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

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Primary Objective:To evaluate long-term safety and tolerability of REN001 in subjects with PMM.Secondary Objective:To evaluate subjects with mtDNA-PMM who are receiving long-term treatment with REN001 in terms of PMM associated symptoms, exercise...

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

Summary

ID

NL-OMON53482

Source
ToetsingOnline

Brief title
Open label study of REN001 in PMM subjects

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: Extension, Open-label, PMM

Outcome measures

Primary outcome

The safety and tolerability of REN001 will be assessed by the following

parameters:

•Number and severity of adverse events (AE)

•Number of AEs leading to study drug discontinuation

•Number of serious adverse events (SAEs)

•Number of adverse events of special interest (AESIs)

•Number of AEs leading to death

These end points will be evaluated throughout the study.

Secondary outcome

Secondary study parameters are as follows:

Absolute values, changes from baseline, and incidence of potentially clinically

significant changes in:

•Laboratory safety tests

•Electrocardiograms (ECG)

•Supine vital signs

•Eye assessments

Absolute values and changes from baseline in:

•Distance walked during the 12-Minute Walk Test (12MWT)

•Modified Fatigue Impact Scale (MFIS) total scores and sub-scale scores

•Patient Global Impression of Severity (PGIS) scores for fatigue and muscle symptoms

•Brief Pain Inventory (BPI) pain severity and pain interference scores

•Patient Reported Outcomes Measurement Information System (PROMIS) Short Form-Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue 13a scores

•36 item Short Form Health Survey (SF-36) domain scores (7-day recall)

•Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) scores

•PGIC (muscle and fatigue symptoms) scores

These end points will be evaluated throughout the study.

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. Three further rhabdomyolysis SAEs also occurred in this FAOD study, which were considered not related to the underlying condition but likely due to underlying factors including exercise and infection. An episode of pancolitis in an individual with underlying bowel disorder was considered possibly related to study drug although the computed tomography scan was consistent with infection

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. Three possibly treatment-related SAEs (in 2 subjects) have been reported in an ongoing FAOD study as noted above. 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.

A Phase 2b study, involving this study drug is currently in progress (study REN001-201, aka "STRIDE"). The aim of STRIDE is to determine how well REN001 works and whether it is safe and well tolerated in patients with PMM. The planned maximum duration for each patient in this study is 36 weeks (8 weeks screening, 24 weeks treatment and 4 weeks follow up). Each patient is given either REN001 treatment or placebo (dummy medication) treatment for 24 weeks. Neither the doctor nor the patient know who is given which study drug treatment

(double-blind).

The aim of this study is to evaluate the long-term safety and tolerability of REN001 administered once daily to subjects with PMM who have previously completed STRIDE or participated in Study REN001-101 and withdrew from that study due to the COVID-19 pandemic.

Study objective

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

Secondary Objective:
To evaluate subjects with mtDNA-PMM who are receiving long-term treatment with REN001 in terms of PMM associated symptoms, exercise endurance, quality of life (QoL) and work productivity

Study design

This is a long-term safety study for subjects who have completed treatment in the STRIDE study or who were participating in the REN001-101 study when it was ended due to the COVID-19 pandemic. (REB001-101 study was open in the UK only). At sites with the IEC and regulatory approvals, eligible subjects will be treated for 24 months. A Safety Review Committee will review safety data during the study.

Subjects enrolling from the STRIDE study will be switching from taking blinded REN001 or placebo in the STRIDE study to open label REN001 in this study. At the time of enrolment into this long-term study, prior treatment allocation in the STRIDE study will be unknown. Subjects who are nearing completion of the STRIDE study will be invited to discuss continuing into this long-term safety study and provide informed consent prior to any study activities. It is expected that most subjects transferring from the STRIDE study will do so at the STRIDE Week 24 visit to prevent an interruption in dosing and reduce the number of study visits and assessments. Subjects who are enrolled at the STRIDE Week 24 visit will not need to complete the STRIDE follow up (FU) visit.

Enrolment at the STRIDE FU visit will require additional baseline assessments. Subjects who wish to take part in this study after leaving the STRIDE study (i.e., after their STRIDE FU visit) and subjects who participated in Study REN001-101, will require additional screening and baseline visits; for details of enrolment options please refer to the protocol Section 6.1 and Table 2.

After the baseline visit, subjects will have study visits at Months 1, 3, 6, 12, 18 and 24 months. As a final follow up there will be a telephone call from the study centre to the subject approximately 30 days after the last dose of

study drug.

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

Intervention

N/A
This is an open-label study and all participants will receive the study drug REN001

Study burden and risks

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.

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 usually 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
A single-species finding of cataract was observed in a high dose 6-month rat chronic toxicology study, but not in any other animal studies (including the 12 month non-human primate study). Taking a conservative approach, ophthalmology examinations were therefore included in all REN001 trials. Slit lamp eye examinations will be conducted, together with assessments of best corrected visual acuity at Screening and months 3, 6, 12, 18 and 24 in this study.

Potential Drug-Drug interactions
REN001 is not a direct or time-dependent inhibitor of CYP3A4. However, REN001 has been shown to be a weak inducer of CYP3A4 in vitro. A potential for drug interactions between REN001 and drugs that are metabolized through the CYP3A4

is considered low but cannot be ruled out. Therefore, drugs that are metabolized primarily by CYP3A4 and have a narrow therapeutic index should be administered with caution in subjects participating in REN001 studies.

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

Fertility and contraception
In accordance with the latest European regulatory discussions and guidelines (Clinical Trials Facilitation Group, 2014 and 2020), 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 (unless permanently sterile by bilateral orchidectomy) with partners who are WOCBP must agree to use a condom from Baseline until at least 14 weeks after the last dose of study medication. A condom must also be used by vasectomized men to prevent delivery of the drug via seminal fluid.

As REN001 is a weak inducer of CYP3A4 in vitro, caution is advised when co-administering REN001 and oral contraceptive agents. Therefore, as a precautionary measure, women receiving highly effective hormonal contraception therapy will be advised to use an additional highly 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 contraception method (i.e., intrauterine device) will not be required to use additional methods of contraception.

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

Bone
Non-Clinical Finding of Premature Bone Plate Closure in Rats: This finding has not been replicated in non-human primates.

Bone Turnover: Currently, it is not known if REN001 (a selective PPARδ agonist) will have any impact on bone mineral density. Nonetheless, given the study requirements for walk tests and taking a highly conservative approach, the Sponsor has excluded subjects with a history of fragility/stress fractures or an osteoporosis concomitant condition which has not been addressed, and will monitor markers of bone turnover during the study. Any reports of bone fracture will be captured as an adverse event 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 a 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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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. mtDNA-PMM subjects:Completed treatment in the STRIDE study or was participating in Study REN001-101, and in the opinion of the Investigator and the Sponsor have been compliant with the study requirements.
Or
nDNA-PMM subjects: Subjects aged 18 years or older with known nuclear (nDNA) pathogenic
variants with a major muscle phenotype consisting of objective myopathy with poor exercise tolerance. Proof of pathogenicity must be provided. Must be able to walk at least 100m in the screening 12MWT and the limitations in walk test must be primarily due to the energy deficit and not due to ataxia or any other condition.
For subjects under 25 years old only: confirmation of bone growth plate closure by wrist radiograph.
2. Have PMM which continues to be primarily characterized by exercise intolerance or active muscle pain.
3. Willing and able to swallow gelatin capsules.
4. Concomitant medications (including supplements) intended for the treatment of PMM or other co-morbidities likely to remain stable throughout participation in the study where clinically possible.

5. Signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
6. Females should be either of non-child-bearing potential or must agree to use highly effective methods of contraception from baseline through to approximately 30 days after last dose of study drug. Males with partners who are WOCBP must also use contraception from baseline through to 14 weeks after last dose of study drug.

Exclusion criteria

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

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Pending

Start date (anticipated):	01-11-2022
Enrollment:	25
Type:	Anticipated

Medical products/devices used

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

Ethics review

Approved WMO Date:	26-07-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-11-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-05-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-07-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-11-2023
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	EUCTR2021-003471-34-NL
ClinicalTrials.gov	NCT05267574
CCMO	NL81753.091.22