STATISTICAL ANALYSIS PLAN

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: 24 November 2023

Statistical Analysis Plan

Sponsor Name: Reneo Pharma Ltd.

Protocol Numbers, Titles, Version and Dates*:

REN001-202
An open-label, multi-centre study to evaluate the long-term safety and tolerability of REN001 in subjects With Primary Mitochondrial Myopathy (PMM)

Version/Dates:
1.0 (4 August 2021)
2.0 (21 December 2022)
3.0 (7 August 2023)

Feeder study: REN001-201
A double-blind, placebo-controlled, study to evaluate the efficacy and safety of 24 weeks treatment with REN001 in patients with Primary Mitochondrial Myopathy (PMM)

Version/Dates:
1.0 (3 September 2020)
Amendment 1, Version 2.0 (3 December 2020)
Amendment 2, Version 3.0 (26 January 2021)
Amendment 3, Version 4.0 (21 July 2022)

Author(s): [redacted]

SAP Version/Date: Final v2.0 / 24 November 2023

** Country specific protocol amendments are listed in Appendix 1 for both studies.*

Signature Page

Protocol Numbers:	REN001-201 & REN001-202
Protocol Titles:	REN001-202 - An open-label, multi-centre study to evaluate the long-term safety and tolerability of REN001 in subjects with Primary Mitochondrial Myopathy (PMM) Feeder study REN001-201 - A double-blind, placebo-controlled, study to evaluate the efficacy and safety of 24 weeks treatment with REN001 in patients with Primary Mitochondrial Myopathy (PMM)
Version:	Final v2.0
Version Date:	24 November 2023

I confirm that I have reviewed this document and agree with the content.

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
AESI	Adverse Events of Special Interest
BCVA	Best Corrected Visual Acuity
BMD	Bone Mineral Density
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
BPI	Brief Pain Inventory
BSAP	Bone Specific Alkaline Phosphatase
CK	Creatine Kinase
CPEO	Chronic Progressive External Ophthalmoplegia
CSR	Clinical Study Report
DXA	Dual Energy X-ray Absorptiometry
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDISH	evaluation of Drug-Induced Serious Hepatotoxicity
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full Analysis Set
HDL	High Density Lipoprotein
KSS	Kearns-Sayre Syndrome
LDL	Low Density Lipoprotein
LLOQ	Lower Limit of Quantification
LOCS III	Lens Opacity Classification System III
MedDRA	Medical Dictionary for Regulatory Activities
MFIS	Modified Fatigue Impact Scale
MELAS	Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-Like Episodes
MERF	Myoclonic Epilepsy with Ragged Red Fibers
MIDD	Maternally Inherited Deafness and Diabetes
MILS	Maternally Inherited Leigh Syndrome

Abbreviation	Description
MNGIE	Mitochondrial Neurogastrointestinal Encephalopathy
mtDNA	mitochondrial DNA mutations
NARP	Neuropathy; Ataxia; and Retinitis Pigmentosa
nDNA	nuclear DNA mutations
NTx	Urine N-terminal telopeptide
PCI	Potentially Clinically Important
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PMM	Primary Mitochondrial Myopathy
PROMIS	Patient-Reported Outcomes Measurement Information System
PK	Pharmacokinetic
PSOC	Patient Screening Oversight Committee
PT	Preferred Term
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SF-36	36 Item Short Form Survey
SOC	System Organ Class
SRC	Safety Review Committee
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TFLs	Tables, Figures and Listings
ULN	Upper Limit of Normal
ULOQ	Upper Limit of Quantification
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problems
WHO	World Health Organization
12MWD	12-minute Walk Distance
12MWT	12-minute Walk Test

2. INTRODUCTION

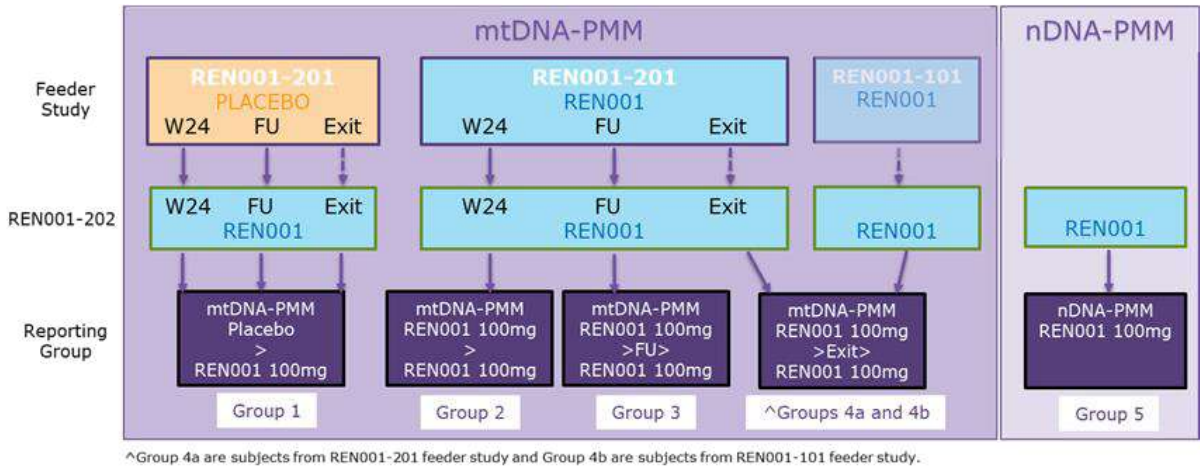
This Statistical Analysis Plan (SAP) details the statistical analyses for the REN001-202 Open Label study. REN001-202 is an open label long term (48 months) safety study in subjects with Primary Mitochondrial Myopathy (PMM) due to mitochondrial DNA mutations (mtDNA-PMM) or nuclear DNA mutations (nDNA-PMM). Subjects with mtDNA-PMM will have previously completed treatment in Study REN001-201 or participated in Study REN001-101. Subjects with nDNA-PMM who enrol in this study will be mavodelpar (REN001) naïve. As this study is an open label extension study to REN001-201 the two studies will be reported together for the REN001-202 clinical study report (CSR). Therefore, this SAP also details the planned integrated analysis for these two studies from a safety perspective and, the planned analysis will provide long term safety data of up to 54 months exposure to mavodelpar for mtDNA subjects who receive mavodelpar in REN001-201.

Figure 1 below shows the different pathways a subject can enter REN001-202 and the 5 distinct reporting groups. These groups provide the following assessments for mavodelpar 100mg once daily:

- Long-term safety data
- Long-term tolerability
- Bridging data (safety and efficacy) between nDNA-PMM subjects and mtDNA subjects

While efficacy data will be presented, these should be interpreted in a descriptive manner since the design of this open label study, does not enable obtaining either reliable or fully interpretable confirmatory evidence of efficacy, including 'durability of effect'. These limitations regarding long-term efficacy assessments are due to several key issues: the lack of a randomized comparator group, the lack of blinding when assessing effects on effort-dependent outcome measures, and the potential impact of meaningfully informative missing data.

Figure 1 Subject Reporting Groups



The data will be presented in different ways:

- from the start of REN001-202. These data presentations will focus on all 5 reporting groups and only consider data collected in REN001-202. This will allow the assessment of mtDNA-PMM and nDNA-PMM over 48 months of mavodelpar treatment. It will also provide an assessment of:
    - the continued safety of mavodelpar for subjects who received mavodelpar for 6 months in REN001-201;
    - the introduction of mavodelpar for subjects who received placebo for 6 months in REN001-201;
    - the re-introduction of mavodelpar for subjects who had a break in mavodelpar treatment in studies REN001-101 or REN001-201; and
    - the introduction of mavodelpar for mavodelpar-naïve nDNA subjects.
- from the start of REN001-201. These presentations will focus on reporting Groups 1, 2, 3 and 4a and include data collected in both REN001-201 and REN001-202, except Group 4a, where only REN001-201 data will be included. This will continue to acknowledge the randomization to treatment groups at the start of the REN001-201. It will provide an insight on the influence of a 6-month delay in beginning mavodelpar on subject safety and efficacy outcomes. Importantly, this will summarize the data for all subjects randomized and dosed in REN001-201.
- from the start of REN001 treatment. These presentations will focus on reporting Groups 1, 2, 3 and 4 and include data collected in both REN001-201 and REN001-202 depending on when mavodelpar is initiated. This provides an overall summary of emergent data following the initiation of mavodelpar treatment to mtDNA-PMM

subjects. This is particularly important with respect to safety data (e.g., overall incidence of AEs with mavodelpar treatment).

For further details on the reporting groups refer to Section 8.2.

The purpose of this SAP is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are comprehensive and appropriate for the assessment of study objectives specified in the study protocol. Changes from the analyses specified in the protocol will be identified in the SAP and any amendments to the SAP will be made prior to database lock. The SAP will be the point of reference for the analyses performed for the CSR. Any additional analyses not described in the final SAP or deviations from the final SAP will be documented in the CSR.

The SAP has been developed based on REN001-202 Protocol Version 3.0 and the latest CRF available (Version 6.0, Date 24 April 2023) and REN001-201 Protocol Version 4.0. The subsequent country specific protocol amendments for REN001-202 (see Appendix 1) do not impact the SAP.

An interim synoptic CSR will be prepared for this study which will be included in the regulatory submission package. The data cut will be the date of the last subject last visit in REN001-201 and the data will be extracted from the database after REN001-201 database has been locked. This CSR will include REN001-202 data up to the data cut date and best efforts will be made to clean data up to this data cut date. In addition, there will be a set of safety outputs generated after submission for the 120-day safety update which is required as part of the submission package. The final CSR will be generated after all subjects have completed participation in REN001-202 and the database is locked.

2.1. RESPONSIBILITIES

Veramed is the Biostatistics vendor for this study and is contracted to prepare the table, figures and listing (TFLs) shells based on this SAP. These shells will detail the format and layout of TFLs and will be presented in a separate document to the SAP. Veramed will perform the statistical analyses and is responsible for the production and quality control of all TFLs.

3. STUDY OVERVIEW

3.1. STUDY OBJECTIVES

3.1.1. Primary Objective

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

3.1.2. 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) for muscle and fatigue, and work productivity.

3.1.3. Pharmacokinetic Objective

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

3.1.4. Exploratory Objective

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) for muscle and fatigue, and work productivity.

3.2. STUDY ENDPOINTS

3.2.1. Primary Endpoints

- 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

3.2.2. Secondary Endpoints

- Absolute values, changes from Baseline and incidence of potentially clinically significant changes in:

  - Laboratory safety tests
  - Electrocardiograms (ECGs)
  - Vital signs
  - Eye assessments

For mtDNA-PMM 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) score 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 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.*

3.2.3. Pharmacokinetic Endpoints

- Mavodelpar plasma concentrations collected pre-dose and 1-, 2-, 4-, 6-, 8-, 12-, and 24-hours post-dose at Month 3 for subjects recruited under Protocol Version 1.0. For subjects recruited under Protocol Version 2.0 plasma concentrations are only collected pre-dose and 1-, 2-, and 4-hours post-dose.
- PK parameters, including C_{trough}, C_{max}, T_{max} and AUC_{τ}, calculated from the Month 3 mavodelpar plasma concentrations of subjects recruited under Protocol Version 1.0.

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-PMM subjects

- Absolute values and changes from Baseline in:
  - Distance walked during the 12-minute walk test (12MWT)*
  - MFIS Total scores and sub-scale scores*
  - Patient Global Impression of Severity (PGIS) score 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 Survey (SF-36) domain scores*
  - 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
- PGIC scores (muscle and fatigue symptoms)

**Collected up to Month 24 only.*

3.3. STUDY DESIGN

REN001-202 is a global Phase 2b open label long-term safety study initially set up for mtDNA-PMM subjects who complete treatment in REN001-201 or who were participating in REN001-101 (a UK only study) when it was ended due to the COVID-19 pandemic. Subjects will receive mavodelpar 100 mg once daily for 48 months.

Protocol Version 2.0 extended recruitment to subjects with nDNA-PMM and increased the predicted sample size. These subjects will enter the study naïve to mavodelpar.

Subjects enrolling from REN001-201 will be switching from taking blinded mavodelpar or placebo in the randomized controlled REN001-201 study to open label mavodelpar in REN001-202. At the time of enrolment into this long-term study, prior treatment allocation in REN001-201 will be unknown. Subjects who are nearing completion of their participation in REN001-201 will be invited to discuss continuing into this long-term safety study.

Hence, subjects may enter REN001-202 via the following pathway options:

1. At REN001-201 Week 24 (REN001-201 W24). Consequently, these subjects will not need to complete the REN001-201 FU visit.
2. At REN001-201 Follow-up (REN001-201 FU).
3. (a) After leaving REN001-201, following their completion of REN001-201 (REN001-201 Exit). This will result in a break in study participation where the subject is off study drug and not monitored in either study.

   (b) After leaving study REN001-101. REN001-101 completed in March 2020 and therefore subjects will have not received mavodelpar for more than 2 years at the time of entry to REN001-202.
4. Recruitment of mavodelpar naïve nDNA-PMM subjects. A Patient Screening Oversight Committee (PSOC) will assess these subjects to confirm the medical diagnosis of nDNA-PMM prior to enrolment.

It is expected that most subjects transferring from REN001-201 will do so at the REN001-201 Week 24 visit to prevent an interruption in dosing and reduce the number of study visits and assessments. Their Week 24 REN001-201 visit will also be used as their Baseline visit for REN001-202.

Enrolment at the REN001-201 FU visit will require additional baseline assessments. Enrolment after exiting REN001-201, after participating in Study REN001-101 and for nDNA-PMM subjects, will require an additional screening visit to complete eligibility checks prior to enrolment. Note, all subjects enrolling from German sites will also need to satisfy additional eligibility checks irrespective of when they roll over from REN001-201.

After the baseline visit, subjects will have study visits at Months 1, 3, 6, 12, 18, 24, 30, 36, 42 and 48 (subjects at the German sites will also have visits at Month 9 and 15) from the start of REN001-202. At 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. The schedule of assessments for REN001-202 is detailed in Section 3.4 and the REN001-201 schedule of assessments is included in Appendix 2.

3.4. SCHEDULE OF ASSESSMENTS

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]
Eye examination	STRIDE Week 24	STRIDE Week 24	X[12]		X[12]	
Wrist radiograph[13]					X	
DXA Scan[14]	STRIDE Week 24	STRIDE Week 24	STRIDE Week 24		X	
Concomitant Medication review	STRIDE Week 24	STRIDE FU	X	X	X	X
AE Review[15]	STRIDE Week 24	STRIDE FU	X	X		X
Dispense Study Drug	X	X		X		X
First dose of study drug[16]	X	X		X		X

[1] Most of baseline data will be STRIDE Week 24 data. Additional assessments to be carried out on the same day.
[2] Baseline tests to be carried out at the STRIDE FU visit.
[3] Separate screening and baseline visits required. 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 8).
[11] There must be a minimum of 4 weeks between the screening and baseline 12MWT.
[12] Eye examination can be done at any time between the screening and baseline visit for scheduling reasons.
[13] Subjects <25 years old.
[14] 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 and perform DXA if subject eligible and not performed in STRIDE.
[15] Review of pre-treatment events for subjects enrolling at option 3 and option 4: after exiting STRIDE or REN001-101, and nDNA-PMM subjects.
[16] 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.

Post Baseline Visits

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				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		X	X	X	X	X	X	X	X	X	X
HbA1c						X			X	X	X
Blood for bone and calcium				X		X		X	X	X	X
PK blood sample for REN001[4]		X	X	X		X		X	X		
Urinalysis inc. pregnancy[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	X----------										----------X
AE review	X----------										----------X
Dosing of study drug	X		X	X		X		X	X	X	

[1] 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.
[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.

3.5. DETERMINATION OF SAMPLE SIZE

The sample size for this study is not based on statistical justification. Recruitment of mtDNA-PMM subjects will be limited to those subjects who participated in REN001-201 or REN001-101, and reside in countries where this long-term safety study is approved. It is estimated that approximately 150 mtDNA-PMM subjects will be enrolled.

It is anticipated that up to 50 nDNA-PMM subjects may also be enrolled.

3.6. TREATMENT ASSIGNMENT AND BLINDING

REN001-202 is an open label study with all subjects receiving mavodelpar 100 mg once daily. Prior treatment allocation in REN001-201 will remain blinded until database lock of REN001-201.

Subjects enrolling from REN001-201 will be assigned the same subject ID they were allocated in REN001-201. Subjects enrolling from study REN001-101 and nDNA-PMM subjects will be assigned a new unique 6-digit subject ID.

A subject, enrolling under pathway options 3 or 4 (Section 3.3), may be rescreened once with prior Sponsor approval and will be given a new subject ID (their original subject ID will be recorded).

3.7. ADMINISTRATION OF STUDY MEDICATION

Subjects will receive 100 mg mavodelpar orally once daily. Study drug should be taken with food at a convenient time to the subject (ideally in the morning). The exceptions to this are:

- at the Baseline visit for subjects enrolled under pathway options 2-4 (Section 3.3) the first dose will be taken with food at the site under the supervision of site staff. Subjects enrolled under pathway option 1 are expected to have taken their last dose of REN001-201 study medication that morning prior to their REN001-201 Week 24 (REN001-202 Baseline) visit, in which case their first dose of mavodelpar in REN001-202 should be taken the following day.
- at the Month 3 visit, where the subject should take the study drug at the study centre with food, when instructed to do so by the site staff.

3.8. APPROACH TO COMBINING REN001-201 DATA

For mtDNA-PMM subjects, the data from REN001-202 will be combined with data from its feeder study, REN001-201. The combined data will be presented from the start of REN001-201 and from the start of REN001 treatment. Presentations from the start of REN001-201 will include all mtDNA-PMM subjects who receive at least one dose of

study drug in REN001-201 and will continue to acknowledge the randomization to treatment groups at the start of REN001-201.

Presentations from the start of REN001 treatment will summarize the data emergent during treatment with mavodelpar. These summaries will include all mtDNA-PMM subjects who receive mavodelpar in REN001-201 and/or REN001-202. In addition to these summaries, data from REN001-202 alone will be reported which will include mtDNA-PMM and nDNA-PMM subjects. These datasets will provide long-term safety, as well as descriptive information on efficacy measures.

As described in Section 3.3 there are 4 pathway options in which subjects can enter REN001-202. The pathway options are described in more detail below:

1. REN001-201 W24

   The majority of subjects enrolling in REN001-202 will enroll at REN001-201 Week 24. This will prevent an interruption in dosing and reduce the number of study visits and assessments for subjects.

   The REN001-201 Week 24 visit will also be the REN001-202 Baseline visit; data in the REN001-201 database for this visit will be copied across programmatically to the REN001-202 database to avoid sites having to re-enter the data. Any data from REN001-201 database repeated in the REN001-202 database will be removed from the tables, listings and analysis datasets prior to reporting the combined data from the two studies. For example, any ongoing AEs or medications at the REN001-201 Week 24 visit will be copied across to the REN001-202 database, where they may be updated if there is any status change (e.g., end date being available); hence the latest information on these events recorded in REN001-202 database will be used for reporting.

   Dosing in REN001-202 will start the day after the REN001-201 Week 24 visit. However, to allow for scheduling of eye examinations and DXA scans these REN001-201 Week 24 assessments can occur up to 14 and 28 days respectively, after the first dose of study drug in REN001-202.

   The schematic below details how subjects transition between the 2 studies and the visit naming convention throughout the 2 studies:

REN001-201 Treatment Group	REN001-201							REN001-202							
	Sc	BL	W2	W4	W12	W18	W24 BL	M1	M3	M6	M12	M18	M24		M48
REN001				REN001							REN001				
	Sc	BL	M0.5	M1	M3	M4.5	M6	M7	M9	M12	M18	M24	M30		M54
Placebo				Placebo							REN001				
	Sc	BL	M0.5	M1	M3	M4.5	M6 *BL	M7 *M1	M9 *M3	M12 *M6	M18 *M12	M24 *M18	M30 *M24		M54 *M48

Footnote: Sc=Screening; BL=Baseline; FU=Follow-up; W=Week; M=Month.
* Baseline visit and nominal visits from start of REN001 treatment.
In REN001-202 visits occur every 6 months between Month 24 and Month 48 (i.e., Months 30, 36 and 42). Where applicable, a final follow up telephone call will occur approximately 30 days after the last dose of study drug.

2. REN001-201 FU

Subjects who enroll at the REN001-201 FU visit will have had an interruption in study drug from the time of the REN001-201 Week 24 visit to the time of the combined REN001-201 FU and REN001-202 Baseline visits. This gap in study treatment is expected to be approximately 4 weeks. For reporting purposes, the nominal study visits in REN001-202 will be considered as a continuation from REN001-201 Week 24.

The REN001-202 Baseline visit data will either be collected at the visit or come from the REN001-201 FU visit if the assessment is performed at the FU visit. The exception to this is the eye examinations and DXA scans which will be taken from REN001-201 Week 24 visit; however, to allow for scheduling of eye examinations and DXA scans these REN001-201 Week 24 assessments can occur after the first dose of study drug in REN001-202. As above for REN001-201 W24 rollover subjects, data in the REN001-201 database for the FU visit will be copied across programmatically to the REN001-202 database to avoid sites having to re-enter the data. Any data from REN001-201 database repeated in the REN001-202 database will be removed from the tables, listings and analysis datasets prior to reporting the combined data from the two studies. For example, any ongoing AEs or medications at the REN001-201 FU visit will be copied across to the REN001-202 database, where they may be updated if there is any status change (e.g., end date being available); hence the latest information on these events recorded in the REN001-202 database will be used for reporting.

Dosing in REN001-202 will start on the day of the REN001-202 Baseline visit.

The schematic below details how subjects transition between the 2 studies and the visit naming convention throughout the 2 studies:

REN001-201 Treatment Group	REN001-201								REN001-202							
	Sc	BL	W2	W4	W12	W18	W24	FU BL	M1	M3	M6	M12	M18	M24		M48
REN001	REN001								REN001							
	Sc	BL	M0.5	M1	M3	M4.5	M6		M7	M9	M12	M18	M24	M30		M54
Placebo	Placebo								REN001							
	Sc	BL	M0.5	W4	W12	W18	W24 *BL	→	M7 *M1	M9 *M3	M12 *M6	M18 *M12	M24 *M18	M30 *M24		M54 *M48

Footnote: Sc=Screening; BL=Baseline; FU=Follow-up; W=Week; M=Month.
* Baseline visit and nominal visits from start of REN001 treatment.
In REN001-202 visits occur every 6 months between Month 24 and Month 48 (i.e., Months 30, 36 and 42). Where applicable, a final follow up telephone call will occur approximately 30 days after the last dose of study drug.

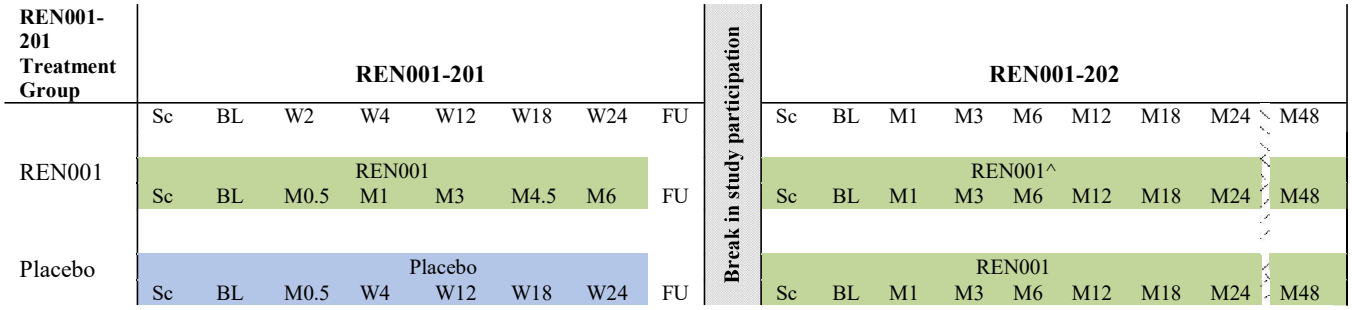
3. (a) <u>REN001-201 Exit</u>

Enrolment after exiting REN001-201 will result in a break in study participation of variable duration where the subject is off study drug and not monitored in either study. Due to the gap in monitoring and dosing, for reporting purposes, the subject's two participations will be considered as two separate subjects and data in REN001-202 will not be considered as a continuation from REN001-201.

These subjects will need to complete Screening and Baseline visits in REN001-202 to check eligibility prior to enrolment. If the subject had a DXA scan in REN001-201, then the REN001-201 Week 24 visit can be used as the Baseline assessment if there is 6 months or less since the assessment. Similarly, the REN001-201 Week 24 eye examination can be used as the Baseline assessment if there is a gap of 6 months or less.

Dosing in REN001-202 will start on the day of the REN001-202 Baseline visit.

The schematic below details how subjects transition between the 2 studies:



Footnote: Sc=Screening; BL=Baseline; FU=Follow-up; W=Week; M=Month.
^ Data from REN001-202 will not be considered a continuation of REN001-201 but will be reported as a separate subject.
In REN001-202 visits occur every 6 months between Month 24 and Month 48 (i.e., Months 30, 36 and 42). Where applicable, a final follow up telephone call will occur approximately 30 days after the last dose of study drug.

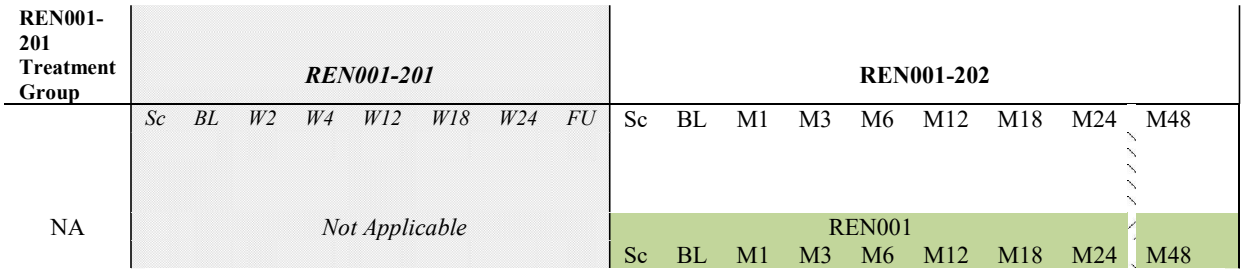
3. (b) REN001-101

REN001-101 completed in March 2020 and therefore subjects will not have received mavodelpar for more than 2 years at the time of entry to REN001-202. For reporting purposes, only data from the start of REN001-202 will be considered.

Subjects will need to perform Screening and Baseline visits in REN001-202 to check eligibility prior to enrolment.

Dosing in REN001-202 will start on the day of the REN001-202 Baseline visit.

The schematic below details the subject visits:



Footnote: Sc=Screening; BL=Baseline; FU=Follow-up; W=Week; M=Month; NA=Not Applicable.
In REN001-202 visits occur every 6 months between Month 24 and Month 48 (i.e., Months 30, 36 and 42). Where applicable, a final follow up telephone call will occur approximately 30 days after the last dose of study drug.

4. nDNA-PMM Subjects

Subjects enrolled with nDNA-PMM will not have received mavodelpar previously so only data from the start of REN001-202 will be available to report.

Subjects will need to perform Screening and Baseline visits in REN001-202 to check eligibility prior to enrolment. Dosing in REN001-202 will start on the day of the REN001-202 Baseline visit.

The schematic below details the subject visits:

REN001-201 Treatment Group	***REN001-201***								**REN001-202**								
	Sc	*BL*	*W2*	*W4*	*W12*	*W18*	*W24*	*FU*	Sc	BL	M1	M3	M6	M12	M18	M24	M48
NA	*Not Applicable*								REN001								
									Sc	BL	M1	M3	M6	M12	M18	M24	M48

Footnote: Sc=Screening; BL=Baseline; FU=Follow-up; W=Week; M=Month; NA=Not Applicable.
In REN001-202 visits occur every 6 months between Month 24 and Month 48 (i.e., Months 30, 36 and 42).
Where applicable, a final follow up telephone call will occur approximately 30 days after the last dose of study drug.

4. EFFICACY ASSESSMENTS

The sections below detail the efficacy assessments, including any derivations required for the efficacy secondary endpoints. The descriptive presentations of data regarding these endpoints are detailed in Section 10.

Details concerning the baseline used in the derivation of changes from baseline are provided in Section 8.6.

4.1. 12-MINUTE WALK TEST (12MWT)

In REN001-201 subjects will perform the 12MWT at Screening, Baseline, Week 12 (Month 3) and Week 24 (Month 6). In REN001-202 subjects will be assessed at Baseline, Months 3, 6, 12, 18 and 24; which from the start of REN001-201 are equivalent to Months 6, 9, 12, 18, 24 and 30. It will also be assessed at an early termination visit if the subject withdraws from the study. In addition, nDNA-PMM subjects will have a screening 12MWT assessment.

The test measures the distance a subject can walk on a flat, hard surface in a period of 12 minutes. To reduce site variability sites will be fully trained to administer the test according to the REN001-202 exercise manual. If the subject does not walk for the full 12 minutes, the distance walked and the duration of time walked will be recorded, along with the reason for stopping prematurely.

Handling of missing or incomplete 12MWT are detailed in Section 8.3.1.

For each visit changes from baseline and percent changes from baseline will be calculated.

Additionally, the exploratory endpoints, distance walked in the first 6 minutes (from start of test up to 6 minutes) and the last 6 minutes (>6 minutes up to 12 minutes) will be derived. As only the number of completed laps are recorded each minute with the final minute recording any partial lap ongoing at the end of the 12 minutes, the distance walked in the first 6 minutes will be the total number of completed laps multiplied by the lap distance (20 meters). The distance walked in the last 6 minutes will then be the total distance walked minus the distance walked in the first 6 minutes. Note, in most cases, this will be an underestimate of the distance walked in the first 6 minutes and an over-estimate of the distance walked in the last 6 minutes.

Pre and post exercise measurements for heart rate and blood pressures are collected. The changes (post – pre) will be calculated.

4.2. PATIENT-REPORTED OUTCOMES MEASUREMENT INFORMATION SYSTEM (PROMIS) SHORT FORM – FUNCTIONAL ASSESSMENT OF CHRONIC ILLNESS THERAPY (FACIT) FATIGUE 13A

The PROMIS short form - FACIT Fatigue 13a is a set of person-centered measures that evaluate a range of fatigue symptoms, from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases a subject'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.

In REN001-201 the PROMIS questionnaire will be used at Screening, Baseline, Week 4 (Month 1), Week 12 (Month 3), Week 18 (Month 4.5) and Week 24 (Month 6). In REN001-202 subjects will be assessed at Baseline, Months 1, 3, 6, 12, 18 and 24; which from the start of REN001-201 are equivalent to Months 6, 7, 9, 12, 18, 24 and 30. It will also be assessed at an early termination visit if the subject withdraws from the study.

There are 13 questions on a 5-point scale ranging from not at all (1) to very much (5). All questions, except Questions 7 and 8, are scaled so that a higher score indicates a greater impact on fatigue. Answers to Questions 7 and 8 will be reversed prior to analysing. The total score is derived by summing the scores and will have a range from 13 to 65. If a subject has a missing response, then the total score will not be derived.

The T-score will be determined using the HealthMeasures Scoring Service (https://www.assessmentcenter.net/ac_scoringservice) (PROMIS 2019). This service uses "response pattern scoring" (Expected A Posteriori estimation) and will also derive a T-score when there is missing data. Subject ID and Visit will be de-identified in the dataset prior to using this scoring service. The T-score rescales the total score into a standardized score, relative to the US general population, with a mean of 50 and a standard deviation of 10. Therefore, an individual with a T-score of 60 is one standard deviation (SD) worse than the mean of the US general population.

For each visit changes from baseline will be calculated for the T-score and total score. The total score data will only be listed.

4.3. PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC) – MUSCLE SYMPTOMS AND FATIGUE SYMPTOMS

In REN001-201 the subject is asked to rate their change in PMM muscle symptoms and their PMM fatigue symptoms at Week 24 (Month 6). In REN001-202 subjects will be assessed at Months 12, 24, 36 and 48; which from the start of REN001-201 are equivalent to Months 18, 30, 42 and 54. It will also be assessed at an early termination visit if the subject withdraws from the study.

The PGIC has a 7-point scale from 'Very Much Improved' to 'Very Much Worse'. This will be converted to a numeric scale from 3 (very much improved) to -3 (very much worse); hence a value of 0 will mean no change in muscle symptoms.

4.4. PATIENT GLOBAL IMPRESSION OF SEVERITY (PGIS) SCORE - MUSCLE SYMPTOMS AND FATIGUE SYMPTOMS

In REN001-201 the PGIS will be used at Screening, Baseline, Week 4 (Month 1), Week 12 (Month 3), Week 18 (Month 4.5) and Week 24 (Month 6). In REN001-202 subjects will be assessed at Baseline, Months 1, 3, 6, 12, 18, 24, 30, 36, 42 and 48; which from the start of REN001-201 are equivalent to Months 6, 7, 9, 12, 18, 24, 30, 36, 42, 48 and 54. It will also be assessed at an early termination visit if the subject withdraws from the study.

The subject will be asked to rate the severity of their PMM for muscle symptoms and for PMM fatigue symptoms over the past 7 days. The scale has 5 levels from 'Absent' to 'Very Severe'.

For each visit changes from baseline will be calculated for the two symptom scores.

4.5. MODIFIED FATIGUE IMPACT SCALE (MFIS)

The MFIS is a detailed tool that is completed by the subject. Scoring is simple, the score reflects functional limitation due to fatigue experienced within the previous 7 days rather than a measure of the current level of fatigue.

In REN001-201 subjects will perform the MFIS at Screening, Baseline, Week 4 (Month 1), Week 12 (Month 3), Week 18 (Month 4.5) and Week 24 (Month 6). In REN001-202 subjects will be assessed at Baseline, Months 1, 3, 6, 12, 18 and 24; which from the start of REN001-201 are equivalent to Months 6, 7, 9, 12, 18, 24 and 30. It will also be assessed at an early termination visit if the subject withdraws from the study.

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 (9 items), cognitive (10 items) and psychosocial functioning (2 items). Physical functioning reflects motivation, effort, stamina and coordination. Cognitive functioning concerns concentration, memory, thinking and organization of thoughts. Psychosocial functioning describes the impact of fatigue upon isolation, emotions, workload and coping. All items are scaled so that a higher score indicates a greater impact of fatigue. The below table shows how to calculate the 3 subscales and the total score:

Subscale	Items	Range
Physical	4+6+7+10+13+14+17+20+21	0 – 36
Cognitive	1+2+3+5+11+12+15+16+18+19	0 – 40

Subscale	Items	Range
Psychosocial	8+9	0 – 8
Total Score	Physical + cognitive + psychosocial subscales	0 – 84

There is no recommended methodology for handling missing component scores for this questionnaire, however, to utilize all available data the following is proposed:

- if 50% or more of the component scores are missing, then the subscale will not be derived and as a result the total score will not be derived. In this situation the subscale(s) with ≥50% missing component scores and the total score will be considered missing
- if less than 50% of the component scores are missing then the average, rounded up to the nearest integer, of the non-missing scores for the subscale will be used to impute each missing value

For each visit changes from baseline and percent changes from baseline will be calculated for each of the sub-scale scores and the total score.

4.6. 36 ITEM SHORT FORM SURVEY (SF-36)

The SF-36 version 2.0 Health Survey asks questions, with a one week recall period, which cover 8 health concepts: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, mental health, social functioning, vitality (referred to in the protocol as energy/fatigue) and general health perceptions. It also includes a single item that provides an indication of perceived change in health. If REN001 is effective greater improvements are anticipated with vitality than the other health concepts.

In REN001-201 the SF-36 will be used at Baseline, Week 4 (Month 1), Week 12 (Month 3), Week 18 (Month 4.5) and Week 24 (Month 6). In REN001-202 subjects will be assessed at Baseline, Months 1, 3, 6, 12, 18 and 24; which from the start of REN001-201 are equivalent to Months 6, 7, 9, 12, 18, 24 and 30. It will also be assessed at an early termination visit if the subject withdraws from the study.

All scale scores will be derived using QualityMetric Health Outcomes Scoring Software 5.0. This software generates standardized scores in accordance with the standards set by the developers of the survey. All items are scored so that a high score defines a more favourable health state. In addition, each item is scored on a 0 to 100 range.

For each visit changes from baseline will be calculated for each health concept scale.

4.7. BRIEF PAIN INVENTORY (BPI) SHORT FORM

The BPI Short Form assesses the severity of pain and its impact on functioning.

In REN001-201 the BPI questionnaire will be used at Baseline, Week 4 (Month 1), Week 12 (Month 3), Week 18 (Month 4.5) and Week 24 (Month 6). In REN001-202 subjects will be assessed at Baseline, Month 12 and Month 24; which from the start of REN001-201 are equivalent to Months 6, 18, and 30. It will also be assessed at an early termination visit if the subject withdraws from the study.

Four severity items will be investigated by the responses to the worst, least and average pain in 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.

In addition, the average pain interference score will be derived as the average of the responses to the 7 components to Question 9 (Cleeland 2009). If there are 3 or fewer responses, then the pain interference score will not be calculated. The higher score indicates more pain interferes with daily functioning.

For each visit changes from baseline will be calculated for the pain severity and pain interference scores.

4.8. WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE: SPECIFIC HEALTH PROBLEMS (WPAI: SHP)

The WPAI questionnaire is a validated instrument to measure impairments in work and activities.

In REN001-201 the questionnaire will be used at Baseline, Week 4 (Month 1), Week 12 (Month 3), Week 18 (Month 4.5) and Week 24 (Month 6). In REN001-202 subjects will be assessed at Baseline, Months 1, 3, 6, 12, 18 and 24; which from the start of REN001-201 are equivalent to Months 6, 7, 9, 12, 18, 24 and 30. It will also be assessed at an early termination visit if the subject withdraws from the study.

Outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes. There are 6 questions defined as:

Questions	Definition
1	currently employed (Yes/No)
2	hours missed because of problems associated with your PMM
3	hours missed because of other reasons
4	hours actually worked
5	how much did your PMM affect productivity while working (scale of 0 [no effect on my work] to 10 [completely prevented me from working])

Questions	Definition
6	how much did your PMM affect regular activities (scale of 0 [no effect on my daily activities] to 10 [completely prevented me from doing my daily activities])

Subjects are asked to answer Questions 2 to 6 with respect to the past 7 days.

The following 4 scores are calculated from the responses, the first 3 will only be calculated if the subject is employed:

Score	Equation
Percent work time missed due to PMM	$100 \times \frac{Q2}{(Q2+Q4)}$
Percent impairment while working due to PMM	$100 \times \frac{Q5}{10}$
Percent overall work impairment due to PMM	$100 \times \left(\frac{Q2}{(Q2+Q4)} + \left[\left(1 - \left(\frac{Q2}{(Q2+Q4)}\right)\right) \times \left(\frac{Q5}{10}\right)\right]\right)$
Percent activity impairment due to PMM	$100 \times \frac{Q6}{10}$

Generally, if a response to a question used in the calculation of a score is missing, the score will be set to missing. The exception to this is the calculation of the percent overall work impairment due to PMM score; if all working hours are missed due to problems associated with PMM (i.e., Question 2≠0 and Q4=0) then (1-(Q2/(Q2+Q4))=0, and so it does not matter if Question 5 (how much did your PMM affect productivity while working) is missing or has a value. Indeed, it is anticipated that the Question 5 response will be missing if they had not worked. In such situations the percent overall work impairment due to PMM will be entirely based on work time missed due to PMM i.e., 100%.

For each visit changes from baseline for each score will be calculated.

4.9. PMM PHENOTYPIC DESCRIPTION

The phenotypic presentation of the subject's disease is rated using 3 questions taken from the Newcastle Mitochondrial Disease Adult Scale. The 3 questions relate to exercise

tolerance, gait stability and myopathy and asked in relation to the previous 4-weeks. Each question has 6 levels (0 to 5), and higher scores indicate a worse rating.

In REN001-201 the questionnaire will be used at Baseline and Week 24 (Month 6). In REN001-202 subjects will be assessed at Baseline, Months 6, 12, 18, 24, 36 and 48; which from the start of REN001-201 are equivalent to Months 12, 18, 24, 30, 42 and 54. It will also be assessed at an early termination visit if the subject withdraws from the study. Where possible the same physician should ask the questions on each occasion to ensure consistency of interpretation.

For each visit changes from baseline for each question will be calculated.

5. PHARMACOKINETIC ASSESSMENT

Plasma mavodelpar concentrations will be determined from samples taken during the study. Samples may be analysed for metabolites, but any analysis of metabolite concentrations will not be part of the CSR and are not detailed in this SAP.

At Month 1 in REN001-202 a single sample will be taken and at Months 6, 12, 18 and 24 two samples will be taken, one on arrival at site, and the second taken at the end of the visit. At Month 3 the timing of samples is dependent on the version of the protocol being used when the subject was recruited:

- Protocol Version 1: pre-dose and 1, 2, 4, 6, 8, 12 and 24 hours post-dose
- Protocol Version 2: pre-dose and 1, 2 and 4 hours post-dose

PK parameters will be calculated from the Month 3 plasma concentrations, for those subjects enrolled under Protocol Version 1.0, by an external vendor using a non-compartmental approach with WinNonlin© software (version 8.3 or higher). Details concerning the derivation of parameters will be documented in a separate non-compartmental analysis plan. The PK parameters estimated will include, but may not be limited to:

C_{trough}	Observed plasma concentration at 24-hours post dose (just prior to next dose)
C_{max}	Maximum observed plasma concentration over the dosing interval
T_{max}	Time of the maximum measured plasma concentration over the dosing interval. If the maximum value occurs at more than one time point, T_{max} is defined as the first time point with this value.
AUC_{τ}	The area under the plasma concentration versus time curve, over the dosing interval (i.e., 0-24 hours), as calculated using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing

The data will also be used for a population pharmacokinetic (PK) analysis which will be detailed in a separate population PK analysis plan and reported separately.

6. SAFETY ASSESSMENTS

The primary purpose of this study is to assess the long-term safety and tolerability of dosing with mavodelpar 100 mg once daily. The sections below detail the safety assessments, including any derivations required. The analyses of the safety endpoints are detailed in Section 10.

Details concerning the baseline used in the derivation of changes from baseline are provided in Section 8.6.

Subjects attending sites in Germany will have additional safety assessments at Month 9 and Month 15. These safety assessments include ECGs, vital signs, safety laboratory evaluation and physical examinations. The data from these assessments will not be included in any 'by visit' summaries but will be listed and will be considered in summaries of results of potential clinical importance.

6.1. ADVERSE EVENTS

The incidence, causality and severity of treatment-emergent adverse events (TEAEs), including treatment-emergent serious adverse events (TESAEs) and adverse events of special interest (AESI), will be investigated.

AESI are those of scientific and medical concern specific to mavodelpar and include:

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

AESI will be identified on the eCRF and will be reported in the same way as serious adverse events (SAEs).

Note in Protocol Versions 1.0 and 2.0, a spherical equivalent loss of ≥0.75 diopters (regardless of changes in lens clarity) was also considered an AESI and reported on the eCRF. However, since the implementation of Protocol Version 3.0 these are no longer routinely reported as AESIs.

6.2. LABORATORY EVALUATIONS

Laboratory safety samples are collected throughout the 2 studies and will be used to determine the following:

- Hematology parameters
- Biochemistry parameters, including:
  - the osteoblastic bone marker - bone specific alkaline phosphatase (BSAP)

  - calcium markers - parathyroid hormone and vitamin D

- Urinalysis parameters, including:
  - the osteoclastic bone marker - Urine N-terminal telopeptide (NTx), via a morning second urinary void

Changes from baseline will be calculated for each laboratory parameter at each scheduled visit.

Laboratory values that are less than the lower limit of quantification (LLOQ) will be set to the LLOQ for the calculation of descriptive statistics. The original recorded value will be displayed in listings.

6.3. DUAL-ENERGY X-RAY ABSORPTIOMETRY (DXA) SCAN

DXA scans will be performed on a subset of subjects at Screening and Week 24 (Month 6) in REN001-201; and in REN001-202 at Baseline, Month 24 and Month 48. Therefore, subjects who have DXA scans throughout the 2 studies will have a total of 4 scans at Screening, Month 6, Month 30 and Month 54 from the start of REN001-201. For subjects who withdraw from the study, it will be performed at an early termination provided the subject has received at least 20 weeks of study drug.

To allow for scheduling of the DXA scans the REN001-201 Week 24 (Month 6) assessment can occur up to 28 days after the visit. Hence, this assessment could occur after the start of administration of mavodelpar in REN001-202; this period is not considered sufficient time to have an impact on DXA results. Therefore, for those mtDNA-PMM subjects who received placebo in REN001-201, enrolled in REN001-202 at REN001-201 Exit, enrol from study REN001-101 or for nDNA-PMM subjects this record will still be considered the baseline record relative to the start of REN001, provided it occurs within 28 days of the first dose of mavodelpar.

Baseline DXA scans will not be required for REN001-201 Exit subjects if within 6 months of the last REN001-201 scan.

The BMD, T-score and Z-score will be measured for 5 spine regions (L1-L4 and total) and for 2 hip regions (total and femoral neck).

Changes from baseline and percent changes from baseline to end of treatment will be calculated for each parameter.

6.4. VITAL SIGNS

Changes from baseline will be calculated for each vital sign parameter (systolic and diastolic blood pressure, pulse, weight and temperature) for each scheduled visit. Change

from baseline for systolic and diastolic blood pressure will be calculated irrespective of whether the arm used for the blood pressure assessment is the same at both visits.

6.5. ECGs

Changes from baseline will be calculated for each ECG parameter (heart rate, QRS duration, PR interval QT interval and QTcF interval) for each scheduled visit.

6.6. Physical Examination

Any physical examination abnormality considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease), will be reported as an AE.

6.7. Eye Examinations

Eye examination data will be performed during the study by an appropriately qualified professional. Any abnormality considered clinically significant, will be reported as an AE.

To allow for scheduling of the eye examinations the REN001-201 Week 24 (Month 6) assessment can occur up to 14 days after the visit. Hence, this examination could occur after the start of administration of mavodelpar in REN001-202; this period is not considered sufficient time to have an impact on eye examination results. Therefore, for those mtDNA-PMM subjects who received placebo in REN001-201, enrolled in REN001-202 at REN001-201 Exit, enrol from study REN001-101 or for nDNA-PMM subjects this record will still be considered the baseline record relative to the start of mavodelpar provided it occurs within 14 days of the first dose of mavodelpar.

Baseline eye examinations will not be required for REN001-201 Exit subjects if the screening visit is within 6 months of the last REN001-201 examination.

Best corrected visual acuity (BCVA) can be assessed using the LogMAR scale, ETDRS letters or Snellen line. All results will be converted to the LogMAR scale before calculating changes from baseline at each visit for left and right eye BCVA (Roy 2003).

Where the Snellen scale has data recorded as x/y the MAR value is calculated by dividing y by x and then the LogMAR is the base 10 logarithm of the MAR value [i.e., LogMAR=log10(MAR)]. Hence, higher scores indicate worse BCVA and increases from baseline indicate deterioration.

A change of 0.02 in LogMAR is equivalent to 1 letter. Hence, a Snellen scores with '-z' or '+z' indicating z letters fewer, or z letters more, respectively, will require an adjustment to the LogMAR score; 0.02 will be added or subtracted, respectively, for each letter (z).

e.g.,

20/15-1: LogMAR = Log10(15 divided by 20)+0.02 = -0.105

20/15+1: LogMAR = Log10(15 divided by 20)-0.02 = -0.145

If the Snellen scale is not reported in x/y format or x/y±z format, then the conversion to logMAR will not be done.

A change of 0.3 LogMAR (equivalent to 15 letters or 3-line change) is considered meaningful.

Refraction error based on spherical equivalent will be derived for each eye using the following formula:

Spherical Equivalent (diopters) = cylinder (diopters)/2 + sphere (diopters)

Changes from baseline at each visit will be calculated.

Cataract are classified and graded against the Lens Opacity Classification System III (LOCS III) for nuclear opalescence, nuclear colour, cortisol and posterior subcapsular cataracts. Changes from baseline will be calculated. Higher scores equate to a deterioration in cataracts. The largest increase from baseline (or smallest decrease if both eyes show a reduction from baseline) across the eyes will be identified at each visit.

6.8. COVID-19 EXPOSURE AND VACCINATION DATA

Information on whether a subject has had exposure to COVID-19 or received a COVID-19 vaccination is collected on a specific eCRF page. Further details of COVID-19 events will be recorded in either medical history or on an adverse event page, depending on the timing; and further details of COVID-19 vaccinations will be recorded on the concomitant page.

7. ANALYSIS SETS AND PROTOCOL DEVIATIONS

7.1. SCREENED ANALYSIS SET

The screened analysis set will include all subjects who signed the REN001-202 informed consent form and are screened for participation in REN001-202.

7.2. SAFETY ANALYSIS SETS

There will be a separate safety set for each of the approaches for summarizing the data.

- from the start of REN001-202 – will include all REN001-202 subjects who signed the REN001-202 informed consent form, completed screening and received at least one dose of mavodelpar study medication in REN001-202.

- From the start of REN001-201 – will include all subjects who signed the REN001-201 informed consent form, completed screening and received at least one dose of study medication in REN001-201.

- from the start of REN001 treatment – will include all subjects who signed the informed consent form (REN001-201 form for mavodelpar REN001-201 subjects and REN001-202 form for REN001-201 placebo subjects), completed screening and received at least one dose of mavodelpar study medication in either REN001-201 (mavodelpar subjects in REN001-201) or REN001-202 (placebo subjects in REN001-201).

The 'from the start of REN001-201' safety analysis set summaries will be based on the actual treatment received. The safety analysis sets will be used for all baseline and safety analyses.

A listing safety analysis set will be used for listings. This will include all subjects who signed the informed consent form and received at least one dose of study medication in either REN001-201 or REN001-202.

7.3. FULL ANALYSIS SETS

There will be a separate full analysis set (FAS) from the start of REN001-202 and from the start of REN001-201 approaches for summarizing the data.

- from the start of REN001-202 – will include all REN001-202 subjects who signed the REN001-202 informed consent form, completed screening, received at least one dose of mavodelpar study medication in REN001-202 and have not been subsequently discontinued from the study for failing eligibility criteria.

- from the start of REN001-201 – will include all subjects who signed the REN001-201 informed consent form, completed screening, received at least one dose of

study medication in REN001-201 and have not been subsequently discontinued from the study for failing eligibility criteria.

Subjects will be analysed according to the treatment they were assigned at REN001-201 randomization for the 'from the start of REN001-201' analyses. The FAS will be the primary analysis set for efficacy.

7.4. PHARMACOKINETIC ANALYSIS SET

The PK set will include all subjects in the safety set who receive mavodelpar in REN001-202 and have at least one evaluable (i.e., not impacted by any important protocol deviations or other events) PK measurement (even if below the limit of quantification) in REN001-202.

Note, intense PK sampling will not be performed on all subjects if it is deemed that sufficient data (i.e., full sampling in approximately 20 -30 subjects) has been collected.

7.5. DXA SCAN ANALYSIS SET

The DXA scan set will include all subjects in the safety set who have a valid REN001-202 Month 24 or Month 48 (or Early Termination) DXA scan (i.e., with parameter measurements). The DXA scan set will be used for analysis of the DXA data.

7.6. PROTOCOL DEVIATIONS

Protocol deviations may be identified by site staff, study monitors and medical monitor reviewers. They may also be identified through programmable checks of the data. Site specific protocol deviations will be provided separately from the subject specific protocol deviations.

Protocol deviations will be reviewed on an ongoing basis and categorized by Reneo Pharma Ltd. as either minor or major prior to database lock. Minor deviations are those that do not produce or have the potential to cause harm, do not impact the integrity of the trial, and cannot be avoided due to the subject's schedule or natural events. In contrast, major deviations are events that may have a significant impact on subject's rights or safety, or the integrity of the clinical study data. No subjects will be excluded from the safety set due to protocol deviations.

Only protocol deviations from REN001-202 will be listed; the REN001-201 protocol deviations will be listed in the REN001-201 CSR. The number of subjects reporting major deviations in either study will be summarized overall and by deviation category.

8. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

8.1. HYPOTHESIS TESTING

No formal statistical testing is planned.

8.2. GENERAL METHODS

Continuous variables will be summarized using the number of non-missing observations (n), mean, SD, median, minimum, and maximum. Categorical variables will be summarized using counts and percentages.

Unless otherwise specified, the estimated mean and median for a set of values should be displayed to 1 more decimal place than the original values, and SD should be displayed to 2 more decimal places than the original values. The minimum and maximum should be displayed to the same number of decimal places as the original values. Deviations from this convention may arise to take account of the relevance of the precision (e.g., the distance walked in the 12MWT is reported to the nearest cm, but there is no relevance in presenting the mean to the nearest mm). These deviations from convention will be documented in the relevant analysis sections below.

Percentages will be displayed with 1 decimal place; except percentages will not be presented when the count is zero and 100% will be presented as an integer. Unless stated otherwise, percentages of subjects will be based on the number of subjects with non-missing data in the analysis set used for the presentation.

Unless stated otherwise, an on-treatment measurement will be any measurement collected (including scheduled and unscheduled visits) up to the date of last dose plus one day. Drug interruptions will not be considered, i.e., data will not be excluded during a drug interruption if the subject resumes study treatment; this includes the follow-up period for subjects who enrol in REN001-202 at the REN001-201 FU.

In by-visit summary tables, the baseline will be summarized using all available data, but also for each visit using only the baseline data from subjects with available data at the visit; hence the mean change from baseline will equal the mean observed visit value – mean baseline value.

Throughout this document ‘change from baseline’ refers to the actual change from baseline (i.e., observed visit value – baseline value). The baseline definitions are detailed in Section 8.6.

There will be 3 approaches to summarising the data and, unless stated otherwise, all presentations will be presented for each approach. Figure 1 in Section 2 shows the different pathway options a subject can enter REN001-202 and the 5 distinct reporting groups these

subjects represent. These 5 reporting groups are referenced in square brackets alongside the descriptions below. The summaries are:

- From the start of REN001-202 Summaries will be presented by mutation group (REN001 100 mg mtDNA-PMM [Groups 1 to 4] and REN001 100 mg nDNA-PMM [Group 5]). The mtDNA-PMM group will also be split by:
    - Placebo > REN001 100 mg [Group 1] – subjects who received placebo in REN001-201 and enrolled at REN001-201 W24, FU or after exit.
    - REN001 100 mg > REN001 100 mg [Group 2] – subjects who received mavodelpar in REN001-201 and enrolled at REN001-201 W24 visit.
    - REN001 100 mg >FU> REN001 100 mg [Group 3] – subjects who received mavodelpar in REN001-201 and enrolled at REN001-201 FU visit.
    - REN001 100 mg >Exit> REN001 100 mg [Groups 4a and 4b] – subjects who received mavodelpar in REN001-201 and enrolled after exiting REN001-201 or subjects who took part in REN001-101 study.

  Summaries will extend out to Month 48, where applicable.
- From the start of REN001-201 which will be split by REN001-201 treatment group (REN001 100 mg [Groups 2, 3 and 4a] and placebo [Group 1]). Subjects who enrol in REN001-202 at REN001-201 Exit will only have their REN001-201 data included in these summaries. Baseline summary tables (disposition, demography, baseline characteristics, medical history and prior medications) will also include an overall summary.

  Summaries will extend out to Month 54, where applicable, for all subjects who complete both studies.
- From the start of REN001 treatment [Groups 1, 2, 3 and 4]. Subjects who enrol in REN001-202 at REN001-201 Exit and receive mavodelpar in REN001-201 [Group 4a] will be counted as 2 separate subjects. Summaries will be presented over all subjects (REN001 100 mg).

  Summaries will extend out to Month 54, where applicable, for subjects who receive mavodelpar in REN001-201 and enrol in REN001-202 at REN001-201 W24 or FU; for all other subjects summaries will extend to Month 48.

In addition, for summaries from the start of REN001 there is only Week 2 (Month 0.5), Week 18 (Month 4.5), Month 1 (Month 7) and Month 3 (Month 9) for subjects who receive mavodelpar in REN001-201 and therefore this visit will not be included in the by visit summaries. Refer to Section 3.8 for diagram of visit assignment.

All data for subjects included in at least one safety analysis set will be listed. For screen failures, only REN001-202 screen failure subjects will have data listed, and this will be limited to disposition (including reason for screen failure), demographics and protocol deviations.

Data listings will be ordered by REN001-201 treatment group (REN001 100 mg, Placebo, Not Applicable), REN001-202 enrolment (REN001-201 W24, REN001-201 FU, REN001-201 Exit, REN001-101 or nDNA-PMM subjects) and subject. For those subjects who do not enter REN001-202 their REN001-202 enrolment will be identified as 'Not Applicable'. Study data from both REN001-201 and REN001-202 will be listed unless stated otherwise, and the listing will indicate the study source of the data. The visit listed will be the original visit for the associated study. A subject's mutational genotype (m.3243A>G, m.8344A>G, mt deletion or Other) will be identified on the listings for mtDNA-PMM subjects. In addition to dates, data listings will present study days relative to:

- Start of REN001-201 dosing (if applicable)
- Start of REN001-202 dosing (if applicable)

Study day will be derived as per SDTM guidelines i.e., study day is derived as (assessment date – first day of dosing +1) after the start of dosing and as (assessment date – first day of dosing) before the start of dosing.

Changes from baseline will be included in listings. More than one change from baseline will be presented if more than one baseline is used (Refer to Section 8.6). All statistical analyses will be performed using SAS® (Version 9.4 or higher, SAS Institute Inc., Cary, NC, USA).

8.3. MISSING DATA

All possible efforts will be made to minimize missing data.

Unless specified otherwise, screening values or pre-dose unscheduled measurements may be used as a baseline value in the event of missing Day 1 pre-dose measurements.

The original data will always be presented in the listings.

8.3.1. Efficacy Data

This is a long-term safety study; since efficacy is a secondary objective and only descriptive presentations of efficacy will be generated there will be no imputation for missing efficacy data. However, all 12MWTs which were stopped prematurely (i.e., before completing 12 minutes) will be reviewed by an adjudication committee to consider whether the reasons are possibly related to the subject's PMM or study treatment. If deemed at least possibly related, then their data recorded will be used in analyses; if

unrelated the data will be considered missing. The adjudication for the REN001-201 12MWTs will have been conducted as part of the REN001-201 reporting and so these decisions will be used for this study as well. As the descriptive presentation of long-term efficacy data is a secondary objective for this study and treatment is open-label the adjudication of the REN001-202 12MWTs will be performed by Reneo.

8.3.2. Pharmacokinetic Data

Missing data will not be imputed.

Mavodelpar concentrations reported as below the limit of quantification (BLQ) will be taken as zero for linear plots, and equal to the LLOQ for log-linear plots. BLQ will be taken as zero for the computation of descriptive statistics except for the geometric mean and geometric CV%, where they will be set to the LLOQ.

8.3.3. Safety Data

AEs with missing classification will be queried prior to database lock. However, if there are missing classifications in the final data the following will be assumed:

- missing causality will be taken as treatment related
- missing severity will be taken as severe

Missing seriousness will not be imputed. Such cases will be discussed in the CSR.

Handling of missing dates/times for the start/stop of medications and adverse events are detailed in Sections 9.4 and 12.1 respectively.

Laboratory values that are less than the LLOQ or greater than the upper limit of quantification (ULOQ) will be set to the LLOQ or ULOQ respectively, for the calculation of descriptive statistics.

There will be no imputation for missing DXA data.

8.4. VISIT WINDOWS

Data will be assigned to 'analysis' visits using windowing (see table below). If more than one assessment (including the early termination or unscheduled assessments) falls within the same defined window, the on-treatment assessment closest to the target day with non-missing data will be used for analysis. If the scheduled visit assessment is on-treatment and within the analysis window, then this will be used irrespective of other unscheduled assessments within the analysis window. If two assessment dates are at the same distance from the target day, the latest on-treatment assessment with non-missing data will be used for analysis. Off-treatment assessments will only be assigned to a visit window in the absence of an on-treatment assessment within the analysis window.

This is the same approach as used in the REN001-201 SAP and therefore the REN001-201 data will have the same analysis visit windowing assigned as per the REN001-201 CSR.

To assess whether a REN001-202 visit is within the analysis window the day relative to the start of REN001-202 will be used. This will mean that for subjects who enrol at REN001-201 FU the interruption in study drug during the REN001-201 FU period will be ignored.

Study	Original Visit	Visit Name for Combined Study Summaries	Target Day[1]	Protocol Visit Window	Analysis Window[1]	Analysis Interval
REN001-201	Baseline	Baseline	1	NA	≤1*	NA
	Week 2	Month 0.5	14	±3	8 – 20	13 (±6)
	Week 4	Month 1	28	±3	21 – 35	15 (±7)
	Week 12	Month 3	84	±7	63 – 105	43 (±21)
	Week 18	Month 4.5	126	±7	106 – 146	41 (±20)
	Week 24	Month 6	168	±7	147 – 189	43 (±21)
REN001-202	Baseline	*Month 6*	1	NA	≤1*	NA
	Month 1	Month 7	28	±3	21 – 35	15 (±7)
	Month 3	Month 9	84	±7	63 – 105	43 (±21)
	Month 6	Month 12	168	±7	147 – 189	43 (±21)
	Month 9^	Month 15^	252	±21	211 – 293	83 (±41)
	Month 12	Month 18	336	±21	294 – 378	85 (±42)
	Month 15^	Month 21^	420	±21	379 – 461	83 (±41)
	Month 18	Month 24	504	±21	462 – 546	85 (±42)
	Month 24	Month 30	672	±21	630 – 714	85 (±42)
	Month 30	Month 36	840	±21	798 – 882	85 (±42)
	Month 36	Month 42	1008	±21	966 – 1050	85 (±42)
	Month 42	Month 48	1176	±21	1134 – 1218	85 (±42)
	Month 48	Month 54	1344	±21	1302 – 1386	85 (±42)

NA=not applicable.
[1] Target day and analysis windows are relative to start of each study.
* Baseline values must be prior to dosing if time of assessment is recorded.
^ Month 9 and Month 15 (original) visits are only applicable for German sites.

Subjects can have more than one baseline defined depending on which reporting group is used. Section 8.6 provides more details on the baseline definitions.

REN001-202 follow-up visit, by design, is after the last dose of study drug and should not be allocated to on-treatment visits. Similarly, REN001-201 follow-up visit should not be assigned to an on-treatment visit in REN001-202.

Windowing will not be used for the DXA scan data. Subjects can have a maximum of 4 DXA scans across the studies and these will be assigned to the nominal scheduled visits.

If an unscheduled or early termination visit is mapped to a scheduled visit, then the type of visit will be identified in the appropriate listing together with the visit that it has been mapped to. In addition, data collected outside these windows will not be attributed to an analysis window and will only be listed, unless specified otherwise in Section 10 and Section 10. Any scheduled visit outside the window will be identified on the appropriate listing.

8.5. SUBGROUPS

Subgroups will only be assessed for the purposes of exploring the consistency of effects. Subgroup analyses are planned for adverse events, 12-minute Walk Distance (12MWD) and DXA endpoints. For these analyses only subgroup categories with 5 or more subjects will be summarized. The subgroups that will be used for each endpoint are defined in the table below, the remaining subgroups will only be used in the summary of baseline characteristics.

Endpoint	Subgroups
Adverse events	Age, sex, race (excluding Other race category)
12MWD	Mutational genotype (both subgroups defined below), baseline 12MWD
DXA	Menopausal status

The subgroups are defined as:

- Age: <65 years or ≥65 years
- Sex: male or female
- Race: black/African American, Asian, American Indian/Alaska Native, Native Hawaiian/Pacific Islander, white or other
- Mutational genotype: there will be 2 subgroups, one which identifies the stratification groups (i.e., m.3243A>G or Other) and a second which further splits out the 'other' category genotype (i.e., m.3243A>G, m.8344A>G, mt deletion or Other). To split out the 'other' genotype category into these extended levels, first the m.8344A>G subjects will be identified from the other description free text

field; then mt deletion subjects will be identified as subjects with a single large deletion gene defect; all remaining subjects will be categorized as Other.

- Syndromatic phenotype: as identified from the additional symptoms of PMM eCRF page.
  - chronic progressive external ophthalmoplegia (CPEO)
  - Kearns-Sayre syndrome (KSS)
  - Leigh and Leigh-like syndrome
  - maternally inherited deafness and diabetes (MIDD)
  - maternally inherited Leigh syndrome (MILS)
  - mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)
  - mitochondrial neurogastrointestinal encephalopathy (MNGIE)
  - myoclonic epilepsy with ragged red fibers (MERF)
  - neuropathy; ataxia; and retinitis pigmentosa (NARP)
  - Pearson syndrome (sideroblastic anemia and pancreatic dysfunction)
  - other
- Baseline 12MWD: there will be 2 subgroups ≤500 m or >500 m and ≤650 m or >650 m
- Country: all countries that randomized a subject
- Region: North America (USA and Canada), Europe or Australia/New Zealand
- Clinically significant vitamin D deficiency at baseline, defined as <30nmol/L: yes, no
- Baseline PROMIS T-score: ≤60 or >60
- Menopausal status: males, pre-menopausal females or post-menopausal females. Post-menopausal females have a screening FSH value ≥ 23.0 IU/L and with either a date of last menstrual period > 1 year ago from date of first dose or a confirmed clinical history of sterility. Female subjects whose last menstrual period was > 1 year ago but do not have a screening FSH value will also be assumed to be post-menopausal. Female subjects who have a clinical history of sterility but do not have a screening FSH value cannot be classified. This subgroup will only be used for DXA and laboratory bone marker analyses.

8.6. BASELINE DEFINITION

Subjects will have up to 2 baselines for endpoints:

- The last available non-missing assessment prior to study drug administration in REN001-201 (Day 1). This baseline will be used for analyses from the start of REN001-201 and, for those who receive mavodelpar in REN001-201, from the start of REN001 treatment analyses.
- The last available non-missing assessment prior to study drug administration in REN001-202. This baseline will be used for analyses from the start of REN001-202, and from the start of REN001 treatment for those subjects who:
    - received placebo in REN001-201
    - enter REN001-202 having exited REN001-201
    - enter REN001-202 having exited REN001-101
    - have nDNA-PMM

  For those subjects who enter REN001-202 from REN001-201 at the REN001-201 W24 or FU visits the baseline should be from the assessments at those visits.

Questionnaires collected on the first day of dosing in either study will be considered as a baseline assessment within the context of the above definitions.

Note, to allow for scheduling of the eye examinations and DXA scans the REN001-201 Week 24 (Month 6) assessment can occur up to 14 days or 28 days respectively, after the visit. Hence, this assessment could occur after the start of administration of mavodelpar in REN001-202; this period is not considered sufficient time to have an impact on the results. Therefore, these assessments can still be considered a baseline record provided it occurs within 14 days for eye examinations or 28 days for DXA scans, of the first dose of mavodelpar.

9. ANALYSIS OF DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS, AND MEDICATION

9.1. SUBJECT DISPOSITION AND WITHDRAWALS

To account for all pathways into REN001-202 a summary including REN001-201 and REN001-202 disposition will be generated. For REN001-201 the summary will be split by REN001-201 treatment groups and present the number (%) of subjects who were:

- Dosed in REN001-201 (% not required)
- Discontinued treatment in REN001-201 (along with reasons)
- Completed treatment in REN001-201 and did not enrol in REN001-202

Percentages will be based on the number of subjects dosed in REN001-201.

For REN001-202 the summary will be split by REN001-101 subjects, nDNA-PMM subjects, and the 6 REN001-201 enrolment pathway options:

1. REN001-201 REN001 enrolled at W24 visit
2. REN001-201 REN001 enrolled at FU visit
3. REN001-201 REN001 enrolled after exiting
4. REN001-201 Placebo enrolled at W24 visit
5. REN001-201 Placebo enrolled at FU visit
6. REN001-201 Placebo enrolled after exiting.

The summary will present the number (%) of subjects who were:

- Screened (for subjects who enrolled after exiting REN001-201, REN001-101 subjects or nDNA-PMM subjects)
- Rescreened (applicable for subjects who enrolled after exiting REN001-201, REN001-101 subjects or nDNA-PMM subjects)[a]
- Not dosed in REN001-202[a]
- Dosed in REN001-202[a]
- Completed REN001-202[b]
- Withdrew from REN001-202 (along with reasons)[b]
- Ongoing in REN001-202 (applicable for interim analyses of REN001-202)[b]
- In each analysis set (safety, FAS, PK and DXA)[b]

[a] Percentages will be based on the number of subjects in the REN001-202 screened set for subjects who enrolled after exiting REN001-201, REN001-101 subjects or nDNA-PMM subjects.
[b] Percentages will be based on the number of subjects dosed in REN001-202.

The number (%) of subjects in the FAS and safety analysis sets will also be summarized from the start of REN001-201 and the number (%) in the safety analysis set from the start of REN001 treatment. The denominator will be based on the number of subjects dosed in REN001-201 and the number of subjects dosed with mavodelpar respectively.

For each scheduled visit the following number (%) of subjects will be presented for each safety analysis set:

- Who attended the visit
- Who missed the visit
- Who withdrew from the study prior to the visit

If a subject does not have a record for a visit and did not withdraw from the study, then the record will be counted as due to missing. For subjects who withdraw from the study then the date of study withdrawal will be used to assess whether the subject missed the visit. Any missing records prior to this date will be classed as missing and any missing records after this date will be classed as a withdrawal.

For interim reporting some subjects will still be ongoing in REN001-202 at the time of the data cut, so in addition to the above categories the number of subjects with the potential to reach a REN001-202 visit will be included; and therefore, the number who attended, missed or were withdrawn prior to visit will be based on those with the potential to reach the REN001-202 visit. Subjects will be assessed as to whether they have the potential to reach a REN001-202 visit using the duration from the first dose in REN001-202 to the date of the data cut. If the duration is greater than the target visit day, then the subject will be deemed to have the potential to reach the REN001-202 visit. If the subject attends a visit they will automatically be categorized as having the potential to reach the visit.

9.2. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demography (sex, race, ethnicity, age at consent [years], weight, height, body mass index (BMI) at screening and menopausal status) will be summarized. Age, weight, height and BMI will be summarized using summary statistics for continuous variables. Sex, categorical age (18 – 25 years, 26 – 45 years and 46 – 64 years and ≥ 65 years), race, ethnicity, and menopausal status (men, pre-menopausal women and post-menopausal women) will be summarized as categorical variables.

The appropriate baseline will need to be used for the subject dependent on their starting position (REN001-201 or REN001-202). For example, the summary of age at consent from the start of REN001 treatment will take their REN001-201 age at consent for subjects who received mavodelpar in REN001-201 and their REN001-202 age at consent for all other subjects.

All subgroups defined in Section 8.5 will be summarized as categorical variables. In addition, the following baseline endpoints will be summarized as continuous variables:

- 12MWD – baseline distance
- PROMIS T-score
- MFIS scale – physical, cognitive, psychosocial and total score
- PGI-S – muscle and fatigue (note, summarized as categorical variables only)

The duration of PMM symptoms (years) will be summarized using summary statistics for continuous variables.

Duration of PMM symptoms (years) = Age at consent – Age at onset of PMM symptoms

These data will be summarised for the safety and DXA scan sets. Menopausal status will only be summarized for the DXA scan set.

9.3. MEDICAL HISTORY AND CONCOMITANT DISEASES

Medical history for subjects who enrol at REN001-201 W24 or FU will come from REN001-201. The only changes to their medical history will be the updating of information (e.g., provision of an end date).

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.1.

Medical history will be presented for each safety set by System Organ Class (SOC) and Preferred Term (PT) with counts and percentages. Each subject will be counted only once in each SOC or SOC/PT summary. In the summary tables, medical history will be presented by decreasing frequency of subjects overall within each SOC and then similarly by decreasing frequency of subjects overall within each PT. In cases of SOCs or PTs with equal frequencies, medical history will be sorted alphabetically.

The following PTs, which are associated with the disease under study, will be listed but excluded from the summaries:

- mitochondrial myopathy
- progressive external ophthalmoplegia
- MELAS syndrome

- myoclonic epilepsy and ragged-red fibres
- Kearns-Sayre syndrome
- gene mutation
- mitochondrial DNA deletion
- mitochondrial encephalomyopathy.

9.4. PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary version WHODRUG GLOBAL B3 September 1, 2020.

Prior medications and concomitant medications are defined in the table below based on the summary being presented.

Presentation	Prior Medication[a]	Concomitant Medication[a]
from start of REN001-201	Medications started prior to the first administration of study drug in REN001-201	Medications taken following first administration of study drug in REN001-201. Medications will be attributed to a treatment period (REN001-201 or REN001-202) if they start or continue into the treatment period.
from start of REN001	Medications started prior to the first administration of mavodelpar[b]	Medications taken following first administration of mavodelpar.
From start of REN001-202	Medications started prior to first administration of study drug in REN001-202[b]	Medications taken following first administration of study drug in REN001-202

[a] Medications started before receiving the study dose but continuing after will be considered as both prior and concomitant medications.
[b] For subjects who participated in REN001-201 only ongoing medications at the time of starting dosing in REN001-202 will be considered as prior medications. Note, from start of REN001 this is relevant only to REN001-201 placebo subjects.

Medication will be summarised for each safety set and the DXA scan set by anatomic therapeutic chemical (ATC) level 2 (therapeutic main group) and ATC level 5 (PT medication name) with counts and percentages. Prior and concomitant medications will be presented by descending frequency in ATC and PT within ATCs over all subjects. A

subject who takes more than one medication will be counted only once if these medications belong to the same extended ATC classification. These summaries will be repeated for medications that have an adverse impact or positive impact on the bones; a medical review of unique medications will be performed prior to database lock to identify these medications.

All data will be listed, and variables will be included to identify the phase of the study when the medication starts and ends (prior, REN001-201 or REN001-202).

If either the start or stop date of medication is missing, the most conservative case will be considered when assigning medications to categories. For a missing start date where stop date is after start date of dosing or missing, the date will be imputed as the dosing start date for the study that the medication was reported in. For a missing start date where stop date is on or before the start date of dosing, the date will be imputed as the day before the stop date and the event will be classified as a prior medication for the study it was reported in, For a missing stop date the date will be imputed as the last study date for REN001-202, except for medications recorded in REN001-201 where the subject enrols after exiting REN001-201; in these cases the last study date in REN001-201 will be used. If a partial date is recorded, the following convention will be used to assign the medication based on the database that the medication was recorded in:

- If a partial date is missing a start day and the month/year is the same as the start date of dosing then use the dose start date if the stop date is after the dose start date or the stop date is missing, else '01' will be used for the day; if a start date is missing a month and the year is the same as the start date of dosing then use the dose start date if the stop date is after the dose start date or the stop date is missing, else January will be used for the start month.
- If a partial date is missing a stop day and month/year is same as last study date then use last study date, else last day of the given month will be used for the stop day; if a stop date is missing a month and the year is the same as last study date then use last study date, else December will be used for the stop month.

Concomitant non-drug therapies will also be listed and the associated phases (prior, REN001-201 or REN001-202) will be included.

9.5. TREATMENT EXPOSURE

Duration of mavodelpar treatment, days on mavodelpar treatment, number of mavodelpar capsules taken, and mavodelpar treatment compliance, will be summarized for each safety analysis set using descriptive statistics. Duration of treatment will also be summarized using 1 month categories up to 3 months and then 3 monthly (84 days) categories (e.g., ≤1 month, >1 to ≤2 months, >2 to ≤3 months, ≤3 month, >3 to ≤6 months, …, >51 to ≤54

months, >54 months); and treatment compliance will also be summarized using the categories <80%, 80-120% and >120%.

- Duration of treatment in days is defined as (date of last mavodelpar dose minus date of first mavodelpar dose plus 1 day). Values will be presented to 1 decimal place
- Days on treatment is defined as the duration of treatment minus the number of days the subject is instructed to not take their mavodelpar medication (e.g., dose interruption due to AE); this will also include the gap in study medication for subjects enrolling at REN001-201 FU
- Number of capsules expected to be taken is defined as the days on mavodelpar treatment multiplied by the number of capsules to be taken each day (2 per day)
- Number of capsules taken is defined as number of capsules dispensed minus number of capsules returned for mavodelpar treatment period
- Treatment compliance (%) is defined as 100 * number of mavodelpar capsules taken / (number of REN001 capsules expected to be taken). Values will be presented to 1 decimal place.

If study drug is not returned, the listing will present a compliance range; the lower limit will assume no study drug taken for the containers not returned and, the upper limit will assume all study drug taken for the containers not returned. The compliance listing will also include number of capsules dispensed and number of capsules returned for mavodelpar treatment period. If study drug is not returned the summary will consider number of capsules taken as missing, and so the subject will be excluded. However, for the treatment compliance categorical summary, the subject may be counted if their range falls entirely within one treatment compliance category (e.g., if the range is 40-60% they will be counted in the count for the <80% category).

As the study will be ongoing at the time of the interim synoptic CSR only duration of treatment and days on treatment will be presented. For ongoing subjects, the date of last dose will be assigned the date of last contact up to the date of the data cut.

Only mavodelpar dosing across the 2 studies will be listed.

10. ANALYSIS OF EFFICACY DATA

All analyses will be based on the FAS for the groups from the start of REN001-202 and from the start of REN001-201 unless stated otherwise.

Missing data will be handled using the complete case methodology described in Section 8.3.1.

As the nDNA-PMM subjects will only be recruited from a subset of the REN001-202 sites, summaries may also be presented only including mtDNA-PMM subjects from the same sites. Two separate sets of subjects may be used: the subjects who received mavodelpar in REN001-201 with their data from the start of REN001-201, and the subjects who received placebo in REN001-201 from the start of REN001-202. Consideration will be given to the duration of exposure for nDNA-PMM subjects when summarising the data from the mtDNA-PMM subjects (e.g., if the duration of exposure of nDNA-PMM subjects is up to 6 months, only the first 6 months of data for the mtDNA-PMM subjects will be used).

10.1. 12-MINUTE WALK TEST (12MWT)

Observed, change from baseline and percent change from baseline values will be summarized by visit using descriptive statistics. The associated 95% confidence intervals for the observed, change from baseline and percent change from baseline means will also be presented. The number of subjects withdrawn prior to the visit or with missing data will also be presented. Note missing data will include those subjects who prematurely stop the 12MWT and their reason for stopping is adjudicated as not being possibly related to the subject's PMM or study treatment.

Mean plots for observed, change from baseline and percent change from baseline values, with 95% confidence intervals will be presented by group with visit on the x-axis. A reference line for no change (i.e., y=0) will be included in the change from baseline and percent change from baseline plots.

Spaghetti plots for the changes from baseline will be plotted over time. The plots will be split by group. The y-axis will be uniform across the plots to allow comparisons. A reference line for no change (i.e., y=0) will be included.

The impact of the subgroups (specified in Section 8.5) on the 12MWD will also be investigated descriptively. Summaries will be presented by subgroup.

The number of stops and the number of falls will be summarized by visit. If a subject does not walk for the full 12 minutes, then this will be counted as an additional stop when summarizing.

All data will be listed together with changes from baseline (from start of REN001-202 and from start of REN001-201) and corresponding percent changes from baseline. Assessments

which were prematurely stopped and adjudicated as being at least possibly related to the subject's PMM will be identified. The pre and post exercise measurement for heart rate, blood pressure and RPP scale score will be listed separately, along with their changes from pre-test.

12MWD values, mean, median, minimum and maximum will all be presented to 2 decimal places and SD will be presented to 3 decimal places.

10.1.1. 6-Minute Walk Distance (Derived from 12MWD)

The first and last 6-minute walk distances derived from the 12MWD will be presented in the same way as the 12MWD. Note that if a subject's 12MWD is incomplete but they walk for longer than 6 minutes then only the last 6-minute period will be classified as incomplete.

In addition to the summary presentation, mean plots for observed, change from baseline and percent change from baseline values, with 95% confidence intervals will be presented by group and 6-minute time period with visit on the x-axis. A reference line for no change (i.e., y=0) will be included in the change from baseline and percent change from baseline plots.

6-minute walk distance values, mean, median, minimum and maximum will all be presented to 2 decimal places and SD will be presented to 3 decimal places.

10.2. MODIFIED FATIGUE IMPACT SCALE (MFIS)

Observed, change from baseline and percent change from baseline values will be summarized by visit using descriptive statistics, for the subscale scores and total score. The associated 95% confidence intervals for the observed, change from baseline and percent change from baseline means will also be presented. The number of subjects withdrawn prior to the visit or with missing data will also be presented.

Mean plots of observed, change from baseline and percent change from baseline values, with 95% confidence intervals will be presented by group with visit on the x-axis. A reference line for no change (i.e., y=0) will be included in the change from baseline plot.

Spaghetti plots for the changes from baseline will be plotted over time. The plots will be split by group. The y-axis will be uniform across the plots to allow comparisons. A reference line for no change (i.e., y=0) will be included.

Categorical shift tables of change from baseline showing improvement (at least a 4-point decrease in score), no change (less than a 4-point change in either direction) or worsening (at least a 4-point increase in score) at each visit will be summarized. The table will include categories for withdrawn and missing. Percentages will not be presented for the withdrawn and missing rows, and the percentages presented will use the number of non-

missing values as the denominator. In addition, to account for subjects at the extreme ends of the scale, the shift table will also include the percent improving or worsening based on those subjects who have the potential to improve or worsen respectively.

10.3. PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC) – MUSCLE SYMPTOMS AND FATIGUE SYMPTOMS

PGIC muscle symptoms and fatigue symptoms scores will be summarized by visit as a categorical variable. The table will include categories for withdrawn and missing. Percentages will not be presented for the withdrawn and missing rows, and the percentages presented will use the number of non-missing values as the denominator.

Stacked bar charts will be presented for the proportion of subjects at each of the PGIC scores by visit for each of the groups. The categories will include each of the PGIC levels and missing and withdrawn.

10.4. PATIENT GLOBAL IMPRESSION OF SEVERITY (PGIS) SCORE - MUSCLE SYMPTOMS AND FATIGUE SYMPTOMS

Categorical shift tables from baseline at each visit will be summarized including marginal totals. The table will include categories for withdrawn and missing. Percentages will not be presented for the withdrawn and missing rows, and the percentages presented will use the number of non-missing values as the denominator. In addition, to account for subjects at the extreme ends of the scale, the shift table will be repeated for improvement or worsening from baseline at each visit, based on those subjects who have the potential to improve or worsen, respectively.

Stacked bar charts will be presented for the proportion of subjects at each of the PGIS scores by visit for each of the groups. The categories will include each of the PGIS levels and missing and withdrawn.

10.5. PATIENT-REPORTED OUTCOMES MEASUREMENT INFORMATION SYSTEM (PROMIS) SHORT FORM – FUNCTIONAL ASSESSMENT OF CHRONIC ILLNESS THERAPY (FACIT) FATIGUE 13A

Observed and change from baseline values will be summarized by visit using descriptive statistics for the T-score. The associated 95% confidence intervals for the observed and change from baseline means will also be presented. The number of subjects withdrawn prior to the visit or with missing data will also be presented.

Mean plots of observed and change from baseline values for the T-score, with 95% confidence intervals will be presented by group with visit on the x-axis. A reference line for no change (i.e., y=0) will be included in the change from baseline plot.

Spaghetti plots for the changes from baseline will be plotted over time. The plots will be split by group. The y-axis will be uniform across the plots to allow comparisons. A reference line for no change (i.e., y=0) will be included.

Categorical shift tables of change from baseline for T-score showing improvement (at least a 5-point decrease in score), no change (less than a 5-point change in either direction) or worsening (at least a 5-point increase in score) at each visit will be summarized. The table will include categories for withdrawn and missing. Percentages will not be presented for the withdrawn and missing rows, and the percentages presented will use the number of non-missing values as the denominator. In addition, to account for subjects at the extreme ends of the scale, the shift table will also include the percent improving or worsening based on those subjects who have the potential to improve or worsen respectively.

10.6. 36 ITEM SHORT FORM SURVEY (SF-36)

Observed and change from baseline values will be summarized at each visit using descriptive statistics for the 8 scale scores. The associated 95% confidence intervals for the observed and change from baseline means will also be presented. The number of subjects withdrawn prior to the visit or with missing data will also be presented.

Mean plots of observed and change from baseline values, with 95% confidence intervals will be presented by group with visit on the x-axis. A reference line for no change (i.e., y=0) will be included in the change from baseline plot.

Categorical shift tables of change from baseline for each scale score showing improvement (at least a 4-point increase in score), no change (less than a 4-point change in either direction) or worsening (at least a 4-point decrease in score) at each visit will be summarized. The table will include categories for withdrawn and missing. Percentages will not be presented for the withdrawn and missing rows, and the percentages presented will use the number of non-missing values as the denominator. In addition, to account for subjects at the extreme ends of the scale, the shift table will also include the percent improving or worsening based on those subjects who have the potential to improve or worsen respectively. Where a 4-point change in score indicates an improvement or worsening, subjects with the potential to improve will have a baseline score of 96 or below; similarly, for those with a potential to worsen they will have a baseline score of 4 or more.

Scale scores and changes from baseline will be listed separately from the raw data.

Scale score values will be presented to 0 decimal places.

10.7. BRIEF PAIN INVENTORY

Observed and change from baseline values will be summarized at each visit using descriptive statistics for the pain severity and pain interference scores. The associated 95% confidence intervals for the observed and change from baseline means will also be presented. The number of subjects withdrawn prior to the visit or with missing data will also be presented.

Mean plots of observed and change from baseline values, with 95% confidence intervals will be presented by group with visit on the x-axis. A reference line for no change (i.e., y=0) will be included in the change from baseline plot.

Categorical shift tables of change from baseline for pain severity and pain interference showing improvement (at least a 1.5-point decrease in score), no change (less than a 1.5-point change in either direction) or worsening (at least a 1.5-point increase in score) at each visit will be summarized. The table will include categories for withdrawn and missing. Percentages will not be presented for the withdrawn and missing rows, and the percentages presented will use the number of non-missing values as the denominator. In addition, to account for subjects at the extreme ends of the scale, the shift table will also include the percent improving or worsening based on those subjects who have the potential to improve or worsen respectively.

Pain severity and pain interference scores and changes from baseline will be listed with the raw data.

10.8. WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE: SPECIFIC HEALTH PROBLEMS (WPAI: SHP)

WPAI scores, except percent activity impairment, will only be summarized for those subjects who are employed. Observed and change from baseline values will be summarized by visit using descriptive statistics for the 4 WPAI scores. The associated 95% confidence intervals for the observed and change from baseline means will also be presented. The number of subjects withdrawn prior to the visit or with missing data will also be presented.

Mean plots of observed and change from baseline values, with 95% confidence intervals will be presented by group with visit on the x-axis. A reference line for no change (i.e., y=0) will be included in the change from baseline plot.

WPAI score values will be presented to 0 decimal places.

10.9. PMM PHENOTYPIC DESCRIPTION

Categorical shift tables from baseline at each visit will be summarized, including marginal totals, for the 3 phenotypic questions. The table will include categories for withdrawn and

missing. Percentages will not be presented for the withdrawn and missing rows, and the percentages presented will use the number of non-missing values as the denominator.

11. ANALYSIS OF PHARMACOKINETIC ENDPOINTS

The mavodelpar concentrations will be evaluated using the PK set. Mavodelpar concentrations will be summarized at each Month 3 scheduled time point using descriptive statistics, including the additional summary statistics geometric mean and geometric CV%. The summary will be repeated for subjects who have completed the 24 h profile. For post-dose samples, only concentrations collected within a 10% window of the protocol specified post dose time point will be included. Similarly, pre-dose concentrations will only be included if the samples were taken prior to dosing on the day. The number of subjects with a BLQ value will also be tabulated.

Linear and log-linear individual concentration profile spaghetti plots against time will be produced for Month 3. All subjects will be displayed on the same plot and mutational genotype (m.3243A>G, m.8344A>G, mt deletion or Other) will be identified for mtDNA-PMM subjects as well as identifying nDNA-PMM subjects. The actual sampling time will be used on the x-axis with pre-dose fixed at zero for all subjects.

Linear and log-linear median concentration profile plots against time will be produced for Month 3. The plots will be repeated for subjects who have completed the 24 h profile. The nominal sampling time will be used on the x-axis. The number of subjects contributing to each time point will be included on the plots. Lines will be included for all subjects and by mutational genotype.

A listing of all REN001-202 concentration data will be presented. The actual time post dose, deviation and percent deviation from nominal post dose time will also be listed for the post dose samples on Day 1 and Weeks 12 and 24. For all other visits the actual time relative to dose the sample was collected will be listed.

Month 3 PK parameters will be summarized for subjects recruited under protocol version 1.0 using descriptive statistics. C_{trough}, C_{max}, and AUC_{τ} will include the additional summary statistics of geometric mean, geometric CV% and CV%; and for T_{max} only the summary statistics median, minimum and maximum will be presented. PK parameters will be listed.

12. ANALYSIS OF SAFETY DATA

All safety evaluations will be performed using each safety analysis set unless specified otherwise.

As the nDNA-PMM subjects will only be recruited from a subset of the REN001-202 sites, summaries may also be presented only including mtDNA-PMM subjects from the same sites. Two separate sets of subjects may be used: the subjects who received mavodelpar in REN001-201 with their data from the start of REN001-201, and the subjects who received placebo in REN001-201 from the start of REN001-202. Consideration will be given to the duration of exposure for nDNA-PMM subjects when summarising the data from the mtDNA-PMM subjects (e.g., if the duration of exposure of nDNA-PMM subjects is up to 6 months, only the first 6 months of data for the mtDNA-PMM subjects will be used).

12.1. ADVERSE EVENTS

AEs will be coded using MedDRA version 23.1.

AEs will be considered treatment-emergent (TE) unless there is a clear indication that the event occurred prior to the first administration of study drug. AEs with missing start dates will be taken as TE unless the end date occurs before Day 1. If there is a partial start date, then the AE will be taken as TE unless suggested otherwise by the partial information provided and the end date.

Any AEs reported prior to dosing in either REN001-201 or REN001-202 (for subjects enrolling at REN001-201 Exit, from REN001-101 or nDNA-PMM subjects) will be reported as pre-treatment AEs in the databases and will therefore not be reported as TE (checks will be made of the AE start date against the start of dosing). Subjects who receive placebo in REN001-201 will have their TE events reported in REN001-201 assigned to placebo. Any events that are ongoing at the start of REN001-202 will only be assigned to mavodelpar if they worsen in severity on or after the start of dosing in REN001-202.

Note, any ongoing AEs at the end of REN001-201 for subjects enrolling at REN001-201 W24 or REN001-201 FU will be recorded on the pre-treatment AE eCRF page for REN001-202; if the event resolves during REN001-202 the record will be updated. These events will be considered TE to the REN001-201 treatment.

If an adverse event has a missing start date where the stop date is after the dosing date, or missing, the date will be imputed as the dosing start date and for a missing start date where the stop date is before the start date of dosing, the date will be imputed as the day of informed consent and classified as a pre-treatment AE; for a missing stop date the TEAE will be considered as ongoing at the last visit date. If a partial date is recorded, the following convention will be used to assign the AE based on the database that the AE was recorded in:

- If a start date is missing the day information and month/year is the same as the dosing start date then use the dose start date, else '01' will be used for the day; if a start date is missing the day/month and the year is the same as the dosing start date then use the dose start date, else January will be used for the start month.
- If a stop date is missing the day information and month/year is same as last study date then use last study date, else last day of the given month will be used for the stop day; if a stop date is missing the day/month and year is the same as last study date then use last study date, else December will be used for the stop month.

Only TEAEs will be included in the summary tables. Summaries will be generated for all TEAEs. Summaries will be presented overall and split by time period looking at AEs reported (based on AE start date) in the first month (up to and including Day 28), 2-6 months (Day 29 to Day 168 inclusive), 6-12 months (Day 169 to Day 336 inclusive) and >12 months (after Day 336). Summaries will be repeated for the subgroups – age (<65 years or ≥65 years), sex and race.

An overall summary will present the number and percentage of subjects with:

- any TEAE
- any TEAE considered as related to study drug (evaluated by the investigator as Possibly Related or Related)
- any TESAE
- any TESAE considered as related to study drug
- any AESI
- maximum severity TEAE of mild, moderate, or severe; i.e. a subject with TEAEs at different intensities will be summarized at the most severe intensity
- maximum severity for TEAE considered as related to study drug
- any TEAE leading to study drug discontinuation
- any TEAE leading to death

The table will include the total number of TEAEs reported. The total number of unique terms within subjects will also be presented, counting each TEAE PT only once within each subject.

The number and percentage of subjects with TEAEs will be presented by System Organ Class (SOC) and PT. Subjects with multiple TEAEs within a SOC or SOC/PT combination will be counted only once for that SOC or SOC/PT combination. Similar summaries will be presented for related TEAEs, AESI and TESAEs.

SOC and PT summaries of TEAEs by maximum severity (mild, moderate or severe) will be presented.

All summaries will be ordered by descending frequency of total number of subjects within each SOC and then similarly by decreasing frequency of total number of subjects within each PT, in the REN001 treatment group (i.e., from start of REN001-201 and from start of REN001 treatment this will be the REN001 100 mg group, and from start of REN001-202 this will be the mtDNA PMM Overall REN001 100 mg group). In cases of SOCs or PTs with equal frequencies, AEs will be sorted alphabetically.

All AEs will be listed with their onset and end study days. AE duration (stop date/time – start date/time or [stop date – start time + 1] for AEs with no time information) will be included in the listing for those AEs no longer ongoing; where applicable imputed data will be used for the calculation of AE duration, but the original date/time information will be presented in the listing. For ongoing AEs the duration will be calculated using the last contact date and presented with a prefix of '>' to indicate it is an estimate. The listing will identify treatment emergent AEs, AESI and SAEs. The associated study (REN001-201 and REN001-202) of AE onset and the assigned treatment emergence period (pre-treatment, REN001-201 or REN001-202) will also be listed.

A separate listing of TESAEs, TEAESI and TEAEs leading to study drug discontinuation will also be generated. If there are any deaths a listing will include the date of death and the adverse event(s) associated with death.

12.2. LABORATORY EVALUATIONS

Observed and change from baseline clinical laboratory data (hematology, biochemistry and continuous urinalysis parameters) will be summarized by visit using descriptive statistics.

Observed, change from baseline and percent change from baseline values for BSAP, parathyroid hormone, vitamin D and urine NTx will be summarized by visit using descriptive statistics. The summary will also be split by sex and baseline menopausal status (i.e., men, pre-menopausal women and post-menopausal women). For NTx only subjects who have a second void collected at the visit will be included in the summary presentations (including the plots specified below).

Urinalysis categorical data will also be summarized by visit. Descriptive statistics will be used for continuous data and counts and percentages for categorical data.

A shift table from baseline to visit, of normal, abnormal low, abnormal high and missing records will also be summarised for hematology, chemistry and urinalysis data, with marginal totals, using counts and percentages. If the reference range does not have a lower bound (e.g., reference range is 0 to x), the low columns/rows will be presented as '-', rather than a count of zero.

Box plots of changes from baseline by visit and group will be presented for the clinical laboratory parameters hemoglobin, HbA1c, high density lipoprotein (HDL), low density

lipoprotein (LDL), lymphocytes, leukocytes, platelets, neutrophils, vitamin D, calcium, CK, ALT, AST, BSAP and urine N-terminal telopeptide (NTx) values. The whiskers will display the 5th and 95th percentiles. For the reporting group from the start of REN001-202 the box plot will be repeated for the overall mt-DNA-PMM versus nDNA-PMM groups and outliers (i.e., outside the 5th to 95th percentile) will be identified on the plot with subject ID. The number of observations contributing to each visit will be included on the plot. The box plot will be repeated for the parameters BSAP and urine N-terminal telopeptide (NTx) however these plots will be presented by sex and baseline menopausal status (i.e., men, pre-menopausal women and post-menopausal women).

Subjects who satisfy the criteria for values of potential clinical importance (PCI), identified in the table below, will be summarized and listed. The summary will present the number of subjects with at least one on-treatment post baseline value (including unscheduled visits) satisfying the criteria. The listing will have a similar layout to the overall laboratory listing but will only include those subjects who satisfy the criteria for a specific parameter. The records satisfying the criteria will be identified on the listing. The criteria are:

Category	Parameter	Criteria
Chemistry	Creatine kinase (CK)	Normal baseline value and post ≥ 5 x ULN > ULN baseline value and post ≥ 5 x baseline level
	Aldolase	Normal baseline value and post > ULN
	Troponin I	> ULN
	Potential Hy's Law (ALT, AST, total bilirubin and alkaline phosphatase)	ALT or AST > 3 x ULN and Total bilirubin > 2 x ULN and Alkaline Phosphatase ≤ 2 x ULN

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will be generated. The plot will include all post baseline data and will present ALT relative to the upper limit of normal (ULN) on the x-axis and total bilirubin relative to the ULN on the y-axis using a log scale for both axes. Reference lines for Hy's law thresholds, i.e., ALT = 3 x ULN and total bilirubin = 2 x ULN, will be added. The plot will identify group and mutational group and separate plots will be done for on-treatment and off-treatment records.

A spaghetti plot for the changes from baseline in creatine kinase (CK) over time will be presented. The actual sampling day will be used on the x-axis (baseline will be set to day 1). A solid line will be used to connect measurements; however, if the measurement was collected after the last dose of study drug plus one day, then a dotted line will be used. Group will be identified on the plot. The plot will be repeated for aldolase and troponin I.

Individual CK, aldolase, ALT, AST and troponin I values relative to the ULN will be plotted over time (i.e., one plot per subject) and group and mutation type will be identified.

The actual sampling day will be used on the x-axis (baseline will be set to day 1). The day of last dose of study drug will be identified on the plot with a vertical reference line.

All individual central laboratory results will be listed. The listing will include change from baseline values and values relative to the ULN. Values outside the laboratory reference range will be identified.

Local laboratory results will not be summarized and will be listed separately from central laboratory results.

12.3. DUAL ENERGY X-RAY ABSORPTIOMETRY (DXA) SCAN

Summaries of DXA data will only be presented from the start of REN001-202 and from the start of REN001 treatment.

Observed, change from baseline and percent change from baseline values for the DXA endpoints will be summarized for the DXA set. The summary will be presented overall within the group and by sex and menopausal status (i.e., men, pre-menopausal women and post-menopausal women).

A box and whisker plot will be presented for each of the parameters measuring the total spine and the 2 hip regions (total and femoral neck), for the DXA set. The whiskers will display the 5th and 95th percentiles and outliers will be identified on the plot with subject ID. The plot will present the visits alongside one another for each group. The plot will be repeated by sex and menopausal status.

For the DXA set, the study day of the follow-up DXA scans (Months 6, 30 and 54 relative to the start of REN001-201) will be summarized using descriptive statistics.

12.4. VITAL SIGNS

Observed and change from baseline values will be summarized by visit using descriptive statistics.

Box plots of change from baseline by visit and group will be presented for measurements. The whiskers will display the 5th and 95th percentiles and outliers will be identified on the plot with subject ID. The number of observations contributing to each visit box plot will be included.

The number and percentage of subjects with an increase or decrease from baseline in systolic blood pressure of <10 mmHg, ≥10 to <20mmHg, ≥20 to <30 mmHg or ≥30 mmHg will be summarized by visit. The denominator for percentages will be the number of subjects still on-treatment. This summary will be repeated for diastolic blood pressure using the following categories <5 mmHg, ≥5 to <10 mmHg, ≥10 to <15 mmHg, ≥15 to <20 mmHg, ≥20 to <25 mmHg or ≥25 mmHg.

Observed and change from baseline values will be listed. The listing will identify the increase or decrease from baseline categories detailed above for systolic and diastolic blood pressure.

12.5. ECG

Observed and change from baseline values will be summarized by visit using descriptive statistics.

A shift table from baseline to visit, for overall ECG interpretation (normal, abnormal not clinically significant, abnormal clinically significant and missing) will be summarised with marginal totals, using counts and percentages.

A shift table from baseline to the maximum post baseline QTcF value will be summarized according to the categories specified in the table below. The maximum will be taken from all scheduled and unscheduled on-treatment values.

Parameter	Criteria
QTcF	< 450 msec ≥ 450 msec and < 480 msec* ≥ 480 msec and < 500 msec* ≥ 500 msec*
QTcF increase from baseline	< 30 msec ≥ 30 msec and < 60 msec* ≥ 60 msec*

* Values of PCI.

Observed and change from baseline values will be listed. The listing will identify QTcF values of PCI (identified in the above table).

12.6. PHYSICAL EXAMINATION

Physical examination data will be listed.

12.7. EYE EXAMINATION

Observed and change from baseline values for the 4 cataract gradings in LOCS III (nuclear opalescence, nuclear colour, cortical and posterior subcapsular cataracts) will be summarized by visit using descriptive statistics. The summary will be across both eyes (i.e., each subject will contribute 2 values if they have a left and right eye reading at the visit) and repeated for the worst change at each visit.

Eye examination data will be listed. Eye examination data will be listed separately - refraction, BCVA, pinhole visual acuity, slit lamp examination, cataract grading, tonometry and irido-corneal drainage angle assessment.

12.8. COVID-19 EXPOSURE AND VACCINATION DATA

The following COVID-19 exposure and vaccination information will be summarized. The number (%) of subjects will be presented:

- Number of vaccination doses (0, 1, 2, 3, >4) received at each visit
- Documented COVID-19 prior to first dose and during the study

All data will be listed.

13. INTERIM ANALYSES

An interim synoptic CSR will be prepared for this study to be included in the regulatory submission package. The data cut will be the date of the last subject last visit in REN001-201 and the data will be extracted from the database after REN001-201 database has been locked. This CSR will include all REN001-202 data up to the data cut date and best efforts will be made to clean data up to this data cut date.

There will be a reduced set of safety outputs generated after submission for the 120-day safety update which is required as part of the submission package. The final CSR will occur after all subjects have had the ability to complete REN001-202, the data has been cleaned and the database locked.

An independently chaired Safety Review Committee (SRC) will review safety data at specified intervals for the duration of the study. The structure, function and operation of the SRC is detailed in the REN001-202 SRC charter. The SRC review of safety data will be limited to data from REN001-202 and will not be combined with REN001-201 data.

14. CHANGES FROM PLANNED ANALYSES SPECIFIED IN THE PROTOCOL

None.

15. REFERENCES

Cleeland CS. *The Brief Pain Inventory User Guide.* 2009:1-66. Published at: https://www.mdanderson.org/documents/Departments-and-Divisions/Symptom-Research/BPI_UserGuide.pdf.

Roy W. Beck, et al. *A Computerized Method of Visual Acuity Testing: Adaptation of the Early Treatment of Diabetic Retinopathy Study Testing Protocol.* American Journal of Ophthalmology February 2003.

Patient-Reported Outcomes Measurement Information System. Published February 28, 2019. https://staging.healthmeasures.net/images/PROMIS/manuals/PROMIS_Fatigue_Scoring_Manual.pdf

APPENDIX 1 – COUNTRY SPECIFIC PROTOCOL AMENDMENTS

The following country specific protocol amendments have been approved for REN001-202:

Country	Amendment, Version (Date)
France	Amendment 1, Version 1.0 (22nd December 2021)
Germany	Amendment 1, Version 1.0 (7th December 2021)
Netherlands	Amendment 1, Version 1.0 (12 July 2022)
Germany	Amendment 2, Version 2.0 (8 February 2023)
Netherlands	Amendment 2, Version 2.0 (1 February 2023)
Germany	Amendment 3, Version 3.0 (18 October 2023)

The following country specific protocol amendments have been approved for REN001-201:

Country	Amendment, Version (Date)
Canada	Amendment 3, Version 4.0 (21st March 2021)
France	Amendment 3, Version 4.0 (1st April 2021)
Germany	Amendment 3, Version 4.0 (20th May 2021)
Canada	Amendment 4, Version 5.0 (29th June 2022)
France	Amendment 4, Version 5.0 (29th June 2022)
Germany	Amendment 4, Version 5.0 (29th June 2022)

APPENDIX 2 – REN001-201 SCHEDULE OF ASSESSMENTS

Time and Events Table	Screening	Baseline[1,2] (Day 1)	Week 2[3] (Day 14)	Week 4[3] (Day 28)	Week 8 (Day 56)	Week 12[2,4] (Day 84)	Week 16 (Day 112)	Week 18[3] (Day 126)	Week 20 (Day 140)	Week 24[2, 4] (Day 168)	Early Termn[2,5]	Follow Up[3] (21-28 days post last dose)
Visit number	**1**	**2**	**3**	**4**		**5**		**6**		**7**		**8**
Window (days)			±3	±3		±7		±7		±7		
Informed Consent[20]	X											
Completion of Proforma and data entered into eCRF[6]	X											
Demographics	X											
Medical/medication/drug/ alcohol/tobacco history[7]	X											
Physician completion of PMM phenotypic description		X								X	X	
Physical exam[8]	X	X				X				X	X	
12-lead ECG	X	X				X				X	X	
Supine Vital signs (BP, PR and temperature)	X	X	X	X		X		X		X	X	X
Serum FSH[9]	X											
HbA1c	X									X	X	
Hepatitis B/C/HIV	X											
Safety labs (inc. urinalysis)	X	X[10]	X	X		X		X		X[11]	X	X[11]
Blood sample for bone and calcium markers		X				X				X	X	
Pregnancy Test (WOCBP only)[12]	X	X		X	X	X	X		X	X	X	X
Blood sample for genotyping[13]	X											
Population PK blood sample[14]		X	X	X		X		X		X	X	
Urine drugs of abuse	X	X				X				X	X	

Time and Events Table	Screening	Baseline[1,2] (Day 1)	Week 2[3] (Day 14)	Week 4[3] (Day 28)	Week 8 (Day 56)	Week 12[2,4] (Day 84)	Week 16 (Day 112)	Week 18[3] (Day 126)	Week 20 (Day 140)	Week 24[2, 4] (Day 168)	Early Termn[2,5]	Follow Up[3] (21-28 days post last dose)
Urine NTX		X				X				X	X	
Sites to provide appropriate snacks and lunch	X	X				X				X	X	
Pedometer eDiary data collection (inc. review)	X	X[15]		X		X		X		X		
MFIS / PGIS (muscle symptoms), PGIS (fatigue symptoms) and PROMIS – Short form FACIT fatigue 13a	X	X		X		X		X		X	X	
SF-36 / BPI and WPAI:SHP		X		X		X		X		X	X	
PGIC (muscle symptoms) and PGIC (fatigue symptoms)										X	X	
12 Minute Walk Test	X[16]	X				X				X	X	
30STS		X				X				X	X	
IMP Capsule Counts			X	X		X		X		X	X	
Eye examination	X[17]					X				X	X	
Wrist radiograph	X[18]											
DXA Scan (REN001-201-DXA sub-study)[21]	X									X	X	
Concomitant medication review	X----------X											
Dosing		X[19]----------X										
AE collection and reporting	X----------X											

1. Screening visit must take place a maximum of 8 weeks before the Baseline visit.
2. If appropriate and feasible Baseline, Week 12, Week 24 /Early Termination visits may be conducted over 2 days at the Investigators discretion.
3. In countries where the regulatory body allows, visit may be in the Study Center or a home nursing visit.
4. Only review of concomitant medications, AE's MFIS and 12MWT will be conducted if the subject has discontinued from study drug treatment but has not withdrawn from the study. If the subjects had an ET visit within 2 weeks of either of these a visit is not required.

5. As a minimum, subjects should have review of concomitant medication and AE's, vital signs (including temperature), complete questionnaires, safety laboratory blood (including HbA1c, bone and calcium markers and PK analysis) and urinalysis (including pregnancy tests for WOCBP, drugs of abuse and NTX) and IMP capsule counts.
6. Patient Screen Oversight Committee will review Proforma data and give a decision or request more information within 7 working days.
7. Subjects will be excluded from the study at the Investigators discretion for alcohol and/or drug dependency. Use of opiates/cannabis for medical reasons is acceptable with prescription evidence or at the Investigators discretion.
8. Full physical exam, height and weight at Screening; full physical exam and weight at Baseline; brief, symptom-directed physical exam and weight only at Weeks 12 and 24.
9. Serum FSH testing for post-menopausal females 45 years and older. Serum FSH test must be performed for all women who participate in the REN001-201-DXA sub-study who have not already had an FSH test as part of the parent REN001-201 study.
10. An additional 10 mL blood sample will be taken pre-dose at baseline and the serum will be stored frozen at the central laboratory as a reference sample in the event that re-analysis of protocol stated tests are required.
11. If any clinically significant abnormalities are noted at the Week 24 visit, these should be followed up until resolved.
12. WOCBP will be supplied with urine home pregnancy test kits at Study Center visits to test at Weeks 8, 16 and 20. The Study Center must contact the subject to confirm the pregnancy test result in a timely manner.
13. Blood sample for local genotype testing will only be conducted with prior Sponsor approval and definitive results must be available prior to the Baseline visit.
14. At the Baseline, Week 12 and Week 24 visits, blood samples will be taken pre-dose and then at 1, 2, 3, and 4 hours post-dose. On the other visits, a single sample can be taken at any time post-dose provided the dosing date and time are recorded.
15. Review of Screening (pre-treatment) pedometer data at Baseline.
16. Screening 12MWT must be at least 4 weeks before the Baseline 12MWT.
17. The Screening eye examination can be performed at any time between the initial Screening and Baseline Visit for scheduling reasons.
18. Subjects <25 years old only.
19. Dosing on Baseline, Week 12 and Week 24 visits should be under the supervision of the site staff.
20. A separate informed consent will be required for the REN001-201-DXA sub-study.
21. Only conducted at sites, on eligible subjects, which are participating in the REN001-201-DXA sub-study. The screening DXA scan should be performed no more than 8 weeks prior to the start of dosing. If a subject discontinues study treatment after at least 20 weeks in the study they will be asked to have a follow-up, scan within 4 weeks of their last dose of study treatment.