Initial experience using intravenous BPM31510 to restore CoQ10 in pediatric patients with Primary CoQ10 deficiency

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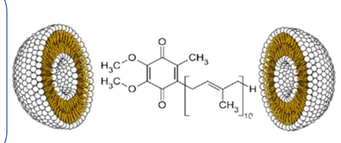
I. BPM31510

- Proprietary & **stable** formulation
- Contains oxidized (active) CoQ10
- High **bioactivity due to presentation of CoQ10 to the cell in the right orientation**
- Lipid nanoparticle suspension **30 to 80 nm size**
- Enrichment in **mitochondria**

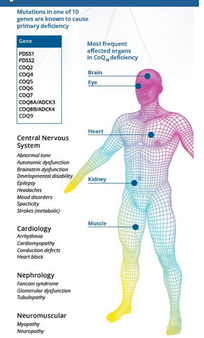


BPM31510 is an investigational drug whose safety and efficacy have not been established by the FDA.

II. 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 involved in many cellular processes such as energy production through the mitochondrial respiratory chain, beta-oxidation of fatty acids, and pyrimidine biosynthesis, but it is also one of the main cellular antioxidants. Its biosynthesis is incompletely characterized and requires products of at least 12 known genes. The pathogenesis is complex and related to the different functions of CoQ10 related to defective ATP production and oxidative stress, but also an impairment of pyrimidine biosynthesis and increased apoptosis. 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 PCD is clearly progressive, serious and potentially life-threatening.



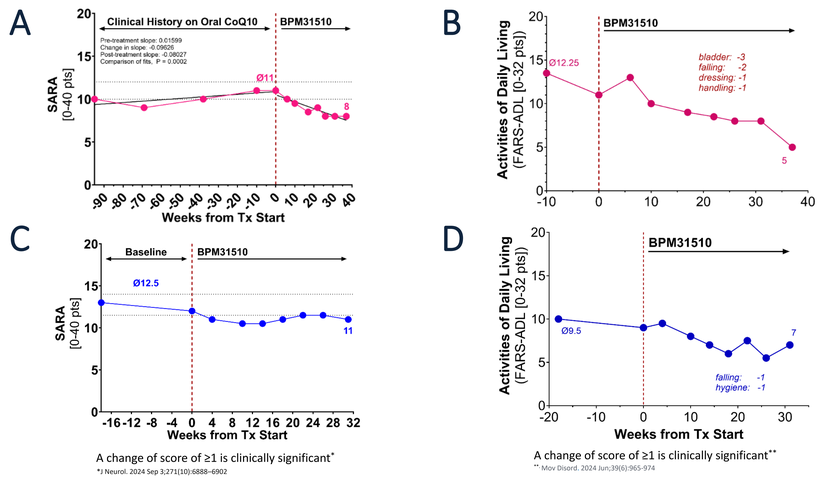
III. Schedule of Assessments (not all assessments done on all pts.)

	Procedures	Specific Tests	Baseline/ Screening	Day 1	Day 8 +/- 1 day	Day 15 +/-1 day	Day 22 +/-1 day	Weekly thereafter +/-2 day	Monthly Starting at Day 29 +/- 2 day	End of Study
All Sites	Informed Consent		X							
	Demographics		X							
	Medical History		X							
	Administer Vitamin K and BPM31510IV			X----------				----------X		
	Concomitant medication review		X	X----------				----------X		
	Physical exam(including height and weight)		X							X
	Vital Signs		X	X----------				----------X		
	Hematology	includes CBC, PT, INR (aPTT), Hb, MCHC, MCH	X	X----------				----------X		
	Serum chemistry	Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium total protein, AST, ALT, sodium	X	X----------				----------X		
	Urinalysis	Appearance, color, pH, specific gravity, ketones, protein, Urine protein creatinine ratio – UPCR, glucose, nitrite, and occult blood (microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation is positive)	X	X----------				----------X		
	Adverse event review and evaluation		X	X----------				----------X		X
	Biomarker assessments		X	X----------				----------X		X
	Pregnacy test	Serum pregnancy test (women of childbearing potential)	X							
	EKG(as indicated)		X							X
	MRI assessment(optional)		X							X
Site 1	Clinician- reported Outcome	SARA (Gait, Stance, Sitting, Speech disturbance, Finger chase, Nose-finger test, Fast alternating hand movements, Heel-shin slide)	X						X	X
		FARS-E	X						X	X
		CGI-C relative to pervious assessment	X						X	X
	Patient reported outcome	FARS-ADL	X						X	X
		PGI-C relative to previous assessment	X						X	X
		Goal Attainment Scale	X						X	X
	Observer-reported Outcome	CaGI-C relative to previous assessment(global + 4 domains)	X						X	X
	Performance Outcome	9-Hole peg test	X						X	X
	Digital-motor outcome	APDM(Gait, Romberg eyes open/closed, Tandemgait/stance if possible)	X						X	X
		Q-motor (Finger Tapping, Diadochokinesia Grip-Lift, Target Reaching)	X						X	X
		Video Recording (2-3 intra-indivdual tasks at home plus APDM gait plus Q-Motor spiral)	X						X	X
Site 2	MM-COAST	Dynamometry (Elbow and hip flexion, wrist extention, ankle dorsiflexion)	X						X	X
		Balance (single leg eyes closed, tandem stance eyes open and closed)	X						X	X
		30 sec sit-to-stand	X						X	X
		6-min walk test	X						X	X
		9-Hole peg test	X						X	X
		Functional dexterity	X						X	X
	Other assessments	CeCEST MRI Scan	X						X	X
		Video Recording	X	X----------				----------X		X

IV. Patient Demographics, Treatment duration and High-level Response

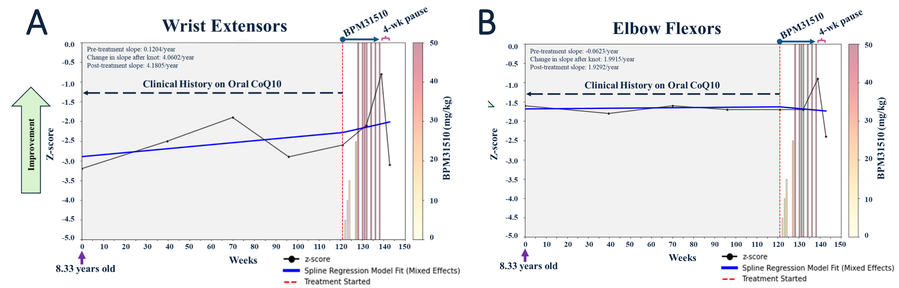
Patient details	Tx Start of weekly infusion	Mutation(s)	Response
P#1 9-year-old Female	10/19/2024	***COQ8A*** (c.812G>A; p.Arg271His; c.1821C>A; p.Tyr607Ter)	Improvements in SARA score, 9HPT (>5sec), activities of daily living, tandem walk, school performance and others *"There have been no more urinary incidences [used to come home from school and had to change her pants]." (parents)* *"Her walking and running is more stable; her legs are more controlled."* (parents)
P#2 17-year-old Male	11/26/2024	***COQ8A*** (c.1042C>T; p.Arg348* homozygous)	Improvements in SARA score, 9HPT (>5sec), activities of daily living, walking speed and endurance, school performance *"I experienced no more falls since I am on treatment"* *"His gait is more stable, his fine motor skills have improved, and his speech is faster"* (parents)
P#3 10-year-old Female	2/7/2025	***COQ8A*** (1q42.13 28kb deletion; c.1390 C>T; p.Arg464Trp)	Improvements in MM-COAST (Flickinger et al. 2021) dynamometry measurements, tandem walk, stair climb, 10MWT, 9HPT etc. *"The patient's school and family have noted significant improvements in cognition, attention, and communication."* (physician) The patient's teacher noted, *"Patient is very engaged and excelling in her schoolwork".*

V. Ataxia Evaluations Indicating Treatment Efficacy in Patients #1 and #2



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.

VI. Patient #3 Improvements in Dynamometry and 9HPT pre- vs. Post-Treatment



Graphs of age-adjusted z-score showing post treatment improvement in strength of A) wrist extensors, 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

- **BPM35510 weekly IV Treatment has been well tolerated with no drug related clinically significant adverse events.**
- **All three patients have demonstrated improvements in ataxia and motility including SARA score (ataxia) and MM-COAST objective assessments (dynamometry)**
- **Noticeable improvements were observed as early as 4 weeks after treatment initiation and sustained past 20 weeks.**
- **Patient #3 showed regression in muscle strength after a 1-month treatment pause.**
- **Parents, teachers, and/or parents of peers have reported substantial improvement in day-to-day activities for all 3 patients.**

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