Protocol for a UK phase-2 clinical trial of 4'-phosphopantetheine for PKAN

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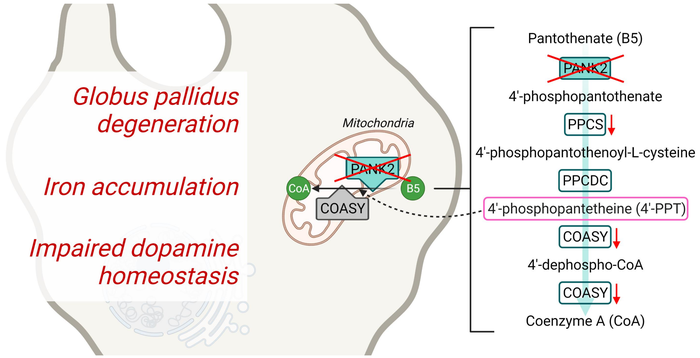
BACKGROUND

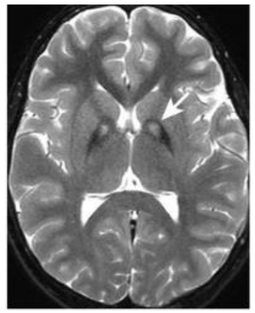
Pantothenate kinase-associated neurodegeneration (PKAN), a Neurodegeneration with Brain Iron Accumulation (NBIA) disorder, is an inborn error of vitamin B5-coenzyme A (CoA) metabolism caused by biallelic mutations in the *PANK2* gene.



Vitamin B5 – CoA pathway and biological consequences of PKAN

Children with classic PKAN present at a mean age of 3.4 years, often with gait difficulties and clumsiness; the atypical form presents later in adolescence or early adult life and progresses more slowly.

PKAN is characterized by a severe movement disorder, cognitive and neuropsychiatric involvement, pigmentary retinopathy and pathological iron accumulation in the basal ganglia; these cause profound disability and risk of premature mortality.



Eye of the tiger sign - pathognomonic of PKAN

PROPOSED THERAPY

There are no proven disease-modifying treatments for PKAN currently.

PKAN is caused by functional loss of the mitochondrially-located PANK2 enzyme which phosphorylates vitamin B5 (pantothenate) in the first step of CoA metabolism. CoA is essential for the tri-carboxylic acid cycle, fatty acid oxidation and synthesis, amino acid metabolism and neurotransmitter synthesis, serving more than 9% of mammalian biochemical reactions.

This trial will assess the safety and tolerability of 4'-phosphopantetheine (4'-PPT):

- Endogenous precursor to CoA
- Found in all cells and many foods
- Corrects disease-specific phenotypes in cultured human cells and the *Pank2*-knock out mouse model
- No toxicity at very high doses in animal models
- Suitable for development as a Food for Special Medical Purpose
- Single daily enteral dose
- Long term aim to license as a food supplement (FSMP)

Single-centre trial based at Great Ormond Street Hospital

Please refer patients for consideration of suitability (contact details below)

TRIAL DESIGN

This is a phase-2 clinical trial of enteral 4'-PPT administered once per day to 24 participants aged 1-25 years. A 6-month placebo-controlled, double-blinded, dose-ranging phase will be followed by an 18-month open-label, single-dose phase.

2022	6 MONTHS	18 MONTHS
Recruitment	Double-blind phase	Open-label phase
• Age 1-25 years • Confirmed PKAN	• Randomised • Placebo-controlled • Dose ranging	• Single-dose

Outcome measures

Primary:

- Safety and tolerability (regular blood test and side effect monitoring)

Secondary:

- Biomarker – blood expression of *COASY* mRNA (last enzyme in the CoA synthesis pathway, *see figure left panel*)

Exploratory:

- Visual electrodiagnostic assessments
- Questionnaire and examination-based disease rating scales
- Activity of daily living scales
- Dystonia scores
- Quality of life scores

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CoA-Z PHASE II TRIAL
GREAT ORMOND STREET HOSPITAL CHARITY
LifeArc