Intravenous BPM31510 for treatment of pediatric patients with primary CoQ10 deficiency

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I. Abstract

Primary CoQ10 deficiency (PCQD) is a mitochondrial disease potentially treatable with CoQ10 replacement therapy. BPM31510 is an intravenously (IV) administered encapsulated ubidecarenone lipid nanosuspension that is designed to overcome the inconsistent GI tract absorption of oral formulations and to address the challenges of delivering CoQ10 into tissues, including the brain. Here, we present preliminary data on the safety and efficacy of BPM31510 compassionate use treatment in four patients with PCQD due to various *COQ8A* variants: P1, 9-year-old [c.812G>A; p.Arg271His; c.1821C>A; p.Tyr607Ter], P2,16-year-old [c.1042C>T; p.Arg348* homozygous], P3, 10-year-old [1q42.13 28kb deletion (pathogenic variant); c.1390 C>T; p.Arg464Trp (likely pathogenic missense variant)], and P4, 17-year-old [c.811C>T; p.Arg271Cys; c.911C>T; p.Ala304Val]. All patients were previously treated with oral CoQ10 supplements (30-50 mg/kg/day) with minimal or unsustained clinical benefit, and in P4, 520 mg/day of idebenone was also added for recurrent stroke-like episodes, with minimal or no benefit. Oral CoQ10 supplements remained unchanged throughout the treatment protocol. Longitudinal patient assessments were performed at baseline and during the treatment period. Overall, substantial clinical improvement was reported in all 4 patients. P1 and P2 were treated ≥9 months with improvements on the Scale for the Assessment and Rating of Ataxia (SARA). P3 was treated for 8 months, with marked improvement in MM-COAST (Mitochondrial Myopathy Composite Assessment Tool) composite score across muscle strength, fatigue, and balance. Improved height and weight trajectories were observed. Subsequent evaluation at 4 months after discontinuation of IV CoQ10 revealed a return to prior baseline MM-COAST trajectory. P4 was treated for > 7 months with improvement on the SARA scale and did not present with any additional stroke-like episodes. No adverse events or any laboratory test safety concerns were reported. BPM31510 was generally well tolerated, was feasible to administer as weekly IV infusions, and was associated with measurable improvement across clinical assessments, showing its potential to modify PCQD's natural history, supporting further investigation. Observed decline in MM-COAST assessments following cessation of treatment in P3 supports the imperative need for continuous treatment, in order to maintain the observed functional benefit on treatment.

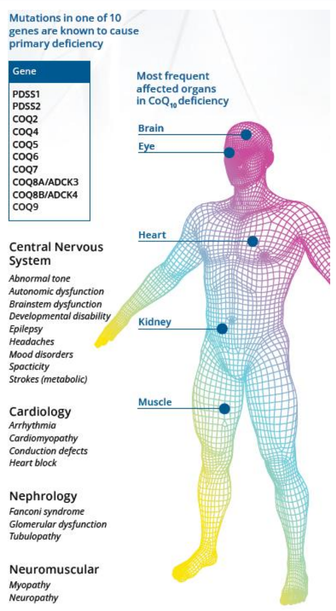
II. BPM31510

- Proprietary & **stable** formulation
- Contains oxidized (active) CoQ10 (red lines in image)
- High **bioactivity due to presentation of CoQ10 to the cell in the right orientation**
- Lipid nanoparticle suspension
- Enrichment in **mitochondria**

III. Primary CoQ10 Deficiency (PCQD)

- Most patients present early in childhood; the earlier the presentation, the worse the prognosis
- Identification of patients has accelerated with the advent of next-gen sequencing (mito panel)
- The current standard of care is based on over-the-counter (OTC) oral CoQ10 supplementation

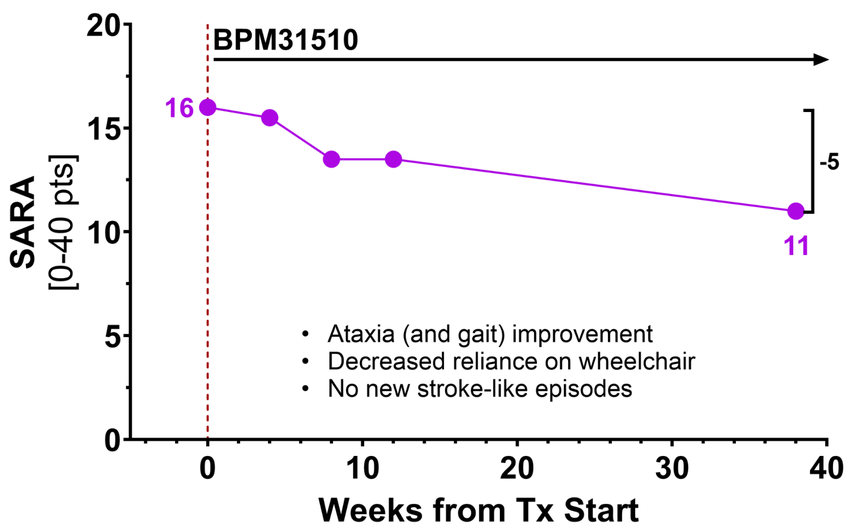
Coenzyme Q10 is a lipid-soluble molecule synthesized endogenously and plays a vital role in several essential cellular processes, including mitochondrial energy production, fatty acid beta-oxidation, pyrimidine biosynthesis, and antioxidant defense. Its biosynthesis is incompletely characterized and requires products of at least 12 known genes. The pathogenesis of PCQD is complex and related to the different functions of CoQ10. PCQD can affect any part of the body, but particularly the brain, muscle and kidney tissues. The common phenotypes are encephalomyopathy, severe infantile multisystemic disease, nephropathy, cerebellar ataxia and atrophy, and mitochondrial myopathy. The clinical trajectory of patients with PCQD is clearly progressive, serious and potentially life-threatening.



IV. Patient Demographics

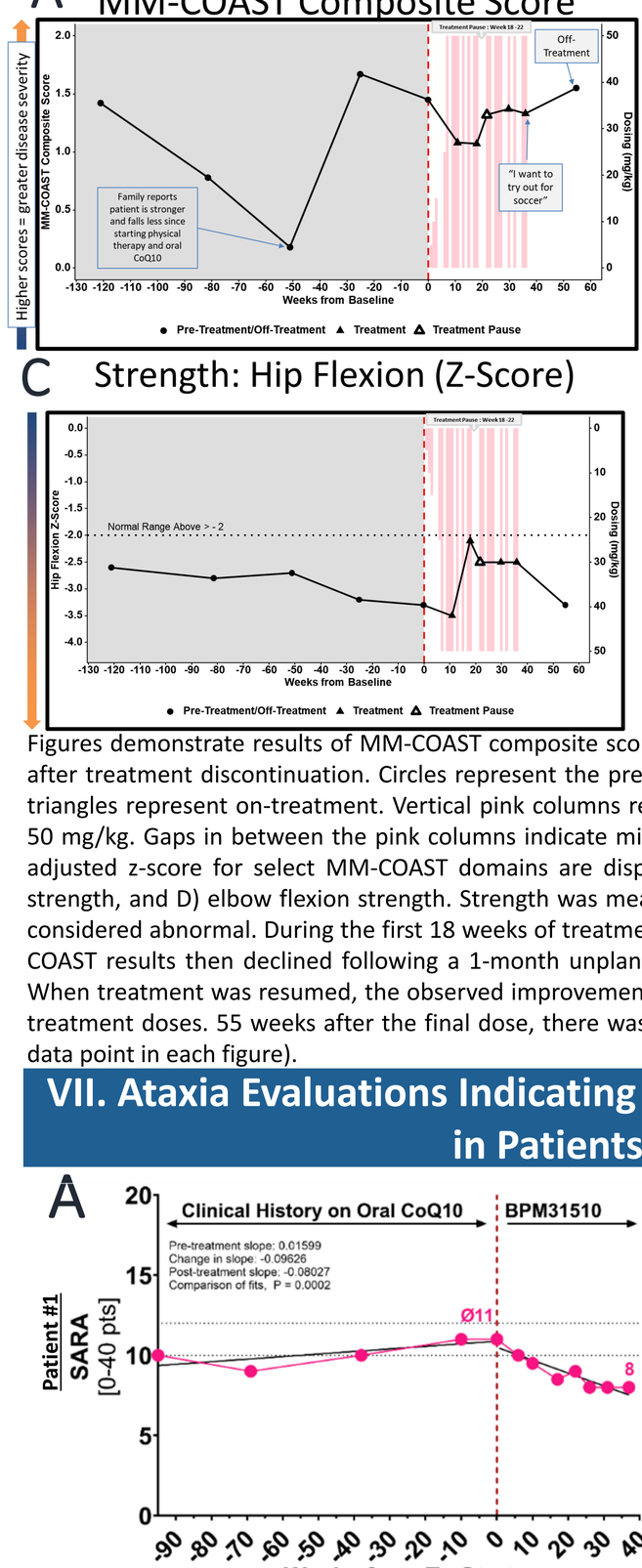
Patient #	Patient details	Time on Tx	Mutation
P1	9-year-old Female	>19 months	***COQ8A*** (c.812G>A; p.Arg271His; c.1821C>A; p.Tyr607Ter)
P2	17-year-old Male	9 months	***COQ8A*** (c.1042C>T; p.Arg348* homozygous)
P3	10-year-old Female	8 months	***COQ8A*** (1q42.13 28kb deletion; c.1390 C>T; p.Arg464Trp)
P4	16-year-old Female	> 9 months	***COQ8A*** (c.811C>T, p.Arg271Cys; c.911C>T, p.Ala304Val)

V. SARA Score Improvement After Treatment in Patient P4



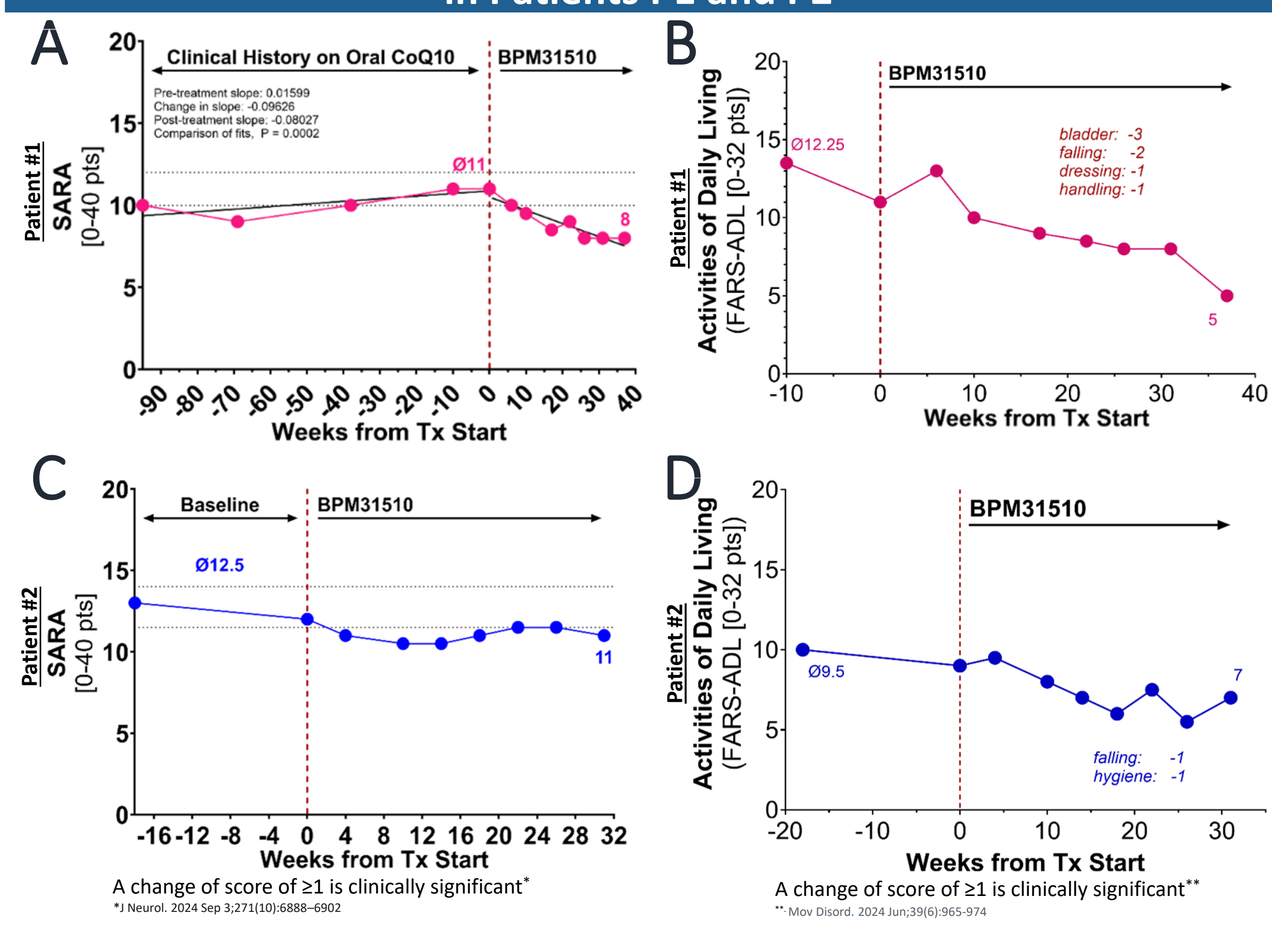
SARA scores (Scale for the assessment and rating of ataxia) indicate an improvement in ataxia symptoms. Patient has increased independence and decreased wheelchair use. Additionally, patient has had no stroke-like episodes since starting treatment. Previously she had experienced these episodes every 2-3 months.

VII. Patient P3 Improvements in Dynamometry, Exercise Intolerance and Overall MM-COAST Score



Figures demonstrate results of MM-COAST composite score and select individual assessments prior to, during, and after treatment discontinuation. Circles represent the pre-treatment (gray background) and off-treatment periods, triangles represent on-treatment. Vertical pink columns represent administered weekly doses up to a max dose of 50 mg/kg. Gaps in between the pink columns indicate missed doses. A) MM-COAST composite score and sex/age-adjusted z-score for select MM-COAST domains are displayed including B) 30 second sit to stand, C) hip flexor strength, and D) elbow flexion strength. Strength was measured by hand-held dynamometry. Z-scores ≤ -2 S.D. are considered abnormal. During the first 18 weeks of treatment, improvement was observed across assessments. MM-COAST results then declined following a 1-month unplanned treatment pause, represented by the open triangle. When treatment was resumed, the observed improvement was not sustained due to intermittent administration of treatment doses. 55 weeks after the final dose, there was a deterioration across all MM-COAST assessments (final data point in each figure).

VII. Ataxia Evaluations Indicating Treatment Driven Improvements in Patients P1 and P2



A change of score of ≥1 is clinically significant*

*J Neurol. 2024 Sep 3;271(10):6888–6902

A change of score of ≥1 is clinically significant**

**. Mov Disord. 2024 Jun;39(6):965-974

SARA scores (Scale for the assessment and rating of ataxia) for A) P#1 and C) P#2, and FARS-ADL scores (Friedreich Ataxia Rating Scale-Activities of Daily Living) for B) P#1 and D) P#2 indicate an improvement in ataxia symptoms.

CONCLUSIONS – Preliminary Evidence of Potential Therapeutic Signal

- **BPM31510 weekly IV treatment has been well tolerated with no drug related clinically significant adverse events.**
- **All four patients have demonstrated improvements in ataxia and mobility by SARA score (ataxia) or MM-COAST objective assessments (including dynamometry)**
- **Noticeable improvements were observed as early as 4 weeks after treatment initiation with discontinuation of treatment resulting in disease progression.**
- **Parents, teachers, and/or parents of peers have reported substantial improvement in day-to-day activities for all 4 patients.**

This preliminary evidence suggests that BPM31510 may have an effect in patients with PCQD, warranting further investigation.

BPM31510 is an investigational drug whose safety and efficacy have not been established by the FDA.