CLINICAL STUDY PROTOCOL

Title: An Open-label, Multi-centre Study to Evaluate the Long-term Safety and Tolerability of REN001 in Subjects With Primary Mitochondrial Myopathy (PMM)

NCTID: NCT05267574

Document Date: 7 August 2023

CLINICAL STUDY PROTOCOL

AN OPEN-LABEL, MULTI-CENTRE STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF REN001 IN SUBJECTS WITH PRIMARY MITOCHONDRIAL MYOPATHY (PMM)

Sponsor:	Reneo Pharma Ltd. Innovation House, Discovery Park Ramsgate Road Sandwich Kent CT13 9FF United Kingdom
Clinical Research Organisation (CRO):	Emmes BioPharma UK Ltd (Formerly Orphan Reach Ltd) The Old School Newport Road Woughton Park Milton Keynes MK6 3AP United Kingdom
Sponsor Protocol No.:	REN001-202
EudraCT No.:	2021-003471-34
IND No.:	Not applicable
Study Drug Name:	REN001
Development Phase:	Phase 2b
Date of Protocol:	07 August 2023
Protocol version:	Version 3.0

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements.

SIGNATURE PAGE

Declaration of Sponsor Chief Medical Officer

Title: An open-label, multi-centre study to evaluate the long-term safety and tolerability of REN001 in subjects with primary mitochondrial myopathy (PMM)

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, as amended in 2013 and the guidelines on Good Clinical Practice.

DocuSigned by:
[redacted]

_____

{*See Electronic Signature Page*}

[redacted]

Institution: Reneo Pharma Ltd.

SIGNATURE PAGE

Declaration of the National Co-ordinating Investigator (use as appropriate)

Title: An open label, multi-centre study to evaluate the long-term safety and tolerability of REN001 in subjects with primary mitochondrial myopathy (PMM)

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure, Case Report Forms, and other scientific data.

The study will not commence without the prior written approval of a properly constituted Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IEC, except where necessary to eliminate an immediate hazard to the subjects.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

National Co-ordinating Investigator **Country**_____

Signature: _____

PLEASE PRINT NAME and TITLE_____

PROTOCOL SYNOPSIS

Title:	**AN OPEN-LABEL, MULTI-CENTRE STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF REN001 IN SUBJECTS WITH PRIMARY MITOCHONDRIAL MYOPATHY (PMM)**
Sponsor Study No:	REN001-202
Compound:	REN001
Phase:	Phase 2b
Sponsor:	Reneo Pharma Ltd.
Design:	This study is designed to evaluate the long-term safety and tolerability of REN001 administered once daily to subjects with PMM due to mitochondrial DNA mutations (mtDNA-PMM) or nuclear DNA mutations (nDNA-PMM). Subjects with mtDNA mutations will have previously completed Study REN001-201 (which is referred to as the STRIDE study) or participated in Study REN001-101. Subjects with nDNA mutations who enrol in this study will be REN001-naïve. nDNA-PMM subjects will not be enrolled in France. Eligible subjects will be treated with REN001 100 mg orally, once daily for 48 months. Following the baseline visit there are 10 planned visits at Months 1, 3, 6, 12, 18, 24, 30, 36, 42 and 48. To satisfy a regulatory agency request for subjects to be assessed every three months for the first 18 months, subjects in Germany will have two additional visits at Month 9 and 15, making it a total of 12 planned visits. A final follow-up telephone call will be made by the study centre to the subject approximately 30 days after the last dose of study drug. A final follow-up telephone call will not be required if mavodelpar has been approved within the country and the subject switches to commercially available medication. As the subjects with nDNA mutations will not have participated in another REN001 study, an independent Patient Screening Oversight Committee (PSOC) will review their screening criteria to ensure they have the appropriate PMM diagnosis for entering this study. The structure, function and operation of the PSOC are detailed in the REN001-202 PSOC Charter. A Safety Review Committee (SRC) will review safety data during the study. The structure, function, and operation of the SRC is detailed in the REN001-202 SRC Charter. Interim data cuts may be taken, and summaries prepared to support regulatory submissions or external communications such as publications.

Objectives:

Primary:
To evaluate long-term safety and tolerability of REN001 in subjects with PMM.

Secondary:
To assess subjects with mtDNA-PMM who are receiving long-term treatment with REN001 in terms of PMM associated symptoms, pain severity and interference, exercise endurance, quality of life (QoL), patient global impression of change (PGIC) and patient global impression of severity (PGIS) for muscle and fatigue, and work productivity.

Pharmacokinetic (PK):
To further characterise the PK profile of REN001 in subjects with PMM receiving long-term treatment

Exploratory:

To evaluate the effect of long-term treatment with REN001 on bone health.

To assess subjects with nDNA-PMM who are receiving long-term treatment with REN001 in terms of PMM associated symptoms, pain severity and interference, exercise endurance, quality of life (QoL), patient global impression of change (PGIC) and patient global impression of severity (PGIS) for muscle and fatigue, and work productivity.

Endpoints

Primary:
For mtDNA and nDNA subjects:

- Number and severity of Adverse Events (AE)
- Number of AEs leading to study drug discontinuation
- Number of serious adverse events (SAE)
- Number of adverse events of special interest (AESI)
- Number of AEs leading to death

Secondary:
For mtDNA and nDNA subjects:

- Absolute values, changes from baseline, and incidence of potentially clinically significant changes in:
    - Laboratory safety tests
    - Electrocardiograms (ECG)
    - Supine vital signs
    - Eye assessments

For mtDNA subjects:

- Absolute values and changes from baseline in:
    - Distance walked during the 12-Minute Walk Test (12MWT)*
    - Modified Fatigue Impact Scale (MFIS) total scores and sub-scale scores*

- Patient Global Impression of Severity (PGIS) scores for fatigue and muscle symptoms
- Brief Pain Inventory (BPI) pain severity and pain interference scores*
- Patient Reported Outcomes Measurement Information System (PROMIS) Short Form-Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue 13a scores*
- 36-item Short Form Health Survey (SF-36) domain scores (7-day recall)*
- Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) scores*
- First 6-minute walk distance and last 6-minute walk distance*
- Phenotypic description question*

- Patient Global Impression of Change (PGIC) scores (muscle and fatigue symptoms).

Pharmacokinetic (PK):
REN001 plasma concentrations and parameters.*

Exploratory:
For mtDNA and nDNA subjects:

- Change from baseline to end of treatment in bone mineral density (BMD) as measured by dual-energy x-ray absorptiometry (DXA), in the following:
  - Lumbar spine (L1 to L4) BMD
  - Total hip BMD and the femoral neck BMD (in the non-dominant hip)
  - Total hip, lumbar spine and femoral neck T-scores and Z-scores

For nDNA subjects:

- Absolute values and changes from baseline in:
  - Distance walked during the 12-Minute Walk Test (12MWT)*
  - Modified Fatigue Impact Scale (MFIS) total scores and sub-scale scores*
  - Patient Global Impression of Severity (PGIS) scores for fatigue and muscle symptoms
  - Brief Pain Inventory (BPI) pain severity and pain interference scores*
  - Patient Reported Outcomes Measurement Information System (PROMIS) Short Form-Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue 13a scores*

- 36-item Short Form Health Survey (SF-36) domain scores (7-day recall)*
- Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) scores*
- First 6-minute walk distance and last 6-minute walk distance*
- Phenotypic description questions*

- Patient Global Impression of Change (PGIC) scores (muscle and fatigue symptoms).

***collected up to Month 24 only**

Number of Subjects:

Recruitment of subjects with mtDNA mutations will be limited to those subjects who participated in the STRIDE study (applicable only for countries where this study is being conducted) or Study REN001-101. It is estimated that approximately 150 mtDNA subjects will be enrolled.

Additionally, up to 50 REN001-naïve subjects with nDNA mutations will be recruited.

Treatment:

Supplies of REN001 will be available as 50mg capsules. Subjects will take REN001, 100mg (2 capsules) once daily with food (preferably with morning meal). Subjects will be treated in the study for 48 months. The study will be considered completed with the last follow-up telephone call of the last subject, unless the subject switches to commercially available medication in which case the follow-up phone call is not required.

Eligibility Criteria:

<u>Inclusion Criteria for all Subjects</u>:

1. mtDNA-PMM subjects: Completed treatment in the STRIDE study or participated in Study REN001-101, and in the opinion of the Investigator and Sponsor have been compliant with the study requirements.

   Or

   nDNA-PMM subjects: Subjects aged 18 years or older with known nuclear (nDNA) pathogenic variants with a major muscle phenotype consisting of objective myopathy with poor exercise tolerance. Proof of pathogenicity must be provided. Must be able to walk at least 100m in the screening 12MWT and the limitations in walk test must be primarily due to the energy deficit and not due to ataxia or any other condition. For subjects under 25 years old only: confirmation of bone growth plate closure by wrist radiograph.

2. Have PMM which continues to be primarily characterized by exercise intolerance or active muscle pain.

3. Willing and able to swallow the REN001 gelatin capsules.
4. Concomitant medications (including supplements) intended for the treatment of PMM or other co-morbidities likely to remain stable throughout participation in the study where clinically possible.
5. Signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
6. Females should be either of non-child-bearing potential or must agree to use highly effective methods of contraception from baseline through to approximately 30 days after the last dose of study drug. Males with partners who are women of childbearing potential (WOCBP) must also use contraception from baseline through to 14 weeks after the last dose of study drug. If subjects are transferred to a commercial supply of REN001 they must be advised to adhere to the contraceptive requirements.

Exclusion Criteria for all subjects:
Subjects who present with any of the following will not be included in the study:

1. Anticipated to need a peroxisome proliferator-activated receptor (PPAR) agonist other than REN001 during the study.
2. Anticipated to need drugs during the study with a narrow therapeutic index and Breast Cancer Resistant Protein (BCRP) mediated absorption, distribution, metabolism and excretion (ADME) (See Table 1).
3. Intent to donate blood, or blood components during the study or within one month after completion of the study.
4. Current drug dependency. Use of opiates/cannabis for medical reasons is acceptable with prescription evidence or at the Investigator's discretion.
5. Current alcohol dependency.
6. Any medical, psychiatric or laboratory condition that may increase the risk associated with study participation or interfere with the interpretation of study results and, in the judgment of the Investigator and Medical Monitor, would make the subject inappropriate for entry into this study.
7. Pregnant or nursing females.

Subjects with mtDNA mutations can enroll at STRIDE Week 24 visit, STRIDE-FU visit, after exiting from STRIDE or after exiting REN001-101 (UK only). Subjects enrolling after exiting from either of the 2 feeder mtDNA studies and all

subjects with nDNA mutations will be required to fulfil additional exclusion criteria during their additional screening visit. This is required for the mtDNA-PMM subjects due to the gap in study drug treatment and period of time without study assessments. The additional exclusion criteria are:

1. Clinically significant kidney disease or impairment, with an eGFR less than 60ml/min/1.73m^2 using the CKD-EPI creatinine equation at baseline. German sites - see alternative criteria below.
2. Clinically significant liver disease or impairment with AST or ALT >2.5 x ULN, or Total bilirubin > 1.6 x ULN or >ULN with other signs and symptoms of hepatotoxicity at baseline. (Subjects with an isolated elevated bilirubin (e.g., < 2 x ULN) may be included after discussion with the Medical Monitor if the cause is due to a benign hereditary disorder of metabolism such as Gilbert's syndrome.)
3. Uncontrolled diabetes and/or a glycosylated hemoglobin (HbA1c) of ≥ 11%. German sites - see alternative criteria below.
4. Evidence of significant concomitant clinical disease that may need a change in management during the study or could interfere with the conduct or safety of this study. (Stable well-controlled chronic conditions such hypercholesterolemia, gastroesophageal reflux, or depression under control with medication are acceptable provided the symptoms and medications would not be predicted to compromise safety or interfere with the tests and interpretations of this study).
5. Clinically significant cardiac disease and/or clinically significant ECG abnormalities including a baseline QTcF of ≥ 450 msec, 2nd degree heart block, symptomatic tachyarrhythmia or unstable arrythmia that in the opinion of the Investigator should exclude the subject from study completion. Subjects with right bundle branch block, left fascicular block and long PR interval which are common in PMM may be enrolled if the Investigator considers that the condition would not compromise their safety in this study.
6. Treatment with an investigational drug, other than REN001, within 3 months or 5 drug half-lives, whichever is longer, prior to Day 1.
7. Have been hospitalized within the 3 months prior to screening for any major medical condition (as deemed by the Investigator).

8. Subject with poor nutritional status as determined by the Investigator.
9. Subjects with positive hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) or positive hepatitis C or human immunodeficiency virus (HIV) at screening. German sites - see alternative criteria below.
10. Subjects who are not eligible or have a contraindication for cataract surgery.
11. Any condition possibly reducing drug absorption (e.g., gastrectomy or increased gastrointestinal motility).
12. History of cancer (except basal cell carcinoma).
13. For subjects from REN001-101 study and nDNA-PMM subjects only, a history of fragility/stress fractures or an osteoporosis concomitant condition which has not been adequately addressed.

For subjects at sites in Germany

For additional criteria 1, 3 and 9, the following alternative criteria apply:

1. Clinically significant kidney disease or impairment, with an eGFR less than 60ml/min/1.73m^2 using the CKD-EPI creatinine equation.
3. Uncontrolled diabetes and/or a glycosylated hemoglobin (HbA1c) of ≥ 8.5%. (NOTE: an HbA1c is not obtained as part of the Week 18 visit in the Stride Study. Nevertheless, the Week 18 blood draw may be used to obtain the test provided the subjects has given the appropriate consent).
9. Subjects with positive hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) or positive hepatitis C or human immunodeficiency virus (HIV). (NOTE: these tests are not obtained as part of the Week 18 or 24 visits in the Stride Study. Nevertheless, the Week 18 or 24 blood draws may be used to obtain the test provided the subjects has given the appropriate consent).

These criteria will require screening assessments to be completed within the 8 weeks prior to the start of dosing in this study.

For subjects wishing to start dosing immediately after the STRIDE Week 24 visit, their STRIDE Week 18 blood tests may be used as the screening assessments; additional blood tests will need to be collected for HbA1c and serology. For mtDNA-PMM subjects wishing to start dosing in this study immediately after the STRIDE -FU visit, their STRIDE

Week 24 blood tests may be used as the screening assessments; additional blood sample will need to be collected for serology.

Study Visits:

It is expected that most STRIDE subjects will enrol at the STRIDE Week 24 visit with the baseline visit for this study coinciding with the STRIDE Week 24 visit. Enrolment at the STRIDE follow-up (FU) visit will require additional baseline assessments. Subjects who wish to take part in this study after leaving the STRIDE study (i.e., after their STRIDE FU visit), subjects who participated in Study REN001-101, and all nDNA subjects will require additional screening and baseline visits, dependent on when the subject enrols in the study:

- Option 1: Enrolment at the STRIDE Week 24 visit: Most of the STRIDE Week 24 assessments will be regarded as the baseline assessments for this study. Additional assessments will be performed as noted in Section 6.1.1.
- Option 2: Enrolment at the STRIDE FU visit: The STRIDE FU visit will be regarded as the baseline visit for this study with additional assessments performed as noted in Section 6.1.2. If a washout period for any prohibited medication started since the STRIDE Week 24 visit, the subject will exit the STRIDE study and will require additional screening and baseline visits to enter the STRIDE AHEAD Study (Option 3 enroller).
- Option 3: Enrolment after exiting Study REN001-101 or STRIDE (mtDNA-PMM subjects): separate screening and baseline visits will be required, with assessments performed as noted in Section 6.1.3.
- Option 4: Enrolment of nDNA-PMM subjects: separate screening and baseline visits will be required, with assessments performed as noted in Section 6.1.4. nDNA-PMM subjects will not be enrolled in France.

Prior to dosing, the PSOC will assess if nDNA-PMM subjects have the appropriate diagnosis for entry into this study.

After the baseline visit each subject will have 10 scheduled visits over a period of 48 months (12 for subjects at sites in Germany). The final follow-up will be conducted by a telephone call approximately 30 days after the last dose of study drug. A final follow-up telephone call will not be required if mavodelpar has been approved within the country and the subject switches to commercially available medication.

Where sites permit, a concierge service will be available to subjects to arrange hotel accommodation and transport to and from the study centre and reimburse any subject study expenses, if applicable. Subjects may be asked to have a negative COVID-19 test prior to undertaking scheduled visits to the study centre.

All protocol assessments are detailed in the study Schedule of Activities (Table 3).

Statistical Methods:

No formal statistical testing is planned.

Endpoints will be summarized by STRIDE treatment (REN001 or Placebo) from the start of STRIDE for mtDNA-PMM subjects. Endpoints will also be summarized from the start of REN001-202, and from the start of REN001 treatment for mtDNA-PMM subjects. Subjects with nDNA-PMM will be summarized from the start of REN001-202.

Treatment-emergent adverse events (TEAEs) will be summarized by System Organ Class (SOC) and preferred term, in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. The number of subjects reporting each AE preferred term will be tabulated for all TEAEs and separately for those considered as at least possibly related to study treatment by the Investigator. Number of subjects reporting AESI and SAEs will also be tabulated.

Absolute values and changes from baseline in clinical laboratory test, vital signs, ECG and eye examination data will be summarized using descriptive statistics by visit.

Absolute values and changes from baseline in 12 Minute Walk Distance (12MWD) and other secondary and exploratory endpoints will be summarized and plotted over time.

LIST OF STUDY PERSONNEL

Sponsor	Reneo Pharma Ltd, Innovation House, Discovery Park, Ramsgate Road, Sandwich, Kent CT13 9FF United Kingdom [redacted]
Contract Research Organisation	Emmes BioPharma UK Ltd The Old School Newport Road Woughton Park Milton Keynes MK6 3AP United Kingdom Telephone: +44 (0)1908 251 480
Medical Monitor	Email: medicalmonitor202@emmes.com
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Statistician	[redacted] ParamStat Limited

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List of Abbreviations and Definitions of Terms

ADR	Adverse Drug Reaction
ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse event
AESI	Adverse Event of Special Interest
AP	Alkaline Phosphatase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area Under the Curve
AUCτ	AUC calculated over the dosing interval
BCRP	Breast Cancer Resistant Protein
BID	*Bis in die* – twice daily
BMD	Bone Mineral Density
BMI	Body Mass Index
BPI	Brief Pain Inventory
CA	Competent Authorities
CFR	Code of Federal Regulations
CK	Creatine phosphokinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum observed concentration
C_{trough}	Observed concentration from sample collected prior to dosing
CoQ10	Coenzyme Q10
COVID -19	Corona Virus Disease 2019
CRO	Clinical Research Organisation
DNA	Deoxyribonucleic acid
DSUR	Drug Safety Update Report
DXA	Dual-energy X-ray Absorptiometry
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
eGFR	Estimated Glomerular Filtration Rate
EIA	Enzyme immunoassay
FAO	Fatty Acid Oxidation
FAS	Full Analysis Set
FU	Follow-up visit
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HbA1c	Glycosylated haemoglobin
HBcAb	Hepatitis B core Antibody
HBsAg	Hepatitis B surface Antigen
hCG	Human Chorionic Gonadotropin
HDL	High Density Lipoprotein
HDPE	High Density Polyethylene
hr	hour
ICH GCP	International Council on Harmonisation Good Clinical Practice
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug

IWRS	Integrated Web-based Response System
kg	Kilogram
LDL	Low Density Lipoprotein
LFT	Liver Function Test
LOQ	Level of Quantification
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MFIS	Modified Fatigue Impact Scale
mg	milligrams
mL	milliliter
mmHg	millimetres of mercury
msec	millisecond
mtDNA	mitochondrial Deoxyribonucleic Acid
nDNA	nuclear Deoxyribonucleic Acid
OLE	Open Label Extension
OXPHOS	Oxidative phosphorylation
PDF	Portable Document Format
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
P-gp	P-glycoprotein
PK	Pharmacokinetic
PMM	Primary mitochondrial myopathy
PPAR	peroxisome proliferator-activated receptor
PRO	Patient Reported Outcome
PSOC	Patient Screening Oversight Committee
PTE	Pre-treatment Events
PV	Pharmacovigilance
QD	*Quaque die* - once daily
QoL	Quality of Life
QT	The interval between the start of the Q wave and the end of the T wave
QTcF	Heart rate corrected QT interval using Fridericia's formula
RR	The interval between the successive R waves
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF-36	36-item Health Survey
SOC	System Organ Class
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to maximum plasma concentration
ULN	Upper Limit of Normal
WOCBP	Women of childbearing potential
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem
12MWD	12-minute walk distance
12MWT	12-minute walk test

1 INTRODUCTION

1.1 Indication

Primary mitochondrial myopathies (PMM) are genetic disorders associated with pathogenic variants in the mitochondrial or nuclear genes that can lead to oxidative phosphorylation (OXPHOS) dysfunction or other disturbances of mitochondrial structure and function. PMM predominantly, but not exclusively, affect the skeletal muscle and present with motor function deficits and poor endurance (Parikh et al 2014; Mancuso et al 2017). In patients with mitochondrial DNA (mtDNA) mutations, inheritance and clinical presentation are further complicated by the presence of multiple mtDNA genomes in an individual cell leading to a mixture of mutated and wild-type genomes (heteroplasmy) in the same cell or tissue.

Onset of PMM can occur at any age, although typically the more severe phenotypes present earlier in life, and milder phenotypes present later in life. Marked clinical variation can be seen in patients and this can delay diagnosis. Because mitochondria are the main source of energy production in mammalian cells, clinical features typically involve the tissues with the highest energy requirements. Furthermore, the presence of mtDNA and nDNA in all human tissues means that dysfunction occurs in multiple organ systems. The most commonly affected organ systems are the nervous, muscular, cardiac and endocrine systems. Individuals with PMM can present with a constellation of clinical features that may be compatible with a discrete clinical syndrome. However, categorizing patients into syndromes is of limited value, as the majority of patients do not fit into discrete categories (Gorman et al, 2016). PMM are usually progressive conditions which produce significant disability and, in some instances, premature death.

The molecular genetic investigation of suspected mitochondrial disease can be complex, and has to be guided by previous clinical, histochemical and biochemical findings. Definitive diagnostic confirmation now relies on genetic testing and the identification of a pathogenic mutation in a recognized mitochondrial or nuclear gene.

The management of patients with mitochondrial diseases is focused on strategies to reduce morbidity and mortality and early treatment of organ-specific complications. Several agents (mostly nutritional supplements) have been investigated in double-blind, placebo-controlled studies. These include carnitine, creatine, Coenzyme Q10 (CoQ10), cysteine, dichloroacetate, dimethylglycine, and the combination of creatine and lipoic acid. No agent or combination regimen has demonstrated efficacy in clinical disease endpoints (Pfeffer & Chinnery, 2013). PMM represents an area of significant unmet medical need; there is currently no available disease-modifying therapy for patients with PMM.

1.2 Background

REN001 is a potent, selective and orally bioavailable PPARδ agonist. PPARδ controls genes involved in cellular metabolic processes such as glucose homeostasis, fatty acid synthesis and storage, and fatty acid mobilization and metabolism. PPARδ is expressed in several metabolically active tissues including liver, muscle, and fat. It is the most abundant PPAR isoform in skeletal muscle and has a higher expression in oxidative type I muscle fibers compared with glycolytic type II muscle fibers. REN001 potently and selectively activates PPARδ and increases fatty acid oxidation supporting the rationale of developing REN001 in the treatment of patients with mitochondrial myopathies.

Full details of the REN001 chemistry, pre-clinical and clinical data can be found in the current Investigator's Brochure.

1.3 Study Rationale

There is a strong rationale for the use of REN001, a selective PPARδ agonist, in patients with PMM. The PPARδ receptor is a nuclear receptor primarily found in skeletal muscle. Patients with PMM caused by genetic mutations in the mitochondrial or nuclear genomes have impaired oxidative phosphorylation. Selective PPAR agonists may ameliorate the cellular energy deficit in patients with these mutations by:

- Increasing fatty acid oxidation (FAO) and OXPHOS activity resulting in enhanced mitochondrial adenosine triphosphate (ATP) generating capacity.
- In mtDNA-PMM, increasing the proportion of wild-type mitochondria. Although mitochondrial disease--induced mitochondrial proliferation may favor mutated mitochondria, pharmacological upregulation of mitochondrial biosynthesis increases the number of both mutated and wild-type mitochondria, which allows wild-type mitochondria to compensate for mutant mitochondria.
- Increasing mitochondrial biogenesis and thereby increasing residual OXPHOS activity, which would enhance the cellular ATP synthesis capacity.

The information collected will support the long-term safety evaluations of REN001 in the total PMM population. Enrolment of PMM patients with nDNA mutations in the REN001-202 OLE study offers the opportunity to rapidly gain safety, tolerability and exploratory efficacy data on the effect of REN001 in these patients. The information obtained will then be used to support further clinical development of REN001 in this population.

This protocol amendment expands the duration of the study to 48 months, to enable subjects who have perceived benefit from therapy to continue to receive REN001.

1.4 Risk-Benefit Assessment

1.4.1 Benefits

In Study REN001-101, an open label Phase 1b study in subjects with mtDNA PMM, oral REN001 dosed at 100mg per day was safe and well tolerated for 12 weeks (Part A) and up to an additional 24 weeks in the subjects who continued into an extension part of the study (Part B). Following 12 weeks of dosing, most subjects experienced improvement in the outcome measures of distance walked in the 12MWT and symptoms of fatigue and pain evaluated with Patient Reported Outcome (PRO) measures. The study was terminated early in 2020 due to the operational obstacles created by the Corona Virus Disease 2019 (COVID-19) pandemic. Subjects who were ongoing in the study when Study REN001-101 was terminated will be given the opportunity for further treatment with REN001 in this study.

The STRIDE study is an ongoing double-blind, placebo-controlled, Phase 2b study to evaluate the efficacy and safety of 24 weeks treatment with REN001, dosed at 100mg per day, in mtDNA PMM subjects. This long-term safety study will offer the opportunity for extended active treatment for those subjects randomized to REN001 in STRIDE, and active treatment for subjects who were randomized to placebo. Neither subjects nor sites will be aware of the allocated treatment in STRIDE when rolling directly into this study, and the Sponsor will remain blinded to this information until the STRIDE database is locked and treatment allocation unblinded.

Patients with nDNA mutations will not have previously participated in studies in the REN001 program (due to eligibility criteria designed to maintain a homogenous population). However, the potential for REN001 to provide benefit for PMM patients is based on the myopathic phenotype, rather than specific genetic cause. Therefore, after gaining experience in the

mtDNA-PMM population, this protocol was amended (Version 2.0) to widen enrollment to include adult PMM patients with nDNA mutations This will provide long-term safety data on the total PMM patient population and provide evidence of potential efficacy in the nDNA-PMM population.

This amendment increases the duration of the study from 24 months to 48 months. The duration of the study has been increased to continue the collection of long-term safety and also to enable access to REN001 therapy to those subjects who may be benefiting from REN001 treatment.

1.4.2 Risks

1.4.2.1 Elevated Creatine Kinase

Subjects with PMM may have asymptomatic benign raised baseline creatine kinase (CK) levels as part of the PMM disease. Even among healthy individuals CK levels rise transiently after exercise or intense physical activity. In patients with PMM, serum CK levels may increase to as much as 30 times the ULN within 24 hours after strenuous physical activity, then slowly decline over the next 7 days. The degree of CK elevation depends on the type and duration of exercise, with greater elevation in those who are untrained (Moghadam-Kia, Oddis, & Aggarwal, 2016). It is possible that improvements in the cellular energy deficit with REN001 treatment may result in increased muscle use and transient benign muscle enzyme elevations.

Serum CK data from subjects with PMM in the Phase 1b study (REN001-101) demonstrated a pattern of transient, elevated CKs following exercise and the collection of muscle biopsies; none of these elevations were associated with myoglobinuria. The elevations seen were self-limited and resolved with no intervention despite continued treatment with REN001 and continuation of the subject's normal activities of daily living, including exercise. In all clinical trials of REN001 to date, elevations in CK tended to be modest and reversible and were usually determined by investigators as unlikely to be associated with REN001 treatment. In the current study as a precautionary measure CK levels will be assessed throughout the study.

1.4.2.2 Cataract Formation

A finding of cataract was observed in a high dose 6-month rat chronic toxicology study. Importantly, no cataracts were observed in any other toxicology studies, including in a 3-month rat study and a 12-month primate study. It is predicated that the changes observed in the 6-month rat study are rat strain specific. Nevertheless, following this observation, taking a conservative approach, ophthalmology examinations are being included in all REN001 trials. Slit lamp eye examinations will be conducted together with assessments of best corrected visual acuity during this study.

1.4.2.3 Potential Drug-Drug Interactions

REN001 is not a direct or time-dependent inhibitor of CYP3A4. However, REN001 has been shown to be a weak inducer of CYP3A4 *in vitro*. A potential for drug interactions between REN001 and drugs that are metabolized through CYP3A4 is considered low but cannot yet be ruled out. Therefore, drugs that are metabolized primarily by CYP3A4 and have a narrow therapeutic index should be administered with caution in subjects participating in REN001 studies.

There are few commonly used CYP3A4 substrates with a narrow therapeutic index which are not already prohibited by the protocol (Table 1). It is standard clinical practice to evaluate every patient as an individual with their own context of comorbid conditions and concurrent

medications. In order to ensure Investigators are checking the most up-to-date references for potential drug-drug interactions, they are referred to their own national medical prescribing guidance if available and to the Flockhart Table[1] maintained by the University of Indiana available at https://drug-interactions.medicine.iu.edu/ if they are in any doubt about the status of a proposed concomitant medication.

REN001 was identified as a P-glycoprotein (P-gp) substrate *in vitro*. Strong P-gp inhibitors may have an impact on the absorption and metabolism of a P-gp substrate, however preliminary human metabolism for REN001 indicates numerous metabolic pathways are involved in the clearance of REN001. Therefore, it is unlikely that co-administration of a strong P-gp inhibitor with REN001 will result in higher systemic exposures of REN001. Co-administration of REN001 with a strong P-gp inducer may reduce REN001 plasma concentrations.

1.4.2.4 Fertility and Contraception

In accordance with the latest European regulatory discussions and guidelines (Clinical Trials Facilitation Group, 2014 and 2020), WOCBP are eligible for the study provided they are using a highly effective form of contraception while taking the study drug and for approximately 30 days after stopping study drug (at least one menstrual cycle after drug exposure). If subjects are transferred to a commercial supply of REN001 they must be advised to adhere to the contraceptive requirements. Serum pregnancy testing will be completed at screening for mtDNA-PMM subjects enrolling after exiting one of the two feeder studies and for nDNA-PMM subjects. Urine pregnancy tests will be carried out at baseline and monthly thereafter until completion of the study for all WOCBP regardless of when they enrolled.

Fertile men (i.e., unless permanently sterile by bilateral orchidectomy) must use a condom during intercourse with a WOCBP from baseline through to at least 14 weeks after stopping study drug (at least one sperm cycle after drug exposure) and should not father a child in this period. A condom is also required to be used by vasectomized men to prevent delivery of the drug via seminal fluid.

As REN001 is a weak inducer of CYP3A4 *in vitro*, caution is advised when co-administering REN001 and oral contraceptive agents. As a precautionary measure, women taking highly effective hormonal contraception therapy will be advised to use an additional effective non-hormonal method of contraception during treatment with REN001 and for 30 days after the final dose of study drug (Section 5.8).

1.4.2.5 Carcinogenicity

Carcinogenicity studies have been initiated but are not yet completed. Animal carcinogenicity data in rodents suggest that some, but not all, PPAR agonists have carcinogenicity potential. The mechanism by which implicated compounds produce tumors in rodents is not well understood and the relevance of these findings for other classes of PPAR agonists, if any, to humans is unknown. Subjects with a history of cancer, except in situ basal cell carcinoma in the skin, are excluded from participation in the study.

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[1] *Flockhart DA, Thacker, D., McDonald, C., Desta, Z. The Flockhart Cytochrome P450 Drug-Drug Interaction Table. Division of Clinical Pharmacology, Indiana University School of Medicine (Updated 2021). https://drug-interactions.medicine.iu.edu/. [Accessed 23 March 2022].*

1.4.2.6 Bone

A finding of premature bone plate closure was observed in toxicology studies in one species of rat. This finding was not seen in the non-human primate studies. As a precaution, treatment-naïve nDNA-PMM subjects under 25 years of age will have a wrist x-ray prior to enrolment to confirm skeletal maturity.

PPARγ agonists have been associated with bone loss. Currently it is not known if REN001 (a selective PPARδ agonist) will have any impact on bone mineral density (BMD). Nonetheless, given the requirements for walk tests and taking a conservative approach, the Sponsor excluded subjects with a history of fragility/stress fractures or an osteoporosis concomitant condition which has not been addressed from the STRIDE study, and will monitor markers of bone turnover during this study. Any reports of bone fracture will be captured as an AESI. Any change in BMD over the course of the study will be assessed using DXA scans where available.

1.4.3 Safety Data Review

The ongoing safety of study subjects will be reviewed by the Medical Monitor and study site physicians as data are received. In addition, safety data will be reviewed in aggregate by the Safety Review Committee (SRC) at pre-defined milestones. See Section 3.11. The safety profile of REN001 to date supports further development in clinical studies subject to appropriate subject selection and safety monitoring.

1.5 Dose Selection Rationale

The dose of 100mg once daily used in this study is the same dose used in the 2 feeder studies for mtDNA-PMM subjects: Study REN001-101 (a UK only study) and the STRIDE study.

To date a total of 163 subjects have been enrolled and 106 subjects received REN001 in four completed clinical trials pertinent to this indication (HPP593-101 (single dose, healthy volunteers); HPP593-102 (14-day, repeat dose study in obese moderately dyslipidemic subjects); HPP593-103, (28-day, healthy volunteer pharmacodynamic study in induced muscle atrophy); REN001-101 (up to 48 weeks, repeat dose in mtDNA-PMM subjects; treatment received for up to 40 weeks due to curtailment of study during the COVID-19 pandemic). In the single dose study, doses ranged from 25mg to 250mg, doses in the 14-day study ranged from 50mg to 200mg QD or 100mg BID, in the 28-day study the dose was 100mg BID and in the 48-week study the dose was 100mg QD. Overall, REN001 was considered safe and well tolerated in all four clinical studies. No treatment related SAEs were reported. No clinically significant abnormalities were observed in any safety parameters including vital signs, ECGs, and physical exams.

In Study REN001-101, most subjects with mtDNA-PMM who received REN001 at an oral dose of 100mg once daily for 12 weeks improved 12MWD, 30 second sit to stand, VO_2 max and gait analysis with these physical function measures being supported by the PRO data. PRO data also reported a reduction in muscle related symptoms and fatigue. Pharmacological activity of the REN001 at 100mg per day was also shown in Phase 1 studies in other indications (see Investigator Brochure for details).

The safety and the pharmacodynamic effects observed in these four completed studies support the 100mg QD dose level in the primary mitochondrial myopathy population evaluated in both the STRIDE study and in this long-term safety study. Although, there is no prior history of REN001 exposure in patients with nDNA mutations, the safety profile of REN001 in this population is not expected to differ significantly from patients with mtDNA mutations. nDNA-PMM patients enrolling in this study must meet similar screening safety

requirements as the naïve mtDNA-PMM patients who previously enrolled in the STRIDE study or in the REN001-101 study.

For completeness, Phase Ib clinical trials have also been completed in Fatty Acid Oxidation Disorder, n= 24 subjects, 50mg or 100mg dose once daily; and McArdle Disease, n= 17 unique subjects, 100mg dose once daily; please see Investigator's Brochure.

2 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate long-term safety and tolerability of REN001 in subjects with PMM.

2.2 Secondary Objectives

To assess subjects with mtDNA-PMM who are receiving long-term treatment with REN001 in terms of PMM associated symptoms, pain severity and interference, exercise endurance, quality of life (QoL), patient global impression of change (PGIC) and patient global impression of severity (PGIS) for muscle and fatigue, and work productivity.

2.3 Pharmacokinetic (PK) Objectives

To further characterise the PK profile of REN001 in subjects with PMM receiving long-term treatment.

2.4 Exploratory Objectives

To evaluate the effect of long-term treatment with REN001 on bone health.

To assess subjects with nDNA-PMM who are receiving long-term treatment with REN001 in terms of PMM associated symptoms, pain severity and interference, exercise endurance, quality of life (QoL), patient global impression of change (PGIC) and patient global impression of severity (PGIS) for muscle and fatigue, and work productivity.

3 OVERALL DESIGN AND PLAN OF THE STUDY

3.1 Overview

This is a long-term safety study for subjects who have completed treatment in the STRIDE study, subjects who participated in the REN001-101 study and nDNA-PMM subjects. At sites with the IEC and regulatory approvals, eligible subjects will be treated for 48 months. A SRC will review safety data during the study. The structure, function, and operation of the SRC is detailed in the REN001-202 SRC Charter. Interim data cuts may be taken, and summaries prepared to support regulatory submissions or external communications such as publications. Subjects with mtDNA mutations enrolling from the STRIDE study will be switching from taking blinded REN001 or placebo in the STRIDE study to open label REN001 in this study. At the time of enrolment into this long-term study, prior treatment allocation in the STRIDE study will be unknown. Subjects who are nearing completion of the STRIDE study will be invited to discuss continuing into this long-term safety study and provide informed consent prior to any study activities. It is expected that most subjects transferring from the STRIDE study will do so at the STRIDE Week 24 visit to prevent an interruption in dosing and reduce the number of study visits and assessments. Subjects who are enrolled at the STRIDE Week 24 visit will not need to complete the STRIDE follow-up (FU) visit.

Alternative exclusion criteria (Section 4.3) apply to subjects who will be enrolled from sites in Germany. These criteria will require screening blood tests within 8 weeks prior to the start of dosing in this study. For those subjects wishing to start dosing immediately after the STRIDE Week 24 visit, their STRIDE Week 18 blood tests may be used as the screening assessments. However, additional blood samples will need to be collected for HbA1c and serology. See section 6.1.1 for details.

Enrolment at the STRIDE FU visit will require additional baseline assessments. For subjects at the German sites wishing to start dosing in this study immediately after the STRIDE FU, their STRIDE Week 24 blood tests may be used as the screening assessments; additional blood samples will need to be collected for serology. See Section 6.1.2 for details.

Subjects who wish to take part in this study after leaving the STRIDE study (i.e., after their STRIDE FU visit), who participated in Study REN001-101 (UK only), and nDNA-PMM subjects will require additional screening and baseline visits; details of enrolment options are provided in Section 6.1 and Table 2.

The PSOC will assess if nDNA-PMM subjects have the appropriate diagnosis for entry into the study prior to dosing. Subjects who successfully complete screening and are approved by the PSOC will then undergo a Baseline Visit.

After the baseline visit, each subject will have study visits at Months 1, 3, 6, 12, 18, 24, 30, 36, 42 and 48 (and Month 9 and 15 for German subjects). As a final follow-up there will be a telephone call from the study centre to the subject approximately 30 days after the last dose of study drug. A final follow-up telephone call will not be required if mavodelpar has been approved within the country and the subject switches to commercially available medication.

Where the site permits, a concierge service will be available to subjects to arrange hotel accommodation and transport to and from study centre visits and to reimburse any subject study expenses, if applicable. If a study centre requires it, subjects may be asked to have a negative COVID-19 test prior to undertaking scheduled visits at the study centre.

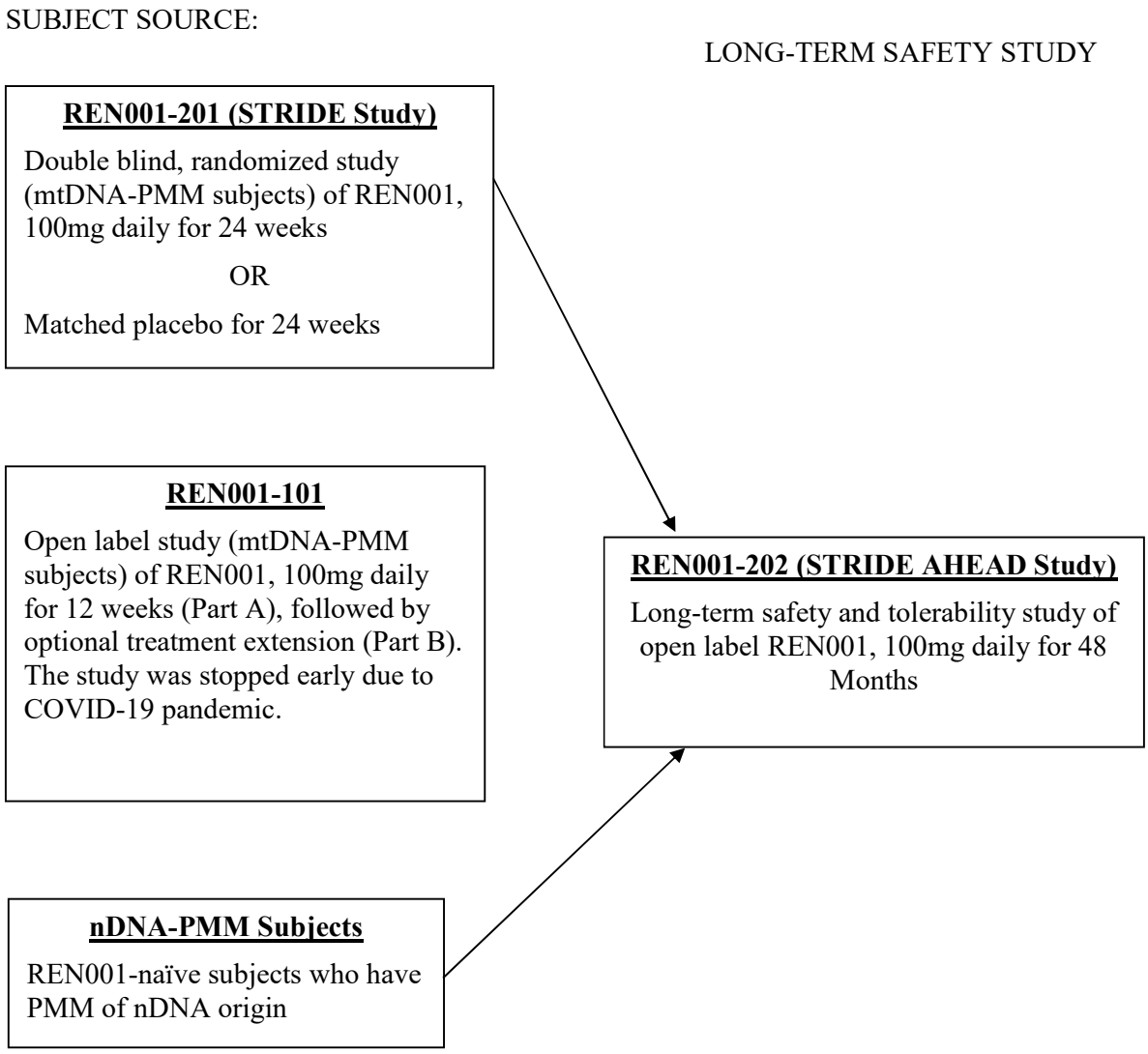
It is expected that most mtDNA-PMM subjects will enrol at the STRIDE Week 24 visit to prevent an interruption in dosing and reduce the number of study assessments. The requirement for screening and baseline visits will be dependent on when the subject enrols in

the study:

- Option 1: Enrolment at the STRIDE Week 24 visit: Most of the STRIDE Week 24 assessments will be regarded as the baseline assessments for this study. Additional assessments will be performed as noted in Section 6.1.1.
- Option 2: Enrolment at the STRIDE FU visit: The STRIDE FU visit will be regarded as the baseline visit for this study with additional assessments performed as noted in Section 6.1.2. If a washout period for any prohibited medication started since the STRIDE Week 24 visit, the subject will exit the STRIDE study and will require additional screening and baseline visits to enter the STRIDE AHEAD Study (Option 3 enroller).
- Option 3: Enrolment after exiting Study REN001-101 or STRIDE (mtDNA-PMM subjects): separate screening and baseline visits will be required, with assessments performed as noted in Section 6.1.3.
- Option 4: Enrolment of nDNA-PMM subjects: separate screening and baseline visits will be required, with assessments performed as noted in Section 6.1.4. nDNA-PMM subjects will not be enrolled in France.

The study design is shown in Figure 1 below. Full details of assessments required for the enrolment options is given below and shown in Table 2.

Figure 1: Study Design



3.2 Endpoints

3.2.1 Primary Endpoints

For mtDNA and nDNA subjects:

- Number and severity of adverse events (AEs)
- Number of AEs leading to study drug discontinuation
- Number of serious adverse events (SAEs)
- Number of adverse events of special interest (AESI)
- Number of AEs leading to death

3.2.2 Secondary Endpoints

For mtDNA and nDNA subjects:

- Absolute values, changes from baseline, and incidence of potentially clinically significant changes in:
    - Laboratory safety tests
    - Electrocardiograms (ECG)
    - Supine vital signs
    - Eye assessments

For mtDNA subjects:

- Absolute values and changes from baseline in:
    - Distance walked during the 12MWT*
    - MFIS total scores and sub-scale scores*

    Patient Global Impression of Severity (PGIS) scores for fatigue and muscle symptoms
    - Brief pain inventory (BPI) pain severity and pain interference scores*
    - Patient Reported Outcomes Measurement Information System (PROMIS) Short Form- Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue 13a scores*
    - 36-Item Short Form Health Survey (SF-36) domain scores (7-day recall)*
    - Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) scores*
    - First 6-minute walk distance and last 6-minute walk distance*
    - Phenotypic description questions*
- Patient Global Impression of Change (PGIC) scores for fatigue and muscle symptoms

3.2.3 PK Endpoints

REN001 plasma concentrations will be measured at each study visit*. The following parameters will be calculated for subjects recruited under Protocol Version 1.0: C_{trough}, $C_{max,}$ T_{max} and Area Under Curve $(AUC)_{\tau}$. The REN001 plasma concentrations may be included in a population PK analysis which will be reported separately to the Clinical Study Report for this study. REN001 metabolite concentrations may also be analyzed and reported.

3.2.4 Exploratory Endpoints

For mtDNA and nDNA subjects:

- Change from baseline to end of treatment in bone mineral density (BMD), as measured by dual energy x-ray absorptiometry (DXA), in the following:
    - Lumbar spine (L1 to L4) BMD
    - Total hip BMD and the femoral neck BMD (in the non-dominant hip)
    - Total hip, lumbar spine, and femoral neck T-scores and Z-scores

For nDNA subjects:

- Absolute values and changes from baseline in:
    - Distance walked during the 12-Minute Walk Test (12MWT)*
    - Modified Fatigue Impact Scale (MFIS) total scores and sub-scale scores*

    Patient Global Impression of Severity (PGIS) scores for fatigue and muscle symptoms
    - Brief Pain Inventory (BPI) pain severity and pain interference scores*

- Patient Reported Outcomes Measurement Information System (PROMIS) Short Form-Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue 13a scores*
- 36-item Short Form Health Survey (SF-36) domain scores (7-day recall)*
- Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) scores*
- First 6-minute walk distance and last 6-minute walk distance*
- Phenotypic description questions*

- Patient Global Impression of Change (PGIC) scores (muscle and fatigue symptoms).

***collected up to Month 24 only**

3.3 Justification of the Study Design

There are no specific regulatory guidelines for the design of studies in patients with PMM and no approved safe and effective treatments for the disease. The STRIDE study is designed to assess the efficacy and safety of REN001 in patients with PMM caused by mtDNA gene mutations treated over a 24-week period.

This long-term safety study is designed to evaluate the safety and tolerability of long-term treatment with REN001 in subjects with PMM. In addition, valuable data regarding PMM associated symptoms, exercise endurance, quality of life and work productivity will be captured. This study will also give the opportunity to evaluate the effects of REN001 on safety and tolerability, any effects of REN001 on other outcome measures, and on quality- of-life measures in PMM subjects with nDNA mutations.

This study will also generate data to support the evaluation of the PK profile of REN001 over time.

3.4 Termination or Suspension of Study

The study will be completed as planned unless one or more of the following criteria occur that require temporary suspension or early termination of the study:

- New information or other evaluation regarding the safety of REN001 that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Occurrence of local or global events (e.g., pandemic) that would impact the safety of subjects in the study.
- A decision by the Sponsor to suspend or discontinue development of the drug for the PMM indication.

3.5 Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the Investigator) is found to be in significant violation of GCP, the protocol, or the contractual agreement, or is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

3.6 Conditions for Individual Subject Withdrawal from the Study

The primary reason for subject withdrawal from the study should be recorded in the electronic Case Report Form (eCRF). Individual subjects may be withdrawn from the study in the following circumstances:

- Concurrent enrolment in other clinical studies involving investigational products or enrolment in other types of clinical research judged not to be scientifically or medically compatible with this study.
- Use of a prohibited concomitant medication.
- Major protocol deviation e.g., the discovery after administration of the first dose of study drug that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health or undermines the ability to achieve the objectives of the trial.
- Lost to follow-up. The subject does not return to the study centre and attempts to contact the subject are unsuccessful. Attempts to contact the subject must be documented.
- Evidence of pregnancy during the treatment period of the study.
- Clinically significant changes from baseline in ECG considered treatment-related including an increase from baseline to an absolute heart rate corrected QT interval using Fridericia's formula (QTcF) value of ≥500 millisecond (msec). Single ECGs should be repeated at 5-minute intervals 3 times to confirm any increased QT interval values. In the event of increased QTcF, the subject must be monitored until the value returns to below 500 msec.
- Clinically significant muscle injury including test abnormalities (e.g., CK) as defined in Section 3.7.1.
- Clinically significant liver toxicity including test abnormalities (e.g., ALT/AST) as defined in Section 3.7.2.
- Clinically significant kidney toxicity including test abnormalities (e.g., creatinine levels) as defined in Section 3.7.3.
- A TEAE that could result in a significant impairment. Subjects should be followed with appropriate medical management until there is a return to normal or baseline values or a clinical diagnosis of an emergent illness is confirmed.
- Voluntary withdrawal. The subject wishes to discontinue study drug and withdraw from the study. Subjects may withdraw from the study at any time without penalty and for any reason without prejudice to their future medical care. In all cases, the reason(s) for withdrawal, including the primary reason, must be recorded in the eCRF. Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

If a subject is prematurely withdrawn from the study drug, the Investigator must make every effort to perform the evaluations described for the Early Withdrawal visit and a further Follow-up contact approximately 30 days after the last does of study drug (if required, see Section 6.14). If the subject is withdrawing consent for continuing in the study and/or further contact no further assessments will be performed.

3.7 Strategy for Potential Withdrawal due to Laboratory Test Abnormalities

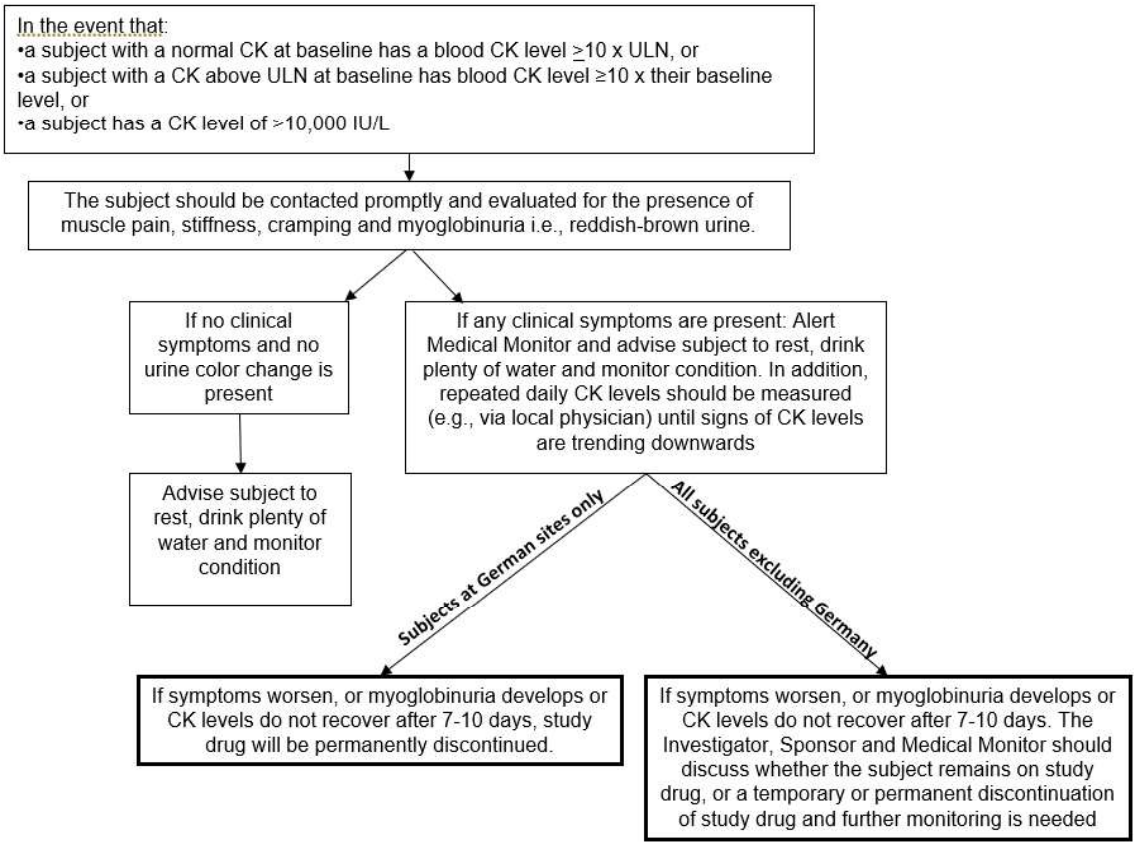
3.7.1 Safety Monitoring for Muscle Injury

Patients with PMM often present with mild to moderate baseline elevations in CK and can experience transient episodes of significantly elevated CK induced by acute illness, vigorous exercise, and other conditions. These elevations are not associated with symptoms or signs and the patients are typically well. CK elevations are generally of the skeletal muscle

fraction. However, a small proportion of the total CK may be from the myocardial fraction reflecting a small amount of this fraction found in skeletal muscle rather than the presence of myocardial injury. Importantly, these elevations are entirely to be expected in this patient population with underlying muscle disease and are not synonymous with clinically significant rhabdomyolysis. Similarly, elevations in serum aminotransferases and uric acid can accompany CK elevations and may not be indicative of liver disease.

True, clinically significant, rhabdomyolysis may also occur in these patients and must be managed appropriately. Rhabdomyolysis is characterized by severe acute muscle injury resulting in muscle pain, weakness, and/or swelling with release of myofiber contents into the bloodstream. Symptoms develop over hours to days following a triggering event and may be associated with dark pigmentation of the urine (Nance & Mammen, 2015). Acute kidney injury is a complication of rhabdomyolysis. The risk of acute kidney injury is low in patients with CK levels less than 15,000 international units per liter (IU/L). The CK algorithm below has been designed to identify those subjects potentially at risk of true rhabdomyolysis and ensure appropriate early action is taken to monitor and treat the subjects accordingly.

Figure 2: CK Algorithm



For the purpose of the different enrollment options, baseline is considered the visit where the subject starts drug.

3.7.2 Safety Monitoring for Liver: Management and Stopping Rules

Subjects with clinically significant liver disease or impairment have been excluded. It would be inappropriate to exclude all subjects with milder elevations in LFTs out of the normal range because subjects with PMM can present with elevations in CK levels that are often accompanied by elevated LFTs (ALT and AST), which are not indicative of liver disease. Accordingly, these elevations appear to be transient and resolve spontaneously (Tarnopolsky 2016). Although serum ALT and AST values have shown good diagnostic accuracy in patients with chronic liver disease, AST and ALT levels can be increased immediately after muscular exertion as well (Lippi 2008).

In the event that a subject presents with raised LFTs during the study the following management guidelines and stopping rules should be followed:

- For subjects who enrol with a baseline below the ULN and present with an increase in serum ALT or AST > 3xULN, repeat testing of ALT, AST, ALP and total bilirubin will be obtained as soon as possible, ideally within 48-72 hours, to confirm the abnormality and whether the abnormality is increasing or decreasing.

- For subjects who enrol with a baseline above the ULN and present with an increase in serum ALT or AST > 3xULN and at least 2x their baseline value, repeat testing of ALT, AST, ALP and total bilirubin will be obtained as soon as possible, ideally within 48-72 hours, to confirm the abnormality and whether the abnormality is increasing or decreasing.
- If symptoms persist or repeat testing shows ALT > 3xULN for subjects with normal baseline measures or 2x their baseline value for subjects with elevated values at baseline, initiate close observation with repeat testing 2-3 times weekly, or as clinically mandated, to determine whether the abnormalities are improving or worsening (see below for further details).
- If close monitoring is not possible, as a precautionary measure study drug should be withheld and continued participation in the study should be discussed with the Medical Monitor.

3.7.2.1 Guidelines for Close Observation

- Repeated ALT, AST, ALP, and total bilirubin tests two or three times weekly.
- Frequency of re-testing can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.
- Obtain a more detailed history of symptoms and prior or concurrent diseases.
- Recheck history of concomitant drug use (including non-prescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and any special diets.
- Rule out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; Non-alcoholic steatohepatitis (NASH); hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtain a history of exposure to environmental chemical agents.
- Obtain additional tests to evaluate liver function, as appropriate (e.g., International normalized ratio (INR) or Prothrombin time (PT), direct bilirubin).
- Consider gastroenterology or hepatology consultations.

3.7.2.2 Discontinuation – All Subjects

Discontinuation or interruption of study drug should be considered, in consultation with the Medical Monitor and the Sponsor where possible, if:

- ALT or AST > 8xULN.
- ALT or AST > 5xULN for more than 2 weeks.
- ALT or AST > 3xULN and total bilirubin > 2xULN or INR >1.5.
- ALT or AST > 3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

3.7.2.3 Discontinuation – Subjects in German sites

Discontinuation of study drug should occur and close monitoring continued, if:

- ALT or AST > 8xULN.
- ALT or AST > 5xULN for more than 2 weeks.
- ALT or AST > 3xULN and total bilirubin > 2xULN or INR >1.5.

- ALT or AST > 3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

3.7.3 Safety Monitoring for Kidney: Management and Stopping Rules

If subjects develop a creatinine elevation > 2xULN and more than 2x baseline value:

- Monitor creatinine 2 times per week, or as clinically indicated, until recovery.
- For subjects with > 3xULN the study drug should be withheld, and the subject should continue to be followed closely.
- In the event of either of the above continued participation in the study should be discussed with the Medical Monitor.

3.7.3.1 Discontinuation – All Subjects

Discontinuation of study drug should be considered, in consultation with the Medical Monitor and the Sponsor where possible, if:

- A > 3xULN creatinine elevation is sustained or deteriorating.
- The subject is unwell and has hyperkalemia.

3.7.3.2 Discontinuation – Subjects in German sites

Study drug must be discontinued if:

- A > 3xULN creatinine elevation is sustained or deteriorating.
- The subject is unwell and has hyperkalemia.

3.8 Replacement of Subjects

Replacement of subjects is not applicable in this study.

3.9 Temporary Discontinuations

Subjects may be temporarily discontinued from study drug while AEs and/or laboratory test abnormalities are being investigated and/or at the request of the Medical Monitor. The Investigator should discuss with the Medical Monitor and Sponsor any subject for whom temporary or permanent discontinuation of study drug is being considered.

If a subject misses several consecutive doses due to personal circumstances or due to an AE not related to study drug, they may be allowed to restart dosing after discussion between the Investigator, Medical Monitor and Sponsor (Section 5.7).

3.10 Review of Screening Eligibility Data for nDNA-PMM subjects

An independent Patient Screening Oversight Committee with experts in the diagnosis of PMM will review screening data to ensure nDNA-PMM subjects have the appropriate diagnosis for entry into the study. Details regarding the structure, function and operation of the PSOC are detailed in the REN001-202 PSOC Charter. nDNA-PMM subjects will not be enrolled in France.

3.11 Safety Review Committee (SRC)

Review of subject safety data (including AEs, ECGs, laboratory safety tests, vital signs, and eye examinations) from this long-term open-label safety study will be performed by the SRC in accordance with the REN001-202 SRC Charter. Safety reviews will be conducted throughout the study to identify any potential safety signals during the trial that may have an impact on the safety of the participants. The SRC may make recommendations concerning continuation, termination or other study modifications based on these reviews.

4 STUDY POPULATION

Protocol inclusion and exclusion criteria in Section 4.1 are intended for all subjects enrolling into the study. These are the only criteria to be assessed for mtDNA-PMM subjects enrolling at the STRIDE Week 24 or STRIDE FU visits. Additional eligibility criteria will need to be met for those mtDNA-PMM subjects enrolling after exiting from either of the 2 feeder studies and nDNA-PMM subjects (Section 4.2). In addition, nDNA-PMM subjects will have some screening data independently reviewed by the PSOC to confirm eligibility. nDNA-PMM subjects will not be enrolled in France.

4.1 Protocol Criteria for All Subjects

4.1.1 Inclusion Criteria

Subjects must meet the following inclusion criteria to be eligible for the study:

1. mtDNA-PMM subjects: Completed treatment in the STRIDE study or participated in Study REN001-101, and in the opinion of the Investigator and the Sponsor have been compliant with the study requirements

   Or

   nDNA-PMM subjects: Subjects aged 18 years or older with known nuclear (nDNA) pathogenic variants with a major muscle phenotype consisting of objective myopathy with poor exercise tolerance. Proof of pathogenicity must be provided. Must be able to walk at least 100m in the screening 12MWT and the limitations in walk test must be primarily due to the energy deficit and not due to ataxia or any other condition. For subjects under 25 years old only: confirmation of bone growth plate closure by wrist radiograph.
2. Have PMM which continues to be primarily characterized by exercise intolerance or active muscle pain.
3. Willing and able to swallow gelatin capsules.
4. Concomitant medications (including supplements) intended for the treatment of PMM or other co-morbidities likely to remain stable throughout participation in the study where clinically possible.
5. Signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
6. Females should be either of non-child-bearing potential or must agree to use highly effective methods of contraception from baseline through to approximately 30 days after last dose of study drug. Males with partners who are WOCBP must also use contraception from baseline through to 14 weeks after last dose of study drug.

4.1.2 Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Anticipated to need a PPAR agonist other than REN001 during the study.
2. Anticipated to need drugs during the study with a narrow therapeutic index and Breast Cancer Resistant Protein (BCRP) mediated absorption, distribution, metabolism and excretion (ADME) (Table 1).

3. Intent to donate blood, or blood components during the study or within one month after completion of the study.
4. Current drug dependency. Use of opiates/cannabis for medical reasons is acceptable with prescription evidence or at the Investigator's discretion.
5. Current alcohol dependency.
6. Any medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or interfere with the interpretation of study results and, in the judgment of the Investigator and Medical Monitor, would make the subject inappropriate for entry into this study.
7. Pregnant or nursing females.

4.2 Additional Exclusion Criteria

Subjects with mtDNA-PMM enrolling after exiting from either of the 2 feeder studies and subjects who have nDNA-PMM will be required to fulfil these additional exclusion criteria:

1. Clinically significant kidney disease or impairment, with an eGFR less than 60ml/min/1.73m^2 using the CKD-EPI creatinine equation at baseline. German sites - see alternative criteria below in Section 4.3.
2. Clinically significant liver disease or impairment with AST or ALT >2.5 x ULN, or Total bilirubin > 1.6 x ULN or >ULN with other signs and symptoms of hepatotoxicity at baseline. (Subjects with an isolated elevated bilirubin (e.g., < 2 x ULN) may be included after discussion with the Medical Monitor if the cause is due to a benign hereditary disorder of metabolism such as Gilbert's syndrome.)
3. Uncontrolled diabetes and/or a glycosylated hemoglobin (HbA1c) of ≥ 11%. German sites - see alternative criteria below in Section 4.3.
4. Evidence of significant concomitant clinical disease that may need a change in management during the study or could interfere with the conduct or safety of this study. (Stable well-controlled chronic conditions such hypercholesterolemia, gastroesophageal reflux, or depression under control with medication, are acceptable provided the symptoms and medications would not be predicted to compromise safety or interfere with the tests and interpretations of this study.)
5. Clinically significant cardiac disease and/or clinically significant ECG abnormalities including a Baseline QTcF of ≥ 450 msec, 2nd degree heart block, symptomatic tachyarrhythmia or unstable arrythmia that in the opinion of the Investigator should exclude the subject from study completion. Subjects with right bundle branch block, left fascicular block and long PR interval which are common in PMM may be enrolled if the Investigator considers that the condition would not compromise their safety in this study.
6. Treatment with an investigational drug, other than REN001, within 3 months or 5 drug half-lives, whichever is longer, prior to Day 1.
7. Have been hospitalized within the 3 months prior to Screening for any major medical condition (as deemed by the Principal Investigator).
8. Subjects with poor nutritional status as determined by the Investigator.
9. Subjects with positive hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb), or positive hepatitis C or human immunodeficiency virus (HIV) at screening. German sites – see alternative criteria below in Section 4.3.
10. Subjects who are not eligible or have a contraindication for cataract surgery.
11. Any condition possibly reducing drug absorption (e.g., gastrectomy or increased gastrointestinal motility).
12. History of cancer (except basal cell carcinoma).

13. For subjects exiting REN001-101 study and nDNA- PMM subjects a history of fragility/stress fractures or an osteoporosis concomitant condition which has not been adequately addressed.

4.3 Alternative Exclusion Criteria for Subjects in Germany

For additional exclusion criteria 1, 3 and 9, the following alternative criteria apply:

1. Clinically significant kidney disease or impairment, with an eGFR less than 60ml/min/1.73m^2 using the CKD-EPI creatinine equation.
3. Uncontrolled diabetes and/or a glycosylated hemoglobin (HbA1c) of ≥ 8.5%. (NOTE: an HbA1c is not obtained as part of the Week 18 visit in the Stride Study. Nevertheless, the Week 18 blood draw may be used to obtain the test provided the subjects has given the appropriate consent).
9. Subjects with positive hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb) or positive hepatitis C or human immunodeficiency virus (HIV). (NOTE: these tests are not obtained as part of the Week 18 or 24 visits in the Stride Study. Nevertheless, the Week 18 or 24 blood draws may be used to obtain the test provided the subjects has given the appropriate consent).

Assessment of these criteria will require screening blood tests within 8 weeks prior to their start of dosing in this study. For those subjects wishing to start dosing immediately after the STRIDE Week 24, their STRIDE Week 18 blood tests may be used as the screening assessments. However, additional blood samples will need to be collected for HbA1c and serology.

For mtDNA-PMM subjects wishing to start dosing immediately after the STRIDE FU visit their STRIDE Week 24 blood tests may be used as the screening assessments. However, additional blood samples will need to be collected for serology.

4.4 Additional Criteria for Subjects at Sites where DXA Scans are Approved

A separate DXA sub-study was set up to collect DXA scans alongside the STRIDE study. In countries and sites where the DXA sub-study was approved by IEC/Regulators, and subjects have a DXA scan at the STRIDE Week 24 time point, this will be taken as baseline for this study and a DXA will be performed at Month 24, and at Month 48, or early withdrawal from this study.

Subjects who did not enter the DXA sub-study during the STRIDE study at sites where the DXA sub-study was approved, subjects who participated in Study REN001-101 and nDNA-PMM subjects must meet the following enrolment criteria. If eligible, these subjects will have a baseline DXA scan on entry to this study and then a DXA scan at Month 24, and one at Month 48 or at early withdrawal. DXA scans are considered optional for all subjects.

Criteria to be eligible for the DXA scan for subjects who did not enter the STRIDE DXA sub-study:

- Must have at least one hip free of metal.
- Signed consent for DXA scan.

Subjects presenting with any of the following will not be eligible for a DXA scan:

- Positive pregnancy test, or possibility of being pregnant.

- Gastrointestinal contrast agents or radionuclides administered within 14 days of the scan, where DXA cannot be rescheduled.
- Severe degenerative changes or fracture deformity in the spine and either fractures in both hips, or double hip replacement.
- Implants, hardware, devices, or other foreign material in both measurement areas.
- Subjects fitted with an implantable cardioverter defibrillator. Pacemakers are permitted.
- Subject unable to attain correct position for both measures and/or remain motionless for the measurement (maximum of 5 minutes scan time, 20 minutes for the entire procedure).
- Absolute weight >136kg (or 300lb).

4.5 Planned Sample Size and Study Centres

Recruitment will be limited to those mtDNA-PMM subjects who participated in the STRIDE study (applicable only for countries where this study is being conducted) or Study REN001-101 (UK only), and nDNA-PMM subjects. It is estimated that approximately 150 mtDNA-PMM and 50 nDNA-PMM subjects may be enrolled. Recruitment will be from across a minimum of 30 centres. nDNA-PMM subjects will not be enrolled in France.

4.6 Study Completion

The study will be considered completed with the last follow-up telephone call of the last subject. A final follow-up telephone call will not be required if mavodelpar has been approved within the country and the subject switches to commercially available medication.

5 STUDY DRUG

5.1 Study Drug Identity

Study drug is presented as orange, hard gelatin capsules, manufactured by Xcelience LLC, a Lonza company. The dosage strength of REN001 capsules is 50mg. Capsules are packaged in 200mL high-density polyethylene (HDPE) bottles, with a heat induction seal and child-resistant lids, containing 100 capsules of 50mg REN001. Labels will contain batch number and expiration date.

5.2 Management of Study Drug

Study drug will be managed using an Integrated Web-Based Response System (IWRS). Sufficient bottles will be supplied to ensure subjects have at least enough capsules to maintain dosing between study centre visits.

5.3 Administration

Subjects will receive once daily 100mg REN001 as 2 x 50mg capsules for oral administration for the duration of the study. Study drug should be taken with food at a convenient time to the subject (ideally in the morning). Subjects will be supplied with a dose record card and will be requested to record the date and time of dosing for all study visit days.

At the Month 3 visit, PK samples will be taken pre and post study drug administration over a 4-hour period (Section 6.3). At this visit the subject should take the study drug at the study centre with food when instructed to do so by the site staff.

5.4 Packaging, Labelling and Storage

Bottles will be labelled and released in accordance with the Clinical Trials Directive 2001/20/EC (European Commission, 2001), GMP Directive 2003/94/EC for Investigational Medicinal Products (European Union, 2003) and US Code of Federal Regulations 21CFR312.6 and 21CFR211.165.

All study drug supplies must be stored in accordance with the manufacturer's instructions. Until dispensed to the subjects, the study drug (REN001 capsules) should be stored at refrigerated temperature (2-8ºC), in a securely locked area, accessible to authorized personnel only. A daily temperature log of the study drug storage area must be recorded and checked every day. Temperature excursions must be reported to the Sponsor or delegate as soon as possible.

Once the study drug has been dispensed to subjects, it should be stored refrigerated (2-8ºC) at the subject's home. Study drug does not need to be kept refrigerated during transport to and from the subject's home and the study centre. Subjects should only open and use one bottle of study drug at a time. Study drug should be kept away from children.

5.5 Excessive Pharmacological Effects

No specific antidotes for REN001 are available and standard supportive measures should be used in the case of excessive pharmacological effects.

5.6 Drug Accountability

The Investigator is responsible for maintaining accurate accountability records for study drug throughout the study. Each dispensing of study drug will be documented in the IWRS.

The subject must bring all study drug (including empty bottles) to the study centre at each visit to monitor compliance, reconciliation, and quarantine of any expired study drug ahead of destruction. Any study drug remaining at the end of study will be returned to the Sponsor

or their representative or destroyed locally on behalf of the Sponsor (with written permission of the Sponsor) and the destruction fully documented.

5.7 Compliance

At all study visits subject compliance with the study drug regimen will be monitored by capsule counts. If a subject consistently fails to take their study drug, the Investigator should alert the site monitor, Medical Monitor and Sponsor and a decision will be made as to whether the subject should be withdrawn for non-compliance.

5.8 Contraceptive Requirements

In countries where the regulatory authority allows, WOCBP will be allowed to enrol into this long-term safety study provided they continue to agree to use adequate contraceptive requirements as outlined for their participating site.

Contraceptive requirements for the study have been defined using the recent recommendations of the Clinical Trials Facilitation Group, Rome September 2014 meeting (Clinical Trials Facilitation Group, 2014 and 2020) and also the International Council on Harmonisation (ICH) M3(R2) guidance (European Medicines Agency, 2009).

5.8.1 Females

Females of child-bearing potential must agree to use highly effective methods of contraception from baseline to approximately 30 days (one menstrual cycle) after the last dose of study drug. Highly effective methods are:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation administered by oral or intravaginal route.
- oral, injectable or implantable progestogen-only hormonal contraception associated with inhibition of ovulation.
- intrauterine device.
- intrauterine hormone-releasing system.
- bilateral tubal occlusion.
- bilaterally orchiectomized or vasectomized partner, provided that partner is the sole sexual partner of the subject, and in the case of a vasectomized partner has received medical assessment of the surgical success.
- true sexual abstinence, where this is in line with the usual lifestyle of the subject.

Periodic (calendar, ovulation, symptothermal or post-ovulation) abstinence and withdrawal are not acceptable methods of contraception.

Caution with co-administration of REN001 and hormonal contraceptives is advised due to the potential for drug-drug interaction (Section 1.4). In addition to highly effective hormonal contraception, WOCBP at risk of pregnancy are advised to also use an additional effective non hormonal method of contraception. Effective methods are male condom, female condom, cervical cap, diaphragm, contraceptive sponge.

Females are considered to be of non-child-bearing potential if they fulfil at least one of the following criteria:

- Post-menopausal, defined as 45 years or older and amenorrhoeic for at least 1 year PLUS have a serum follicle stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women, at screening or baseline visit.
- Have undergone a documented hysterectomy and/or bilateral oophorectomy.

5.8.2 Males who are considered fertile and with partners who are WOCBP

Males are considered fertile after puberty unless permanently sterile by bilateral orchidectomy or vasectomy (following medical assessment of surgical success). Fertile males with partners who are WOCBP must agree to use contraception (condom) from baseline until 14 weeks after the last dose of study drug. A condom is required to be used by vasectomized men to prevent delivery of the drug via seminal fluid. In addition, they must be advised not to donate sperm during this period.

5.9 Concomitant Medications

Any medication other than the study drug is considered a concomitant medication. The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, dose, start and stop date (and whether it is a prior medication) and indication.

At baseline, subjects will be asked what medications they are currently taking. At each subsequent study visit, subjects will be asked what medications they have taken since the last study visit. If the subject is enrolled at the STRIDE Week 24 or FU visits, then their ongoing concomitant medications at the time of transition from one study to the other will be recorded for both studies. For those mtDNA-PMM subjects enrolling from Study REN001-101 (UK only), or after exiting the STRIDE study, and nDNA-PMM subjects, any medications taken prior to the start of dosing will be documented as prior medications. Subjects who are receiving prohibited medications must suspend the medications if this can safely and appropriately be done and have sufficient washout during the screening period (See Table 1). Re-screening of subjects is allowed only once and requires prior approval by the Sponsor.

If a mtDNA-PMM subject who wishes to enrol at the STRIDE FU visit has started taking prohibited medications between their Week 24 and FU visits, they will not be allowed to start dosing until they have had a sufficient washout of the medications (Table 1). The subject will exit the STRIDE study and have a screening and baseline visit for this study. Subjects may not use the medications and treatments listed in Table 1 and these medications must be withheld for the duration of the study.

5.9.1 *Statins*

Concomitant statin therapy should be initiated based on a consideration of risk-benefit, given the inherent risk of myopathy from statin treatment.

Potential identified individual risk factors for statin-induced myopathy include age, sex, race and clinical co-morbidities (history of elevated CK, family history of muscle symptoms induced by lipid lowering therapy, hypothyroidism, McArdle disease, diabetes mellitus, current infection, renal disease, hyperuricemia, alcohol overconsumption, trauma and intense physical activity). Identified pharmacodynamic genetic markers that appear to increase statin risk for myopathy include CPT2, COQ2 and RYR2 (Feng et al. 2012).

In addition, pharmacokinetic interactions, arising from concomitant drug therapy or genetic polymorphisms in enzymes and transporters that decrease statin elimination by mechanisms including metabolism and transport by CYP3A4, SLCO1B1, OAT3, P-gp and BCRP, are risk factors for statin-induced myopathy. The contribution of each of these is dependent on the individual statin with the dose intensity of the statin being a high predictor of risk.

Mavodelpar does not appear to be an inhibitor of any of the above processes with perhaps the exception of BCRP. Therefore, a clinical study to examine the impact of mavodelpar on a single 20mg rosuvastatin dose, the statin predicted to be most affected by mavodelpar, was conducted in healthy subjects. Based on preliminary data from the study, a chronic 100 mg

daily regimen resulted in a weak interaction, increasing the AUC_{inf} by 58% (90% CI; 40% to 78%) and C_{max} by 81% (90% CI; 61% to 103%); i.e., 1.58 and 1.81-fold increase respectively. These data indicate that this weak interaction is likely to be inhibition of BCRP in the intestine, leading to a small increase in the extent of rosuvastatin absorption. Based on the pharmacokinetic changes alone, rosuvastatin use may be considered.

Additional physiologically-based pharmacokinetic (PBPK) modelling was conducted with a model that predicted the changes in rosuvastatin and applied to predict pharmacokinetic changes that mavodelpar might have on atorvastatin and pravastatin. Based on the findings from this model, no significant PK drug-drug interactions are anticipated for these statins as well. Therefore, these statins could also be used based on pharmacokinetic changes. The use of any of these statins in this population should be initiated based on consideration of risk-benefit.

5.9.2 Sensitive BCRP substrates with narrow therapeutic indices

Based on in vitro data and a clinical drug-drug interaction study with the index BCRP substrate, rosuvastatin, mavodelpar is a weak inhibitor of BCRP. Therefore, drugs with narrow therapeutic indices and whose dispositions are affected by BCRP should not be used (Table 1).

5.9.3 Treatment with moderate or strong inhibitors or inducers of cytochrome P450 (CYP)2C8

Approximately half of mavodelpar clearance is estimated to be mediated by oxidative metabolism, mediated primarily by CYP2C8. In a clinical drug-drug interaction study with gemfibrozil, a strong index CYP2C8 inhibitor, mavoldelpar exposure (AUC_{inf}) was increased (preliminary data) by 257 (90% CI; 216% to 305%). Also, steady-state carbamazepine, an identified PXR and CAR activator responsible for induction of various CYP enzymes, on mavodelpar exposure was also investigated in a clinical drug-drug interaction study. Carbamazepine reduced (preliminary data) mavodelpar exposure (AUC_{inf}) by 60%. The AUC ratio of mavodelpar + carbamazepine compared to mavodelpar alone was 39% (90% CI; 37% to 42%). . Such a decrease might result in loss of efficacy. Therefore, the use of moderate or strong inhibitors of CYP2C8 and PXR/CAR inducers are prohibited (See Table 1).

Table 1: Prohibited Medication

Medication	**Washout period (Prior to Day 1)[1]**
Statins (including simvastatin and lovastatin)[2]	1 week
Anticoagulants[2]	1 week or 5 half-lives: (whichever longer)
Bezafibrate and other PPAR agonists	4 weeks
Cyclosporine and other immunosuppressive drugs	4 weeks
Oral or systemic steroids[2]	4 weeks
Investigational drugs (other than REN001)	3 months or 5 half-lives (whichever longer)
Moderate or strong CYP2C8 inhibitors and CAR/PXR activators, including clopidogrel, deferasirox, gemfibrozil, teriflunomide, trimethoprim, tucatinib, rifampin, carbamazepine	3 months or 5 half-lives (whichever longer)
Drugs with a narrow therapeutic index and BCRP mediated ADME e.g., aliskiren, ambrisentan, colchicine, digoxin, everolimus, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan, methotrexate, mitoxantrone, irinotecan, and sulfasalazine.	No washout period applicable, subjects should be excluded from the study (section 4.1.2)

[1] Only applies to mtDNA-PMM subjects enrolling at STRIDE FU, after exiting STRIDE or Study REN001-101, and nDNA-PMM subjects

[2] pravastatin, atorvastatin and rosuvastatin may be used after careful consideration of the benefit/risk assessment. Other statins, anticoagulants and steroids may be allowed if considered medically appropriate following discussion with the Medical Monitor/Sponsor

6 STUDY CONDUCT

Depending on IEC and regulatory approvals, this study may be conducted at a minimum of 30 study sites. Details of study assessments are provided in Section 7.

Following baseline, visits should occur within the scheduled timeslot for the visit; see Table 3, Schedule of Activities. Where possible, visits should occur on the target visit day in relation to the first day of study drug dosing.

Site staff will provide subjects with meals and snacks at appropriate times during the visit so that study drug is taken with food and to ensure subjects have enough energy prior to completing the exercise tests as required.

All PROs should, where possible, be completed prior to the 12MWT, and the 12MWT should be performed at least 2 hours after a snack. The 12MWT should be conducted at the same time of day on every occasion where possible.

Where a study centre requires, subjects may be asked to have a negative COVID-19 test prior to undertaking scheduled visits at the study centre.

6.1 Screening and Baseline Visits

It is expected that most mtDNA-PMM subjects will enrol at the STRIDE Week 24 visit to prevent an interruption in dosing and reduce the number of study assessments. The requirement for screening and baseline visits will be dependent on when the subject enrols in the study:

- Option 1: Enrolment at the STRIDE Week 24 visit: Most of the STRIDE Week 24 assessments will be regarded as the baseline assessments for this study. Additional assessments will be performed as noted in Section 6.1.1.
- Option 2: Enrolment at the STRIDE FU visit: The STRIDE FU visit will be regarded as the baseline visit for this study with additional assessments performed as noted in Section 6.1.2. If a washout period for any prohibited medication started since the STRIDE Week 24 visit, the subject will exit the STRIDE study and will require additional screening and baseline visits to enter the STRIDE AHEAD Study (Option 3 enroller).
- Option 3: Enrolment after exiting Study REN001-101 or STRIDE (mtDNA-PMM subjects): separate screening and baseline visits will be required, with assessments performed as noted in Section 6.1.3.
- Option 4: Enrolment of nDNA-PMM subjects: separate screening and baseline visits will be required, with assessments performed as noted in Section 6.1.4. nDNA-PMM subjects will not be enrolled in France.

Full details of assessments required for the enrolment options is given below and shown in Table 2.

6.1.1 Option 1: Enrolment at STRIDE Week 24

As a subject nears completion of the STRIDE study, the possibility of participation in this long-term safety study should be discussed with the subject and the approved patient information sheet supplied to the subject. Subjects should be given adequate time to think about whether they want to participate and to ask questions. The Investigator (or an appropriate delegate at the site) will obtain written informed consent from each subject prior to commencing any specific study related activities or assessments. Subjects who are enrolled at the STRIDE Week 24 visit will not need to complete the STRIDE FU visit.

Subjects enrolling in Germany will require screening blood tests within 8 weeks prior to the start of dosing in this study. For subjects wishing to start dosing immediately after the STRIDE Week 24 visit, their STRIDE Week 18 blood tests may be used as the screening assessments. However, additional blood samples will need to have been collected for HbA1c and serology with results available for review prior to dosing in this study.

Medical histories and demography reported in STRIDE will be transferred to this study. The following procedures taking place at STRIDE Week 24 will be regarded as baseline assessments for this long-term safety study:

- Second morning void urine sample for:
  - Urine NTX bone markers
  - Urinalysis and drugs of abuse testing
  - Urine pregnancy testing (WOCBP)
- Blood samples for:
  - Haematology and biochemistry (including HbA1c)
  - Bone and calcium markers
  - Pre-dose plasma sample for PK analysis of REN001
- Review of ongoing concomitant medications and non-drug treatments.
- Review of ongoing AEs.
- Physician completion of subject's PMM phenotypic description.
- Physical examination (including weight).
- ECG.
- Vital signs (including temperature).
- Patient Reported Outcome (PRO) Questionnaires
  - MFIS
  - PGIS – muscle symptoms and fatigue symptoms
  - PROMIS Short Form – 13a (FACIT Fatigue)
  - SF-36
  - WPAI:SHP
  - BPI
- 12MWT.
- Eye examination.
- DXA Scan (if participating in DXA sub-study of STRIDE study).

Additional procedures required specifically for enrolment into this long-term safety study at Week 24 of STRIDE are:

- Obtain written informed consent. In Germany written informed consent should be obtained prior to the additional screening samples for HbA1c and serology tests taken within 8 weeks prior to baseline, these may be done at STRIDE Week 18 visit.
- Optional DXA Scan (if not performed as part of the STRIDE DXA sub-study in those countries and sites where this is permitted). It should be scheduled as close as possible to this baseline visit, however if this is not feasible, then it must be performed within the 4 weeks after the baseline visit. Subjects must be checked against the Additional Criteria for Sites with approvals for DXA Scans (Section 4.3). All WOCBP must have

a negative pregnancy test prior to the scan. All female subjects will require an FSH test if not confirmed as post-menopausal on the STRIDE Study. Details of how the DXA scan will be performed can be found in the DXA Manual.

- Urine pregnancy test for women aged ≥45 years, not confirmed as post-menopausal in the STRIDE study and if not already conducted at Week 24 STRIDE visit.
- Dispense study drug, first dose to be taken the following day with food at home. Subject should be instructed on study drug dosing requirements and reminded of the study restrictions. Study centre will telephone the subject the day after this baseline visit to confirm administration of first dose of study drug (Day 1) and record any change in AEs or concomitant medications (ongoing or new) since leaving the study centre on the previous day. Additional telephone contact will be made with the subject until first administration of study drug is confirmed. The contact and the first dose date will be reported in the eCRF.

6.1.2 Option 2: Enrolment at STRIDE FU

Subjects will be required to attend the study centre for the STRIDE FU visit to allow the additional assessments required for enrolment into this study.

Subjects enrolling in Germany will require screening blood tests within 8 weeks prior to the start of dosing in this study. For subjects wishing to start dosing immediately after the STRIDE FU visit, their STRIDE Week 24 blood tests may be used as the screening assessments. However, additional blood samples will need to have been collected for serology with results available for review prior to dosing in this study.

Subjects who plan to roll over at the STRIDE FU visit should be provided with a urine collection cup and instructions for collecting a second morning void, *at the STRIDE Week 24 visit*. This is provided in case the subject has their second morning void before attending the study centre at their next study visit.

Medical histories and demography reported in STRIDE will be transferred to this study. The following procedures taking place at the Week 24 or the FU visit for the STRIDE study will be regarded as baseline assessments for this long-term study:

- Review of ongoing AEs (part of STRIDE FU assessments).
- Vital signs (including temperature, part of STRIDE FU assessments).
- Urine pregnancy testing (WOCBP, part of STRIDE FU assessments).
- Eye examination (part of Week 24 assessments)
- DXA Scan (if participating in DXA sub-study of STRIDE study, part of Week 24 assessments)
- Review of ongoing concomitant medications and non-drug treatments (part of STRIDE FU assessments).

Additional procedures required specifically for enrolment into this long-term safety study at the STRIDE FU visit are:

- Obtain written informed consent. In Germany written informed consent should be obtained prior to the additional screening samples for serology tests taken within 8 weeks prior to baseline, these may be done at STRIDE Week 24 visit.

If subject started on any prohibited medications (Table 1) since STRIDE Week 24, a washout period will be required and the subject will need to exit the STRIDE study and return for screening and baseline visits after the washout period, as an Option 3 enroller;

the screening visit should be scheduled as soon as possible after the washout period.

For subjects who do not need a washout period of prohibited medications the following procedures should be carried out at the STRIDE FU visit:

- Second morning void urine sample for:
  - Bone marker – NTX
  - Urinalysis, drugs of abuse testing
- Blood samples for:
  - Haematology and biochemistry (including HbA1c)
  - Bone and calcium metabolism markers
  - Serum FSH testing for all females (aged ≥45 years) who were not confirmed as post-menopausal in the STRIDE study
  - Pre-dose plasma sample for PK analysis of REN001
- Physician completion of subject's PMM phenotypic description.
- Full physical examination (including weight and height).
- ECG.
- Patient Reported Outcome (PRO) Questionnaires
  - MFIS
  - PGIS – muscle symptoms and fatigue symptoms
  - PROMIS Short Form – 13a (FACIT Fatigue)
  - SF-36
  - WPAI:SHP
  - BPI
- 12MWT.
- Optional DXA Scan (in those countries and sites where this is permitted), if not performed as part of the STRIDE DXA sub-study. It should be scheduled as close as possible to this baseline visit, however if this is not feasible, then it must be performed within the 4 weeks after the baseline visit. Subjects must be checked against the Additional Criteria for Sites with approvals for DXA Scans (Section 4.4). All WOCBP must have a negative pregnancy test prior to the scan. All female subjects will require an FSH test if not confirmed as post-menopausal on the STRIDE Study. Details of how the DXA scan will be performed can be found in the DXA Manual.
- Dispense study drug, first dose to be taken at the site with food under the supervision of study staff. The time of dosing will be recorded. Subject should be instructed on study drug dosing requirements and reminded of the study restrictions.

6.1.3 Option 3: Enrolment of mtDNA-PMM subjects from Study REN001-101 or after exiting STRIDE

Separate screening and baseline visits are required when enrolling mtDNA-PMM subjects into this study after exiting from either of the 2 feeder mtDNA-PMM studies, as screening blood and urine test results must be available at the baseline visit for clinical review. Subjects who are receiving prohibited medication must suspend the medication if this can safely and appropriately be done. If a washout period is required for any prohibited medications this may extend the time between the screening and baseline visits (Table 1). The assessments to be carried out at each visit are as follows:

6.1.3.1 Screening Visit

- Obtain written informed consent. Subjects should be given adequate time to think about whether they want to participate and to ask questions. The Investigator (or an appropriate delegate at the site) will obtain written consent from each subject prior to commencing any specific study related activities or assessments.
- Subject Demography.
- Complete Medical History (including prescription and non-prescription drugs/treatment, non-drug treatments, topical products, vitamins and dietary supplements taken in the last 4 weeks, alcohol, drugs of abuse and tobacco use. (See Table 1 for prohibited medication and washout times).
- Review of ongoing concomitant medications and non-drug treatments. If subject is on any prohibited medications (Table 1), a washout period will be required and the baseline visit should be scheduled after the washout period.
- Review of pre-treatment events (Section 7.1.1.1).
- Full physical examination (including weight and height).
- ECG.
- Vital signs (including temperature).
- Urinalysis and drugs of abuse testing.
- Blood samples for:
    - Haematology and biochemistry (including HbA1c, HIV/Hepatitis B/C serology)
    - Serum pregnancy test (WOCBP)
    - Serum FSH testing for all females (≥ 45 years) enrolling from Study REN001-101 (UK only) or not confirmed as post-menopausal in the STRIDE study
- Eye examination (may be completed between Screening and Baseline visits). Eye examinations will not be repeated if within 6 months of a previous test within STRIDE.
- Optional DXA Scan (in those countries and sites where this is permitted). It should be scheduled as close as possible to the baseline visit, however if this is not feasible, then it must be performed within the 4 weeks after the baseline visit. Subjects must be checked against the Additional Criteria for Sites with approvals for DXA Scans (Section 4.4). All WOCBP must have a negative pregnancy test prior to the scan. All female subjects will require an FSH test if not confirmed as post-menopausal on the STRIDE Study. A STRIDE subject will not have a baseline DXA in this study if they had a Week 24 DXA in the STRIDE study. Details of how the DXA scan will be performed can be found in the DXA Manual. DXA scans will not be repeated if within 6 months of a previous scan within STRIDE.
- Provide a urine collection cup and instructions for collecting a second morning void for next study visit. This is provided in case the subject has their second morning void before attending the study centre at their next study visit.

6.1.3.2 Baseline visit

This should be scheduled when results from all screening tests are available for clinical review against the protocol criteria. Maximum time between screening and baseline visits should be 8 weeks. Re-screening of subjects is allowed only once and requires prior approval by the Sponsor, for instance, if the wash out of prior medication is longer than 8 weeks.

The following assessments should be performed:

- Second morning void urine sample for:
  - Bone marker – NTX
  - Urinalysis and drugs of abuse testing
  - Pregnancy testing (WOCBP)
- Blood samples for:
  - Haematology and biochemistry (including HbA1c)
  - Bone and calcium metabolism markers
  - Plasma sample for PK analysis of REN001
- Review of concomitant medication including contraception and non-drug treatments.
- Review of pre-treatment events (Section 7.1.1.1).
- Physician completion of subject's PMM phenotypic description.
- Full physical examination (including weight).
- ECG.
- Vital signs (including temperature).
- Patient Reported Outcome (PRO) Questionnaires
  - MFIS
  - PGIS – muscle symptoms and fatigue symptoms
  - PROMIS Short Form – 13a (FACIT Fatigue)
  - SF-36
  - WPAI:SHP
  - BPI
- 12MWT.
- Dispense study drug. First dose to be taken with food at the site under the supervision of site staff. The time of the first dose will be recorded. Subject should be instructed on study drug dosing requirements and reminded of the study restrictions.

6.1.4 Option 4: Enrolment of nDNA-PMM subjects

Separate screening and baseline visits are required when enrolling nDNA-PMM subjects, as screening blood and urine test results must be available at the baseline visit for clinical review. There must be a minimum of 4 weeks between the screening 12MWT and the baseline 12MWT. Subjects who are receiving prohibited medication must suspend the medication if this can safely and appropriately be done. If a washout period is required for any prohibited medications this may extend the time between the screening and baseline visit (Table 1). The assessments to be carried out at each visit are as follows:

6.1.4.1 Screening Visit

- Obtain written informed consent. Subjects should be given adequate time to think about whether they want to participate and to ask questions. The Investigator (or an appropriate delegate at the site) will obtain written consent from each subject prior to commencing any specific study related activities or assessments.
- Subject Demography.
- Complete Medical History (including prescription and non-prescription drugs/treatment, non-drug treatments, topical products, vitamins and dietary

supplements taken in the last 4 weeks, alcohol, drugs of abuse and tobacco use. (See Table 1 for prohibited medication and washout times).

- Review of ongoing concomitant medications and non-drug treatments. If subject is on any prohibited medications (Table 1), a washout period will be required, and the baseline visit should be scheduled after the washout period.
- Full physical examination (including weight and height).
- ECG.
- Vital signs (including temperature).
- Urinalysis and drugs of abuse testing.
- Blood samples for:
    - Haematology and biochemistry (including HbA1c, HIV/Hepatitis B/C serology)
    - Serum pregnancy test (WOCBP)
    - Serum FSH testing for all females (≥ 45 years)
- Eye examination (may be completed between Screening and Baseline visits).
- For subjects <25 years old (only) a wrist radiograph will be required to confirm bone growth plate closure.
- Optional DXA Scan (in those countries and sites where this is permitted). It should be scheduled as close as possible to the baseline visit, however if this is not feasible, then it must be performed within the 4 weeks after the baseline visit. Subjects must be checked against the Additional Criteria for Sites with approvals for DXA Scans (Section 4.4). All WOCBP must have a negative pregnancy test prior to the scan. All female subjects, regardless of child-bearing potential, must have an FSH test. Details of how the DXA scan will be performed can be found in the DXA Manual.
- 12MWT. Subjects must be able to walk at least 100m in the screening 12MWT and the limitations in walk test must be primarily due to the energy deficit and not due to ataxia or any other condition.
- Provide a urine collection cup and instructions for collecting a second morning void for next study visit. This is provided in case the subject has their second morning void before attending the study centre at their next study visit.
- Input of the Pro-forma Screening data into eCRF for PSOC approval. Provided the subject fulfils all the inclusion and none of the exclusion criteria, and the PSOC has confirmed their agreement, the subject may enter the study and proceed with the Baseline Visit.

6.1.4.2 Baseline visit

This should be scheduled when results from all screening tests are available for clinical review against the protocol criteria. Maximum time between screening and baseline visits should be 8 weeks. Re-screening of subjects is allowed only once and requires prior approval by the Sponsor, for instance, if the wash out of prior medication is longer than 8 weeks.

The following assessments should be performed:

- Second morning void urine sample for:
    - Bone marker – NTX
    - Urinalysis and drugs of abuse testing
    - Pregnancy testing (WOCBP)

- Blood samples for:
  - Haematology and biochemistry
  - Bone and calcium metabolism markers
  - Plasma sample for PK analysis of REN001
- Review of concomitant medication including contraception and non-drug treatments.
- Review of pre-treatment events (Section 7.1.1.1).
- Physician completion of subject's PMM phenotypic description.
- Full physical examination (including weight).
- ECG.
- Vital signs (including temperature).
- Patient Reported Outcome (PRO) Questionnaires
  - MFIS
  - PGIS – muscle symptoms and fatigue symptoms
  - PROMIS Short Form – 13a (FACIT Fatigue)
  - SF-36
  - WPAI:SHP
  - BPI
- 12MWT
- Dispense study drug. First dose to be taken with food at the site under the supervision of site staff. The time of the first dose will be recorded. Subject should be instructed on study drug dosing requirements and reminded of the study restrictions.

6.2 Month 1 (Day 28)

Visits should be scheduled relative to the first day of study drug administration (Day 1). The following assessments will be carried out at the first post baseline visit:

- The subject should take their study drug with food at their usual dosing time. The actual time of dosing should be recorded by the patient on a dosing card.
- Review concomitant medications, non-drug treatments and study drug compliance including capsule counts of remaining study drug.
- Review of AEs.
- Vital signs (including temperature).
- Obtain blood samples for:
  - Haematology and biochemistry
  - Single plasma sample for PK analysis of REN001, time to be recorded
  - FSH test for females aged ≥45 years who were not confirmed as post-menopausal in the STRIDE study or at the STRIDE AHEAD Screening visit, and/or if menopausal symptoms develop.
- Urinalysis and drugs of abuse testing.
- Urine pregnancy testing (WOCBP).
- PRO Questionnaires:
  - MFIS
  - PGIS – muscle symptoms and fatigue symptoms

  - PROMIS Short Form – 13a (FACIT Fatigue)
  - SF-36
  - WPAI:SHP
- Provide home pregnancy testing kits for WOCBP for use after 2 months of dosing. Study centre will telephone the subject and remind them of the need to complete the test and confirm the test has been carried out. The date of test and result will be recorded in the eCRF.
- Provide a urine collection cup and instructions for collecting a second morning void for next study visit. This is provided in case the subject has their second morning void before attending the study centre at their next study visit.
- Subject should be instructed on study drug dosing requirements and reminded of the study restrictions. Subject should be reminded that the study drug should be taken at the study centre for the Month 3 visit after a pre-dose blood sample for PK is taken.

6.3 Month 3 (Day 84)

Site staff will provide subjects with meals and snacks at appropriate times during the visit. Where possible and applicable the 12MWT should be performed at the same time of day as in the Week 24 Visit of the STRIDE study. A sample Schedule for Study Visit is in Appendix 5.

The urine and blood samples should be carried out **prior to dosing**:

- Obtain urine sample for:
  - Urinalysis (and pregnancy testing if WOCBP)
- Obtain blood samples for:
  - Pre-dose plasma sample for PK analysis of REN001
  - Haematology and biochemistry
  - FSH test for females (if menopausal symptoms develop)

Following these tests, the study drug should be administered with food under the supervision of clinical staff and the time of dosing recorded.

- Plasma samples for PK analysis of REN001 will be taken at 1, 2, and 4 hours post dose. Other assessments below should be scheduled in between blood samples. Exact time of collection of all blood samples to be recorded.

Other assessment to be performed at this visit:

- Review concomitant medications, non-drug treatments and study drug compliance including capsule counts of remaining study drug.
- Review of AEs.
- Brief physical examination (including weight).
- ECG.
- Vital signs (including temperature).
- PRO Questionnaires (to be completed prior to exercise testing)
  - MFIS
  - PGIS – muscle symptoms and fatigue symptoms
  - PROMIS Short Form – 13a (FACIT Fatigue)
  - SF-36
  - WPAI:SHP

- 12MWT (to be completed at the same time of day as previously).
- Eye examination (may be completed ± 14 days of the visit if required).
- Provide home pregnancy testing kits for WOCBP for use at Months 4 and 5 of dosing. Study centre will telephone the subject and remind them of the need to complete the test and confirm the test has been carried out. The date of test and result will be recorded in the eCRF.
- Provide a urine collection cup and instructions for collecting a second morning void for next study visit. This is provided in case the subject has their second morning void before attending the study centre at their next study visit.
- Dispense study drug and remind subject of study drug dosing requirements and study restrictions.

6.4 Month 6 (Day 168)

Site staff will provide subject with meals and snacks at appropriate times during the visit. The following assessments will be carried out:

- The subject should take their study drug with food at their usual dosing time. The actual time of dosing should be recorded by the patient on a dosing card.
- Obtain second morning void urine sample for:
  - Bone marker – NTX
  - Urinalysis and drugs of abuse testing
  - Urine pregnancy testing (WOCBP)
- Obtain blood samples for:
  - Haematology and biochemistry
  - Bone and calcium metabolism markers
  - 2 plasma samples for PK analysis of REN001, sample 1 to be taken on arrival at site, sample 2 to be taken at end of visit. Time of samples to be recorded.
  - FSH test for females (if menopausal symptoms develop)
- Review concomitant medications, non-drug treatments and study drug compliance including capsule counts of remaining study drug.
- Review of AEs.
- Physician completion of subject's PMM phenotypic description.
- Brief physical examination (including weight).
- ECG.
- Vital signs (including temperature).
- PRO Questionnaires (to be completed prior to exercise testing)
  - MFIS
  - PGIS – muscle symptoms and fatigue symptoms
  - PROMIS Short Form – 13a (FACIT Fatigue)
  - SF-36
  - WPAI:SHP
- 12MWT (to be completed at same time of day as previously).
- Eye examination (may be completed ± 14 days of the visit if required).
- Provide home pregnancy testing kits for WOCBP to enable monthly pregnancy

testing. Study centre will telephone the subject and remind them of the need to complete the test and confirm the test has been carried out each month. The date of test and result will be recorded in the eCRF.

- Provide a urine collection cup and instructions for collecting a second morning void for next study visit. This is provided in case the subject has their second morning void before attending the study centre at their Month 12 study visit.
- Dispense study drug and remind subject of study drug dosing requirements and study restrictions.

6.5 Month 9 (Day 252) – German sites only

Site staff will provide subject with meals and snacks at appropriate times during the visit. The following assessments will be carried out:

- The subject should take their study drug with food at their usual dosing time. The actual time of dosing should be recorded by the patient on a dosing card.
- Urinalysis and drugs of abuse testing
- Urine pregnancy testing (WOCBP)
- Obtain blood samples for:
    - Haematology and biochemistry
    - FSH test for females (if menopausal symptoms develop)
- Review concomitant medications, non-drug treatments and study drug compliance including capsule counts of remaining study drug.
- Review of AEs.
- Brief physical examination (including weight).
- ECG.
- Vital signs (including temperature).
- Provide home pregnancy testing kits for WOCBP to enable monthly pregnancy testing. Study centre will telephone the subject and remind them of the need to complete the test and confirm the test has been carried out each month. The date of test and result will be recorded in the eCRF.

6.6 Month 12 (Day 336)

Site staff will provide subjects with meals and snacks at appropriate times during the visit. The following assessments will be carried out:

- The subject should take their study drug with food at their usual dosing time. The time of dosing should be recorded by the patient on a dosing card.
- Obtain second morning void urine sample for:
    - Bone marker – NTX
    - Urinalysis and drugs of abuse testing
    - Urine pregnancy testing (WOCBP)
- Obtain blood samples for:
    - Haematology and biochemistry (including HbA1c)
    - Bone and calcium metabolism markers
    - 2 plasma samples for PK analysis of REN001, sample 1 to be taken on arrival at site, sample 2 to be taken at end of visit. Time of sample collection to be

recorded.
    - FSH test for females (if menopausal symptoms develop)
- Review concomitant medications, non-drug treatments and study drug compliance including capsule counts of remaining study drug.
- Review of AEs.
- Physician completion of subject's PMM phenotypic description.
- Brief physical examination (including weight).
- ECG.
- Vital signs (including temperature).
- PRO Questionnaires (to be completed prior to exercise testing)
    - MFIS
    - PGIS – muscle symptoms and fatigue symptoms
    - PROMIS Short Form – 13a (FACIT Fatigue)
    - SF-36
    - WPAI:SHP
    - PGIC muscle and fatigue symptoms
    - BPI
- 12MWT (to be completed at same time of day as previously).
- Eye examination (may be completed ± 14 days of the visit if required).
- Provide home pregnancy testing kits for WOCBP to enable monthly pregnancy testing. Study centre will telephone the subject and remind them of the need to complete the test and confirm the test has been carried out each month. The date of test and result will be recorded in the eCRF.
- Provide a urine collection cup and instructions for collecting a second morning void for next study visit. This is provided in case the subject has their second morning void before attending the study centre at their Month 18 study visit.
- Dispense study drug and remind subject of study drug dosing requirements and study restrictions.

6.7 Month 15 (Day 420) – Germany only

Site staff will provide subject with meals and snacks at appropriate times during the visit. The following assessments will be carried out:

- The subject should take their study drug with food at their usual dosing time. The actual time of dosing should be recorded by the patient on a dosing card.
- Urinalysis and drugs of abuse testing
- Urine pregnancy testing (WOCBP)
- Blood samples for:
    - Haematology and biochemistry
    - FSH test for females (if menopausal symptoms develop)
- Review concomitant medications, non-drug treatments and study drug compliance including capsule counts of remaining study drug.
- Review of AEs.

- Brief physical examination (including weight).
- ECG.
- Vital signs (including temperature).
- Provide home pregnancy testing kits for WOCBP to enable monthly pregnancy testing. Study centre will telephone the subject and remind them of the need to complete the test and confirm the test has been carried out each month. The date of test and result will be recorded in the eCRF.

6.8 Month 18 (Day 504)

Site staff will need to provide subject with meals and snacks at appropriate times during the visit. The following assessments will be carried out:

- The subject should take their study drug with food at their usual dosing time. The time of dosing should be recorded by the patient on a dosing card.
- Obtain second morning void urine sample for:
  - Bone marker – NTX
  - Urinalysis and drugs of abuse testing
  - Pregnancy testing (WOCBP)
- Obtain blood samples for:
  - Haematology and biochemistry
  - Additional bone and calcium metabolism markers
  - 2 plasma samples for PK analysis of REN001, sample 1 to be taken on arrival at site, sample 2 to be taken at end of visit. Time of samples to be recorded.
  - FSH test for females (if menopausal symptoms develop)
- Review concomitant medications, non-drug treatments and study drug compliance including capsule counts of remaining study drug.
- Review of AEs.
- Brief physical examination (including weight).
- ECG.
- Vital signs (including temperature).
- PRO Questionnaires (to be completed prior to exercise testing):
  - MFIS
  - PGIS – muscle symptoms and fatigue symptoms
  - PROMIS Short Form – 13a (FACIT Fatigue)
  - SF-36
  - WPAI:SHP
- 12MWT (to be completed at same time of day as previously).
- Eye examination (may be completed ± 14 days of the visit if required).
- Provide home pregnancy testing kits for WOCBP to enable monthly pregnancy testing. Study centre will telephone the subject and remind them of the need to complete the test and confirm the test has been carried out each month. The date of test and result will be recorded in the eCRF.

- Provide a urine collection cup and instructions for collecting a second morning void for next study visit. This is provided in case the subject has their second morning void before attending the study centre at their next study visit.
- Dispense study drug and remind subject of study drug dosing requirements and study restrictions.

6.9 Month 24 (Day 672) or Early Withdrawal Visit (Prior to Month 24)

Site staff will provide subjects with meals and snacks at appropriate times during the visit.

If the subject discontinues study treatment prior to Month 24 they will be withdrawn from the study. If they discontinue study treatment between visits, they will be required to attend an early withdrawal visit as soon as possible after their last dose of REN001. If their withdrawal is prior to the Month 24 visit, the below assessments should be carried out:

The following assessments will be carried out:

- The subject should take their study drug with food at their usual dosing time. The actual time of dosing should be recorded by the patient on a dosing card.
- Obtain second morning void urine sample for:
  - Bone marker – NTX
  - Urinalysis and drugs of abuse testing
  - Pregnancy testing (WOCBP)
- Obtain blood samples for:
  - Haematology and biochemistry (including HbA1c)
  - Bone and calcium metabolism markers
  - 2 plasma samples for PK analysis of REN001, sample 1 to be taken on arrival at site, sample 2 to be taken at end of visit. Time of samples to be recorded.
  - FSH test for females (if menopausal symptoms develop)
- Review concomitant medications, non-drug treatments and study drug compliance including capsule counts of remaining study drug.
- Review of AEs.
- Physician completion of subject's PMM phenotypic description.
- Brief physical examination (including weight).
- ECG.
- Vital signs (including temperature).
- PRO Questionnaires (to be completed prior to exercise testing)
  - MFIS
  - PGIS – muscle symptoms and fatigue symptoms
  - PROMIS Short Form – 13a (FACIT Fatigue)
  - SF-36
  - WPAI:SHP
  - PGIC muscle and fatigue symptoms
  - BPI
- 12MWT (to be completed at same time of day as previous visits).
- Eye examination (may be completed ± 14 days of the visit if required).

- Optional DXA Scan
    - Eligible subjects must have had a DXA scan at baseline, either as part of the STRIDE study or at entry into this long-term safety study. If subject is an Early Withdrawal, a scan will only be performed if there has been at least 20 weeks of dosing following the baseline scan. All female subjects not confirmed as post-menopausal should have an FSH test performed. All WOCBP must have a negative pregnancy test prior to the scan. Where possible, the same scanner should be used at this visit as at the baseline visit. Details can be found in the DXA Manual.

The following items must be completed for subjects continuing dosing beyond Month 24:

- Provide home pregnancy testing kits for WOCBP to enable monthly pregnancy testing. Study centre will telephone the subject and remind them of the need to complete the test and confirm the test has been carried out each month. The date of test and result will be recorded in the eCRF.
- Provide a urine collection cup and instructions for collecting a second morning void for next study visit. This is provided in case the subject has their second morning void before attending the study centre at their Month 30 study visit.
- Dispense study drug and remind subject of study drug dosing requirements and study restrictions.

6.10 Month 30 (Day 840)

Site staff will need to provide subject with meals and snacks at appropriate times during the visit. The following assessments will be carried out:

- The subject should take their study drug with food at their usual dosing time. The time of dosing should be recorded by the patient on a dosing card.
- Obtain second morning void urine sample for:
    - Bone marker – NTX
    - Urinalysis and drugs of abuse testing
    - Pregnancy testing (WOCBP)
- Obtain blood samples for:
    - Haematology and biochemistry
    - Additional bone and calcium metabolism markers
    - FSH test for females (if menopausal symptoms develop)
- Review concomitant medications, non-drug treatments and study drug compliance including capsule counts of remaining study drug.
- Review of AEs.
- Brief physical examination (including weight).
- ECG.
- Vital signs (including temperature).
- PRO Questionnaire:

  PGIS – muscle symptoms and fatigue symptoms
- Eye examination (may be completed ± 14 days of the visit if required).
- Provide home pregnancy testing kits for WOCBP to enable monthly pregnancy testing. Study centre will telephone the subject and remind them of the need to

complete the test and confirm the test has been carried out each month. The date of test and result will be recorded in the eCRF.

- Provide a urine collection cup and instructions for collecting a second morning void for next study visit. This is provided in case the subject has their second morning void before attending the study centre at their Month 36 study visit.
- Dispense study drug and remind subject of study drug dosing requirements and study restrictions.

6.11 Month 36 (Day 1008)

Site staff will need to provide subject with meals and snacks at appropriate times during the visit. The following assessments will be carried out:

- The subject should take their study drug with food at their usual dosing time. The time of dosing should be recorded by the patient on a dosing card.
- Obtain second morning void urine sample for:
  - Bone marker – NTX
  - Urinalysis and drugs of abuse
  - Pregnancy testing (WOCBP)
- Obtain blood samples for:
  - Haematology and biochemistry
  - Additional bone and calcium metabolism markers
  - FSH test for females (if menopausal symptoms develop)
- Review concomitant medications, non-drug treatments and study drug compliance including capsule counts of remaining study drug.
- Review of AEs.
- Brief physical examination (including weight).
- ECG.
- Vital signs (including temperature).
- PRO Questionnaire:
  - PGIS – muscle symptoms and fatigue symptoms
  - PGIC – muscle symptoms and fatigue symptoms
- Eye examination (may be completed ± 14 days of the visit if required).
- Provide home pregnancy testing kits for WOCBP to enable monthly pregnancy testing. Study centre will telephone the subject and remind them of the need to complete the test and confirm the test has been carried out each month. The date of test and result will be recorded in the eCRF.
- Provide a urine collection cup and instructions for collecting a second morning void for next study visit. This is provided in case the subject has their second morning void before attending the study centre at their Month 42 study visit.
- Dispense study drug and remind subject of study drug dosing requirements and study restrictions.

6.12 Month 42 (Day 1176)

Site staff will need to provide subject with meals and snacks at appropriate times during the visit. The following assessments will be carried out:

- The subject should take their study drug with food at their usual dosing time. The time of dosing should be recorded by the patient on a dosing card.
- Obtain second morning void urine sample for:
  - Bone marker – NTX
  - Urinalysis and drugs of abuse
  - Pregnancy testing (WOCBP)
- Obtain blood samples for:
  - Haematology and biochemistry
  - Additional bone and calcium metabolism markers
  - FSH test for females (if menopausal symptoms develop)
- Review concomitant medications, non-drug treatments and study drug compliance including capsule counts of remaining study drug.
- Review of AEs.
- Brief physical examination (including weight).
- ECG.
- Vital signs (including temperature).
- PRO Questionnaire:

  PGIS – muscle symptoms and fatigue symptoms
- Eye examination (may be completed ± 14 days of the visit if required).
- Provide home pregnancy testing kits for WOCBP to enable monthly pregnancy testing. Study centre will telephone the subject and remind them of the need to complete the test and confirm the test has been carried out each month. The date of test and result will be recorded in the eCRF.
- Provide a urine collection cup and instructions for collecting a second morning void for next study visit. This is provided in case the subject has their second morning void before attending the study centre at their Month 48 study visit.
- Dispense study drug and remind subject of study drug dosing requirements and study restrictions.

6.13 Month 48 (Day 1344) or Early Withdrawal Visit (Post Month 24)

Site staff will need to provide subject with meals and snacks at appropriate times during the visit.

If the subject discontinues study treatment prior to Month 48 they will be withdrawn from the study. If they discontinue study treatment between visits, they will be required to attend an early withdrawal visit as soon as possible after their last dose of REN001. If their withdrawal is after the Month 24 visit, the below assessments should be carried out. The following assessments will be carried out:

- The subject should take their study drug with food at their usual dosing time. The time of dosing should be recorded by the patient on a dosing card.
- Obtain second morning void urine sample for:
  - Bone marker – NTX
  - Urinalysis and drugs of abuse

  - Pregnancy testing (WOCBP)
- Obtain blood samples for:
  - Haematology and biochemistry
  - Additional bone and calcium metabolism markers
  - FSH test for females (if menopausal symptoms develop)
- Review concomitant medications, non-drug treatments and study drug compliance including capsule counts of remaining study drug.
- Review of AEs.
- Brief physical examination (including weight).
- ECG.
- Vital signs (including temperature).
- PRO Questionnaires:
  - PGIS – muscle symptoms and fatigue symptoms
  - PGIC – muscle symptoms and fatigue symptoms
- Eye examination (may be completed ± 14 days of the visit if required).
- Optional DXA Scan
  - Eligible subjects must have had a DXA scan at baseline and/or at the Month 24 visit. If subject is an Early Withdrawal after M24, a scan will only be performed if there has been at least 20 weeks of dosing following the M24 scan. All female subjects not confirmed as post-menopausal should have an FSH test performed. All WOCBP must have a negative pregnancy test prior to the scan. Where possible, the same scanner should be used at this visit as at the baseline and Month 24 visits. Details can be found in the DXA Manual.
- Provide home pregnancy testing kit for WOCBP for final pregnancy test prior to the follow-up telephone contact at approximately 30 days after the last dose of study drug.

6.14 Follow-up Telephone Contact

If subject has completed 48 Months treatment or is an Early Withdrawal from the study, there will be a FU telephone contact from the study centre to the subject approximately 30 days after their last dose of study drug. If the Early Withdrawal visit is 21 or more days after the last dose of study drug, then the FU telephone contact is not needed. The following activities will be completed:

- Review of any AEs that were ongoing at the final study centre visit or Early Withdrawal visit.
- Document result of pregnancy testing (WOCBP only).

Any clinically significant abnormalities noted at the final treatment visit should be followed up until resolved or stabilized.

The follow up phone call is not required if mavodelpar has been approved within the country and the subject switches to commercially available medication.

6.15 Unscheduled Visits

Unscheduled visits may also be arranged at any time at the discretion of the investigator as clinically indicated. These visits should be recorded on the unscheduled study visit pages in the electronic Case Report Form (eCRF).

Table 2: Screening and Baseline Visits

Assessments	Option 1 Enrolment at STRIDE Week 24[1]	Option 2 Enrolment at STRIDE FU[2]	Option 3 mtDNA-PMM subjects from REN001-101 or after exiting STRIDE[3]		Option 4 nDNA-PMM subjects[3]	
	Baseline	Baseline	Screening	Baseline	Screening	Baseline
Informed Consent	X	X	X		X	
Demography	STRIDE Baseline	STRIDE Baseline	X		X	
Medical History	STRIDE Baseline	STRIDE Baseline	X		X	
Physician completion of PMM Phenotype	STRIDE Week 24	X		X		X
Physical Exam (inc weight and height)[4]	STRIDE Week 24	X	X	X	X	X
ECG	STRIDE Week 24	X	X	X	X	X
Vital signs	STRIDE Week 24	STRIDE FU	X	X	X	X
Safety labs	STRIDE Week 24	X	X	X	X	X
HbA1c[5]	STRIDE Week 24	X	X	X	X	X
HEP B/C/HIV[6]			X		X	
Blood for bone and calcium markers	STRIDE Week 24	X		X		X
PK blood sample for REN001	STRIDE Week 24[7]	X		X		X
Urinalysis, inc pregnancy testing[8]	STRIDE Week 24	STRIDE FU		X		X
Serum pregnancy testing			X		X	
Urine drugs of abuse[9]	STRIDE Week 24	X	X	X	X	X
Serum FSH		X[10]	X		X	
Urine NTX bone markers	STRIDE Week 24	X		X		X
PROs	STRIDE Week 24	X		X		X
12MWT	STRIDE Week 24	X		X	X	X[11]

[1] Most of baseline data will be STRIDE Week 24 data. Additional assessments to be carried out on the same day (Section 6.1.1).
[2] Baseline tests to be carried out at the STRIDE FU visit.
[3] Separate screening and baseline visits required (Section 6.1.3). nDNA subjects will not be recruited in France.
[4] Height only collected at screening/baseline visits
[5] Subjects enrolling in Germany require a HbA1c to be performed 8 weeks prior to baseline. For subjects enrolling at STRIDE Week 24 or FU these samples could coincide with STRIDE Week 18 or 24 visits respectively. Informed consent must be obtained prior to these samples being taken.
[6] Subjects enrolling in Germany require a Hepatitis B/C/HIV to be performed 8 weeks prior to baseline. For subjects enrolling at STRIDE Week 24 or FU these samples could coincide with STRIDE Week 18 or 24 visits respectively. Informed consent must be obtained prior to these samples being taken.
[7] Data will only be reported in the REN001-201 CSR
[8] Urine pregnancy testing will be carried out at all visits, excluding the option 3 & option 4 screening visit which will be a serum pregnancy test. Women aged ≥45 years will receive a urine pregnancy test at the STRIDE Week 24 visit in lieu of an FSH test which will be conducted at Month 1, if required.
[9] Subject will be excluded at the Investigator's discretion for alcohol/drug dependency. Use for medical reason is acceptable with prescription evidence.
[10] FSH for females aged ≥45 years not confirmed as post-menopausal in the STRIDE study (FSH not conducted at STRIDE Week 24 visit, see footnote 5).
[11] There must be a minimum of 4 weeks between the screening and baseline 12MWT.

Eye examination	STRIDE Week 24	STRIDE Week 24	X[1]		X[1]	
Wrist radiograph[2]					X	
DXA Scan[3]	STRIDE Week 24	STRIDE Week 24	STRIDE Week 24		X	
Concomitant Medication review	STRIDE Week 24	STRIDE FU	X	X	X	X
AE Review[4]	STRIDE Week 24	STRIDE FU	X	X		X
Dispense Study Drug	X	X		X		X
First dose of study drug[5]	X	X		X		X

[1] Eye examination can be done at any time between the screening and baseline visit for scheduling reasons.
[2] Subjects <25 years old.
[3] Optional. Only conducted at sites which participated in the DXA sub-study. If a DXA scan was performed at STRIDE Week 24 it will be regarded as the baseline. Sites with approvals in place should review all subjects against the additional protocol criteria (Section 4.3) and perform DXA if subject eligible and not performed in STRIDE.
[4] Review of pre-treatment events for subjects enrolling at option 3 and option 4: after exiting STRIDE or REN001-101, and nDNA-PMM subjects.
[5] Subject enrolling at STRIDE Week 24 should take the first dose the day after the Baseline visit, this will be confirmed with a telephone call from site the next day. Subject enrolling at STRIDE FU or after exiting STRIDE or Study REN001-101, and nDNA-PMM subjects should take the first dose at the study centre baseline visit.

Table 3: Schedule of Activities

Assessments/Time*	Screening / Baseline Visits[1]	Month 1 (Day 28)	Month 3 (Day 84)	Month 6 (Day 168)	Month 9 (Day 252) Germany only	Month 12 (Day 336)	Month 15 (Day 420) Germany only	Month 18 (Day 504)	Month 24 (Day 672) or pre M24 Early Withdrawal[2]	Month 30 (Day 840), M36 (Day 1008), M42 (Day 1176)	Month 48 (Day 1344) or post M24 Early Withdrawal[2]
Window for visit		±3 days	±7 days	±7 days	±21days	±21days	±21days	±21 days	±21 days	±21 days	±21 days
Physician-PMM phenotypic description				X		X			X	X	X
Physical exam[3] (inc. weight)			X	X	X	X	X	X	X	X	X
ECG			X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X	X
Safety bloods haematology/biochemistry		X	X	X	X	X	X	X	X	X	X
HbA1c						X			X	X	X
Blood for bone and calcium markers				X		X		X	X	X	X
PK blood sample for REN001[4]		X	X	X		X		X	X		
Urinalysis inc. pregnancy testing[5]		X	X	X	X	X	X	X	X	X	X
Urine drugs of abuse		X	X	X	X	X	X	X	X	X	X
Serum FSH[6]		X[7]	X	X	X	X	X	X	X	X	X
Urine NTX bone markers				X		X		X	X	X	X
PROs[8]		X	X	X		X		X	X	X	X
12MWT			X	X		X		X	X		
Eye examination			X	X		X		X	X	X	X
DXA Scan[9]									X		X
Dispense Study Drug			X	X		X		X	X	X	
Concomitant medication review	X----------										----------X
AE review	X----------										----------X
Dosing of study drug	X		X	X		X		X	X	X	

[1] See Table 2. It is expected that most subjects will enrol at the STRIDE Week 24 visit with the baseline visit for this study coinciding with the STRIDE Week 24 visit. With additional assessments subjects can also enrol at the STRIDE FU visit, or at any time after exiting Study REN001-101 or STRIDE, and nDNA-PMM subjects (Table 2 and Section 6.1).
[2] If subject discontinues study drug, they will be required to attend an early withdrawal visit as soon as possible after their last dose of study drug. A FU telephone call by the site approx. 30 (±7) days after last dose of study drug is required unless subject transfers to commercially available mavodelpar. Clinically significant abnormalities should be followed up until resolved/stabilized.
[3] Brief symptom directed physical exam can be done post baseline.
[4] PK samples (1 or 2) will be collected at all visits except Month 3 when 4 PK samples will be collected at 0,1,2,4 hrs post dose.
[5] Urine home pregnancy test kits will be supplied to WOCBP to enable monthly pregnancy testing. The study centre must contact the subject to confirm the pregnancy test results. The final test will be performed prior to the follow-up telephone contact approximately 30 days after the last dose of study drug.
[6] FSH test should be done during study if menopausal symptoms develop.
[7] FSH to be measured for all females (aged ≥45 years) not confirmed as post-menopausal.
[8] PROs include MFIS, PGIS and PGIC (muscle and fatigue symptoms), SF-36, PROMIS, WPAI:SHP, BPI. BPI will be carried out at Month 12 and Month 24 only. After the M24 visit, only the PGIS will be conducted at each visit. The PGIC will be carried out at Month 12, 24, 36 and 48 only.
[9] Optional DXA scan will only be conducted at sites which participated in the DXA sub-study. Eligible subjects must have had a DXA scan at baseline.
*Additional unscheduled visits may be arranged at any time at the discretion of the investigator as clinically required.

7 PARAMETERS AND METHODS OF ASSESSMENT

7.1 Safety Parameters

7.1.1 Adverse Events

7.1.1.1 Definitions

Pre-treatment Event (PTE):

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study drug; it does not necessarily have to have a causal relationship with study participation. Hence, occurrences between the screening and baseline visits for those mtDNA-PMM subjects enrolling from REN001-101 (UK only), or after exiting the STRIDE study, and nDNA-PMM subjects will be reported as PTEs. For those mtDNA-PMM subjects who transition to this study immediately from STRIDE, only ongoing adverse events at the time of enrolling in this study will be reported as a PTE (see Section 7.1.1.3).

Adverse Event (AE):

- An AE is any untoward medical event that occurs in a subject who has received study drug and does not necessarily have a causal relationship with study treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the product.
- A TEAE will be defined as an AE that begins or that worsens in severity after the first dose of study drug has been administered.
- An adverse drug reaction (ADR) is any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.
- An unexpected adverse reaction is an adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in the Investigator's Brochure.

All PTEs/AEs, including intercurrent illnesses, occurring during the study will be documented in the eCRF.

Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

7.1.1.2 Laboratory values and ECG findings

Changes in laboratory values or ECG parameters are only considered to be AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the Investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional non-invasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

7.1.1.3 Pre-existing conditions

For STRIDE subjects the handling of pre-existing conditions (present at the time of signing of informed consent) will be dependent on their reporting in the STRIDE study and when the subject is enrolled into this study.

If the subject is enrolled at the STRIDE Week 24 or FU visits the following will apply:

- If the condition was reported as an ongoing AE at the end of the STRIDE study then the details concerning the AE will be transferred to a PTE eCRF page in this study and followed up during this study.
- If the condition was reported as pre-existing in the STRIDE study (i.e., present at the time of signing STRIDE informed consent) then it would have been reported in medical history for STRIDE. Such information will be transferred to this study's database and may be updated (e.g., end date provided).

For mtDNA-PMM subjects enrolled from Study REN001-101 or after exiting STRIDE, and nDNA-PMM subjects, then the following will apply:

- Baseline evaluations (e.g., laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs.
- Pre-existing conditions (present at the time of signing REN001-202 informed consent) are considered concurrent medical conditions and should be recorded as medical history. They should NOT be recorded as PTEs. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE/AE. Investigators should ensure that the event term recorded captures the change in the condition (e.g., "worsening of…"). For example,
    - episodic conditions asthma or epilepsy: if episodes become more frequent, serious or severe in nature, the AE term recorded should capture the change in the condition from baseline (e.g., "worsening of…").
    - degenerative concurrent conditions (e.g., cataracts): if the worsening of the condition occurs to a greater extent to that which would be expected the AE term recorded should captures the change in the condition from baseline (e.g., "worsening of…").

7.1.1.4 Worsening of PTEs and AEs

If the subject experiences a worsening or complication of PTE or an AE after starting the study drug in this study, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

7.1.1.5 Adverse Events of Special Interest (AESI)

AESI are those of scientific and medical concern specific to the Sponsor's product for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be warranted. These events require further investigation to fully characterize. Based on this assessment, the Sponsor plans to include AESI as follows:

- Changes in laboratory parameters of muscle injury associated with clinically significant AEs
- Changes observed after baseline in formation or exacerbation of cataracts.
- Occurrence of fractures after baseline

While an AESI may not meet the definition of an SAE, it should be reported in the same manner as SAE (See Section 7.1.1.9). This allows the event to be tracked in more detail and followed up for additional information if required. When completing the SAE form there is an extra box to check to confirm that the event is an AESI. AESIs will not be reported to the Regulatory Authorities unless they are also suspected unexpected serious adverse reactions (SUSARs).

7.1.1.6 Assessment of Adverse Event

Each AE will be assessed by the Investigator with regard to the following categories.

7.1.1.6.1 Seriousness

An SAE (or serious ADR or unexpected SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (this means that the subject is at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalisation or prolongs existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event(s) that may not be immediately life-threatening or result in death or hospitalisation but that may jeopardize the subject or require intervention to prevent one of the above outcomes. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalisation, or the development of drug dependency or drug abuse.

Note: Cases of potential drug-induced liver injury as assessed by laboratory test values ("Hy's Law Cases") are also reportable. If a subject develops abnormal values in AST or ALT or both, concurrent with abnormal elevations in total bilirubin and no other known cause of liver injury, that event would be classified as a Hy's Law Case. In this clinical study, the term SAE will be understood to also include Hy's Law Cases.

Medical and scientific judgment should be exercised in deciding whether a case is serious and whether expedited reporting is appropriate.

7.1.1.6.2 Severity

The intensity of each AE must be assessed by the Investigator using one of the following categories, and recorded in the eCRF:

- Mild: An AE that does not interfere with usual activities.
- Moderate: An AE that interferes with usual activities.
- Severe: An AE that prevents usual activities.

7.1.1.6.3 Causality

The Investigator will assess the causality / relationship between the study drug and the AE and record that assessment in the eCRF. Causality will be shown as Related, Possibly Related, or Not related.

7.1.1.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all AEs.

The relationship should be assessed as Yes if the Investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as No.

7.1.1.8 Collection and Reporting of AEs

7.1.1.8.1 PTE and AE Collection Periods

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study drug (Day 1) or until screen failure.

Collection of AEs will commence from the time that the subject is first administered study drug (Day 1). Routine collection of AEs will continue until the follow-up telephone contact (if required, see Section 6.14) approximately 30 days after the last study drug dose.

7.1.1.8.2 PTE and AE Reporting

AEs at the end of the STRIDE study for subjects enrolled at the STRIDE Week 24 or FU visits that are still present at the time the subject signs the informed consent to participate in this study should be followed up in this study and recorded in the eCRF as PTEs.

At each study visit, the Investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked.

Subjects may report AEs occurring at any other time during the study.

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All PTEs/AEs will be documented in the PTE/AE page of the eCRF, whether or not the Investigator concludes that the event is related to the study drug. The following information will be documented for each event:

- Event term
- Start and stop date {and time}
- Severity
- Investigator's opinion of the causal relationship between the event and administration of study drug
    - If no, provide alternative aetiology or explanation
- Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure
- Action concerning study drug
- Outcome of event
- Seriousness.

7.1.1.9 Reporting Serious Adverse Events

All SAEs that occur during the study from the signing of the informed consent and up to approximately 30 days after receiving the last dose of study drug, whether considered to be associated with the study drug or not, must be reported within 24 hours by email or fax to the study Pharmacovigilance (PV) team. The minimum information required for an initial report is:

- Sender of report (name, address of Investigator)

- Subject identification (screening number, initials, NOT subject name)
- Protocol number
- Description of SAE and reason why the event is categorized as serious
- Causality assessment, if possible

As far as possible all points on the SAE form should be covered in the initial report and the completed SAE form faxed to the PV team (details below). The original SAE form should be sent to the address below and the Medical Monitor and the Sponsor Chief Medical Officer informed by email. In addition, the event must be documented in the eCRF.

SAE information to be sent to PV Team:
Bionical Emas
Spirella Building
Bridge Road
Letchworth Garden City, Hertfordshire
SG6 4ET
United Kingdom
Email: Drug.safety@bionical-emas.com
Fax: +44 (0) 1462 600 456

After receipt of the initial report, the PV team will review the information and, if necessary, contact the Investigator, to obtain further information for assessment of the event. Bionical Emas, the PV vendor will be responsible for all information processing and reporting according to local legal requirements. Where necessary, Investigators will inform the authorities in their own countries.

7.1.1.10 Reporting Pregnancies

Although pregnancy should not be considered as an SAE *per se*, any pregnancies occurring in a study subject between baseline and the end of the contraception requirements (14 weeks after last dose for males, 30 days (approximately 1 menstrual cycle) after last dose for WOCBP) must be reported and captured as if they were SAEs.

If any subject is found to be pregnant during the study, the subject should be withdrawn, and study drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 14 weeks after the last dose of study drug should also be recorded following authorisation from the subject's partner.

All reported pregnancies will be followed up to final outcome, using the paper pregnancy follow-up form. The outcome, including any premature termination, must be reported to the Sponsor. An evaluation after the birth of the child will also be conducted.

Reports should be sent within 24 hours using the Pregnancy Report Form. If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the Investigator should notify the primary care physician that the subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of treatments the subject received.

7.1.1.11 Follow-up of Adverse Events

All AEs experienced by a subject, irrespective of the suspected causality, will be monitored until the event has resolved, any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Investigator, Medical Monitor and/or the Sponsor, or until there is a satisfactory explanation for the changes observed, or until the subject is lost to follow-up.

7.1.1.12 Safety Reporting to Investigators, IECs, and Regulatory Authorities

The Sponsor will be responsible for reporting all SUSARs and any other applicable SAEs to regulatory authorities, Investigators and IECs, as applicable, in accordance with national or regional regulations in the countries where the study is conducted. Day zero is the first day of awareness of the event by the Sponsor or Sponsor's designee. SUSARs will be submitted within 7 days for fatal and life-threatening events and within 15 days for other SUSARs, unless otherwise required by national regulations. The Sponsor will also prepare an expedited report for Events Requiring Other Actions, where these might materially alter the current risk-benefit assessment of the study drug or that would be sufficient to consider changes in the study drug administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IECs in accordance with national regulations. In addition, once a year throughout the clinical trial or upon request, a Development Safety Update Report (DSUR) will be submitted to the concerned regulatory authority and IEC taking into account all new available safety information received during the reporting period.

7.1.2 Clinical Laboratory Safety Tests

Laboratory assessments will be performed by a central laboratory. Details of the urine and blood sampling procedures and any subject restrictions (e.g., withholding supplements) and subsequent storage and shipment of samples can be found in the REN001-202 Laboratory Manual. Sites will be provided with laboratory kits from the central laboratory. Details of parameters to be tested are listed in Table 4. Approximate volume of blood to be taken from each subject during the study is detailed in Table 5. Additional blood may be required for repeats of safety laboratory tests.

Table 4: Safety Laboratory Parameters

Biochemistry Albumin, Alanine aminotransferase (ALT), Aldolase Alkaline phosphatase (AP), Aspartate aminotransferase (AST) Bilirubin (Total, direct and indirect) Calcium, Cholesterol (Total, LDL and HDL), C-reactive protein Creatinine, Creatine Kinase (CK) eGFR using CKD-EPI Gamma glutamyl transferase (GGT), Glucose (non-fasted) Lipase Magnesium Phosphate, Potassium, Protein (Total) Sodium Triglycerides, Urea, Uric acid **Bone and Calcium Markers** Bone Specific alkaline phosphatase (BSAP) Parathyroid Hormone Vitamin D **Endocrine and biomarker assays** FSH (females ≥45 years not confirmed as post-menopausal, or if menopausal symptoms develop) Human chorionic gonadotropin (hCG) (WOCBP only) Troponin 1	**Haematology** Basophils Eosinophils Haemoglobin Haematocrit (Packed cell volume) Large unstained cells Lymphocytes Mean corpuscular volume (MCV) Monocytes Neutrophils Platelet count Red cell count Reticulocytes White cell count HbA1c
Serological Markers HBsAg, HBcAb, Anti-hepatitis C virus serology (by multi-antigen enzyme immunoassay (EIA), HIV	
Urinalysis -Blood, Glucose, Ketone, Protein, pH, Specific Gravity, Nitrite, Leukocytes, Bilirubin and Urobilinogen. Any significant abnormalities should be investigated via microscopy -Pregnancy Testing: hCG. Urine home pregnancy test kits will be supplied to allow monthly testing between study centre visits. -Testing for drugs of abuse: cocaine, cannabinoids, opiates, barbiturates, benzodiazepines, methadone, and amphetamines. Urine Biomarker assay -Urine N-terminal telopeptide (NTX).	

Laboratory tests results can be repeated if necessary. Any clinically significant abnormal laboratory test result (e.g., findings that lead to more extensive investigation and/or indicate a risk to the health of the subject) should be reported as an AE. The Investigator should assess the possible relationship to study drug as is the case for all other AEs.

Table 5: Approximate Blood Volume Required for Study

Test	No. samples after baseline over 48 months[1]	Vol (ml)	Total (ml)
Haematology (including HbA1c)[2]	10	2	20
Biochemistry (including aldolase, troponin I, FSH and hCG as applicable)[3]	10	5	50
PK samples	14	4	56

[1]Two additional samples needed for screening and baseline safety bloods if enrolment of mtDNA-PMM subjects is after participating in Study REN001-101 or after exiting STRIDE, and nDNA-PMM subjects (maximum of 14 ml extra taken over the screening and baseline period).

[2] There will be an additional 2 Haematology samples collected for German subjects (8 samples rather than 6), totaling 16ml

[3] There will be an additional 2 Biochemistry samples collected for German subjects (8 samples rather than 6), totaling 40ml

Test	No. samples after baseline over 48 months[1]	Vol (ml)	Total (ml)
Bone and calcium markers (including BSAP, PTH, and vitamin D)	9	4	36
Total volume over study (mL)			162

7.1.3 Physical Examination (including weight and height)

All physical examinations will be carried out by a qualified person. Subjects enrolling at STRIDE Week 24 will have had a symptom-directed physical examination in STRIDE.

Subjects with mtDNA-PMM enrolling at STRIDE FU or from study REN001-101 (UK only), or after exiting STRIDE, and nDNA-PMM subjects will have a full physical examination at baseline, to include an assessment of head, neck, heart, lungs, abdomen, skin (including hair and nails), peripheral circulation, joints, general appearance, and a neurological examination.

Post baseline, subjects will have a brief symptom-directed physical examination, which should include general appearance, heart, lungs, skin, and a neurological examination. Clinically significant changes from the baseline examination should be assessed. Other systems examined should be determined by clinical findings and any AEs reported.

Height collected at screening/baseline visits only. Subjects should have weight and height measured while wearing indoor clothing and with shoes off.

7.1.4 Vital Signs

Blood pressure (systolic and diastolic mmHg) will be measured after subject has been supine for at least 5 minutes. The subject's dominant arm, where possible should be used throughout the study (and, where applicable, the same arm as used in the STRIDE study) and recorded to the nearest mmHg. Pulse (beats per minute) should be measured in the brachial/radial artery for at least 30 seconds. Body temperature will be recorded at all visits using a digital thermometer. Any results <35^{o}C should be repeated to ensure correct placement of the thermometer.

7.1.5 Electrocardiogram (ECG) Recording

Single ECG measurements will be taken after the subject has rested for at least 10 minutes in a supine position using a 12-lead ECG machine.

To ensure safety of the subjects, a qualified individual at the site will evaluate all ECGs. If the QTcF is ≥500 msec for any post baseline ECG, the ECG intervals should be inspected carefully to ensure that the RR interval has been recorded correctly, and a single ECG will be repeated at 5-minute intervals 3 times. If these values are consistently high (>500 msec), as a precautionary measure, the subject will discontinue treatment. If a machine read QTcF value is prolonged, as defined above, repeat measurement may not be necessary, provided a qualified physician interpretation determines that the QTcF values are acceptable for the individual. In some cases, it may be necessary to repeat abnormal ECGs to rule out improper lead placement as contributing to the EC abnormality. ECGs may be sent to an ECG vendor for centralised reading at a later date if deemed necessary.

7.1.6 Eye Examination

All eye examinations should be carried out by an appropriately qualified professional. Best efforts should be made to ensure the same professional undertakes the slit lamp examinations for a particular subject in both the STRIDE study and in this long-term safety study. If the lens is clear, that should be recorded. If a cataract is identified, the cataract should be

classified and graded against the Lens Opacity Classification System III, (Chylack et al, 1993).

In addition, best corrected distance visual acuity (including refraction) should be assessed.

For scheduling reasons, the above assessments may be conducted ± 14 days of the visit window given for the eye assessments.

In addition, any subject who experiences any visual symptoms during the study should have an additional eye examination as appropriate.

Eye examinations will not be repeated if within 6 months of a previous test within STRIDE.

7.1.7 Dual-energy X-ray absorptiometry (DXA) Scans

Eligible subjects can choose to have a DXA scan (in those countries and sites where this is permitted), of the non-dominant hip and spine. If the non-dominant hip is unsuitable for scanning (e.g., fractures, hip replacement etc.) then the dominant hip can be used instead.

The same DXA scanner should be used for all scans on an individual subject to aid interpretation of the scans. Subject weight and height are required for scan data, further details can be found in the DXA Scanning Manual. Scans which are not of sufficient quality, as determined by an independent assessor, will not be included in the database.

DXA scans will not be repeated if within 6 months of a previous test within STRIDE.

7.2 Exercise Endurance

7.2.1 12-Minute Walk Test (12MWT)

The 12MWT is a practical test that requires simple equipment to execute. This test measures the distance a subject can walk on a flat, hard surface in a period of 12 minutes. It is important that operators administering the test are fully trained to reduce variability across study centres and that the test is conducted at the same time of the day at each visit. Time of the test will be recorded in the eCRF. Further details are given in the REN001-202 Exercise Manual.

Note: nDNA-PMM subjects must be able to walk at least 100m in the screening 12MWT and the limitations in walk test must be primarily due to the energy deficit and not due to ataxia or any other condition. There must be a minimum of 4 weeks between the screening 12MWT and the baseline 12MWT.

7.3 Quality of Life PROs

7.3.1 Modified Fatigue Impact Scale (MFIS)

The MFIS is a 21-item scale, the score reflects functional limitation due to fatigue experienced within the previous 7 days rather than a measure of the level of fatigue. It may be used in both the clinical and the research setting in people for whom fatigue is a predominant symptom.

There are 21 items, each of which is scored 0 (never) to 4 (almost always), providing a continuous scale of 0–84. It is composed of three subscales that describe the impact of fatigue on physical, cognitive and psychosocial functioning:

Physical functioning (9 items) reflects motivation, effort, stamina, and coordination. The physical subscale can range from 0 to 36. It is calculated by adding items 4+6+7+10+13+14+17+20+21.

Cognitive functioning (10 items) concerns concentration, memory, thinking and organization

of thoughts. The cognitive subscale can range from 0 to 40. It is calculated by adding items 1+2+3+5+11+12+15+16+18+19.

Psychosocial functioning (2 items) describes the impact of fatigue upon isolation, emotions, workload, and coping. The psychosocial subscale can range from 0 to 8. It is calculated by adding items 8+9.

All items are scaled so that a higher score indicates a greater level of fatigue. See Appendix 2.

7.3.2 Patient Global Impression of Severity (PGIS): Muscle and Fatigue

7.3.2.1 Muscle Symptoms

The patient will be asked to rate the severity of their PMM muscle symptoms over the past 7 days.

Overall, how would you rate the severity of your muscle symptoms related to your Primary Mitochondrial Myopathy over the past 7 days?

a. □ Absent
b. □ Mild
c. □ Moderate
d. □ Severe
e. □ Very Severe

7.3.2.2 Fatigue Symptoms

The patient will be asked to rate the severity of their PMM fatigue symptoms over the past 7 days.

Overall, how would you rate the severity of your fatigue symptoms related to your Primary Mitochondrial Myopathy over the past 7 days?

a. □ Absent
b. □ Mild
c. □ Moderate
d. □ Severe
e. □ Very Severe

7.3.3 Patient Global Impression of Change (PGIC): Muscle and Fatigue

7.3.3.1 Muscle Symptoms

The subject will be asked to rate their degree of improvement or worsening of PMM muscle symptoms compared to before the start of study drug in this open label study, using a 7-point scale, standardized PGIC scale.

Overall, how would you rate the change in the severity of your muscle symptoms related to your Primary Mitochondrial Myopathy **since starting the study**?

a. □ Very much improved
b. □ Moderately improved
c. □ Minimally improved
d. □ No change

e. ☐ Minimally worse

f. ☐ Moderately worse

g. ☐ Very much worse

7.3.3.2 Fatigue Symptoms

The subject will be asked to rate their degree of improvement or worsening of PMM fatigue symptoms compared to before the start of study drug in this open label study, using a 7-point scale, standardized PGIC scale.

Overall, how would you rate the change in the severity of your fatigue symptoms related to your Primary Mitochondrial Myopathy **since starting the study**?

a. ☐ Very much improved

b. ☐ Moderately improved

c. ☐ Minimally improved

d. ☐ No change

e. ☐ Minimally worse

f. ☐ Moderately worse

g. ☐ Very much worse

7.3.4 PROMIS Short Form 13a (FACIT-Fatigue)

The PROMIS® Short Form-13a Functional Assessment of Chronic Illness FACIT-Fatigue items assess a range of self-reported symptoms, from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases one's ability to execute daily activities and function normally in family or social roles. The fatigue short forms are universal rather than disease-specific. All assess fatigue over the past 7 days. The score is calculated by adding all the individual question scores (scores of 1 to 5) together to give a total score. Hence a range of scores between 13 and 65 are possible with a higher score indicating a greater level of fatigue. See Appendix 3.

7.3.5 36-item Health Survey V2.0® (SF-36)

The 36-Item Health Survey Version 2.0® asks questions which cover eight health concepts: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health. A one-week recall period will be used.

7.4 Work Productivity PRO

The Work Productivity and Activity Impairment: Specific Health Problem (WPAI:SHP) questionnaire is a well validated instrument to measure impairments in work and activities due to a specific disease over the last 7 days. Outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes. See calculation below:

Scores:

Percent work time missed due to PMM: 100 x Q2 / (Q2 + Q4)
Percent impairment while working due to PMM: 100 x Q5 / 10

Percent overall work impairment due to PMM: 100 x {Q2 / (Q2 + Q4) + [(1-(Q2 / (Q2 + Q4))) x (Q5 / 10)]}
Percent activity impairment due to PMM: 100 x Q6 / 10
See Appendix 4.

7.5 Pain Severity and Interference PRO

The Brief Pain Inventory (BPI) Short Form rapidly assesses the severity of pain and its impact on functioning. It is well used in research and clinical settings.

Four severity items will be investigated by the responses to the worst, least and average pain in the last 24 hours and the pain right now (Questions 3, 4, 5 and 6). The higher score indicates worse pain. A pain severity score will be calculated as the mean of the non-missing 4 severity items. A higher score indicates greater pain severity. In addition, the average pain interference score will be derived as the average of the responses to the 7 components to Question 9. A higher score indicates the more pain interferes with daily functioning. See Appendix 5.

7.6 PMM Phenotypic Description

To enable comparative descriptions of the phenotypic state of each subject's disease, 3 questions, taken from the Newcastle Mitochondrial Disease Adult Scale (NMDAS) will be completed by the physician.

While the questions do not need to be read verbatim, the subject should be questioned to determine the response which best describes the subject's function. To ensure consistency in interpretation the same physician (where possible) should assess subjects on all occasions.

Rate function over the preceding **4-week period, according to patient and/or caregiver** interview only. The physician's subjective judgement of functional ability should not be taken into account.

Question 1 – Exercise Tolerance

0 Normal
1 Unlimited on flat – symptomatic on inclines or stairs.
2 Able to walk <1000m on the flat. Restricted on inclines or stairs – rest needed after 1 flight (12 steps).
3 Able to walk <500m on the flat. Rest needed after 8 steps on stairs.
4 Able to walk <100m on the flat. Rest needed after 4 steps on stairs.
5 Able to walk <25m on the flat. Unable to do stairs alone.

Question 2 – Gait Stability

0 Normal
1 Normal gait – occasional difficulties on turns, uneven ground, or if required to balance on narrow base.
2 Gait reasonably steady. Aware of impaired balance. Occasionally off balance when walking.
3 Unsteady gait. Always off balance when walking. Occasional falls. Gait steady with support of stick or person.
4 Gait grossly unsteady without support. High likelihood of falls. Can only walk short distances (< 10m) without support.
5 Unable to walk without support. Falls on standing.

Rate current status according to examination performed at **the time of** assessment

Question 3 – Myopathy

0 Normal
1 Minimal reduction in hip flexion and/or shoulder abduction only (e.g., MRC 4+/5).
2 Mild but clear proximal weakness in hip flexion and shoulder abduction (MRC 4/5). Minimal weakness in elbow flexion and knee extension (MRC 4+/5 – both examined with joint at 90 degrees).
3 Moderate proximal weakness including elbow flexion and knee extension (MRC 4/5 or 4 -/5) or difficulty rising from a 90-degree squat.
4 Waddling gait. Unable to rise from a 90-degree squat (=a chair) unaided.
5 Wheelchair dependent **primarily** due to proximal weakness.

7.7 PK Blood Samples

Blood samples for determination of REN001 concentrations and possibly REN001 metabolite concentrations will be collected via a direct venipuncture or indwelling cannula. A 4.0 ml blood sample, to provide approximately 2 ml of plasma for PK analysis, will be collected into a labelled tube. Sample handling instructions are provided in the REN001-202 Laboratory Manual. The plasma samples will be stored at the central laboratory prior to analysis. Plasma samples will be transferred to the bioanalytical laboratory on dry ice to maintain frozen conditions. Analysis of REN001 concentrations in plasma will be performed using a validated analytical method.

Subjects will be supplied with a dose record card and will be requested to record the date and time of dosing for all study visit days. At each of the Baseline and Month 1 visits a single PK sample will be taken. At Months 6, 12, 18 and 24 two plasma samples will be taken for PK analysis of REN001, sample 1 to be taken on arrival at site, sample 2 to be taken at end of visit. At the Month 3 visit, PK samples will be taken pre and post study drug administration over a 4-hour period (pre-dose and at 1, 2 and 4 hours post dose (Section 6.3); The subject should take the study drug at the study centre with food when instructed to do so by the site staff, time of dose and time of all PK samples should be recorded.

8 STATISTICAL METHODS

A formal Statistical Analysis Plan (SAP) will be finalized prior to locking the study database. The full details of data presentations and analyses will be provided in the SAP. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and included in the SAP. Any deviations from the final SAP will be discussed in the final Clinical Study Report.

As this study is the open-label extension study to STRIDE, the two studies will be reported together. In addition to data being presented from the start of REN001-202, the data will also be presented from the start of STRIDE and from the start of REN001 treatment for mtDNA-PMM subjects. This will allow the assessment of long-term safety and efficacy from the start of dosing in STRIDE for those who received REN001 in STRIDE, as well as from the start of REN001 in this study.

Presentations from the start of REN001-202 will include all mtDNA-PMM subjects who receive at least one dose of REN001 in this study. The presentations will be split by the various options for entering the study, and by the STRIDE treatment group (REN001, Placebo) for those subjects who participated in STRIDE. nDNA-PMM subjects will also be summarized from the start of REN001-202.

Presentations from the start of STRIDE will include all mtDNA-PMM subjects who receive at least one dose of study drug in the STRIDE study. These will be split by the STRIDE treatment groups (REN001, Placebo). For those subjects who are enrolled into this study after exiting STRIDE only the data collected in STRIDE will be summarized in these presentations.

Presentations from the start of REN001 treatment will summarize the data emergent during treatment with REN001. These summaries will include all mtDNA-PMM subjects who receive REN001 in STRIDE and/or this study.

8.1 Study Subjects

8.1.1 Disposition of Subjects

The number and percentage of subjects entering and completing the study will be presented by treatment group, where treatment groups will be detailed in the SAP.

Reasons for withdrawal will also be summarized.

8.1.2 Protocol Deviations

Deviations from the protocol will be categorized as “minor” or “major”. Full details of the handling of protocol deviations can be found in the Protocol Deviation Management Plan. Deviations will be assessed regularly and finalized prior to database lock.

8.1.3 Analysis Populations

Separate safety and full analysis sets will be identified for the different approaches to summarizing the data (start of REN001-202, start of STRIDE or start of REN001 treatment). Precise details of the analysis sets are dependent on the approach and will be defined further in the SAP, but the general definitions are:

Screened Set	All subjects who sign the informed consent form.
Safety Set/Full Analysis Set (FAS)	All subjects who receive at least one dose of study treatment .
PK Set	All subjects in the FAS who have at least 1 evaluable post-dose PK measurement (even if this is <Level of

	Quantification (LOQ)) in this study.
Scan Set	All subjects in the FAS who have evaluable post-baseline DXA endpoint data.

Safety and efficacy analyses will be based upon the Safety and FAS analysis sets, respectively.

After all the data have been verified/coded/entered into the database, a review will be performed. The purpose of this review will be to define the analysis populations. The review will also check the quality of the data, identify outliers, and make decisions on how to deal with any data issues (e.g., missing values, withdrawals, protocol deviations). After the pre-analysis review, resolution of all issues and documentation of all decisions, the database will be locked.

8.2 General Considerations

8.2.1 Statistical Hypotheses

No formal statistical testing is planned.

8.2.2 Determination of Sample Size

Recruitment of mtDNA-PMM subjects will be limited to those who participated in the STRIDE study (applicable only for countries where this study is being conducted) or Study REN001-101. It is estimated that approximately 150 mtDNA-PMM subjects will be enrolled.

Up to 50 nDNA-PMM subjects will be recruited.

8.2.3 Data Summaries

Continuous data will be summarized using descriptive statistics (e.g., mean and standard deviation) and categorical data will be summarized using frequency tables (counts and percentages).

For both safety and efficacy analyses, data used as a baseline measurement will be dependent on the approach to summarizing the data:

- For presentations from the start of REN001-202, baseline will be taken as the last measurement prior to dosing in this study.
- For presentations from the start of STRIDE, baseline will be taken as the last measurement prior to dosing in STRIDE.
- For presentations from the start of REN001 treatment, baseline will be taken as the last measurement prior to REN001 dosing. This will be prior to REN001 dosing in this study for all subjects except those who receive REN001 in STRIDE, where it will be the last measurement prior to dosing in STRIDE.

8.3 Demographics, Baseline Characteristics and Concomitant Medications

Demographics, baseline characteristics, and concomitant medication data will be summarized. Prior medications will also be summarized.

The WHO Drug coding dictionary will be used for the concomitant medications.

8.4 Treatment Compliance

Treatment compliance will be assessed through capsule counts and will be summarized.

8.5 Efficacy Analyses

Absolute values and, where applicable, changes from baseline in 12MWD and other secondary endpoints will be summarized and may be plotted over time.

8.6 Safety Analyses

No imputation will be used for handling missing data, with the exception of conservative approaches taken for missing AE information (e.g., intensity). Details of such conventions will be documented in the SAP.

Treatment-emergent adverse events will be summarized by SOC and Preferred Term, in accordance with the MedDRA coding dictionary. The number of subjects reporting each AE preferred term will be tabulated for all TEAEs and separately for those considered as at least possibly related to study treatment by the Investigator. Number of subjects reporting SAEs and AESIs will also be tabulated.

Changes from baseline in laboratory parameters (including bone and calcium markers), vital signs, ECG and eye examinations data will be summarized by visit.

The incidence of potentially clinically significant laboratory and ECG values (e.g., increase in QTcF ≥30 msec from baseline or an absolute QTcF value of ≥500 msec).

Absolute values and changes from baseline for the DXA endpoints will be summarized. Summaries will be presented over all subjects and for the following demographic sub-groups:

- Men
- Pre-menopausal women
- Post-menopausal women

8.7 PK Analysis

REN001 plasma concentrations will be summarized over time. Individual and median concentration over time profile plots will be presented for concentrations measured from samples collected at the Month 3 visit. Both linear-linear and linear-log plots will be presented.

PK parameters will be calculated from the Month 3 plasma concentrations for subjects who had their Month 3 visit completed under Protocol Version 1.0. The parameters will include C_{trough}, C_{max}, T_{max} and AUC_{τ}. These parameters will be summarized.

The data may be used for a population PK analysis which will be reported as a standalone report to the Clinical Study Report.

9 ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

9.1 Data Quality Assurance

The Sponsor (or its delegate) will conduct a site visit/telephone call to verify the qualifications of each Investigator, inspect the site facilities, and inform the Investigator of responsibilities and the procedures for ensuring adequate and correct documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded in the eCRFs for this study must be consistent with the subjects' source documentation (i.e., medical records).

9.2 Electronic Case Report Forms (eCRF) and Source Documentation

All data obtained during this study should be entered in the eCRFs promptly. All source documents from which eCRF entries are derived should be placed in the subject's medical records. Measurements for which source documents are usually available include laboratory assessments, and ECG recordings.

The original eCRFs for each subject will be checked against source documents at the study site by the site monitor.

After review by the site monitor, completed eCRFs will be marked as complete and verified. Data Management will review the eCRFs within the electronic data capture (EDC) system. Where data is discrepant, Data Management will raise queries for the site to resolve within the EDC.

9.3 Access to Source Data

During the study, a monitor will make site visits to review protocol compliance, compare eCRFs and individual subject's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained.

Checking of the eCRFs for completeness and clarity and cross-checking with source documents in the presence of the Investigator will be required to monitor the progress of the study. Moreover, regulatory authorities of certain countries, IECs, and/or the Sponsor's Clinical Quality Assurance consultant may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures the CRO and the Sponsor of the necessary support at all times.

9.4 Data Processing

The site will be supplied with a web browser address for an EDC system that has been fully validated and conforms to 21CFR11 requirements. The trained Investigator site staff will enter the data required by the protocol into the eCRFs from source documents (e.g., medical records and study-specific data capture tools as needed) using the supplied data collection tool. All information in the eCRFs must be traceable to these source documents. Data recorded directly into the eCRFs will be defined before study start and the eCRFs will be considered the source data. Clinical Research Associates and Data Managers will review eCRFs entered by investigational staff for completeness and accuracy. Automatic quality programs check for data discrepancies in the eCRFs and the resulting queries will be notified to the investigational site using an electronic data query process within the EDC system.

Designated Investigator site staff are required to respond to queries and make any necessary changes to the data. Details of the data correction process will be specified in the Data Management Plan. After database lock, the Investigator will receive a CD-ROM of the subjects' eCRFs (portable document format [PDF]) for archiving at the investigational site.

An audit trail of all changes to the database, including the date, reason for the data change and who made the change, will be maintained within the clinical database. The audit trail will be part of the archived data at the end of the study.

9.5 Archiving Study Records

Adequate records as required by ICH GCP and Food and Drug Administration (FDA) Code of Federal Regulations (CFR), will be maintained for the study. This will include subject medical records, Investigator logs, eCRFs, laboratory reports, work sheets, signed ICFs, drug dispensing records, AE reports, information regarding subjects' discontinuation and electronic data. Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the final discontinuation of clinical development of the investigational product. However, if required by the applicable regulatory requirements or by an agreement with the Sponsor these documents should be retained for a longer period (e.g., retention period in Canada is 25 years). It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

9.6 Good Clinical Practice (GCP)

The procedures set out in this study protocol are designed to ensure that the Sponsor and Investigator abide by the principles of ICH GCP and the Declaration of Helsinki (2013). The study also will be carried out in keeping with local legal requirements.

9.7 Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating subjects must be maintained. Subjects will be identified in eCRFs and other documents submitted to the CRO by their subject number and/or birth year, not by name. Documents that identify the subject (e.g., the signed informed consent) must be maintained in confidence by the Investigator.

9.8 Informed Consent

Before each subject is admitted to the study, a personally signed and dated informed consent will be obtained from the subject according to the regulatory and legal requirements of the participating country (i.e., Declaration of Helsinki, ICH GCP, and other applicable local regulations). This consent form must also be signed by the person collecting the informed consent and a copy retained by the Investigator as part of the study records. The subject will also receive a copy of the signed consent. The Investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must also be documented in the eCRF.

If a protocol amendment is required, the informed consent form may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and

approved by the appropriate IEC and signed by all subjects subsequently enrolled in the study as well as those currently enrolled in the study.

9.9 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC and CA's, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IEC and CA approval prior to implementation (if appropriate). All amendments will be distributed to all protocol recipients, with appropriate instructions.

9.10 Premature Termination of the Study

If the Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to subjects if the study continues, the study may be terminated after appropriate consultation between the relevant parties. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study.
- A decision on the part of the Sponsor to suspend or discontinue development of the drug.

9.11 Liability and Insurance

The Sponsor will obtain reasonable third-party liability insurance cover in accordance with all local legal requirements. The civil liability of the Investigator, the persons instructed by him and the hospital, practice or institute in which they are employed and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

The Sponsor will arrange for subjects participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

9.12 Publication Policy

By signing the study protocol, the Investigator agrees with the use of results of the study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

After study completion, data from the entire study will be considered for reporting at a scientific meeting and for publication in a scientific journal. The Sponsor will coordinate these activities and will work with the Principal Investigator to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted and other related issues. Authorship will be based on criteria stipulated by leading clinical journals (e.g., contribution to one or more areas of study design, data analysis and interpretation, manuscript preparation and review, etc.).

An Investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the Sponsor in advance.

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