur before conducting the test with trial subjects.
- Evaluating the physical location of the 6MWT course to ensure it meets standard criteria.
- Review of trial specific source documentation.
- Answering any questions regarding the conduct of the 6MWT.

The purpose of the SEEV is to ensure standards by which the 6MWT is performed do not differ from person to person within a site as well as helping to create consistency across this multicenter trial.

Additionally, the 6MWT should be administered by a clinical site staff member trained on the conduct of the 6MWT and not involved in other aspects of the study.

6.3.14. Pharmacokinetic (PK) Sampling

To characterize the PK of elamipretide, PK sampling will be conducted at defined time points. PK sampling will identify and characterize the influence of demographic factors (e.g., age, gender, race), health status, drug-drug interaction and other covariates on the PK of elamipretide. The PK sampling schedule is as follows:

- Week 4: 1 hour post dose (± 10 min)
- Week 12: 30 min, 2 hours, and 4 hours post dose (± 10 min)
- Week 24: pre-dose (-10 min)

6.3.15. 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 during the Treatment Period in PART 1 (Baseline, Week 4, Week 12, and Week 24 Visits) and PART 2 (Week 28, Week 36, Week 48, Week 72, Week 96, Week 120, Week 144, Week 168). The skin examination should occur at 30 (±5) minutes after the IMP 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 Appendix 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 9.9.1.4. Any ISR that meets any of the criteria of a SAE/serious adverse device effect (SADE) (Section 9.8) should be reported within 24 hours of the clinical site first becoming aware of the event (as outlined in Section 9.10).

7. SELECTION AND WITHDRAWAL OF SUBJECTS

The inclusion and exclusion criteria for participation in PART 1 and PART 2 are provided below. All screening assessments must be completed during the SPIMM-301 Screening Period, but may be performed on different days. Screening assessments should not be repeated, and subjects cannot be re-screened without the Sponsor's approval. If a subject is re-screened, they will maintain their original screening number. Subjects may only be enrolled into the trial one time.

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

While there is no screening period for PART 2, subjects continuing into PART 2 must meet the PART 2 Continuation Criteria. Subjects who decide not to continue in the PART 2 at the PART 1 Week 24 Visit are not eligible to participate in PART 2.

7.1. SPIMM-301 Eligibility

7.1.1. Subject Inclusion Criteria

A subject must meet all of the following Inclusion Criteria at the Baseline Visit to be eligible for inclusion in the SPIMM-301 trial:

1. Willing and able to provide a signed informed consent form (ICF) prior to participation in any trial-related procedures.
2. Agrees and is able to adhere to the trial requirements for the length of the trial, including the use of the elamipretide delivery system.
3. Subject is ≥16 and ≤80 years of age. In Germany, subjects must be ≥18 years of age.
4. Enrolled (signed ICF) in SPIMM-300 or have prior approval from the Sponsor to enroll without SPIMM-300 participation.
5. Diagnosed with PMM in the opinion of the Investigator, consisting of:
    a. Molecular genetic abnormality of the mitochondrial respiratory chain, and
    b. Subject reported symptoms (i.e., exercise intolerance, fatigue, muscle weakness) or physical examination findings of myopathy that are the predominant symptoms of the subject's mitochondrial respiratory chain disorder.
6. The subject's molecular genetic abnormality is consistent with PMM as confirmed by the Adjudication Committee.
7. Women of childbearing potential must agree to use 1 of the following methods of birth control from the date they sign the ICF until 28 days after the last dose of IMP:
    a. Abstinence, when it is in line with the preferred and usual lifestyle of the subject. Subject agrees to use a highly effective method of contraception should they become sexually active.

b. Relationships with male partners who have been surgically sterilized by vasectomy (the vasectomy procedure must have been conducted at least 60 days prior to the Screening Visit).

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).

8. Male subjects with female partners of child-bearing potential must be willing to use a highly effective method of contraception from the date they sign the ICF until 28 days after the last dose of IMP.

7.1.2. SPIMM-301 Exclusion Criteria

A subject CANNOT meet any of the following Exclusion Criteria at the SPIMM-301 Baseline Visit to be eligible for inclusion in the trial:

1. Subject has myopathic signs and/or symptoms due to a neuropathic process (i.e. cerebellar dysfunctions and peripheral neuropathies) or a gait problem that would interfere with the 6MWT, in the opinion of the Investigator.
2. Female subjects who are pregnant, planning to become pregnant, or breastfeeding/lactating.
3. Walks < 100 meters or > 450 meters during the 6MWT at either the Screening Visit OR Baseline Visit.
4. At the Baseline Visit, the estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2, using the Screening Visit value with the Modification of Diet in Renal Disease (MDRD) Study equation.
5. Subject has undergone an in-patient hospitalization within the 30 days prior to the Baseline Visit or has a planned hospitalization or a surgical procedure during the trial.
6. Subject has clinically significant respiratory disease and/or cardiac disease (medical history or current clinical findings), in the opinion of the Investigator, or prior interventional cardiac procedure (e.g., cardiac catheterization, angioplasty/percutaneous coronary intervention, balloon valvuloplasty, etc.) within 3 months of the Baseline Visit.
7. Subject has a pacemaker, implantable cardioverter-defibrillator, or cardiac resynchronization therapy device OR QTc elongation (using the correction factor utilized at the clinical site) defined as a QTc >450 msec in male subjects and >480 msec in female subjects.

   Note: At the initial electrocardiogram (ECG), if QTc exceeds these parameters, the ECG may be repeated 2 more times (during the same visit), and the average of the 3 QTc values used to determine the subject's eligibility.

8. ECG evidence of acute ischemia, atrial fibrillation, or active conduction system abnormalities with the exception of any of the following:
    a. First degree AV-block
    b. Second degree AV-block Type 1 (Mobitz Type 1 / Wenckebach type)
    c. Right bundle branch block
9. Subject has severe vision impairment that, in the opinion of the Investigator, may interfere with their ability to complete all trial requirements
10. Subject has a seizure disorder that, in the opinion of the Investigator, may interfere with their ability to complete all trial requirements.
11. Active malignancy or any other cancer from which the subject has been disease-free for < 2 years.
12. Subject has a solid organ transplant and/or is currently receiving treatment with therapy for immunosuppression, in the opinion of the Investigator.
13. Subject has been previously diagnosed with human immunodeficiency virus (HIV), hepatitis B, or hepatitis C infection.
14. Subject has a history of a systemic eosinophilic illness and/or an eosinophil count >1,000 cells $x10^6$/L at the Screening Visit.
15. Subject is currently participating or has participated in an interventional clinical trial (i.e., investigational product or device, stem cell therapy, gene therapy) within 30 days of the Baseline Visit; or is currently enrolled in a non-interventional clinical trial (except for SPIMM-300) at the Baseline Visit which, in the opinion of the Investigator, may be potentially confounding to the results of the current trial (e.g. exercise therapy trial).
16. Subject has previously received elamipretide (MTP-131), for any reason.
17. Subject has a history of active substance abuse during the year before the Baseline Visit, in the opinion of the Investigator.
18. 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.

7.2. PART 2 Eligibility

7.2.1. PART 2 Subject Continuation Criteria

A subject must meet all of the following PART 2 Continuation Criteria at the Week 24 Visit in PART 1 to be eligible for PART 2:

1. Subjects must continue to be able and willing to adhere to the trial requirements.
2. Subject is appropriate to continue in PART 2 (i.e. subject was compliant in SPIMM-301), in the opinion of the Investigator.
3. Subject has not had a serious adverse event (SAE)/serious adverse device effect (SADE) attributed to the elamipretide delivery system.

4. Subject has not permanently discontinued the elamipretide delivery system.

7.3. Prohibited Medications

The use of any other investigational drug except elamipretide 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 attempts should be made to keep all medications, including over-the-counter treatments, vitamins, or supplements constant during the SPIMM-301 trial and to not initiate new therapy during the trial, unless in response to an AE. All concomitant medications will be recorded in the source data and the Electronic Case Report Form (eCRF). Changes in dosages of current medications (including over-the-counter vitamins or supplements) during the conduct of the trial will be discouraged, unless required to treat an AE/ADE.

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

7.4. Criteria for Subject or Trial Discontinuation

7.4.1. Discontinuation of Subjects

Subjects may be discontinued from the trial for the following reasons:

- Investigator Decision
  - The Investigator decides that the subject should be discontinued from the trial for any reason (e.g., the eGFR is <30 mL/min/1.73 m^2, using the MDRD study equation).
- Subject Decision
  - The subject or the subject's designee, (e.g., parents or legal guardian), requests to be withdrawn from the trial.
  - Subjects who withdraw should be explicitly asked about the contribution of possible AEs/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 clinical site 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 trial or stops the subject's participation in the trial for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP guidelines.

- Adverse Event (AE)/ADE
  - If the Investigator decides that the subject should be withdrawn because of an AE/ADE or a clinically significant laboratory value, the investigational product is to be discontinued and appropriate measures are to be taken. The Sponsor or its designee is to be alerted immediately.

For all subjects, it is the intent that subjects who discontinue IMP (at any time) for any reason will continue to be followed for all protocol-planned trial visits through the completion of the PART 1 Treatment Period, and will have all endpoints (including efficacy) collected accordingly. In the interest of the subject, subjects who withdraw consent or are withdrawn from the trial by the investigator should be encouraged to complete an Early Discontinuation Visit as soon as possible and an effort should be made to complete and report the observations as thoroughly as possible up to the date of withdrawal.

7.4.2. Discontinuation of Clinical Site Participation

A clinical site participation may be discontinued if the Sponsor or its designee, the Investigator, the Regulatory Authority, or the Ethics Committee (EC) judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP guidelines.

7.4.3. Discontinuation of the Trial

The trial may 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. INVESTIGATIONAL MEDICINAL PRODUCT MATERIALS AND MANAGEMENT

8.1. Treatments Administered

PART 1 is a 24-week, randomized, double-blind, parallel-group, placebo-controlled trial will enroll approximately 202 subjects who have PMM. Subjects will be randomized (1:1) to one of two groups: 24 weeks of single daily SC doses of 40 mg elamipretide administered with the elamipretide delivery system or 24 weeks of single daily SC doses of placebo.

PART 2 is an up to 144-week, open-label assessment of the long-term safety and tolerability of single daily SC doses of 40 mg elamipretide administered with the elamipretide delivery system in subjects with PMM. Subjects who continue into PART 2 will receive treatment with 40 mg SC elamipretide for up to 144 weeks.

Elamipretide injection and placebo will be supplied as a labeled sterile 3.0 mL 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 2.5 mL of sterile elamipretide solution for 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. The placebo solution is composed of sodium chloride, sodium phosphate buffer, and benzyl alcohol.

8.1.1. Elamipretide Pen Injector

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

The elamipretide pen injector has a common classification of Piston Syringe Class II in accordance with 21 CFR 880.5860 and a classification of IIa in accordance with Medical Device Directive 93/42/EEC Annex IX. The elamipretide delivery system is designated system A in accordance with ISO 11608-1:2014.

In accordance with MDD 93/42/EEC, Annex IX, Classification Criteria, I. Definitions, the elamipretide pen injector is transient (normally intended for continuous use for less than 60 minutes) and surgically invasive device (penetration other than through an established body orifice), sections 1.1 and 1.2, respectively. In accordance with Annex IX, Section III Classification, Rule 6, the elamipretide pen injector is Class IIa, “all surgically invasive devices for transient use are in Class IIa”. Further to Rule 6, the elamipretide pen injector is intended to administer medicines by means of a delivery system, but **not** done in a manner that is potentially hazardous taking account the mode of application. This classification is further supported by the fact that the device (elamipretide pen injector) is intended to administer a daily fixed dose of medicine where the dosage level and nature of the medicinal product is not critical, i.e., elamipretide has demonstrated an acceptable safety profile at the proposed fixed daily clinical dose.

In Canada, the reusable elamipretide pen injector is considered a surgically invasive device classified as Class II by rule 1(1) of the Medical Device Regulations (SOR/98-282) Rule 1 states:

Rule 1:

1. Subject to sub-rules (2) and (3), all surgically invasive devices are classified as Class II.
2. A surgically invasive device that is intended to diagnose, monitor, control or correct a defect of the central cardiovascular system or the central nervous system or of a fetus in utero is classified as Class IV.

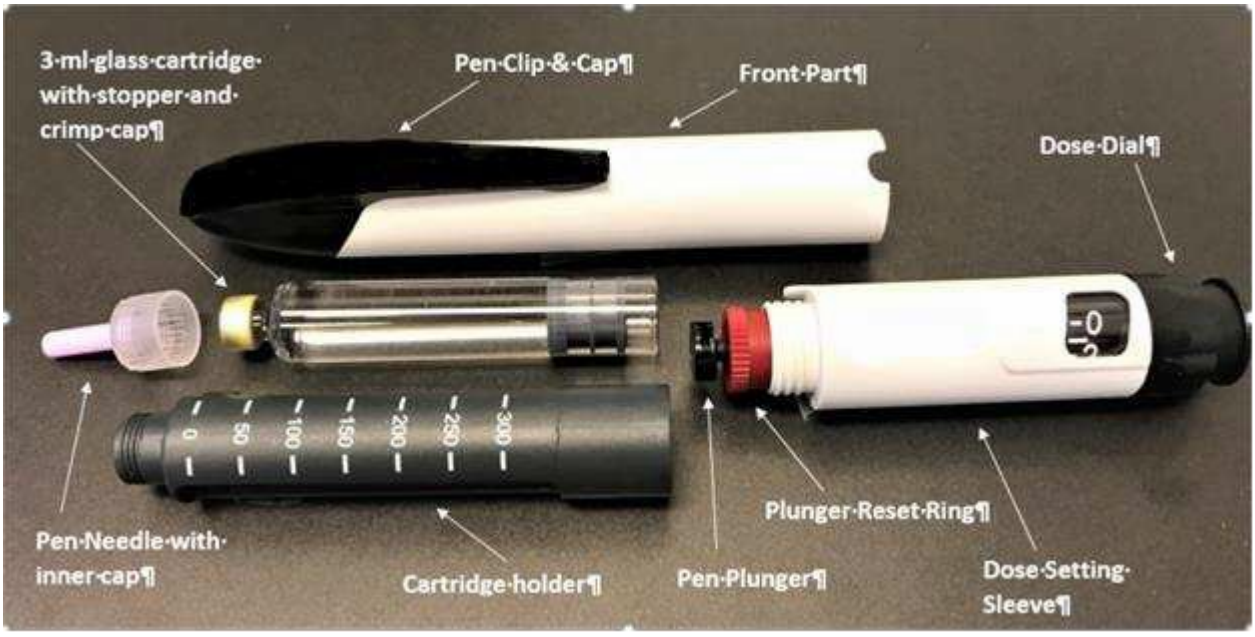
A surgically invasive device that is intended to be absorbed by the body, or that is normally intended to remain in the body for at least 30 consecutive days, is classified as Class III.

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 IMP cartridge and the pen needle constitutes the elamipretide delivery system which will be used in SPIMM-301. The elamipretide delivery system is for personal use (single subject) for SC administration of a fixed dose (0.5 mL) of elamipretide injection or placebo. The needle provided should be used. The elamipretide delivery system is operated mechanically and contains no electronics. The elamipretide delivery system is depicted in Figure 4. The user will assemble and use the elamipretide delivery system per the IFU that will be provided to each subject.

Figure 4: 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 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 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 the IMP 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 the IMP 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 IMP, independent from the location of the concomitant therapy injections, should be used. At the Baseline Visit, the IMP will be administered with the elamipretide delivery system after completion of all baseline procedures (Section 6.2.1.2).

8.2. Materials and Supplies

The placebo and elamipretide multidose glass cartridge and delivery system will be dispensed and stored according to the Pharmacy Manual. The placebo and elamipretide multidose glass cartridges are to be stored refrigerated at 2 to 8°C (36 to 46°F) in a secure area. 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 multi-use cartridge, while in use in the elamipretide delivery system, may 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 may be stored at room temperature.

Additional information will be provided in the Pharmacy Manual. An Instructions for Use (IFU) pamphlet will be provided to assist in training.

8.3. Investigational Medicinal Product Accountability

IMP will be assigned for both PART 1 and PART 2 through an Interactive Web Response System (IWRS). All drug accountability records must be kept current, and the Investigator must be able to account for all used and unused elamipretide delivery system supplies. These records should contain the dates, quantity, and elamipretide delivery system:

- Received at clinic
- Administered to each subject
- Dispensed to each subject

- Returned from each subject
- Disposed of at the clinical site or returned to the Sponsor or designee

The clinical monitor responsible for the clinical site will provide written approval for the destruction or return of used and unused elamipretide delivery system supplies following reconciliation of all clinical supplies.

8.4. Treatment Compliance

During the treatment period, IMP will be administered with the elamipretide delivery system daily by a trained caregiver, or self-administration. A diary will be used to document administration.

8.5. Randomization

The randomization for PART 1 will be based on a 1:1 ratio of elamipretide to matching placebo. The randomization will be centrally administered through an IWRS. Subjects will be stratified by the subclassification of the mutation determined to be the primary cause of the subject's PMM (DiMauro 2003) as determined by the Adjudication Committee:

- Disorders involving mtDNA mutations that impair mitochondrial protein synthesis in toto
- Disorders involving mtDNA mutations that affect the subunits of the respiratory chain
- Disorders involving nDNA mutations in genes encoding subunits or ancillary proteins of the respiratory chain
- Disorders involving nDNA mutations causing defects of intergenomic signaling
- Disorders involving nDNA mutations causing defects of mitochondrial protein importation
- Disorders involving nDNA mutations causing alterations of the lipid milieu of the inner mitochondrial membrane
- Disorders involving nDNA mutations causing alterations of mitochondrial motility or fission

There is no randomization for PART 2.

8.6. Blinding and Unblinding Procedures

Trial personnel and subjects will be blinded to treatment in PART 1 until the PART 1 database is locked.

The Investigator will contact the Sponsor prior to unblinding any subject's treatment sequence unless in the instance of a medical emergency.

In case of an immediate medical emergency or if directed by the Sponsor, and only if the information is required by the Investigator to manage a subject's AE, is a subject's treatment assignment to be unblinded prematurely. In cases of medical emergency, the Investigator may

unblind a subject's treatment assignment using the computerized system according to the instructions received. The Sponsor must be notified as soon as possible regarding the reason for unblinding.

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

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

9. EFFICACY AND SAFETY EVALUATIONS AND APPROPRIATENESS OF MEASUREMENTS

9.1. Efficacy Endpoints

Efficacy will only be assessed for PART 1.

9.1.1. Primary Endpoints

The primary endpoints are:

- Distance walked (meters) during the 6MWT
- Total Fatigue score on the PMMSA

9.1.2. Secondary Endpoints

The secondary endpoints are:

- Fatigue During Activities score on the PMMSA
- Neuro-QoL Fatigue Short Form score
- Most bothersome symptom score on the PMMSA
- Neuro-QoL Fatigue activities of daily living (specific items from the Neuro-QoL Item Bank)

9.1.3. Exploratory Endpoints

There will be a number of exploratory endpoints investigated, including:

- Individual symptom scores on the PMMSA
- Alternate version of the PMMSA Total Fatigue Score
- Individual item scores of the Neuro-QoL Fatigue
- EQ-5D-5L scores
- Patient Global Impression (PGI) Scales
  - PGI of Symptom scores
  - PGI of Change scores
- Clinician Global Impression (CGI) Scales
  - CGI of Symptom scores
  - CGI of Change scores

9.1.4. Pharmacokinetic (PK) Endpoints

The PK endpoints are:

- PK parameters

9.2. Safety Endpoints

For both PART 1 and PART 2, safety will be assessed through collection of the following data:

- AEs/ADEs
- Vital Signs
- Electrocardiograms
- Clinical laboratory evaluations
- C-SSRS

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 post treatment follow-up period.

Subjects must be seen by a physician or designee (an appropriately trained healthcare professional) at every trial visit and the evaluation must be documented. Clinical site staff will report any AE/ADEs, 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 trial in the subject's eCRF and applicable forms. The reporting period for AEs/ADEs is described in Section 9.9.2.

The Sponsor will periodically review trial safety data as outlined in the Medical Monitoring Plan.

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

Any untoward medical occurrence in a subject 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 unfavorable 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 instructions 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.

The safety profile 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 trial's post treatment follow-up period.

Subjects must be seen by a physician or designee (an appropriately trained healthcare professional) at every trial 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 trial in the subject's eCRF and applicable forms.

Should the IMP be discontinued due to an AE/ADE deemed probably or possibly related to the IMP (per Section 9.9.1.2), reinitiating (rechallange) of the IMP may be possible, after consultation with the Sponsor.

9.3. Pre-Treatment Adverse Events

Untoward events that occur prior to the first IMP administration (pre-treatment event) and assessed by the Investigator as related to a trial procedure and/or meeting seriousness criteria will be recorded as an AE/SAE on the subject's electronic case report form (eCRF) and applicable forms, processed, and followed accordingly. AEs/SAEs that occur prior to IMP administration are by definition, unrelated to the IMP and will be reported as such in the data listings.

9.4. Medical History Conditions

Pre-treatment events or diagnoses not related to a trial procedure and/or meeting seriousness criteria will be recorded as medical history on the subject's eCRF. Medical history conditions, related or not related to the therapeutic area of interest/investigation, that worsen in severity or frequency during the trial 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.

9.5. Medical and Surgical Procedures

Medical or surgical procedures (including hospitalizations) scheduled prior to signing the informed consent, but occurring during the trial 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 informed consent 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 or SAE/SADE and the procedure should be captured on the concurrent procedures page.

9.6. 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 or SAE/SADE, 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.

9.7. Symptomatic Overdose

In the event of an overdose of trial 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 trial Medical Monitor (or designee).

9.8. 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 in-patient 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.

An 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 subject 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 a SAE/SADE should be reported as a SAE/SADE. The start date of the SAE/SADE 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 subject's eCRF.

As part of the routine medical monitoring, the medical monitor (or designee) will review all SAEs/SADEs reported in the SPIMM-301 trial, looking for any safety data trends or trial IMP-related issues.

9.9. 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 subject's eCRF. All

SAEs/SADEs must be reported using the trial specific SAE Report Form, in addition to the subject's eCRF.

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

Investigators should use the AE/ADE definitions provided in the above sections and should observe the following guidelines when completing the subject's eCRF:

- 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 with a definite diagnosis (if available). Similarly, a fatal event with an unknown cause should be recorded as "Unknown"
- 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.

9.9.1. Investigator Assessments

9.9.1.1. Severity

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 IMP administration; and/or not needing therapeutic intervention.
- **Moderate:** Associated with limitation of usual activities or significant discomfort; generally requiring alteration or cessation of IMP administration; and/or requiring therapeutic intervention.
- **Severe:** Associated with inability of subject to carry out usual activities or very marked discomfort; considered to be life-threatening; resulting in significant disability or incapacity; and requiring therapeutic intervention.

9.9.1.2. Relationship to the Investigational Medicinal Product (IMP)/Elamipretide Delivery System

Investigators must systematically assess the causal relationship of AEs/ADEs to the IMP 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 IMP/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 IMP/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 IMP/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.

9.9.1.3. Outcome of an Adverse Event (AE)/Adverse Device Effect (ADE)

Investigators must follow all AEs/ADEs and SAEs/SADEs until the clinical trial'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.

9.9.1.4. 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 Appendix 14.

- Any ISR that meets any of the criteria of a SAE/SADE (Section 9.8) should be reported within 24 hours of the clinical site first becoming aware of the event (as outlined in Section 9.10).
- 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.

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

The AE/ADE reporting period begins when the subject signs the informed consent and continues through the clinical trial post treatment follow-up period. Note that AEs that occur between the time subject signs the ICF and the time the subject is dosed with IMP will be summarized in the medical history eCRF and not as an AE unless the event meets the definition of a SAE or is related to a trial procedure.

After trial 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.

9.10. 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 the Sponsor by telephone, by fax or by e-mail as detailed in the SAE form, completion instructions, eCRF completion guidelines, and/or Safety Management Plan (SMP). Reporting responsibilities for SAEs/SADEs are detailed in the SMP. For sites in Germany, see Appendix 15.

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

- Investigator/Reporter with full contact information,
- Subject identification details (trial number, center number, subject number),
- IMP administration details (dose and dates),
- Event Verbatim, a brief description of signs/symptoms/or diagnosis and the date of onset,
- Seriousness criteria (ion) met.

Within 24 hours, the relationship of the event to the IMP (e.g., the causality according to the Investigator) and/or to the elamipretide delivery system (serial number) and needle (e.g., the causality according to the Investigator) should be provided.

All SAE/SADE reports should be transmitted according to the Safety Management Plan.

The Investigator/Reporter must provide follow-up information as available or requested by the Sponsor.

9.10.1. Pregnancy and Contraception

For male subjects with female partners of child-bearing potential, highly effective methods of contraception must be adhered to from the date they sign the ICF until 28 days after the last dose of IMP. Highly effective methods of contraception are defined as the usage by the female partner of any form of hormonal contraception or intra-uterine device (which should be established prior to the start of the trial) plus usage by one of the partners of an additional spermicide-containing barrier method of contraception. Male subjects with pregnant partners must use a condom from the start of treatment until 28 days after the last dose of IMP. Sperm or egg donation by subjects is not permitted from the start of treatment until 28 days after the last dose of IMP.

Any pregnancy in a female partner of a male subject during the course of the trial and until the last follow-up visit must be reported even if no AE/ADE has occurred, as detailed in the Safety Management Plan. If the investigator suspects the pregnancy has resulted from an interaction of the trial medication with contraceptives, then the pregnancy is considered as an AE.

The Investigator must notify the Sponsor of any pregnancy using the Pregnancy Notification Form and the reporting procedure as described in the Safety Management Plan. Investigators must actively follow up, document, and report on the outcome of every pregnancy, even if the subject is withdrawn from the trial, as detailed in the Safety Management Plan.

9.10.2. Responsibilities to Regulatory Authorities, Investigators and Ethics Committees

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

The Investigator must comply with (and inform the Sponsor of) any applicable center-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 IMP/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 IEC/central IRB and will maintain records of these

notifications. When direct reporting by the Sponsor is not clearly defined by national or center-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety reports provided by the Sponsor and of 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 Guidances.

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 clinics, as appropriate
- Sponsor start-up training to instruct the Investigators and trial coordinators. This training will give instruction on the protocol, the completion of the eCRFs, and trial procedures.
- Make periodic visits to the clinic
- Be available for consultation and stay in contact with the clinical site staff 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 subject data recorded against source documents at the clinic. The trial 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 trial, 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 trial. If requested, the Investigator will provide the Sponsor, applicable regulatory agencies, and applicable ECs with direct access to original source documents.

10.1. Data Capture System

An electronic data capture system (eDC) will be used in this trial. The clinical site will maintain a separate source for the data entered by the clinical site into the Sponsor-provided electronic data capture system.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data or ECG data, or any data for which electronic documentation is provided by the subject, 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 clinical site in that center's trial 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

The sample size of 202 subjects provides 90% power to detect a 30-meter difference between treatment groups in the 6MWT and also 90% power to detect a one unit difference in the PMMSA Total Fatigue Score, assuming standard deviations of 60 meters for 6MWT and 2 units for the PMMSA Total Fatigue Score, at an alpha-level of 0.025. The two-sided alpha-level of 0.025 is to account for a possible multiplicity adjustment as given in Section 11.2.5.5.

11.2. Statistical and Analytical Plans

11.2.1. General Considerations

Data will be tabulated (by treatment group) using descriptive statistics (number of subjects, mean, median, standard deviation, minima, and maxima) for continuous variables and using frequencies and percentages for discrete variables. Inferential statistics will be presented where specified. A comprehensive statistical analysis plan (SAP) will be written and approved prior to database lock. This SAP will detail how missing values are to be handled, windows for trial visits, and how other analysis considerations will be addressed.

Statistical tests (where performed) will be 2-sided at the alpha=0.05 level of significance, except where otherwise noted to adjust for multiplicity.

11.2.2. Analysis Populations

Statistical analysis will be performed using the following populations:

- Safety Population – Includes all trial subjects who receive at least 1 dose of IMP. Subjects will be analyzed according to the actual treatment they receive.
- Intent-to-Treat (ITT) Population – Includes all trial subjects who receive at least one dose of IMP. Subjects will be analyzed according to the treatment group they were randomized to and generally included in efficacy analyses for which post-baseline data are available.
- Per-Protocol (PP) Population – Includes all ITT subjects without major protocol violations/deviations. The list of major protocol violations/deviations will be identified and specified in the SAP prior to final database lock for the trial that would lead to exclusion for the PP analysis.
- Pharmacokinetic (PK) Population - Includes all trial subjects who have at least one PK sample taken during their participation.

11.2.3. Subject Disposition

Subject disposition (including the number and percent of subjects who are randomized, who receive randomized treatment, who are included in each analysis population, who prematurely discontinue and reasons for discontinuation, and who complete the trial) will be tabulated by treatment group. The number and percentage of subjects by exposure duration will be tabulated.

11.2.4. 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.

11.2.5. Efficacy Analyses

Details regarding the final analyses will be included in a comprehensive SAP, which will be written and approved prior to database lock.

11.2.5.1. Primary Efficacy Endpoints

The distance walked (meters) during the 6MWT and Total Fatigue score on the PMMSA constitute the primary endpoint family. Efficacy analyses will be conducted on the ITT population.

For the analysis of the primary endpoint family, the following two-sided hypotheses will be carried out to evaluate the treatment effect of elamipretide group against the placebo group in the 6MWT and Total Fatigue score on the PMMSA (i=1 and 2, respectively):

$$H_{0i}: \mu_i^{MTP} = \mu_i^{PLB} \; vs. \; H_{ai}: \mu_i^{MTP} \neq \mu_i^{PLB}$$

where μ_i^{PLB} is the mean change from baseline on either the 6MWT (i=1) or the Total Fatigue score on the PMMSA [4 item] (i=2) at the end of the treatment period (Week 24) for the placebo treatment group, and μ_i^{MTP} is the respective mean change from baseline at the end of the treatment period (Week 24) for the elamipretide treatment group.

Analyses of continuous endpoints will be conducted utilizing a mixed model repeated measures (MMRM) approach, with fixed effects for treatment, genetic abnormality subclassification strata, visit, the treatment-by-visit interaction, and subject as a random effect. The outcome is the change from baseline to each on-treatment time point. The baseline value for the endpoint and a baseline by visit interaction term will be included as covariates. The primary time point is at Week 24; however, all protocol-scheduled time points will be included in the model. The exact details of the model, including variance-covariance structure and denominator degrees of freedom will be specified in the SAP.

11.2.5.2. Secondary Efficacy Endpoints

The secondary endpoints are:

- Fatigue During Activities score on the PMMSA
- Neuro-QoL Fatigue Short Form score
- Most bothersome symptom score on the PMMSA
- Neuro-QoL Fatigue activities of daily living (specific items from the Neuro-QoL Item Bank)

These endpoints will be assessed in a similar manner as the primary efficacy endpoints.

11.2.5.3. Exploratory Endpoints

There will be a number of exploratory endpoints investigated, including:

- Individual symptom scores on the PMMSA
- Alternate version of the PMMSA Total Fatigue Score
- Individual item scores of the Neuro-QoL Fatigue
- EQ-5D-5L scores
- Patient Global Impression (PGI) Scales
  - PGI of Symptom scores
  - PGI of Change scores
- Clinician Global Impression (CGI) Scales
  - CGI of Symptom scores
  - CGI of Change scores

These endpoints will be assessed in a similar manner as the primary efficacy endpoints.

11.2.5.4. Pharmacokinetic (PK) Endpoints

The PK endpoints are:

- PK parameters

11.2.5.5. Adjustments for Multiplicity

A family-wise alpha level of 0.05 will be maintained for the primary endpoint family, using Hochberg's procedure at the primary time point of 24 weeks. If both primary endpoints are significantly different from placebo at the 0.05 (two-sided) level of significance (in favor of treatment), then both will be considered statistically significant. Otherwise the endpoint with the smaller p-value of the two will be considered statistically significant, if statistically significant at the 0.025 (two-sided) level of significance.

Select secondary and exploratory endpoints will be alpha-level protected in a hierarchical fashion, conditional upon the statistical significance of both endpoints in the primary endpoint family. Additional details will be specified in the SAP.

11.2.5.6. Handling of Missing Data

A significant amount of missing data are not anticipated, given characteristics of the subject population from which subjects will be enrolled. In addition, the mixed model repeated measures approach is valid under a missing at random (MAR) missingness mechanism. Nevertheless, depending on the extent of missing data, additional sensitivity analyses may be considered.

11.2.6. Pharmacokinetics (PK)

Elamipretide plasma concentration data collected on repeated occasions in all subjects (Week 4, Week 12 and Week 24) will be used in a non-linear mixed effects model to assess the characteristics of elamipretide PK in the PK population.

The PK model will be generated and validated using data reported from historical, thorough PK studies. Where sufficient data allows, covariates will include age, gender, race, renal function (as described by eGFR), ordinal grouping of genetic abnormalities, intercurrent conditions and concomitant medications.

Plasma samples will be analyzed for elamipretide using a validated liquid chromatography/ tandem mass spectrometry assay. Pharmacokinetic modelling will be performed using NONMEM computer software.

All model assumptions, validation and data analysis will be detailed in the PK Analysis Plan prior to database lock.

11.2.7. Safety Analyses

Safety data analysis will be conducted for the Safety Population.

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

All AEs/ADEs will be coded to system organ class (SOC) and preferred term (PT) using the latest Medical Dictionary for Regulatory Activities coding dictionary. All reported AEs/ADEs will be listed, but only treatment-emergent AEs (TEAEs)/treatment-emergent adverse device effects (TEADEs) will be summarized.

The incidence of all TEAEs/TEADEs, drug relationship with TEAEs, device relationship with TEADEs, and severity of TEAEs/TEADEs will be summarized by treatment group. In the summary tables, subjects may be counted under multiple SOCs and PTs, but for each SOC and PT, subjects are only counted once for each treatment group. If a subject has the same AE/ADE on multiple occasions, the highest severity (severe > moderate > mild) or drug relationship (probable > possibly related > unlikely related > unrelated) recorded for the event will be presented. If severity is missing, subjects will be included as missing (for severity). If drug relationship is missing, subjects will be included in related tables (i.e., considered related). Summary tables will be organized by SOC, then PT.

Local tolerability (pain/tenderness, erythema, induration/swelling, and pruritus) of the injection site will be evaluated as an AE and summarized.

11.2.7.2. Deaths and Other Serious Adverse Events (SAEs)/Serious Adverse Device Effects (SADEs)

Listings will be provided for the following:

- Deaths
- SAEs/SADEs
- AEs/ADEs leading to discontinuation of double-blind IMP

11.2.7.3. Clinical Laboratory Evaluations

Summary tables for laboratory parameters included in Appendix 4 (including clinical hematology and chemistry laboratory parameters, 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 parameter and visit for each treatment group. Shift tables for urinalysis will show the number of subjects who are normal/abnormal at baseline and normal/abnormal at the end of trial.

11.2.7.4. Vital Signs

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

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

11.2.7.5. Electrocardiogram

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

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

Similar data will be reported for ambulatory arrhythmias.

11.2.7.6. Other Safety Parameters

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

12. INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

12.1. Informed Consent

The Investigator is responsible for identifying potential subjects from the SPIMM-300 study or subjects that otherwise meets trial Inclusion/Exclusion Criteria. The Investigator is responsible for ensuring that the subject understands the potential risks and benefits of participating in the trial, including answering any questions the subject may have throughout the trial 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 trial.

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

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

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

12.2. Ethical Review

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

Documentation of EC approval of the protocol and the ICFs must be provided to the Sponsor, or designee before the trial may begin at the clinical site.

12.3. Regulatory Considerations

This trial will be conducted in accordance with:

1. Consensus ethics principles derived from international ethics guidelines, including the CIOMS International Ethical Guidelines
1. The ICH GCP Guideline [E6]
2. European Directive 2001/20/EC
3. Applicable laws and regulations

The Investigator, Sponsor, or designee will promptly submit the protocol to applicable EC(s), IRBs, Regulatory Authorities and other Regulatory bodies as required. Some of the obligations of the Sponsor may be assigned to a third-party organization. Clinical sites will not commence enrollment until Regulatory Authority submission/approval and site EC/IRB favorable opinion/approval are granted.

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/ADEs and/or other trial-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 trial.

12.3.2. Final Report Approval

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

12.3.3. Trial Monitoring

The Investigators and institution(s) will permit trial-related monitoring of the eCRF data by Stealth BioTherapeutics Inc., or their assignee by providing direct access to source data and/or documents. The trial monitor will verify the eCRFs 100% against the source documentation. Deviations from the protocol with regard to subject enrollment or trial conduct will be noted in a database. Serious/major protocol deviations may be reported to EC(s), IRBs, Regulatory Authorities and other Regulatory bodies as required. A Sponsor representative will visit the clinical site to initiate the trial, prior to the first treatment of the first subject, and at agreed times throughout the trial, including at the end of the trial. Drug dispensing and clinical drug supply records will be 100% verified at the clinical site by the trial monitor. It is understood that all subject specific information is confidential and no documentation that can link trial information to the specific subject will be collected or retained by the Sponsor. Additional details will be provided in a Clinical Monitoring Plan.

12.3.4. Retention of Records

All trial-related material including source documents, eCRFs, Central Authority, EC correspondence, and analyses and any other documentation required by applicable laws and regulations will be maintained for 15 years after completion of the trial 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 trial only. It is understood by the Investigator that Stealth BioTherapeutics Inc., will use information developed in this clinical trial 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 trial, the Investigator understands that he/she has an obligation to provide complete test results and all data developed during this trial to the Sponsor.

The Investigator may not submit for publication or presentation the results of this trial without first receiving written authorization from Stealth BioTherapeutics Inc. Stealth BioTherapeutics

Inc., agrees that before it publishes any results of the trial, it shall provide the Investigator with at least 30 days for review of the pre-publication manuscript prior to the submission of the manuscript to the publisher.

13. REFERENCES

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APPENDIX 1. PART 1 SCHEDULE OF ASSESSMENTS

Period	**Screening Period[a]**	**Treatment Period**				**Follow-Up Period**
Visit[b]	**Visit 1 (Screening)**	**Visit 2 (Baseline/Day 1)[c]**	**Visit 3 (Week 4)**	**Visit 4 (Week 12)**	**Visit 5 (Week 24)**	**Visit 6A (End-of-Trial or Early DC)**
Window	**-28 Day to -1**	**Day 1**	**Day 29 ±2**	**Day 85 ± 4**	**Day 169 + 14**	**Day 197 +14**
Informed Consent[d]	X					
Demographics	X					
Review Inclusion/Exclusion Criteria	X	X				
Review PART 2 Continuation Criteria					X	
Medical/Surgical History[n]	X	X (update)				
Concomitant Medication/Procedure Review	X	X (update)	X	X	X	X
Review AEs/ADEs	X	X	X	X	X	X
Physical Examination[e]	X	X	X	X	X	X
Vital Signs[f]	X	X	X	X	X	X
12-Lead ECG[g]	X	X	X	X	X	X
C-SSRS "Baseline/Screening"	X					
C-SSRS "Since Last Visit"		X	X	X	X	X
Clinical chemistry and hematology laboratory parameters[h]	X	X	X	X	X	X
Clinical Urinalysis[h]	X	X	X	X	X	X
Pregnancy Test[i]	X	X				X
PK Samples[j]			X	X	X	
PMMSA	X[o]----------Daily----------X					
Neuro-QoL Fatigue	X	X	X	X	X	
EQ-5D-5L	X	X	X	X	X	
PGI Scales	X	X	X	X	X	
CGI Scales	X	X	X	X	X	
6MWT[k]	X	X	X	X	X	
IMP Administration[l]		X----------Daily---------- X				
ISR Assessment[m]		X	X	X	X	

a. Screening will begin with the subject's signature of the informed consent form (ICF) and will last a minimum of 7 days to a maximum of 28 days. Subjects not previously enrolled in SPIMM-300, however, may have a longer screening period for review by the Adjudication Committee to determine their eligibility for study enrollment.

b. All clinical site visits should occur at approximately (±2 hours) the same time during the day and subjects should have at least 1 hour of fasting (e.g. no large meals) prior to the 6MWT. Trial Days are relative to the Baseline Visit (Day 1).

c. Baseline assessments must be completed within 24 hours prior to receiving IMP.
d. The ICF must be signed prior to any trial-related procedures are performed.
e. Height will only be measured at the Screening Visit, and used in the trial to calculate BMI. Physical examination will include: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, extremities, nervous system, and weight.
f. Vital signs will include HR, RR, and BP after sitting for 5 min, and temperature.
g. All scheduled ECGs must be performed after the subject has rested quietly for at least 5 min in the supine position.
h. Blood samples will be collected prior to the IMP administration on the Baseline Visit. Analysis will include testing for parameters included in Appendix 4. Additional blood samples at the Baseline, Week 24 Visit, and Early Discontinuation Visit (if applicable) will be collected and stored for assessing the immunogenicity potential of the IMP.
i. Serum pregnancy test will be done for women of childbearing potential at the Screening Visit. Results of the Baseline Visit pre-dose urine pregnancy test must be evaluated before randomization to ensure eligibility. Urine pregnancy test will also be performed for women of childbearing potential at the End-of-Trial/Early Discontinuation Visit.
j. PK Schedule: Week 4: 1 hour post dose (± 10 min); Week 12: 30 min, 2 hours, and 4 hours post dose (± 10 min); Week 24: pre-dose (-10 min).
k. The 6MWT should be performed after all other trial procedures (except for PMMSA at the Screening Visit and the IMP administration at the Baseline Visit). The 6MWT instructions are provided in Appendix 13.
l. Subjects (and caregivers if needed) will be trained on the procedure for administration of the elamipretide delivery system (the investigational medicinal product [IMP] [elamipretide or placebo], the elamipretide pen injector, and needle). On days of trial visits, the IMP administered with the elamipretide delivery system should be administered at the clinical site. At Baseline Visit, the IMP administration will occur after the completion of all Visit procedures. At the Week 4, Week 12, and Week 24 Visits, the IMP administration should occur after all other trial procedures. The location (injection in the abdomen, rotating around the four abdominal quadrants, or other appropriate location [after Investigator consultation with the Sponsor]) and time (at approximately the same time each day [e.g., early morning, noon, or early afternoon]) of the IMP administration will be recorded daily in a diary. Supplies will be collected, compliance will be assessed, and new supplies will be provided at clinical site visits. For subjects continuing into PART 2 of the trial, IMP administration the day of the Week 24 Visit will use the PART 2 supply of IMP. Subjects not continuing into PART 2 will not be administered IMP at the Week 24 Visit.
m. The skin examination should occur at 30 (±5) minutes after the IMP 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 Appendix 14.
n. Obtain previous genetic testing results from subjects not previously enrolled in SPIMM-300.
o. The PMMSA at the Screening Visit should be the last trial assessment completed.

APPENDIX 2. PART 2 SCHEDULE OF ASSESSMENTS

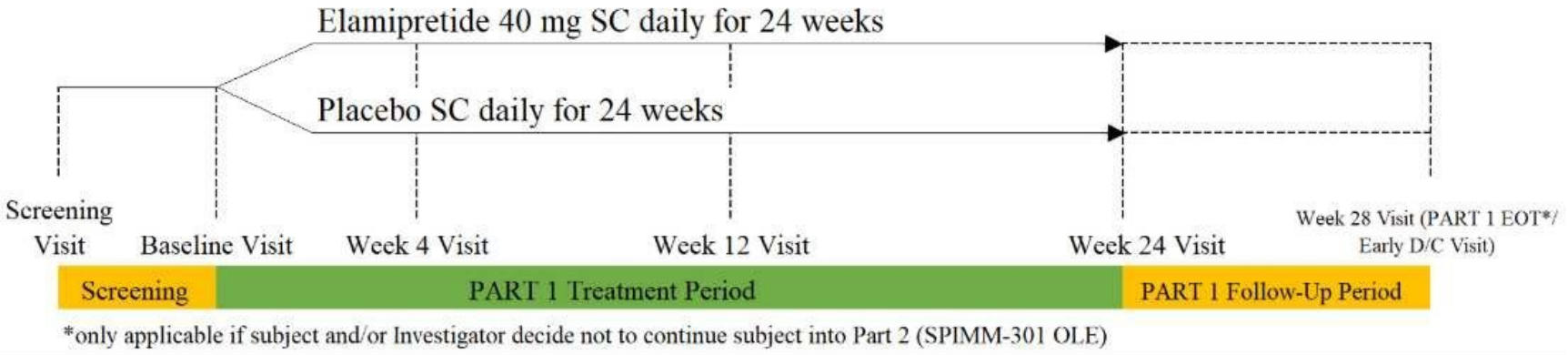
Period	Treatment Period					Follow-Up Period
Visit	**Visit 6B (Week 28)**	**Visit 7 (Week 36)**	**Visit 8 (Week 48)**	**Visits 9-13 (Week 72, 96, 120, 144, 168)**	**Phone Call (Week 60, 84, 108, 132, 156)**	**Visit 14 (Week 172) End-of-Trial or Early DC**
Window	**± 1 week**	**± 2 weeks**	**± 2 weeks**	**± 2 weeks**	**± 2 weeks**	**+ 7 days**
Concomitant Medication/Procedure Review	X	X	X	X	X	X
Review AEs/ADEs	X	X	X	X	X	X
Physical Examination[a]	X	X	X	X		X
Vital Signs[b]	X	X	X	X		X
12-Lead ECG[c]	X	X	X	X		X
C-SSRS "Since Last Visit"	X	X	X	X		X
Clinical chemistry and hematology laboratory parameters[d]	X	X	X	X		X
Clinical Urinalysis[d]	X	X	X	X		X
Urine Pregnancy Test[e]						X
IMP Administration[f]	X----------Daily---------- X					
ISR Assessment[g]	X	X	X	X		

a. Physical examination will include: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, extremities, nervous system, and weight.
b. Vital signs will include HR, RR, and BP after sitting for 5 min, and temperature.
c. All scheduled ECGs must be performed after the subject has rested quietly for at least 5 min in the supine position.
d. See Appendix 4 for clinical laboratory tests. Additional blood samples at the Early Discontinuation Visit (if applicable) will be collected and stored for assessing the immunogenicity potential of the IMP.
e. Urine Pregnancy test will be performed for women of childbearing potential at the End-of-Trial/Early Discontinuation Visit.
f. On days of trial visits, the IMP administered with the elamipretide delivery system should be administered at the clinical site. The location (injection in the abdomen, rotating around the four abdominal quadrants, or other appropriate location [after Investigator consultation with the Sponsor]) and time (at approximately the same time each day [e.g., early morning, noon, or early afternoon]) of the IMP administration will be recorded daily in a diary. Supplies will be collected, compliance will be assessed, and new supplies will be provided at clinical site visits.
g. The skin examination should occur at 30 (±5) minutes after the IMP 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 Appendix 14.

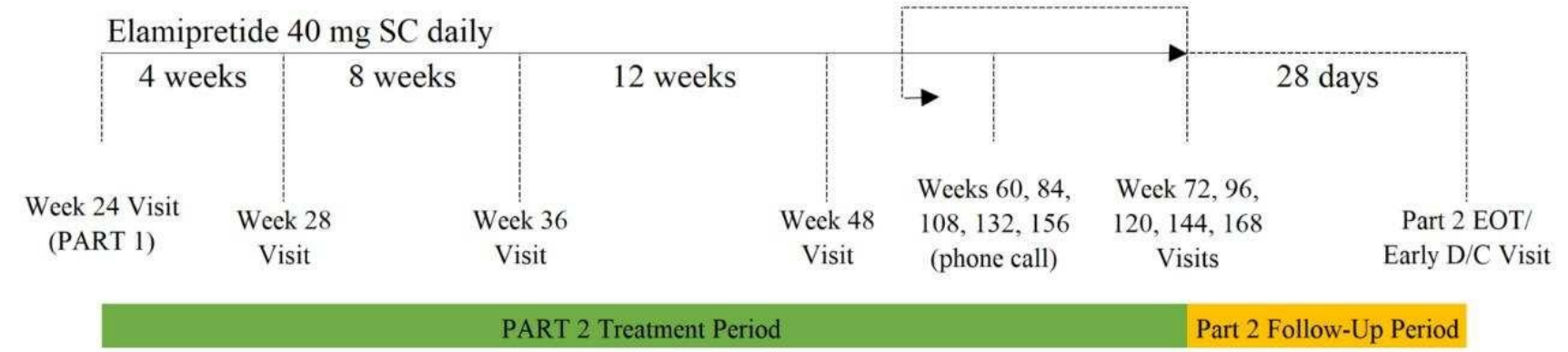
APPENDIX 3. TRIAL DESIGN SCHEMATIC

PART 1

Trial site(s): Multicenter (North America and Europe); approximately 27 sites



PART 2



APPENDIX 4. LIST OF CLINICAL LABORATORY TESTS TO BE PERFORMED

Hematology:	**Chemistry:**
Haemoglobin	Sodium
Haematocrit	Potassium
Erythrocyte count (RBC)	Total bilirubin
MCH	Direct bilirubin
MCHC	Indirect bilirubin
MCV	Bicarbonate
RBC morphology	Alkaline phosphatase (ALK-P)
Leukocytes (WBC)	Alanine aminotransferase (ALT)
Neutrophils (ANC, segmented %)	Aspartate aminotransferase (AST)
Lymphocytes (absolute, %)	Blood urea nitrogen (BUN)
Monocytes (absolute, %)	Gamma-glutamyl transpeptidase (GGTP)
Eosinophils (absolute, %)	Creatine kinase (CK)
Basophils (absolute, %)	Creatinine
Platelets	LDH
	Uric Acid
Urinalysis:	Phosphate
Color & Clarity	Total Protein
Specific Gravity	Globulin
pH	Magnesium
Protein	Calcium
Glucose	Glucose (non-fasting)
Ketones	Albumin
Bilirubin	Chloride
Urobilinogen	Triglycerides
Blood	Cholesterol
Nitrite	HDL
Leukocyte esterase	LDL
	VLDL
	Lactate
Immunogenicity sample (Baseline and Week 24 ONLY)	eGFR

APPENDIX 5. 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* _____

APPENDIX 6. 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* _____

APPENDIX 7. SAMPLE SAFETY TELEPHONE CALL SCRIPT

This page provides a sample script for the phone call that will be made to the subject occur approximately every 12 weeks between clinical site visits after the subject is enrolled in PART 2 to ensure the safe and compliant use of the study drug and to appropriately collect the safety events with use of the study drug.

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

During each 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 about 3 months since we last spoke about your experience using elamipretide, the study drug in the PART 2 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 had any problems with the study drug device?

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).

APPENDIX 8. PRIMARY MITOCHONDRIAL MYOPATHY SYMPTOM ASSESSMENT (PMMSA)

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 (for example, when sitting or lying down)?	☐	☐	☐	☐
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 (for example, when sitting or lying down)?	☐	☐	☐	☐
4. During the past 24 hours, how severe was your worst feeling of muscle weakness during activities?	☐	☐	☐	☐
5. During the past 24 hours, how severe were your worst balance problems?	☐	☐	☐	☐
6. During the past 24 hours, how severe were your worst vision problems?	☐	☐	☐	☐
7. During the past 24 hours, how severe was your worst abdominal discomfort (feeling nauseous, bloated, or in pain)?	☐	☐	☐	☐
8. During the past 24 hours, how severe was your worst muscle pain?	☐	☐	☐	☐
9. During the past 24 hours, how severe was your worst numbness?	☐	☐	☐	☐
10. During the past 24 hours, how severe was your worst headache?	☐	☐	☐	☐

At Screening Visit Only:

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

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

APPENDIX 9. NEURO-QOL FATIGUE

Fatigue

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

	In the past 7 days…	Never	Rarely	Sometimes	Often	Always
NQFTG13	I felt exhausted……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG11	I felt that I had no energy……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG15	I felt fatigued……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG06	I was too tired to do my household chores.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG07	I was too tired to leave the house……...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG10	I was frustrated by being too tired to do the things I wanted to do……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG14	I felt tired……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG02	I had to limit my social activity because I was tired…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG01	I needed help doing my usual activities because of my fatigue…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG03	I needed to sleep during the day…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG04	I had trouble <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

APPENDIX 10. 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

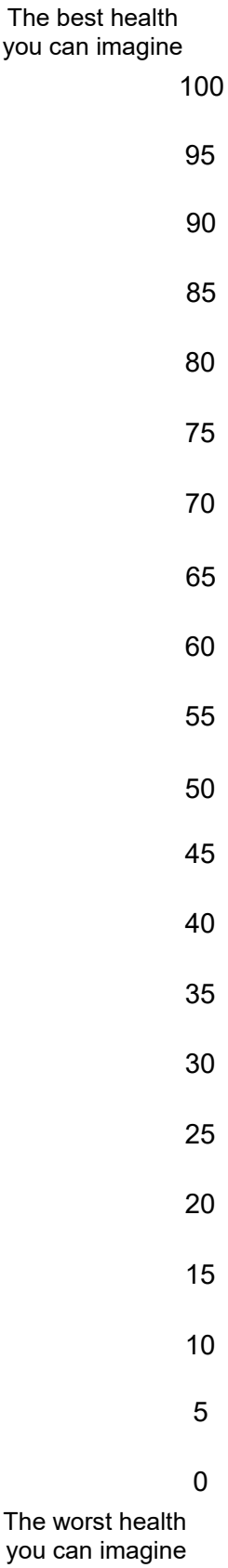
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 = [ ]



APPENDIX 11. PATIENT GLOBAL IMPRESSION (PGI) SCALES

Patient Global Impression of Symptoms

Date Completed: _____

The following questions ask you about your primary mitochondrial myopathy symptoms OVER THE PAST WEEK.

1. Please choose the response below that best describes the severity of your primary mitochondrial myopathy symptoms over the past week.
   - ☐ No Symptoms
   - ☐ Mild Symptoms
   - ☐ Moderate Symptoms
   - ☐ Severe Symptoms
   - ☐ Very Severe Symptoms

2. Please choose the response below that best describes the severity of your fatigue (tiredness and muscle weakness) over the past week.
   - ☐ No Fatigue
   - ☐ Mild Fatigue
   - ☐ Moderate Fatigue
   - ☐ Severe Fatigue
   - ☐ Very Severe Fatigue

3. Please choose the response below that best describes the severity of your tiredness at rest over the past week.
   - ☐ No Tiredness
   - ☐ Mild Tiredness
   - ☐ Moderate Tiredness
   - ☐ Severe Tiredness
   - ☐ Very Severe Tiredness

4. Please choose the response below that best describes the severity of your tiredness during activities over the past week.
   - ☐ No Tiredness
   - ☐ Mild Tiredness
   - ☐ Moderate Tiredness
   - ☐ Severe Tiredness
   - ☐ Very Severe Tiredness

5. Please choose the response below that best describes the severity of your muscle weakness at rest over the past week.
   - ☐ No Muscle Weakness
   - ☐ Mild Muscle Weakness

- ☐ Moderate Muscle Weakness
- ☐ Severe Muscle Weakness
- ☐ Very Severe Muscle Weakness

6. Please choose the response below that best describes the severity of your muscle weakness during activities over the past week.
   - ☐ No Muscle Weakness
   - ☐ Mild Muscle Weakness
   - ☐ Moderate Muscle Weakness
   - ☐ Severe Muscle Weakness
   - ☐ Very Severe Muscle Weakness

7. Please choose the response below that best describes the severity of your balance problems over the past week.
   - ☐ No Balance Problems
   - ☐ Mild Balance Problems
   - ☐ Moderate Balance Problems
   - ☐ Severe Balance Problems
   - ☐ Very Severe Balance Problems

8. Please choose the response below that best describes the severity of your vision problems over the past week.
   - ☐ No Vision Problems
   - ☐ Mild Vision Problems
   - ☐ Moderate Vision Problems
   - ☐ Severe Vision Problems
   - ☐ Very Severe Vision Problems

9. Please choose the response below that best describes the severity of your abdominal discomfort (feeling nauseous, bloated, or in pain) over the past week.
   - ☐ No Abdominal Discomfort
   - ☐ Mild Abdominal Discomfort
   - ☐ Moderate Abdominal Discomfort
   - ☐ Severe Abdominal Discomfort
   - ☐ Very Severe Abdominal Discomfort

10. Please choose the response below that best describes the severity of your muscle pain over the past week.
    - ☐ No Muscle Pain
    - ☐ Mild Muscle Pain
    - ☐ Moderate Muscle Pain
    - ☐ Severe Muscle Pain
    - ☐ Very Severe Muscle Pain

11. Please choose the response below that best describes the severity of your numbness over the past week.
    - ☐ No Numbness
    - ☐ Mild Numbness
    - ☐ Moderate Numbness
    - ☐ Severe Numbness
    - ☐ Very Severe Numbness

12. Please choose the response below that best describes the severity of your headache over the past week.
    - ☐ No Headache
    - ☐ Mild Headache
    - ☐ Moderate Headache
    - ☐ Severe Headache
    - ☐ Very Severe Headache

Patient Global Impression of Change

Date Completed: _____

Please think about how your primary mitochondrial myopathy symptoms have changed from the time just before you started the study medication to today. The following questions ask you about how your symptoms have changed SINCE THE TIME JUST BEFORE YOU STARTED THE STUDY MEDICATION TO TODAY.

1. Please choose the response below that best describes the overall change in your primary mitochondrial myopathy symptoms since you started taking the study medication. My primary mitochondrial myopathy symptoms are:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

2. Please choose the response below that best describes the overall change in your fatigue (tiredness and muscle weakness) since you started taking the study medication. My fatigue is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

3. Please choose the response below that best describes the overall change in your tiredness at rest since you started taking the study medication. My feeling of tiredness at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

4. Please choose the response below that best describes the overall change in your tiredness during activities since you started taking the study medication. My feeling of tiredness during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

5. Please choose the response below that best describes the overall change in your feeling of muscle weakness at rest since you started taking the study medication. My feeling of muscle weakness at rest is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

6. Please choose the response below that best describes the overall change in your feeling of muscle weakness during activities since you started taking the study medication. My feeling of muscle weakness during activities is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

7. Please choose the response below that best describes the overall change in your balance problems since you started taking the study medication. My balance problems are:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

8. Please choose the response below that best describes the overall change in your vision problems since you started taking the study medication. My vision problems are:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

9. Please choose the response below that best describes the overall change in your abdominal discomfort (feeling nauseous, bloated, or in pain) since you started taking the study medication. My abdominal discomfort is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

10. Please choose the response below that best describes the overall change in your muscle pain since you started taking the study medication. My feeling of muscle pain is:
    - ☐ Very much Better
    - ☐ Moderately Better
    - ☐ A Little Better
    - ☐ No Change
    - ☐ A Little Worse
    - ☐ Moderately Worse
    - ☐ Very much Worse

11. Please choose the response below that best describes the overall change in your numbness since you started taking the study medication. My feeling of numbness is:
    - ☐ Very much Better
    - ☐ Moderately Better
    - ☐ A Little Better
    - ☐ No Change
    - ☐ A Little Worse
    - ☐ Moderately Worse
    - ☐ Very much Worse

12. Please choose the response below that best describes the overall change in your headache since you started taking the study medication. My feeling of headache is:
    - ☐ Very much Better
    - ☐ Moderately Better
    - ☐ A Little Better
    - ☐ No Change
    - ☐ A Little Worse
    - ☐ Moderately Worse
    - ☐ Very much Worse

APPENDIX 12. CLINICIAN GLOBAL IMPRESSION (CGI) SCALES

Clinician Global Impression of Symptoms

Date Completed: _____

1. Overall, how severe are the patient's primary mitochondrial myopathy symptoms today?
   - ☐ No Symptoms
   - ☐ Mild Symptoms
   - ☐ Moderate Symptoms
   - ☐ Severe Symptoms
   - ☐ Very Severe Symptoms

2. Overall, how severe is the patient's fatigue (tiredness and muscle weakness) today?
   - ☐ No Fatigue
   - ☐ Mild Fatigue
   - ☐ Moderate Fatigue
   - ☐ Severe Fatigue
   - ☐ Very Severe Fatigue

Clinician Global Impression of Change

Date Completed: _____

Please think about how the patient's primary mitochondrial myopathy symptoms have changed from the time just before he/she started the study drug in SPIMM-301 to today. The following questions ask you about how the patient's symptoms have changed SINCE THE TIME JUST BEFORE HE/SHE STARTED THE STUDY DRUG IN SPIMM-301 TO TODAY.

1. Please choose the response below that best describes the overall change in the patient's primary mitochondrial myopathy symptoms since he/she started taking the study drug in SPIMM-301. The patient's primary mitochondrial myopathy symptoms are:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

2. Please choose the response below that best describes the overall change in the patient's fatigue (tiredness and muscle weakness) since he/she started taking the study drug in SPIMM-3ど. The patient's fatigue is:
   - ☐ Very much Better
   - ☐ Moderately Better
   - ☐ A Little Better
   - ☐ No Change
   - ☐ A Little Worse
   - ☐ Moderately Worse
   - ☐ Very much Worse

APPENDIX 13. 6-MINUTE WALK TEST (6MWT)

A 6MWT will be performed to assess the distance a subject is able to walk in six minutes on a fixed course length. The subject will be instructed to walk as far as possible for 6 minutes. Subjects may stop to rest as needed but should continue walking as soon as they are able.

If a test is unusable the Core Lab will instruct the site to repeat the test, if possible.

CPC Clinical Research (CPC) will provide training to all individuals who will be administering the 6MWT for this trial and pre-approving the 6MWT course at each clinical site. Subjects should only be walked on a course that is approved by CPC.

The following instructions should be provided to the subject prior to each visit that includes a 6MWT:

1. Do not eat or smoke within 1 hour prior to the test,
2. Wear comfortable, low-heeled walking shoes for the test, and
3. Bring your usual walking aid (cane, walker, etc.) with you to the visit.

Please refer to the Study Manual and CPC 6MWT Reference Tool for the full instruction on how to conduct the 6MWT.

APPENDIX 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.

APPENDIX 15. COUNTRY-SPECIFIC APPENDIX--GERMANY

The SAE definition and reporting of SAEs will conform to the Medical Devices Safety Plan Ordinance (Medizinprodukte-Sicherheitsplanverordnung) that is valid for Germany.

SAE definition:

“Ein Schwerwiegendes unerwünschtes Ereignis” ist jedes in einer genehmigungspflichtigen klinischen Prüfung oder einer genehmigungspflichtigen Leistungsbewertungsprüfung auftretende ungewollte Ereignis, das unmittelbar oder mittelbar zum Tod oder zu einer schwerwiegenden Verschlechterung des Gesundheitszustands eines Probanden, eines Anwenders oder einer anderen Person geführt hat, geführt haben könnte oder führen könnte ohne zu berücksichtigen, ob das Ereignis vom Medizinprodukt verursacht wurde; das Vorgesagte gilt entsprechend für schwerwiegende unerwünschte Ereignisse, die in einer klinischen Prüfung oder Leistungsbewertungsprüfung, für die eine Befreiung von der Genehmigungspflicht nach § 20 Absatz 1 Satz 2 des Medizinproduktegesetzes erteilt wurde, aufgetreten sind.

SAE reporting responsibilities for Germany are detailed in the SMP.

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