1. SYNOPSIS

Name of Sponsor/Company: Reneo Pharma Ltd **Name of Finished Product:** REN001 **Name of Active Ingredient:** REN001	Individual Study Table Referring to Part of the Dossier Volume: Page:	(*For National Authority Use Only)*
Title of Study: An open-label study to evaluate the safety and tolerability of 12-weeks treatment with oral REN001 in patients with primary mitochondrial myopathy (PMM), with an optional extension of treatment.		
Principal Investigators: Professor Gráinne Gorman (Newcastle) and Dr. Rob Pitceathly (London)		
Study Centres: Wellcome Centre for Mitochondrial Research, Newcastle University, Newcastle upon Tyne NE2 4HH, United Kingdom. Queen Square Clinical Research Facility (Leonard Wolfson Experimental Neurology Centre), London WC1N 3BG, United Kingdom.		
Publication (reference): None at the time of this report.		
Studied period (years): 0.83 years Date of first enrollment: 10 May 2019 Date of last subject visit: 23 March 2020 Date of study termination: 24 March 2020	**Phase of Development:** Phase 1b	
Objectives: **Primary Objective:** To evaluate the safety and tolerability of REN001 in subjects with PMM, during 12 weeks of treatment. **Secondary Objective:** To evaluate the safety and tolerability of REN001 in subjects with PMM, during 48 weeks of treatment. **Pharmacokinetic Objective:** To investigate the pharmacokinetics (PK) of REN001 in subjects with PMM treated for 12 weeks with REN001, administered as a capsule, using population PK methodology. **Pharmacodynamic Objective:** To investigate the pharmacodynamic (PD) effects of REN001 in subjects with PMM treated for 12 weeks		

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Methodology:

An open-label, multicenter study that evaluated the safety and tolerability of REN001 in subjects with PMM.

This study was conducted in two parts: Part A and Part B. During Part A, all subjects received 100 mg REN001 orally once daily for 12 weeks. Part B of the study was an optional dosing extension of 36 weeks during which subjects remained on the REN001 dose they had received in Part A of the study.

This study was prematurely stopped on 24 March 2020 to ensure the safety of trial participants during the public health emergency related to the coronavirus disease (Covid-19) pandemic. As of this date the study had provided safety and exploratory outcome measure data for 12 weeks of dosing for 17 subjects. Thirteen subjects had entered Part B, of which 7 subjects had provided additional, longer term safety data for at least 24 weeks of dosing. The longest total duration of dosing was 39.9 weeks; therefore, no subjects completedthe planned 48 weeks of dosing in the study due to the pandemic.

Number of subjects (planned and analyzed): The study aimed to recruit approximately 12 subjects with m.3243A>G mutations and 12 subjects with other mitochondrial deoxyribonucleic acid (mtDNA) mutations. The actual number of subjects enrolled was 23 (11 with the m.3243A>G mutation and 12 with other mtDNA defects).

Diagnosis and main criteria for inclusion: Male or female subjects aged 16 years or older with an established diagnosis of PMM according to the 2016 Rome Consensus recommendations. Subjects had to score 2–4 on Question 5, Section III, of the Newcastle Mitochondrial Disease Adult Scale (NMDAS) based on the subjects' medical history or at screening.

Subjects had to either have a confirmed m.3243A>G mutation or other mtDNA defects, with myopathy.

Test product, dose and mode of administration, batch number: REN001 (formerly referred to as HPP593). Dose administered was 100 mg REN001 as 4x25 mg oral capsules once daily. Medication was taken at a convenient time for the subject, ideally in the morning and without regard for food. The exception was when the subject was required to attend the study center for their baseline, Week 12, and Week 48 Visits (if applicable), when they took the study medication at the study center, when instructed to do so, by the site staff.

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Duration of treatment: (Intended)Twelve weeks for Part A of the study and an additional 36 weeks in Part B.

Criteria for evaluation:

Primary endpoint: Number and severity of adverse events (AEs).

Secondary endpoints:

- Absolute values and changes from baseline (at 12 and 48 weeks if applicable) and the incidence of potentially clinically significant changes in:
  - Laboratory safety tests
  - Electrocardiograms
  - Supine vital signs

Pharmacokinetic endpoints:

- REN001 plasma concentrations using population PK methodology
- Identification of metabolites using pooled plasma

Pharmacodynamic endpoints:

- Absolute values and changes from baseline in serum biomarkers (fibroblast growth factor-21 [FGF 21] and growth differentiation factor-15 [GDF-15] at baseline and Week 12)
- Absolute values and changes from baseline in acylcarnitine panel (baseline and Week 12)
- Changes from baseline in muscle histopathology (Week 12; reported separately to the Clinical Study Report [CSR])

Statistical Methods:

No formal statistical testing was planned for this study. All summaries were presented overall and by mutation type (m.3243A>G or other mtDNA defects).

Results:

Twenty-three subjects received REN001. When the study was prematurely terminated,17 subjects had completed 12 weeks of treatment in Part A, and 13 (56.5%) subjects had entered Part B of the study. Seven subjects received REN001 for at least 24 weeks. All the subjects who had the potential to reach their Week 12 visit had completed the Week 12 visit.

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Pharmacokinetic Results:

Median REN001 plasma concentrations increased up to the final sampling time of 4 hours on Day 1; the median concentration at 4 hours was 3870 ng/mL (minimum, maximum: 1300 ng/mL, 5820 ng/mL, respectively).

At Week 12, the median plasma concentration in subjects was 1060 ng/mL at pre-dose. Concentrations increased after dosing to a maximum median value of 4800 ng/mL at 2 hours, before reducing to 4040 ng/mL at 4 hours. Median plasma concentration for subjects with m.3243A>G mutation, and for subjects with other mtDNA defects, showed similar profiles to subjects overall.

Pharmacodynamic Results:

Concentrations of both FGF-21 and GDF-15 were highly variable. Baseline GDF-15 concentration means were similar for the two mutation groups, however, the mean baseline FGF-21 concentration was higher with m.3243A>G mutation subjects compared to that for subjects with other mtDNA defects.

There was a small change in mean FGF-21 and GDF-15 concentrations from baseline to Week 12 (-10.4 pg/mL [95% CI: -103.3, 82.8] and 140.6 pg/mL [95% CI: -12.6, 293.7], respectively).

Safety Results:

Overall, two subjects each experienced a serious AE (SAE). Both SAEs were single events that were considered to be of moderate severity and were judged to be related to the muscle biopsy done at baseline, therefore, they were recorded as not related to REN001 by the Investigator:

- Subject 02/003, a white female of 57 years with the m.3243A>G mutation experienced a hematoma (reported term: hematoma post muscle biopsy). Although the event was judged as related to the baseline muscle biopsy, the onset occurred on Day 2 of dosing; consequently, it was summarized as a treatment-emergent adverse event (TEAE). The SAE resolved after 52 days and the subject continued in the study
- Subject 01/004, a white female of 55 years with the other mtDNA mutation type experienced a hematoma (reported term: post-biopsy hematoma) which was reported days before the start of dosing. The SAE resolved after 3 days and the subject continued in the study.

No subjects died during the study.

Overall, 21 (91.3%) subjects experienced 114 TEAEs, of which 109 were unique TEAEs, suggesting very few repeated TEAEs were reported.

Of these, 15 (65.2%) subjects experienced TEAEs that were considered as at least possibly related to REN001 by the Investigator; moreover, five (21.7%) subjects experienced TEAEs that were considered as probably related to REN001.

All TEAEs were of mild or moderate severity. There were no severe TEAEs reported.

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Overall, the most frequently reported (more than 25% subjects) system organ class (SOCs) were:

- Gastrointestinal disorders (11 [47.8%] subjects)
- Infections and infestations (10 [43.5%] subjects)
- Musculoskeletal and connective tissue disorders (eight [34.8%] subjects)
- Nervous system disorders (eight [34.8%] subjects)
- Skin and subcutaneous tissue disorders (eight [34.8%] subjects)
- General disorders and administration site conditions (six [26.1%] subjects)

Of these, the most frequently reported treatment-related TEAEs by SOC were:

- Gastrointestinal disorders (nine [39.1%] subjects)
- Skin and subcutaneous tissue disorders (seven [30.4%] subjects)
- Nervous system disorders (six [26.1%] subjects)

The most frequently (more than 10% subjects) reported preferred terms (PTs) were:

- Constipation (four [17.4%] subjects)
- Headache (four [17.4%] subjects)
- Dry skin (four [17.4%] subjects)
- Fatigue (four [17.4%] subjects)
- Gastroesophageal reflux disease (three [13.0%] subjects)
- Diarrhea (three [13.0%] subjects)
- Neutropenia (three [13.0%] subjects)

Of these, the most frequently reported treatment-related TEAEs by PT were:

- Dry skin (four [17.4%] subjects)
- Headache (four [17.4%] subjects)

- Constipation (three [13.0%] subjects)
- Fatigue (three [13.0%] subjects)
- Gastroesophageal reflux disease (three [13.0%] subjects)
- Diarrhea (three [13.0%] subjects)

It is noted that gastrointestinal disorders occur frequently in subjects with PMM.

Several individuals reported maximum creatine phosphokinase (CPK) values in the first 7–10 days after dosing and thereafter were somewhat variable; however, values appeared generally to be slightly higher in subjects with other mtDNA defects than in subjects with the m.3243A>G mutation. As expected some subjects had elevations in CPK levels following exercise or other precipitating factors which resolved without intervention or interruption of study drug.

No subject experienced a Hy's law event (i.e., elevated bilirubin and/or aspartate aminotransferase [AST]). No trends in mean laboratory values were noted. Several subjects experienced out-of-range laboratory values that were reported as AEs; all of these AEs resolved. The majority of AE's resulting from out-of-range laboratory values can be easily interpreted from the review of the data listings. The observations for five subjects are further discussed in this document.

Overall, 11 subjects had abnormal chemistry values of potential clinical importance (as defined by the sponsor in the statistical analysis plan), all in Part A. There were no chemistry parameters of potential clinical importance in Part B.

Pulse rate (beats/min) values showed no notable changes across all the weeks of treatment compared with baseline values and there were no pulse rate values of potential clinical importance (<45 beats/min; >130 beats/min).

Systolic and diastolic blood pressure (mmHg) values showed no notable changes compared with baseline values in any subjects across all weeks of treatment and there were no blood pressure values of potential clinical importance (defined as <80 and <50 mmHg OR >155 and >100 mmHg; for systolic and diastolic blood pressure, respectively).

Overall, there were no notable trends for any electrocardiogram (ECG) parameters at any visit. Some subjects had abnormal ECG values across all visits in Parts A and B but none were reported as clinically significant by the Investigator.

Retinal examination showed one abnormal value in one subject which was not considered clinically significant by the Investigator.

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Conclusions:

Safety Conclusions:

REN001 was considered to be safe and well tolerated in this Phase 1b study.

- Two SAEs were reported following the muscle biopsy at baseline and were therefore not related to treatment. No other SAEs were reported in this study. No serious adverse drug reactions were identified
- All TEAEs were considered mild or moderate by the Investigator
- As CPK is of particular interest in this population, values have been thoroughly reviewed. Elevations typically followed exercise or other precipitating factors and were resolved without intervention or interruption of study drug
- The safety parameters assessed and described above did not identify any safety concerns

Pharmacokinetic Conclusions:

- Median REN001 plasma concentrations increased up to the final sampling time of 4 hours on Day 1 median concentration at 4 hours was 3870.0 ng/mL (minimum, maximum: 1300 ng/mL, 5820 ng/mL)
- At Week 12 concentrations increased after dosing to a maximum median value of 4800 ng/mL at 2 hours

Date of the Report:

02 September 2021