A within subject dose escalation study of a vitamin supplement for PKAN

Published: 29-07-2020
Last updated: 27-12-2024

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Iron and trace metal metabolism disorders
Study type	Interventional

Summary

ID

NL-OMON55013

Source
ToetsingOnline

Brief title
PKAN-II

Condition

- Iron and trace metal metabolism disorders
- Movement disorders (incl parkinsonism)

Synonym
Hallervorden-Spatz, PKAN

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: ZonMw;Hersenstichting

Intervention

Keyword: 4-PPT, Phase II, PKAN, Vitamin supplement

Outcome measures

Primary outcome

Main study parameter/endpoint:

1) 4*-PPT will be measured in the collected blood samples (collected at 10 time points, according to Table 1).

2) COASY biomarker mRNA expression levels measured in lymphocytes extracted from blood at 10 time points during the study.

Secondary outcome

Secondary study parameters/endpoints:

1) Safety outcome measures will include study product-emergent adverse events and abnormalities on routine laboratory tests collected at 10 time points over 2 years of the study.

2) In addition, at 6 time points during the study video recordings will be performed to objectively measure the neurological examination.

3) Tolerability outcomes will be assessed via participant retention in the study and adherence to the study product regimen.

Study description

Background summary

Pantothenate kinase-associated neurodegeneration (PKAN) is an ultra-rare neurodegenerative disease affecting children and adults, with a prevalence of 1 case per 1-3 million in the general population. Patients suffer from progressive generalised dystonia, parkinsonism and brain iron accumulation. The progression of PKAN is relentless but unpredictable and variable between patients. No treatment exists for this painful, disabling and fatal disease. PKAN patients lack an enzyme required for biosynthesis of coenzyme-A, an essential metabolic co-factor. We have compelling preclinical evidence that 4*-PPT completely rescues the disease phenotype in PKAN animal and human cell models. Preclinical studies also identified a promising biomarker. In the long term we hypothesise that 4*-PPT will slow or stop disease progression in PKAN patients. It is currently unknown whether 4*-PPT, which is normally not present in plasma, can be detected in a dose dependent manner in plasma of PKAN patients when it is orally provided. Our study aims to collect for the first time in vivo pharmacokinetic information of 4*-PPT, when orally provided, in PKAN patients. Based on preclinical and limited clinical data we hypothesize that 4*-PPT will be detectable in plasma of PKAN patients after several days when daily orally provided.

We propose a within-subject dose-escalation study, investigating 3 subsequent increasing doses during 5 months followed by an open label extension study of 19 months on the middle dose.

Study objective

The primary objectives are:

1) to obtain in vivo pharmacokinetic data of 4*-PPT (the study product) measured in plasma of PKAN patients;

2) to obtain pharmacodynamic data of the biomarker COASY in circulating lymphocytes of PKAN patients, when 4*-PPT is provided daily at 3 subsequent increasing doses (7,5 mg/m2, 15 mg/m2 and 30 mg/m2) for a month each;

3) to collect data regarding plasma levels of CoA-Z and 4) the biomarker COASY when 4*-PPT has been orally provided over a period of 19 months on a fixed dose. We will start a fixed dose of 15 mg/m2 as the default dose, but may adjust to the lower or higher dose based on the biomarker measurements obtained from the dose-escalation phase.

The secondary objectives are:
1) To assess safety and tolerability of the used doses of 4*-PPT in PKAN

patients when 4*-PPT is orally provided;
2) Objective neurological examination (video) .

Study design

The proposed trial is a single-center study in which patients receive an initial daily dose of 7,5 mg/m2 4*-PPT during one month (M0), followed by a wash-out period of one month (M1). Subsequently a dose of 15 mg/m2 will be provided (one month; M2), a washout will follow (one month; M3) and finally a dose of 30 mg/m2 (one month; M4) will be provided. This dose-escalation phase will be followed up by an open label extension phase of 19 months on a fixed dose. The default dose will be a daily dose of 15 mg/m2. This dose may be adjusted per patient, based on the biomarker results obtained in the dose-escalation phase.

Intervention

All patients will be given 4*-PPT. Patients will be assigned a daily dose of 4*-PPT, which will be provided in the form of capsules. The content will be dissolved in water and the desired amount will be orally administered or via gastronomy tube.
Patients will be visited at home or at a nearby location 10 times during the first 5 months (M0-M4) of the dose-escalation phase. During the extension stud, 1 visit after 1 year will occur and 1 visit at the end of the trial. Blood collection will occur at 10 visits for 4*-PPT and COASY, plus routine safety laboratory tests. A standard video-recording will be taken at 6 of the visits (visit 2, after each period of increased dose, after 1 year and at the last visit) to monitor the neurological status of the patient, and regular telephone contact will occur between the visits as needed.

Study burden and risks

All PKAN patients participating in the study will receive 4*-PPT. Results from unpublished clinical studies show that 4*-PPT is well tolerated and no side effects are reported. However, we cannot 100% exclude that the study product poses risks, when taken over an extended period. All clinical procedures involved in this research (blood draws and neurological evaluation using video recording) are judged to pose minimal risk to even the youngest of participants.

Previous trials in this patient group have showed that traveling, for instance to the hospital, is a stressful event for patients, not only putting them at medical risk by increasing neurological symptoms, but also potentially confounding the study results. Therefore, during the proposed trial, the clinician will travel to the patients instead of patients traveling to the clinic and all study procedures including the consent process for the study

will be performed at the residency of the patients. This approach was important for ZonMw to commit funding for the study. In previous international trials Dutch PKAN patients were never able to participate. Here for the first time, they will have access to a possibly lifesaving treatment.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)

Inclusion criteria

1. Have a diagnosis of PKAN confirmed by genetic testing showing two pathogenic mutations, OR one found mutation and typical clinical and imaging features of the disease.
2. aged >12 months at the time of screening.

3. Be able to take the study product by mouth or via gastrostomy tube.
4. Informed consent is provided by the patient and/or parents, and/or legal representative.
5. Be resident in The Netherlands or Belgium for the duration of the trial.
6. Have a valid Dutch or Belgian health insurance.

Exclusion criteria

1. subjects must NOT have been exposed to a putative PANK2 *bypass* therapeutic agent in the 30 days prior to screening.
2. subjects must NOT be concurrently enrolled in another interventional clinical trial.
3. subjects must NOT have concurrent medical or other conditions that in the opinion of the investigators are expected to preclude completion of study procedures or confound the assessment of clinical and laboratory measures of safety.
4. subjects must be able to understand Dutch.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-09-2021
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	29-07-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-07-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-12-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-03-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 24533
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL73850.000.20