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)

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Main Objective:To evaluate the efficacy of REN001 in subjects with PMM treated for 24 weeks, assessed by the effect on exercise endurance.Secondary Objective:To evaluate the efficacy of REN001 in subjects with PMM treated for 24 weeks, assessed by…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neurological disorders congenital
Study type	Interventional

Summary

ID

NL-OMON51665

Source
ToetsingOnline

Brief title
Phase 2b Safety and Efficacy Study of REN001 in Mitochondrial Myopathy

Condition

- Neurological disorders congenital
- Neurological disorders NEC

Synonym
PMM, Primary Mitochondrial Myopathy

Research involving
Human

Sponsors and support

Primary sponsor: Reneo Pharma Ltd
Source(s) of monetary or material Support: By the industrial sponsor of the study

Intervention

Keyword: PMM, Primary Mitochondrial Myopathy

Outcome measures

Primary outcome

Change from baseline in distance walked during the 12 minute walk test.

Secondary outcome

Change from Baseline in the Modified Fatigue Impact Scale (MFIS) Physical

sub-scale score;

Patient Global Impression of Change (PGIC) score (muscle symptoms).

Study description

Background summary

Primary mitochondrial myopathy (PMM) is an illness that results in muscle symptoms including muscle weakness, fatigue and pain. These symptoms are extremely common and often debilitating in patients with PMM. To date, there are no effective treatments and no cures. Hence, there is an urgent need to find an effective drug treatment.

To date, five clinical studies (HPP593-101, HPP593-102, HPP593-103, REN001-101 and REN001-103), involving a total number of 181 PMM subjects, of which 124 received the study drug REN001, have been conducted in accordance with GCP principles. Study results indicate that REN001 was overall considered safe and well tolerated. No treatment-related SAEs were reported, and in the randomised trials the incidence of AEs was similar between REN001 treated and placebo arms. In another clinical study REN001-102, which involved PMM subjects with FAOD, REN001 was similarly considered to overall be safe and well tolerated.

Elevations in serum CPK have been reported in all studies conducted with REN001. It should be noted that CPK levels were raised in some subjects at the time of screening and/or baseline, and most were considered clinically mild by the treating investigator, and typically related to the underlying condition. As a conservative measure, the Sponsor does not rule out a potential association between treatment with REN001 and elevations on CPK. The Sponsor concludes that, if elevations in CPK are associated with treatment with REN001, such elevations are typically modest and reversible.

In the Phase 1b FAOD study, SAEs of rhabdomyolysis and acute renal failure were reported following unspecified COVID-19 vaccination which were considered possibly related to vaccination, underlying FAOD, and REN001. Two further rhabdomyolysis SAEs also occurred in this FAOD study, which were considered related to the underlying condition.

No clinically important abnormalities were observed in vital signs, ECGs, urinalysis or ophthalmic examinations, and clinically significant physical examination findings were rare. The majority of AEs were considered mild to moderate in severity, with no treatment-related SAEs reported in the completed clinical studies. Three possibly treatment-related SAEs (in 2 subjects) have been reported in an ongoing FAOD study. There were no deaths in any study conducted to date. Weight gain or oedema, complications known to be associated with other PPAR agonists, were not observed in any studies.

The planned maximum duration for each patient in this study will be 36 weeks (8 weeks screening, 24 weeks treatment and 4 weeks follow up). Each patient will be given either REN001 treatment or placebo (dummy medication) treatment for 24 weeks. Neither the doctor nor the patient will know who is given which study drug treatment (double-blind). This is important to ensure that any effects are due to the medication and not to any other potential factors (e.g. more interaction with medical staff or hospital visits).

This study will determine how well REN001 works and whether it is safe and well tolerated in patients with PMM.

Study objective

Main Objective:To evaluate the efficacy of REN001 in subjects with PMM treated for 24 weeks, assessed by the effect on exercise endurance.

Secondary Objective:To evaluate the efficacy of REN001 in subjects with PMM treated for 24 weeks, assessed by the effect on fatigue.

Other Objectives:
Safety:
To evaluate the safety and tolerability of REN001 in subjects with PMM during 24 weeks of treatment.

Pharmacokinetic (PK):
To investigate the pharmacokinetics of REN001 in subjects with PMM.

Exploratory:
To evaluate the efficacy of REN001 in subjects with PMM treated for 24 weeks, assessed by the effect on functional capacity.
To evaluate the effect of REN001 on quality of life (QoL) of subjects with PMM after treatment for 24 weeks.

Study design

This is a randomised, double-blind, placebo-controlled, parallel group, multicentre study in patients with PMM.

Approximately 200 subjects will be recruited into the study.

There will be a total of 8 visits for each subject.

Each subject who provides informed consent will complete screening activities to confirm eligibility to enter the study.

The Screening Visit (Visit 1) must be completed no more than 8 weeks prior to the start of dosing and will take place at the Study Center. There must be a minimum of 4 weeks between the Screening 12MWT and the Baseline 12MWT. If laboratory tests are outside of the normal range at initial screening, tests may be repeated once (this can be done as a home nurse visit). Where possible subjects should be pre-screened to assess the requirement for genotyping. The Screening Visit may be accomplished over more than 1 day. Subjects who are receiving prohibited medications must suspend the medications, if this can safely and appropriately be done and have sufficient washout during the screening period prior to randomization. Re-screening of subjects is allowed only once and requires prior approval by the Sponsor, for instance, if the wash-out of prior medications or genotyping is longer than 6-8 weeks. Where a Study Center requires it, subjects may be asked to have a negative COVID-19 test prior to undertaking scheduled visits at the Study Center.

At selected sites, subjects may choose to participate in study exit interviews upon their completion in the study.

Intervention

Each patient will be given either REN001 treatment or placebo (dummy medication) treatment for 24 weeks. Neither the doctor nor the patient will know who is given which study drug treatment (double-blind).

Study burden and risks

There will be 8 site visits, as follows:

The Screening Visit (Visit 1) must be completed no more than 8 weeks prior to the start of dosing and will take place at the Study Center. There must be a minimum of 4 weeks between the Screening 12MWT and the Baseline 12MWT. If laboratory tests are outside of the normal range at initial screening, tests may be repeated once (this can be done as a home nurse visit). Where possible subjects should be pre-screened to assess the requirement for genotyping. The Screening Visit may be accomplished over more than 1 day. Subjects who are receiving prohibited medications must suspend the medications, if this can safely and appropriately be done and have sufficient washout during the screening period prior to randomization. Re-screening of subjects is allowed only once and requires prior approval by the Sponsor, for instance, if the wash-out of prior medications or genotyping is longer than 6-8 weeks. Where a Study Center requires it, subjects may be asked to have a negative COVID-19 test prior to undertaking scheduled visits at the Study Center.

The following procedures will be performed:

SCREENING: VISIT 1
• Subject demography
• Complete medical history (including prescription and non-prescription drugs/treatments, non-drug treatments,
topical products, vitamins and dietary supplements taken in the last 4 weeks, alcohol, drugs of abuse and tobacco use)
• Full physical examination (including height and weight)
• 12-lead ECG
• Vital signs (including temperature)
• Obtain blood samples for:
o Hematology and HbA1c
o Biochemistry, HIV/Hepatitis B/C serology, serum FSH test (post-menopausal females only) and serum pregnancy
test (WOCBP only)
o Genotyping (only with prior approval of Sponsor)
• Obtain urine samples for:
o Urinalysis
o Drugs of abuse
• MFIS
• PGIS - muscle symptoms
• PGIS - fatigue symptoms
• PROMIS Short Form - FACIT Fatigue 13a
• 12MWT
• Eye examination (maybe completed at any time between the initial Screening and Baseline visits)
• For subjects <25 years old (only) a wrist radiograph will be required to confirm bone growth plate closure.
• Input of the Pro-forma Screening data into eCRF for Patient Screening

Oversight Committee (PSOC) approval
• Subjects will be provided with a pedometer and instructions on how to use the device and complete the eDiary prior to leaving the Study Center (including the requirement for collecting the Screening, pre-treatment, pedometer data for 14 days from the Screening visit)
• Subjects will be provided with a urine collection cup and instructions for collecting a second morning void at the Baseline visit if they are unable to do this at the Study Center for any reason.
Provided the subject fulfils all the inclusion and exclusion criteria, and the PSOC has confirmed their agreement, the subject may enter the study and proceed with the Baseline Visit.

BASELINE (DAY 1): VISIT 2
Subjects will attend the Study Center for the Baseline Visit when the following assessments will be carried out prior to dosing:
• Obtain second morning void urine sample for:
o Bone marker - N-terminal telopeptide (NTX)
o Urinalysis
o Drugs of abuse
o Urine for pregnancy testing (WOCBP only)
• Obtain blood samples for:
o Hematology
o Biochemistry
o Additional bone and calcium metabolism markers
o Additional serum for possible use as baseline reference, to be stored frozen at the central laboratory through to completion of the study
o Pre-dose plasma sample for pharmacokinetic analysis of REN001
• Review of concomitant medications including contraception and non-drug treatments
• Review of pre-treatment events (see Section 7.1.1.1 of protocol)
• Physician completion of subjects PMM phenotypic description
• Review of Screening pedometer eDiary data
• Full physical examination (including weight)
• 12-lead ECG
• Vital signs (including temperature)
• MFIS
• BPI
• SF-36
• PGIS - muscle symptoms
• PGIS - fatigue symptoms
• PROMIS Short Form - FACIT Fatigue 13a
• WPAI:SHP
• 12MWT
• 30STS
Assessments should be conducted to ensure that the PRO questionnaires are completed prior to exercise testing and the 12MWT must be done at least 1 hour before the 30STS. Provided the subject meets all the study entry criteria they

will be randomized to study treatment. The IWRS will allocate study drug to be dispensed to the subject. The first dose should be taken with food under the supervision of site staff and the time of dosing recorded. Subjects will remain in the Study Center after study drug administration for the following assessments to be carried out:
• Obtain plasma samples for pharmacokinetic analysis of REN001 (1, 2, 3 and 4* hours post dose)
• Review of adverse events
• Subjects will be provided with a urine collection cup and instructions for collecting a second morning void at the Week 12 visit if they are unable to do this at the Study Center for any reason
* To ease subject burden, the 4-hour post dose blood may be omitted if the visit is extending beyond what is reasonable, at the Investigator*s discretion. Subjects may then leave the Study Center at the discretion of the supervising clinical staff after being provided with sufficient study medication to last until their next scheduled Study Center visit. Subjects will be reminded of the study restrictions and instructed on study medication dosing requirements. If feasible, and at the Investigator*s discretion, the Baseline Visit may be conducted over two days.

WEEK 2 (DAY 14): VISIT 3
Subjects will either attend the Study Center or receive a home nursing visit (in countries where the regulatory authority allows) on Day 14. On this day, the subject will take their daily dose at home as usual and record the time of dose on the subject dosing card. The following assessments will be carried out:
• Review concomitant medications, non-drug treatments and study medication compliance
• Review of adverse events
• Vital signs (including temperature)
• Obtain blood samples for:
o Haematology
o Biochemistry
o Plasma sample for pharmacokinetic analysis of REN001
• Obtain urine samples for:
o Urinalysis
• Capsule counts of remaining capsules including any opened IMP bottles
Subjects will be reminded of the study restrictions and instructed on study medication dosing requirements.

WEEKS 4 and 18 (DAYS 28 and 126): VISITS 4 and 6
Subjects will either attend the Study Center or receive a home nursing visit (in countries where the regulatory authority allows) on Days 28 and 126. On these days, the subject will take their daily dose at home as usual and record the time of dose in the subject dosing card. The following assessments will be carried out:
• Review concomitant medications, non-drug treatments and study medication compliance

• Review of adverse events
• Vital signs (including temperature)
• Obtain blood samples for:
o Haematology
o Biochemistry
o Plasma sample for pharmacokinetic analysis of REN001
• Obtain urine samples for:
o Urinalysis
o Urine for pregnancy testing (WOCBP Week 4 only)
• Review of last 7 days pedometer data
• MFIS
• BPI
• SF-36
• PGIS - muscle symptoms
• PGIS - fatigue symptoms
• PROMIS Short Form - FACIT Fatigue 13a
• WPAI:SHP
• Capsule counts of remaining capsules including any opened IMP bottles

Subjects will be reminded of the study restrictions and instructed on study medication dosing requirements.

WEEKS 8, 16 and 20 (DAYS 56, 112 and 140)
Subjects who are WOCBP at risk of pregnancy will be supplied with urine pregnancy tests to use at home at Weeks 8,16 and 20. Study Center staff will need to contact the subjects by telephone to obtain the result of the pregnancy test and enter the result into the eCRF. Subjects may be given a reminder telephone call to conduct the test if necessary.

WEEKS 12 and 24 (DAYS 84 and 168): VISITS 5 and 7
Site staff will need to provide subjects with meals and snacks at appropriate times during the visit to ensure subjects have enough energy prior to completing the exercise tests.
Subjects will attend the Study Center on Days 84 and 168. On these days, the subject will take their daily dose in the Study Center. The following assessments will be carried out:
• Obtain second morning void urine sample for:
o Bone marker - NTX
o Urinalysis
o Drugs of abuse
o Urine for pregnancy testing (WOCBP only)
• Obtain blood samples for:
o Haematology (including HbA1c at Week 24 only)
o Biochemistry
o Additional bone and calcium metabolism markers
o Pre-dose plasma sample for pharmacokinetic analysis of REN001
• Administer the study drug with food under supervision of clinical staff and

the time of dosing recorded.
• Review concomitant medications, non-drug treatments and study medication compliance
• Review of adverse events
• Physician completion of subjects PMM phenotypic description (Week 24 only)
• Review of pedometer eDiary data
• Brief physical examination (including weight)
• 12-lead ECG
• Vital signs (including temperature)
• Obtain plasma samples for pharmacokinetic analysis of REN001 (1, 2, 3 and 4* hours post dose)
• Review of last 7 days pedometer data
• MFIS
• BPI
• SF-36
• PGIS - muscle symptoms
• PGIS - fatigue symptoms
• PGIC - muscle symptoms (Week 24 only)
• PGIC - fatigue symptoms (Week 24 only)
• PROMIS Short Form - FACIT Fatigue 13a
• WPAI:SHP
• 12MWT
• 30STS
• Capsule counts of remaining capsules including any opened IMP bottles
• Subjects will be provided with a urine collection cup and instructions for collecting a second morning void at the Week 24 visit if they are unable to do this at the Study Center for any reason (Week 12 only)
• Eye examinations (may be completed ± 14 days of the visit if required)

Assessments should be conducted to ensure that the PRO questionnaires are completed prior to exercise testing and
the 12MWT must be done at least 1 hour before the 30STS.

*To ease subject burden, the 4-hour post dose blood may be omitted if the visit is extending beyond what is reasonable, at the Investigator*s discretion.
At the end of Visit 7 (Week 24) subjects must return all their unused study medication and may then leave the Study Center at the discretion of the supervising clinical staff after being provided with details of their Follow Up visit.

FOLLOW UP VISIT
Subjects will either attend the Study Center or receive a home nursing visit (in countries where the regulatory authority allows), 21-28 days following the last dose of study medication for a Follow Up Visit. This visit will not be required if a REN001 open label extension study is recruiting and subjects choose to enter the extension study at their Week 24 visit.
At this visit, the following activities will be completed:

• Review concomitant medications and non-drug treatments
• Review of adverse events
• Vital signs (including temperature)
• Obtain a urine sample for pregnancy testing (WOCBP only)
If clinically significant safety laboratory findings were apparent at the subjects last visit these should be followed up until resolved with blood samples for haematology and biochemistry and a urine sample for urinalysis as appropriate.

EARLY TERMINATION VISIT
Subjects who discontinue taking study drug early should, if possible, have an Early Termination visit as soon as possible after the subject stops taking study drug. Where possible the Early Termination visit assessments should be completed in the study center as listed below. Site staff will need to provide subjects with meals and snacks at appropriate times during the visit to ensure subjects have enough energy prior to completing the exercise tests.
• Review concomitant medications and non-drug treatments*
• Review of adverse events*
• Brief physical examination (including weight)
• Physician completion of subjects PMM phenotypic description
• 12-lead ECG
• Vital signs (including temperature) *
• Obtain blood samples for:
o Haematology (inc HbA1c)*
o Biochemistry*
o Additional bone and calcium metabolism markers
o Plasma sample for pharmacokinetic analysis of REN001*
• Obtain second morning void urine sample for:
o Bone marker - NTX*
o Urinalysis*
o Drugs of abuse*
o Urine for pregnancy testing (WOCBP only) *
• MFIS*
• BPI*
• SF-36*
• PGIS - muscle symptoms*
• PGIS - fatigue symptoms*
• PROMIS Short Form - FACIT Fatigue 13a*
• PGIC muscle symptoms (with respect to how they were on their last dosing day) *
• PGIC fatigue symptoms (with respect to how they were on their last dosing day) *
• WPAI:SHP*
• 12MWT
• 30STS
• Capsule counts of remaining capsules including any opened IMP bottles*
• Eye examination (may be completed ± 14 days of the visit if required)

If the subject is unable to attend the Study Center for the full visit, then every effort should be made to complete the assessments marked with an asterisk (*).

If the subject is withdrawing from the study: after their Early Termination Visit they should be instructed to return for the Follow Up Visit 21-28 days after their last dose of study medication. If the Early Termination Visit is 21 or more days after the last dose, then the Follow Up Visit is not needed.

The Risk:Benefit profile of REN001 is overall considered positive for subjects with PMM participating in this study, subject to appropriate subject selection and safety monitoring.

FORESEEABLE RISKS AND MEASURES TO PREVENT/TREAT UNFORESEEABLE/UNDESIRABLE EVENTS:

Elevated CPK
Serum CPK data from subjects with PMM in the Phase 1b study (REN001-101) demonstrated a pattern of transient, elevated CPKs following exercise and the collection of muscle biopsies; none of these elevations were associated with myoglobinuria. The elevations seen were self-limiting and resolved with no intervention despite continued treatment with REN001 and continuation of the subject*s normal activities of daily living including exercise. In all the clinical trials that have included REN001 to date, elevations in CPK tended to be modest and reversible and were determined by investigators as unlikely to be associated with REN001 treatment. In the current study CPK levels will be assessed throughout the study with particular emphasis at Baseline and Week 2, based on the expected (asymptomatic) increases in CPK previously observed in subjects with PMM.

Cataract formation
Cataracts were observed in a 6-month rat chronic toxicology study, but not in any other animal studies. As a precaution, ophthalmology examinations were therefore included in all REN001 trials. Although no safety findings have been identified during the detailed ophthalmological examinations conducted to date, slit lamp eye examinations will be conducted during this study, at screening and at the end of REN001 treatment (week 24) and a visual acuity test will be conducted at week 12 as part of the safety evaluations. Any clinically significant finding will require a further slit lamp eye examination.

Potential Drug-Drug interactions
There may be a potential for drug interactions between REN001 and drugs that are metabolized through the CYP3A4 pathway. Therefore, drugs metabolized by CYP3A4 should be administered with caution.

REN001 has also been identified as a P-glycoprotein (P-gp) substrate in vitro. Substrates of P-gp are susceptible to changes in pharmacokinetics due to drug

interactions with P-gp inhibitors or inducers. However previous clinical studies have demonstrated relatively high absorption of REN001 following multiple oral doses likely saturating REN001 P-gp efflux and hence a drug-drug interaction with P-gp inhibitors is unlikely to be a clinical issue.

The Sponsor anticipates that exposure to REN001 concomitant to short-term exposure to a P-gp inducer is not a major concern. However, a subset of subjects with PMM present with seizures and it is possible that some of these subjects may need to receive long-term antiepileptic drugs known to induce P-gp function (i.e., Carbamazepine, Phenobarbital, Phenytoin, Fosphenytoin). At low free concentrations in plasma REN001 could be expected to be subject to P-gp mediated efflux. Thus, strong P-gp inhibitors and inducers should be used with caution.

Fertility and contraception
Women of child-bearing potential (WOCBP) are eligible for the study provided they are using a highly effective form of contraception from Screening, whilst taking the drug and for 30 days after stopping investigational medication. Serum pregnancy testing will be completed at Screening. In addition, urine pregnancy tests will be carried out monthly and at Follow Up.

Fertile males with partners who are WOCBP must agree to use a condom from Baseline until 14 weeks after the last dose of study medication. A condom must also be used by vasectomized men.

Since REN001 is a weak inducer of CYP3A4 in vitro, it could potentially decrease concentrations of CYP3A4 substrates such as hormonal contraceptives. Therefore, caution with co-administration of REN001 and hormonal contraceptives is advised. Women receiving highly effective hormonal contraception therapy will be required to also use an effective non-hormonal method of contraception during treatment with REN001 and for 30 days after the final dose. Women using a highly effective non-hormonal contraceptive will not be required to use additional methods of contraception.

Carcinogenicity
Preclinical findings suggest that some PPAR agonists may have carcinogenicity potential.

Subjects with a history of cancer, except in situ basal cell carcinoma in the skin, will not be allowed to participate in the study. Close safety monitoring will occur during the study.

Bone
Non-Clinical Finding of Premature Bone Plate Closure in Rats: This finding has not been replicated in non-human primates. As a precaution, subjects under 25 years of age in studies over 12 weeks duration will have a wrist radiograph (x-ray) prior to enrolment to confirm skeletal maturity.

Bone Turnover:
Given the study requirements for walk tests, and taking a highly conservative approach, Reneo has excluded subjects with osteoporosis, defined as a previous fragility/stress fracture or a documented history of osteoporosis (for example, a previous T-score of -2.5 or lower). Currently, it is not known if REN001 will have any impact on bone density. Nonetheless, Reneo has excluded subjects with a history of fragility/stress fractures or an osteoporosis concomitant condition and will monitor markers of bone turnover and capture any reports of fracture as adverse events of special interest.

Blood draws
There may be some slight discomfort involved in taking blood by venepuncture. There may be slight discomfort or pain in the area around the vein when the blood is taken. There may be bruising, swelling and discomfort over the vein after the procedure. There is a small risk of infection. The risks involved in donating blood samples by needle are the same as for the routine blood tests subjects have in routine clinic visits.

Risks associated with study procedures.
Measurements of blood pressure and pulse rate are well established methods. Subjects may experience some discomfort during blood pressure measurements when using the blood pressure cuff. Subjects may experience skin irritation from the electrodes or gel used during the ECG. Eye drops are used to dilate the pupils for the slit-lamp eye test, the effects are temporary but subjects should not drive until the effects have fully worn off. All of the study and exercise tests are safe and regularly used in clinics. Subjects may feel tired after the exercise tests.

Possible Side Effects And Risks of Taking The Study Medication
REN001 has been given to healthy volunteers, to obese subjects and to subjects with PMM in previous clinical studies. REN001 was considered to be safe and well tolerated in all these trials with no drug-related side effects (adverse drug reactions) identified.

In the PMM subject study, involving 23 subjects, the most common side effects reported were
• constipation in 4 out of 23 subjects and
• headache in 4 out of 23 subjects
which may have been due to the subject*s underlying PMM.

Contacts

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Scientific
Reneo Pharma Ltd

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Subjects aged 18 years or older with PMM
2. A confirmed PMM diagnosis due to known pathogenic gene mutation or deletion of the mitochondrial genome.
3. Documented PMM primarily characterized by exercise intolerance or active muscle pain.
4. Subjects must be ambulatory and able to perform the 12MWT independently (walking aids are allowed).
5. Distance walked of <=1000 meters at Screening in the 12MWT (must be obtained at least 4 weeks before randomization).
6. Have no changes to any therapeutic exercise regimen within 30 days prior to Day 1 and be willing to remain on the same therapeutic exercise regimen for the duration of the study.
7. Be willing and able to swallow gelatin capsules.
8. Females should be either of non-child-bearing potential or must agree to use highly effective methods of contraception from Screening through to 30 days after last dose in the study. Males with partners who are WOCBP must also use contraception.
9. Concomitant medications (including supplements) must be stable for at least

1 month prior to enrolment and throughout participation in the study.
10. For subjects under 25 years of age, confirmation of bone growth plate closure by wrist radiograph
11. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

Exclusion criteria

1. Participation in a prior REN001 study.
2. Currently taking or anticipated to need a PPAR agonist during the study.
3. Bone deformities or motor abnormalities other than related to the mitochondrial myopathy that may interfere with the outcome measures.
4. Treatment with an investigational drug within 3 months or 5 drug half-lives, whichever is longer, prior to Day 1.
5. Anticipated to need a prescription and/or non-prescription drug that might interfere with the study endpoints
6. Currently taking drugs with a narrow therapeutic index and BCRP mediated ADME
7. Clinically significant kidney disease or impairment with an eGFR less than 60ml/min/1.73m2 using the CKD-EPI creatinine equation at Screening.
8. Clinically significant liver disease or impairment of AST or ALT Grade 2 or above (>2.5 x ULN), or Total bilirubin > 1.6 x ULN or >ULN with other signs and symptoms of hepatotoxicity at Screening.
9. Uncontrolled diabetes and/or a Screening HbA1c of >=11%.
10. Uncontrolled epilepsy.
11. Evidence of significant concomitant clinical disease that may need a change in management during the study or could interfere with the conduct or safety of this study.
12. A history of cancer. A history of in situ basal cell carcinoma in the skin is allowed.
13. Have been hospitalized within the 3 months prior to Screening for any major medical condition (as deemed by the Investigator).
14. Clinically significant cardiac disease and/or clinically significant ECG abnormalities including a screening QTcF of >= 450 msec, 2nd degree heart block, symptomatic tachyarrhythmia or unstable arrythmia that in the opinion of the Investigator should exclude the subject from completing exercise tests (i.e. study 12 MWT and 30 STS tests).
15. Any condition possibly reducing drug absorption.
16. Evidence of hospitalization for rhabdomyolysis within the year prior to enrolment.
17. Positive HBsAg and HBcAb at screening or positive for hepatitis C or HIV at Screening..
18. Pregnant or nursing females.
19. History of sensitivity to PPAR agonists.

20. Donation or intent to donate blood, or blood components during the study or within one month after completion of the study.
21. A history of drug dependency. Use of opiates/cannabis for medical reasons is acceptable with prescription evidence or at the Investigators discretion.
22. A history of alcohol dependency.
23. Significant impairment due to central or peripheral nervous system involvement that would interfere with the exercise tests.
24. Significant weakness not caused by the underlying primary muscle disease such as post stroke or neurogenic weakness.
25. Have had an organ transplant.
26. Are not eligible or have a contraindication for cataract surgery.
27. A history of osteoporosis as evidenced by non-traumatic (stress) fractures or a prior T-score of -2.5 or worse which has not been adequately addressed.
28. Inability to comprehend or unwilling to follow the study requirements including restrictions on treatments, attendance at the study center, completion of questionnaires and participation in laboratory testing as called for by the protocol.
29. Any other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator and in discussion with the Medical Monitor, would make the subject inappropriate for entry into this study.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-05-2022

Enrollment:	21
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	REN001
Generic name:	REN001

Ethics review

Approved WMO Date:	22-03-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-05-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-10-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-10-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-10-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-11-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	17-01-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2020-002855-40-NL
ClinicalTrials.gov	NCT04535609
CCMO	NL80335.091.22