Intravenous BPM31510 for treatment of pediatric patients with primary CoQ10 deficiency

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I. Abstract

Introduction: Primary CoQ10 deficiency (PCQD) is a mitochondrial disease potentially treatable with CoQ10 replacement therapy. BPM31510 is an intravenously administered lipid nanoparticle encapsulated ubidecarenone 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.

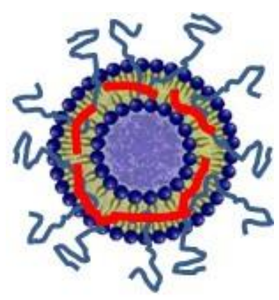
Methods: Here, we present preliminary data on the safety and efficacy of BPM31510 compassionate use treatment in four patients with PCQD due to *COQ8A* variants: P1, 9-years-old; P2,16-years-old; P3, 10-years-old; and P4, 17-years-old. All patients were previously treated with oral CoQ10 supplements (30-50 mg/kg/day), and in P4, 520 mg/day of idebenone was also added for recurrent stroke-like episodes, with minimal or no benefit. Multiple functional assessment scales were performed at baseline and during the follow-up.

Results: Overall, a 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 has 6 months of follow-up treatment with marked improvement in MM-COAST (Mitochondrial Myopathy Composite Assessment Tool) composite score across muscle strength, fatigue, balance, dexterity, and exercise intolerance tests. P4 was treated for more than 9 months with improvement on the SARA scale and didn't present any additional stroke-like episodes. No adverse events or any laboratory test safety concerns were reported.

Conclusion: BPM31510 was generally well tolerated and demonstrated encouraging clinical activity, supporting its potential to modify PCQD's natural history.

II. BPM31510

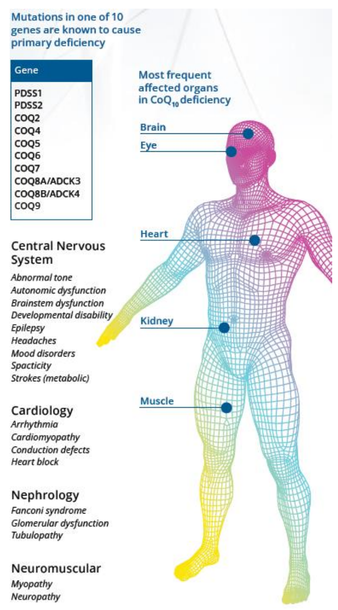
- Proprietary & **stable** formulation
- Contains oxidized (active) CoQ10 (red lines in image)
- High **bioactivity due to presentation of CoQ10 to the cell in the right orientation**
- Lipid nanoparticle suspension
- Enrichment in **mitochondria**



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

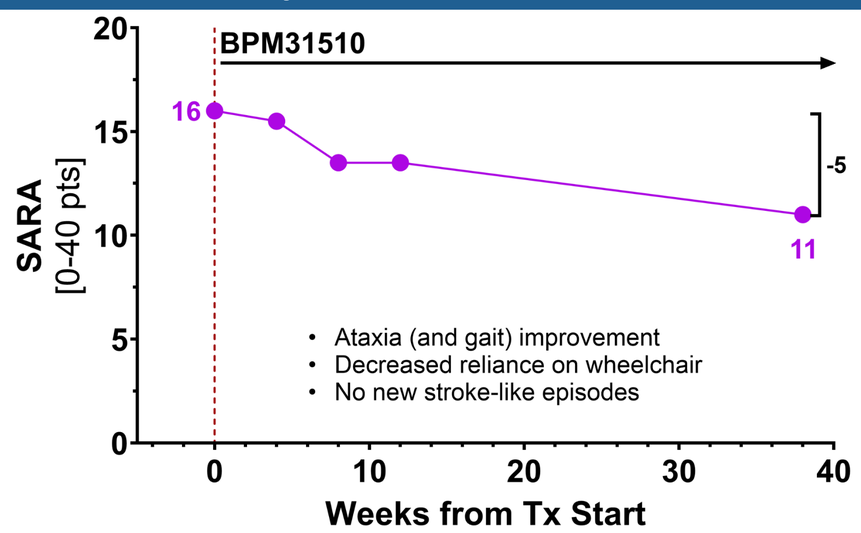
Coenzyme Q10 is a lipid-soluble molecule synthesized endogenously and plays a vital role in several essential cellular processes, including mitochondrial energy production, fatty acid beta-oxidation, pyrimidine biosynthesis, and antioxidant defense. Its biosynthesis is incompletely characterized and 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

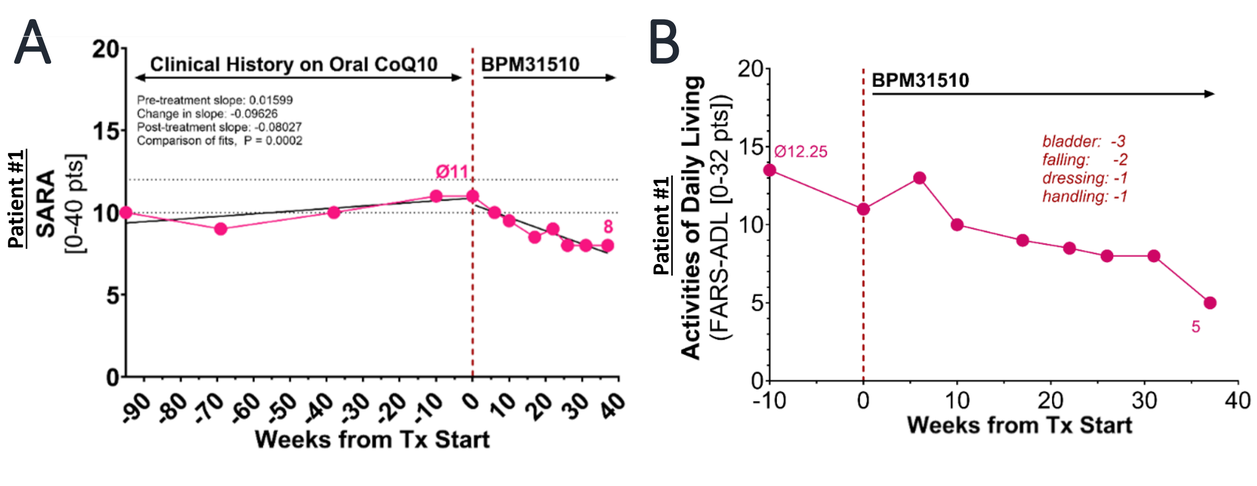
Patient #	Patient details	Time on Tx	Mutation
P1	9-year-old Female	>19 months	***COQ8A*** (c.812G>A; p.Arg271His; c.1821C>A; p.Tyr607Ter)
P2	17-year-old Male	9 months	***COQ8A*** (c.1042C>T; p.Arg348* homozygous)
P3	10-year-old Female	8 months	***COQ8A*** (1q42.13 28kb deletion; c.1390 C>T; p.Arg464Trp)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

VI. Ataxia Evaluations Indicating Improvement in Patients P1 and P2



A change of score of ≥1 is clinically significant*

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

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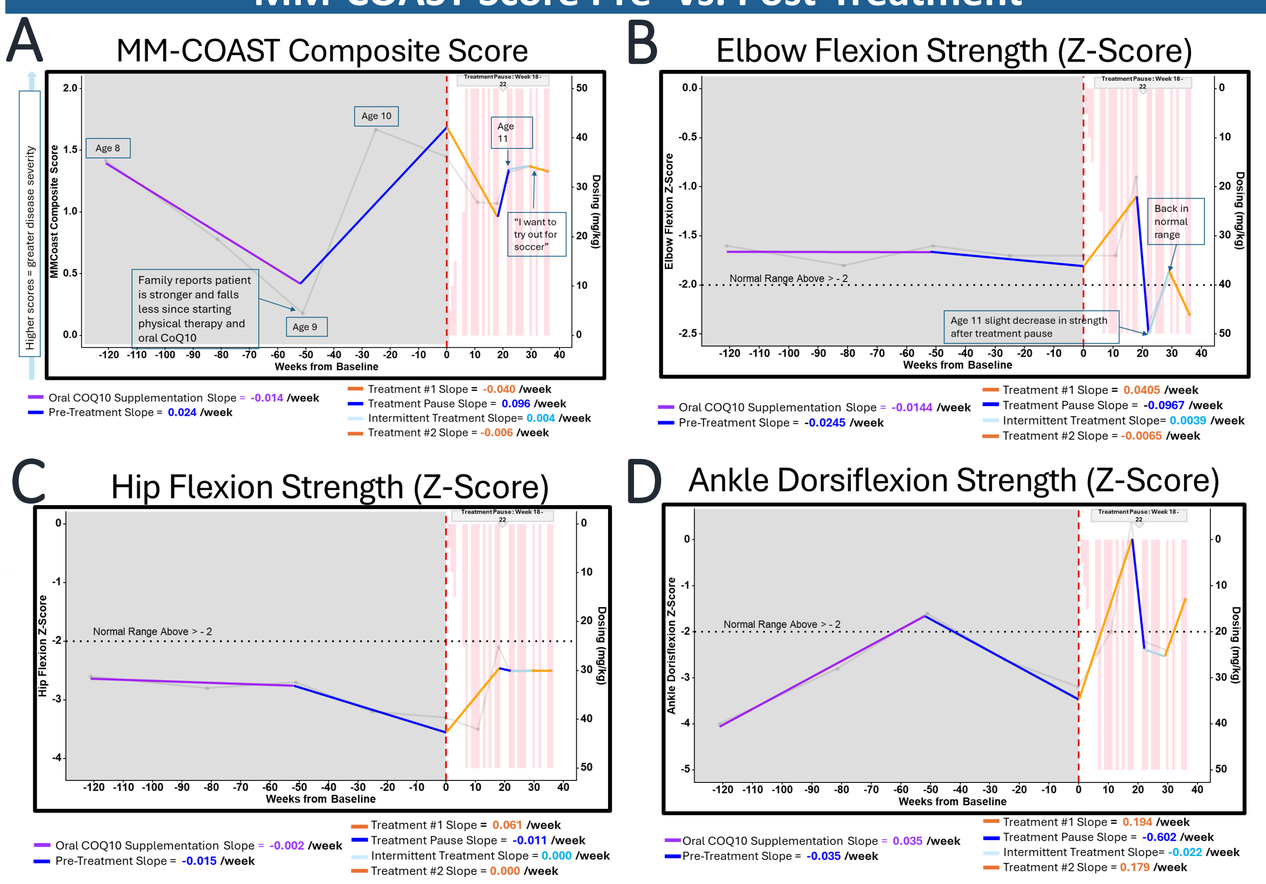
**. Mov Disord. 2024 Jun;39(6):965-974

SARA scores (Scale for the assessment and rating of ataxia) for A) P1 and C) P2, and FARS-ADL scores (Friedreich Ataxia Rating Scale-Activities of Daily Living) for B) P1 and D) P2 indicate an improvement in ataxia symptoms.

VII. Patient P3 Improvements in Dynamometry and Overall MM-COAST Score Pre- vs. Post-Treatment



Graphs showing post treatment improvements in A) MM-COAST composite score and of age-adjusted z-score showing improvement in strength (components of MM-COAST) of B) elbow flexors, C) hip flexors, and D) ankle dorsiflexors measured by hand-held dynamometry. Z-scores ≤ -2 S.D. are considered abnormal. This improvement regressed at the last data point following a 1-month unplanned treatment pause.

Spline regression analysis (blue line) demonstrates the pre-treatment and post-treatment MM-COAST trajectories. Vertical red line indicates initiation of treatment. Vertical yellow columns represent administered weekly doses up to a max dose of 50 mg/kg. Gaps in between the yellow columns indicate missed doses.

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 (dynamometry)**
- **Noticeable improvements were observed as early as 4 weeks after treatment initiation and sustained past 20 weeks.**
- **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 a substantial effect in patients with PCQD, warranting further investigation.

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