A double-blind, randomized, placebo-controlled, single-center, two-way cross-over study with KH176 in patients with the mitochondrial DNA tRNALeu(UUR) m.3243A>G mutation and clinical signs of mitochondrial disease

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Objectives: Primary Objective1. To evaluate the effect of KH176 on gait (Gaitrite®) parameters: step-length and variability in step-time and step-width in patients with a m.3243A>G mutationSecondary Objectives2. To explore the effect of KH176 on...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON42839

Source
ToetsingOnline

Brief title
The KHENERGY study

Condition

- Other condition

Synonym
dysfunctional energy metabolism, Oxidative Phosphorylation Disorders

Health condition

Mitochondriale aandoeningen

Research involving
Human

Sponsors and support

Primary sponsor: Khondrion B.V.
Source(s) of monetary or material Support: Khondrion B.V.

Intervention

Keyword: Efficacy, KH-176, Mitochondria, proof-of-concept

Outcome measures

Primary outcome

Efficacy:

Change from baseline (defined as the value measured at pre-dose Day -2 and -1)

in:

- Gait parameters: cadence, walking speed, right and left step and stride

lengths, and right and left step times

- NMDAS Score

- Spirometric parameters: Forced Vital Capacity (FVC), Forced Expiratory Volume

in 1 sec (FEV1), Peak Expiratory Flow (PEF), Maximal inspiratory mouth pressure

(MIP), Maximal Expiratory mouth pressure (MEP)

- 30-Seconds sit - stand test: Number of standings

- Handgrip dynamometry: Maximum grip strength

- 6 Minutes Chewing test: VAS pain, VAS tiredness, Rate of Mastication, quality

of movement

- 6 Minutes Walk Test (part of the gait evaluation protocol): Distance and

Distance/minute

- RAND-SF36 score

- Hospital Anxiety and Depression Scale (HAD), supplemented with a Beck Depression Index (BDI)

- Checklist Individual Strenght (CIS)

- Test of Attentional Performance (TAP): Alertness and Mental Flexibility

A Dutch reading task for adults will be performed once as an indication of intelligence

In addition, in each period the following assessemens will be performed:

- an assessment of a Goal Attainment Scale (GAS)

- a diary of Diet and Gastro-Intestinal Functioning

- and a continuous registration of motor activity and sleeping pattern (accelerometer): sleep schedule variability, sleep quantity, sleep quality, overall motor activity (sedentary, low, light, moderate, vigorous activity as a percentage of time)

Secondary outcome

Safety and Tolerability:

• Change from baseline (defined as the value measured at pre-dose assessment on day 1) for body weight, height, BMI, bio-impedance, physical examinations and cardiac echo *

• Change from baseline (defined as the pre-dose assessment on day 1) to each time point for vital signs (supine and standing blood pressure, and heart rate). *

• Change from baseline (defined as the pre-dose assessment on day 1) to each time point for ECG variables *

• Change from baseline (defined as the pre-dose assessment on day 1) to each time point for clinical laboratory variables (clinical chemistry, haematology and urinalysis)

• Treatment-emergent laboratory abnormalities up to Follow-up *

• Treatment-emergent ECG abnormalities up to Follow-up

• Treatment-emergent abnormalities in cardiac monitoring (bedsite/Holter registration)*

• Treatment-emergent AEs up to Follow-up *

• Treatment-emergent AEs leading to discontinuation of study drug *

• Treatment-emergent SAEs up to 28 days after last study drug intake

Pharmacokinetics:

Plasma concentrations of KH176 and its metabolite KH183 will be used to calculate the following parameters derived with non-compartimental analysis: Cmax, tmax, and AUCtau, AUC0-t and time to reach steady state following multiple dose administration.

Pharmacodynamics:

At timepoints indicated in the flow-chart, a blood and urine (24-hour collection) sample will be taken for:

- bioanalysis of Glutathione (GSH/GSSG)

- bioanalysis of FGF21, GDF15 and PRDX1

- a whole metabolome analysis

- Oxidative stress platform analysis

For all parameters and their respective ratio*s a change from baseline to each

timepoint of measurement will be calculated.

Study description

Background summary

This study is a Phase II, Proof of Concept clinical trial with KH176 with the promise to develop a novel treatment for mitochondrial diseases, specifically for patients with a m.3243A>G mutation, resulting in oxidative phosphorylation (OXPHOS) deficiency, for whom currently no clinically relevant treatment is available.

Inherited Mitochondrial OXPHOS disorders are a group of clinically heterogeneous diseases defined by lack of cellular energy production due to defects in the mitochondrial OXPHOS process, affecting ~1/5000 of the population. Several debilitating mitochondrial OXPHOS diseases exist like MELAS, LHON, and Leigh syndrome. The disease course depends on the primary defect, is severely debilitating and progressive, involving dysfunction of neuromuscular and other organ systems and can result in early death. The majority of OXPHOS disorders are caused by isolated or combined (involving other OXPHOS enzyme complexes) OXPHOS Complex I deficiencies.

Despite advances in understanding these disorders, treatment options are extremely limited and only supportive. Therefore, there is an urgent need for novel treatments.
Within all cells of the human body, mitochondria act as a powerhouse - collectively producing energy that is essential for life. When these mitochondria are defective, the result can take the form of a wide range of serious and debilitating illnesses. Signs and symptoms of mitochondrial diseases can include: fatigue, intolerance to exercise, muscle weakness and loss of muscle coordination, heart failure, diabetes, deafness, blindness, stunted growth, and learning disabilities. Leigh Disease, MELAS and LHON belong to the ever-expanding group of mitochondrial diseases.
Mitochondrial diseases refers to disorders whose underlying genetic cause directly or indirectly impairs the composition or function of the 5-complexes forming the oxidative phosphorylation system (OXPHOS), localized within the inner mitochondrial membrane in which the end products of intermediary metabolism are oxidized to generate energy in the form of adenosine

triphosphate (ATP).
Mitochondrial failure is usually the result of genetic defects in either the mitochondrial DNA or the nuclear DNA, but can also be caused by environmental factors, including adverse reactions to certain drugs.
Because of the multifactorial genetic background and the interaction of heteroplasmy, replicative segregation and the threshold effect, mitochondrial diseases present as a very wide range of phenotypes.
Scharfe et al. (2009) established a clinical phenotype catalogue of 174 mitochondrial disease genes associated with 191 diseases and studied the association of diseases and genes. They noted that most mitochondrial disease phenotypes involve several clinical categories including neurologic, metabolic, and gastrointestinal disorders. All these phenotypes, however, share the common feature of being based on inadequate OXPHOS within the mitochondria of the affected tissues.
It has been recognised for more than a decade that cell redox imbalance play a key role in the pathogenesis of many of the clinical manifestations of mitochondrial diseases (Atkuri 2009, Hargreaves 2005, Wallace 2010, Kirkinezos & Moraes, 2001, Scialo, 2016, Koopman 2016). Mitochondrial redox chemistry is of profound importance to the redox balance of the entire cell and is central to the signal transduction of many cellular pathways. For example, disruption of mitochondrial redox circuitry will lead to an increased oxidative stress in the cells (Jones 2006).

1.2 Mitochondrial DNA 3243A>G mutation, MELAS and MIDD and mixed types
Mitochondrial disorders can be caused by mutations of nuclear DNA or mitochondrial DNA. The classification of mitochondrial disorders is hampered by the wide variety in resulting phenotypes, with also a wide variety of clinical syndromes. In this study, the mitochondrial DNA 3243A>G mutation is chosen as the clinical syndromes resulting from this mutation are, although variable, relatively well described. Despite being caused by one mutation, the clinical syndromes resulting from this mutation are still heterogeneous. In Nijmegen about 150 carriers of this mutation are involved in a detailed clinical follow up study.

MELAS (Mitochondrial Epilepsy Lactic Acidosis and Stroke like episodes) is a well-known syndrome that can be caused by the m.3243A>G mutation. The encephalopathy is characterized by epilepsy or dementia, often with additional neurological symptoms like migraine or psychiatric problems. Elevated lactic acid levels are present in most patients. Stroke like episodes may arise at any age (typically before the age of 40 years) and are characterized by the same neurological abnormalities as seen in strokes (hemianopia, hemiparesis, aphasia, hemineglect), associated with additional symptoms like seizures, ataxia, migraine-like headaches, impaired vision or hearing, or disturbances in consciousness. After stroke-like episodes, some patients retain a normal intelligence, whereas others have severe mental and physical disabilities.

MIDD (Maternally Inherited Diabetes and Deafness) is the most common syndrome caused by the m.3243A>G mutation and is a syndrome of early onset sensorineural hearing loss and a defect in insulin secretion. The mean age at onset is 30 years for diabetes and 40 years for sensorineural hearing loss. MIDD typically presents as early onset diabetes without obesity, rapid progression to insulin requirement, high likelyhood of microvascular complications, and family history suspicious of maternal inheritance. Other symptoms associated with the mutation may also occur. These symptoms include: focal segmental glomerulosclerosis, hypertrophic cardiomyopathy, macular retinal dystrophy, short stature, ptosis, myopathy, neuropathy, and also MELAS syndrome.

The study will allow both phenotypes as well as mixed types to be included. Although different in phenotype and clinical syndrome, several symptoms seem a common denominator for all phenotypes. Fatique and tiredness is a clear symptom present in all patients and disturbances in Gait appears to be present in the vast majority.

CPEO (Chronic Progressive External Ophthalmoplegia) is another syndrome caused by the m.3243A>G mutation. It can occur as an isolated ophthalmologic syndrome, which would mean that most assessments done in this trial would not be affected. Therefore, patients with CPEO can only participate if associated with other features, such as abnormal gait.

1.3 Mitochondrial dysfunction and redox/ROS-imbalance
Mitochondria constantly metabolize oxygen thereby producing reactive oxygen species (ROS) as a by-product. These organelles have their own ROS scavenging mechanisms that are required for cell survival. It has been shown, however, that mitochondria produce ROS at a rate higher than their scavenging capacity, resulting in the incomplete metabolism of approximately 1-3% of the consumed oxygen.
The by-products of incomplete oxygen metabolism are superoxide (O_2^-), hydrogen peroxide (H_2O_2), and the hydroxyl radical (OH•).
The formation of superoxide occurs via the transfer of a free electron to molecular oxygen. This reaction occurs at specific sites of the electron transport chain (ETC), which resides in the inner mitochondrial membrane. ETC complexes I (NADH: ubiquinone oxidoreductase) and III (cytochrome bc1 complex) produce most of the superoxide, which is then scavenged by the mitochondrial enzyme manganese superoxide dismutase (MnSOD) to produce H_2O_2.
Since mitochondria do not contain catalase, their only defence against the potentially toxic properties of H_2O_2 is the enzyme glutathione peroxidase (GSPx). GSPx requires reduced glutathione (GSH) as a coenzyme and converts H_2O_2 to water, thus completely detoxifying ROS. However, in the presence of reduced transition metals, H_2O_2 can produce the highly reactive OH•, which can cause extensive damage to DNA, proteins, and lipids.
Two other important radical species are nitric oxide (NO) and peroxynitrite (ONOO*). Mitochondria possess their own nitric oxide synthase (mtNOS) and can produce endogenous NO and ONOO*. Mitochondrial NO decays mainly via ONOO*

formation, ubiquinol oxidation, and reversible binding to cytochrome c oxidase. Under normal conditions, the effects of ROS are counteracted by a variety of antioxidants, by both enzymatic and non-enzymatic mechanisms. Oxidative stress is considered to be the result of an imbalance of two opposing and antagonistic forces, ROS and antioxidants, in which the effects of ROS are more potent than the compensatory capacity of antioxidants. In the case of mitochondrial-derived ROS, superoxide is the first radical produced. It is a highly reactive species and does not diffuse easily throughout the cell. H2O2 is the next key player in mitochondrially derived ROS, as it is the product of superoxide detoxification by MnSOD.
H2O2 is not a free radical by definition because it lacks free electrons. Nevertheless, its role in ROS-mediated damage is extremely significant by virtue of chemical versatility and diffusibility. H2O2 is a substrate in many physiological and abnormal chemical reactions both intracellularly and extracellularly. Due to its small size and relatively benign reactivity, compared to the rest of the ROS, H2O2 can diffuse freely across several cell radii; therefore, it is able to mediate toxic effects far from the site of ROS production. Although by itself H2O2 is not a major source of oxidative damage, it can react with free transition metals via the Fenton reaction (Fe2+ + H2O2 * Fe3+ + OH + OH•), producing the extremely reactive hydroxyl radical. OH• has a very short half-life and reacts with virtually any molecules in close proximity. There is no known scavenger for OH•, but OH• toxicity can be avoided by minimizing the levels of H2O2 and most importantly the availability of free transition metals (e.g. Fe2+, Cu+).
Nitric oxide has also been implicated in ROS mediated damage. NO has a dual personality, which is both beneficial, and detrimental. In some instances, different intracellular levels of NO can mediate diverse effects. For example, physiological levels of NO inhibit the opening of the mitochondrial permeability transition pore (PTP), whereas high NO concentrations promote PTP opening. High levels of NO are cytotoxic, although the exact mechanism associated with this effect is still unclear. It may be involved in inflammatory, neurodegenerative, and cardiovascular pathological processes.

1.4 KH176

Khondrion has identified a class of highly active compounds that are capable of preventing the negative cellular consequences of OXPHOS dysfunction. The most promising lead compound is KH176, a redox modulator, currently under development. KH176 acts as a potent intracellular redox-modulating agent targeting the reactive oxygen species as demonstrated by a number of in vitro and in vivo assays.

Khondrion has recently received Orphan Drug Designation (ODD) status for KH176 to treat Leigh and MELAS syndrome by the European Medicines Agency (EMA) and by the FDA for the treatment of all inherited mitochondrial respiratory chain disorders. Leigh syndrome is actually a pediatric indication and it should be noted that translation of a successful proof of concept in this study to a

pediatric dosing regimen is foreseen.

KH176 underwent pre-clinical testing to ensure its activity and safety before entering clinical studies. Further details can be found in the Investigator*s Brochure. In brief KH176 showed a potent intracellular redoxmodulating capacity to target the reactive oxygen species that have been shown in different in vitro and in vivo models to play an important role in the pathogenesis of the above described conditions. The metabolite KH183 has been shown to have a pharmacological activity that is (in vitro) at least comparable to the activity of KH176.
The genotoxicity studies (Ames test, Chromosomal Aberration test and in vivo Micronucleus test) revealed no mutagenic nor clastogenic effects. Also the safety pharmacology studies showed no relevant KH176-related effects, i.e. for both the CNS rat study and the respiratory rat study, the No Observed Adverse Effect Levels (NOAELs) were indicated to be higher than the highest dose level administered (250 mg/kg/dose BID). For the dog cardiovascular study the NOAEL was set at the highest dose level of 45 mg/kg/dose BID. Moderate adverse effects (vomiting, salivation and tremors in dogs, and histopathological findings in the rat, including phospholipidosis in a broad range of organs (high dose only) and follicular cell hypertrophy in the thyroid glands up to the lowest dose level tested (25 mg/kg/dose BID)) were recorded in the repeated dose toxicity studies. Effects as described in these studies were mainly showing reversibility in the 2 week treatment free period.
A Phase I study in healthy male participants was performed to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics in a Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) design.

KH176 was well tolerated by healthy subjects up to 800 mg as a single dose and up to 400 mg BID for 7 days, with mild to moderate headache as the only possibly drug related adverse event. A dose of 2000 mg, which was administered as a single dose, was however not tolerated. At 2000 mg participants experienced dizziness, nausea and vomiting, oral paraesthesia and psychiatric symptoms (depersonalisation, bradyphrenia and visual hallucinations). Furthermore, telemetry and ECG recordings post-dosing showed a marked QTc prolongation and to a lesser extent a QRS prolongation. To follow up on these findings, an extensive evaluation of the ECG*s and an analysis of the different intervals were performed and a PKPD evaluation was performed to understand the relation of the ECG changes with dose and exposure of KH176. In addition, an in vitro study was conducted to determine the ion channel-blocking profile of KH176 and KH183. The following currents were examined; hERG, Nav1.5 (peak and late), Cav1.2, and KvLQT1/mink. These currents are known to be relevant for conduction and repolarization. The results of this analysis are described in paragraph 1.4.4. dose justification.

The pharmacokinetics of KH176 shows a rapid absorption profile with a time to reach maximum concentrations (Tmax) of around 2 hours. Half live of KH176 was around 9 h for KH176 and around 15 hours for its active metabolite KH183. Which

results in an accumulation factor of 2.5 for KH176 and a factor 2 for KH183 with 100 mg BID dosing in steady state conditions. Steady state conditions were reached within 3 days of dosing.

With increasing dose, the plasma-exposure increased slightly more than proportional, although half-live remained the same across doses, indicating a potential difference in bioavailability with dose. This seems in line with the observation that KH176 is a substrate for Cytochrome P450 3A4 and the efflux pump P-glycoprotein. Saturation of this efflux pump typically results in this type of disproportional increases of plasma concentrations with increasing dose.

The intake of food with the administration of KH176 had no relevant influence on the pharmacokinetics of KH176 and KH183 and therefore administration of KH176 in this study will be done just prior to a meal for compliance reasons.

Pharmacodynamic evalutions in these healthy participants did not reveal any relevant signs related to mitochondrial functioning, however, it should be noted that the lack of impairment in mitochondrial functioning in this population hampers any conclusions.

Study objective

Objectives:
Primary Objective
1. To evaluate the effect of KH176 on gait (Gaitrite®) parameters: step-length and variability in step-time and step-width in patients with a m.3243A>G mutation

Secondary Objectives
2. To explore the effect of KH176 on biomarkers of mitochondrial functioning in patients with an m.3243A>G mutation.
3. To explore the effect of KH176 on functional clinical measures of mitochondrial disease in patients with an m.3243A>G mutation.
4. To investigate the tolerability and safety of KH176 following 28 days of oral administration to patients with an m.3243A>G mutation.
5. To investigate the multiple dose pharmacokinetics of KH176 following 28 days of oral administration in patients with an m.3243A>G mutation.

Study design

Methodology:
The trial will be a double blind, randomized, placebo-controlled, single-centre, two-way cross-over trial. Twenty patients, with a confirmed mitochondrial DNA tRNALeu(UUR) m.3243A>G mutation and with clinical signs of mitochondrial disease, will be randomized over 2 groups (active or placebo first). After a screening period and a training session, each group will have 2

dosing periods of 28 days, with a washout period of at least 28 days in between. On these occasions, patients will receive 100 mg KH176 twice daily (treatment A) or a matching placebo (treatment B) twice daily for 28 days.

Below the design of the trial has been presented
Week
Group -3 - -1 -1 1-4 5-8 9-12 14
I Screening Training Treatment A Washout Treatment B Follow up
II Screening Training Treatment B Washout Treatment A Follow up

Clinical assessments will be performed once in a training session prior to baseline, at baseline and in week 4 post dosing during each treatment phase (A and B), details can be found in the flow chart (paragraph 3.2). Testing conditions and circumstances, with respect to timing of the assesments, hospitilization and meals, will be standardized for each assessement period. Furthermore, assessments of biomarkers for mitochondrial functioning, pharmacokinetics and specific safety assessments will be performed weekly according to the time points indicated in the flowchart.
In each treatment phase (A and B), patients will be hospitalized for the baseline assessments and for safety monitoring for the first 3 days of treatment (Day*s 1, 2 completely and Day 3 until discharge in the afternoon). As an interim evaluation for safety monitoring, and as a part of the pharmacokinetic evaluation, 3 plasma samples will be taken on Day 1 after the morning dose, shipped and analysed immediately, with the aim to have results prior to discharge on Day 3. The results will not be reported to the study team (as the study team should remain blinded), but only the conclusion whether or not the safety treshold (1000 ng/mL) was exceeded will be reported. The objective of this interim evaluation is to compare plasma exposure in these patients with the plasma exposure of KH176 and its metabolite KH183 in healthy participants. In case the treshold of 1000 ng/mL is exceeded, investigators and sponsor will discuss options for continuation, including a dose reduction, taking all safety and pharmacokinetic results into account.
For logistical reasons of the intense safety monitoring on Days 1 to 3 participants will be scheduled in groups of maximally 3 participants. Participants will be randomized in such a way that no more than 2 participants will have active treatment at the same time during those first 3 days of intense monitoring.

Intervention

Investigational Drug:
Treatment A: Twice daily dosing of 100 mg (100 mg BID/ 200 mg per day). KH176 will be administered as an oral liquid, just before a meal.
Comparative Drug:

Treatment B: Twice daily dosing of a matching placebo as an oral liquid, just before a meal.

Study burden and risks

Side effects/risks as described in the subjects Information

When we administered KH176 in very high doses (1 x 800 mg or 2 x daily 400 mg) in healthy men, changes were seen on the heart tracing (ECG). It concerns a change in the conduction of the electric stimulation of the heart. More specifically, an extension of the so-called QT-time (the time between the control of the contraction of the heart to the recovery phase of the conduction) was observed. This change will not be noticed by the patient. However, if this change is larger (the QT interval is longer), this could lead to arrhythmia. The arrhythmia that can occur if you receive too high of a dose can be fatal if they are not observed or treated.

There are drugs that are prescribed by doctors that affect the conduction of the heart, such as anti-psychotic, some antidepressants and anti-vomiting medication. In high doses, these frequently prescribed drugs can also lead to arrhythmia. Persons with a sensitive heart muscle, for example, after a myocardial infarct, are hereby more sensitive to the onset of arrhythmia of the heart.

Despite the fact that we will investigate a lower dose of KH176 in this study and we estimate the risk is very low for these changes, we will take strict security measures to prevent KH176 to cause arrhythmia. Below are the steps we have taken:
- You will receive 2 x daily 100 mg KH176. To illustrate: The first changes in the conduction of the heart were observed at 2 x 400 mg per day.
- We know that patients with abnormal cardiac muscle are more sensitive to cardiac arrhythmia. Therefore only in this study m.3243A> G carriers participate with no or very mild abnormalities of the heart muscle. This will be assessed on the basis of your medical information. If necessary, we will perform an additional cycling test to assess the function of your heart during exercise.
- The transformation of a normal conduction to arrhythmia is gradual. If we see that your ECG shows any change, we will monitor you extra well and possibly stop the medication so that the conduction can recover. This is to prevent you from getting heart arrhythmia. You will be at the medium or intensive care during the first period of treatment to ensure maximum monitoring.
- We determine the amount of KH176 in your blood after the first dose to see if you have an amount of KH176 in your blood that we would expect
- We will make multiple heart movies during the entire treatment period, a few per day during the first doses and subsequently 1 x weekly at home
- You will receive a box (Holter) to take home on which your heart rhythm is registered.

KH176 is ingested only by 30 healthy men for 7 days. They did not give more complaints than healthy men who received a placebo. The study drug could have side effects which are unknown.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Males and females aged 18 years or older at screening
2. Ability and willingness to sign the Informed Consent Form prior to screening evaluations.
3. Confirmed mitochondrial DNA tRNALeu(UUR) m.3243A>G mutation
4. Heteroplasmy level as measured in urine >= 20 %.
5. Body Mass Index (BMI) 18.0-30.0 kg/m2 (extremes included) at screening
6. Clinical evidence of mitochondrial disease, positive NMDAS score (including but not limited to MELAS, MIDD and mixed types). CPEO patients with signs restricted to the eye only are not

considered eligible.
7. Disease appropriate physical and mental health as established by medical history, physical examination, electrocardiogram (ECG) and vital signs recording, and results of biochemistry, hematology and urinalysis testing within 3 weeks prior to the first dose as judged by the Investigator.
8. Appropriate cardiac functioning as assessed by medical history, ECG and Echo, evaluated by a cardiologist.
9. Able to comply with the study requirements, including exercise testing and swallowing study medication
10. Willingness to use adequate contraceptive methods (male and female) and negative urine pregnancy test (females) at screening and first baseline assessment.
11. Able and willing to refrain from the use of (multi)vitamins, co-enzyme Q10, Vitamine E, riboflavin, and anti-oxidant supplements (and idebenone/EPI-743), as well as any medication negatively influencing mitochondrial functioning (including but not limited to valproic acid, glitazones, statins, anti-virals, amiodarone, and NSAID*s) as well as any strong Cytochrome P450 inhibitors (all *conazoles-anti-fungals*, HIV antivirals, grapefruit) and strong Cytochrome P450 inducers (a.o. carbamazepine, phenobarbital, phenytoin, rifampicine, St Johns wort, pioglitazone, troglitazone) as well as any medication known to affect cardiac repolarization (all anti-psychotics, several anti-depressants: nor/amytriptilline, fluoxetine, anti-emetics: domperidone (motilium) granisetron, ondansetron).

Exclusion criteria

1. Motoric abnormalities other than related to the mitochondrial disease interfering with the outcome parameters.
2. CPEO patients with clinical signs and symptoms restricted to the eye only
3. Heteroplasmy level as measured in urine < 20%
4. Poor nutritional state as judged by the investigator
5. Body Mass Index (BMI) not within 18.0-30.0 kg/m2 at screening.
6. History of cancer
7. Surgery or active illness of gastro-intestinal tract that might interfere with absorption.
8. Participation in a trial of an investigational product in the preceding 3 months prior to the first dose or during this trial.
9. Positive drug, alcohol or cotinine test at screening and/or admission (Day 1 of the first dosing period).
10. Clinically relevant abnormal laboratory, ECG recordings, cardiac echo (within 1 year prior to screening), vital signs or physical or mental findings at screening as judged by the Investigator.
11. Clinically relevant abnormal ECG or cardiac functioning as judged by a cardiologist.
12. ECG: QTc > 450 ms, abnormal T-wave
13. Symptomatic heart failure or signs of ischemic heart disease
14. Left Ventricular Ejaction Fraction <45%
15. History or family history of congenital Long QT syndrome
16. Increased or decreased potassium (local laboratory normal range)
17. Inadequate contraception use, pregnancy or breast feeding (females)

18. Clinically significant presence or history of allergy as judged by the Investigator.
19. History of hypersensitivity or idiosyncrasy to any of the components of the investigational drug.
20. Within 4 weeks prior to dosing, the use of (multi)vitamins, co-enzyme Q10, Vitamine E, riboflavin, and anti-oxidant supplements (and idebenone/EPI-743), as well as any medication negatively influencing mitochondrial functioning (including but not limited to valproic acid, glitazones, statins, anti-virals, amiodarone, and NSAID*s) as well as any strong Cytochrome P450 inhibitors (all *conazoles-anti-fungals*, HIV antivirals, grapefruit) and strong Cytochrome P450 inducers (a.o. carbamazepine, phenobarbital, phenytoin, rifampicine, St Johns wort, pioglitazone, troglitazone) as well as any medication known to affect cardiac repolarization (all anti-psychotics, several anti-depressants: nor/amytriptilline, fluoxetine, anti-emetics: domperidone (motilium) granisetron, ondansetron)

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	21-09-2016
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO

Date:	18-08-2016
Application type:	First submission

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-09-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-03-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-001696-79-NL
CCMO	NL57767.091.16