**Treatment with REN001, a Novel PPARδ Agonist, Preserves Muscle Strength and Promotes Recovery of Muscle Atrophy After Prolonged Leg Immobilization**

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Introduction: REN001 is an oral, once-daily peroxisome proliferator-activated receptor delta (PPARδ) agonist being investigated for the treatment of PMM.

Methods: A randomized, investigator and subject blind, placebo-controlled phase 1 study in healthy volunteers was conducted to evaluate the safety of oral REN001 (formerly known as HPP593), 100 mg twice daily, administered during and after limb immobilization. All subjects had the left leg immobilized with a knee brace (30° flexion) and used crutches from Day 1 to Day 14. Changes in muscle strength, gene expression from muscle biopsies, and cross section area (CSA) in the immobilized leg was evaluated. After 14 days of dosing the brace was removed and the subjects continued to take REN001 for an additional 14 days and gradually resumed regular physical activity of their previously immobilized limb.

Results: A total of 24 subjects (all men) were randomized to receive 28 days treatment with REN001 (n=12, mean [SD] age 42 [8.9] years) or placebo (n=12, mean [SD] age 39 [8.2] years).

After removal of the knee brace at Day14, subjects receiving REN001 had significantly less loss of knee strength compared to those receiving placebo (Mean change: REN001 = -5.8 lb, Placebo = -36.2 lb; p=0.01). The primary pharmacodynamic endpoint was change in single knee extension strength at Day 21 from baseline. REN001 treated subjects had a significant increase in knee extension strength compared to placebo (Mean change: REN001 = 32.8 lb, Placebo = 2.7 lb; p<0.001, mixed model repeated measures analysis; p=0.004, with baseline as a covariate). At day 29, change in mean knee extension strength was greater for the REN001 group compared to placebo (Mean change: REN001 = 25.5 lb, Placebo = 13.7 lb; p<0.2.). No differences in CSA were noted.

Muscle biopsies were analyzed for changes in mRNA expression of PPARδ-regulated genes involved in mitochondrial biogenesis and function. Compared to placebo, REN001-treated individuals had significant increases (>4-fold) in pyruvate dehydrogenase lipoamide kinase isozyme 4 (PDK4), angiopoietin-like 4 (ANGPTL4) and solute carrier family 25 member 34 (SLC25A34).

REN001 was safe and well tolerated in this study. No serious adverse events were reported. Most treatment-emergent adverse events (TEAEs) were mild in severity and similar in placebo

or REN001 treated subjects. The most common TEAEs were headache, post-procedural hematoma and rash. Mild elevation in CPK, not related to study drug, were observed. All TEAEs resolved with no sequelae.

Conclusions: REN001, 100 mg given orally twice daily for 28 days to healthy volunteers was safe and well tolerated. Compared to placebo, treatment with REN001 increased expression of genes involved in mitochondrial biogenesis and oxidative phosphorylation, prevented muscle wasting and promoted recovery of muscle atrophy after prolonged leg immobilization. This is the first demonstration of the impact of REN001 directly on human muscle and these results offer a rationale to evaluate REN001 in patients with mitochondrial myopathies.

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