A Phase IIb double-blind, randomised, placebo-controlled, multi-centre, confirmative three-way cross-over study on cognitive function with two doses of KH176 in subjects with a genetically confirmed mitochondrial DNA tRNALeu(UUR) m.3243A>G mutation.

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To evaluate the effect of KH176 during a 4 week treatment period on the attention domain score of cognitive functioning, as assessed by the visual identification test of the Cogstate computerised cognitive testing battery.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON49029

Source
ToetsingOnline

Brief title
KHENERGYZE

Condition

- Other condition
- Congenital and hereditary disorders NEC
- Neurological disorders NEC

Synonym
metabolic diseases

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: Cognitive function, KH176-202, Mitochondrial Diseases, Nutritional and Metabolic Diseases

Outcome measures

Primary outcome

Changes from baseline (measured at pre-dose Day 1) to end of treatment (Day 28

of each treatment period) in:

• the attention domain score of cognitive functioning, as assessed by the

visual identification test of the Cogstate computerised cognitive testing

battery

Secondary outcome

Changes from baseline (measured at pre-dose Day 1) to end of treatment (Day 28

of each treatment period) in the following domains of cognitive functioning:

• executive

• working memory

• psychomotor function

• visual learning

• verbal learning

Changes from baseline (measured at pre-dose Day 1) to end of treatment (Day 28 of each treatment period) in:

• Test of Attentional Performance (TAP): Alertness

• Hospital Anxiety and Depression Scale (HADS), supplemented with a Beck Depression Index (BDI)

• NMDAS Score

• number of headache days, intensity and duration and use of medication to relieve headache

• hearing (PTA)

• smell identification test (UPSIT)

• Cognitive Failure Questionnaire (CFQ)

• Neuro-QoL Fatigue Short Form

Study description

Background summary

Mitochondrial diseases, estimated prevalence 1 in 4,300 adults, is caused by pathogenic mutations in genes finally encoding for mitochondrial proteins of the various enzyme complexes of the OXPHOS. Among these mutations, the 3243A>G nucleotide change in the mitochondrially encoded transfer RNALeu(UUR) leucine 1 gene (MT TL 1) is the most prevalent one. When mitochondria are defective, this may result in a wide range of serious and debilitating illnesses, especially in energy-demanding tissues like the muscles and the brain. Signs and symptoms of mitochondrial diseases can therefore include a variety of symptoms like fatigue, exercise intolerance, muscle weakness and ataxia, heart failure, deafness, blindness, stunted growth, and cognitive dysfunction including learning disabilities.

Despite advances in the understanding of mitochondrial disorders, treatment options are extremely limited and, to date, largely supportive. Therefore,

there is an urgent need for novel treatments. KH176, a new active pharmaceutical ingredient (API), is an orally bio-available small molecule under development for the treatment of these disorders. 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. A previous phase II study showed positive effects of KH176 on alertness and mood. The current study will further evaluate the effect of KH176 in various cognitive domains and evaluate the effect of different doses of KH176.

In view of the growing recognition of the importance of mitochondrial function in maintaining cognitive processes in the brain, as well as the understanding of the safety profile and pharmacokinetics of KH176 following previous clinical studies, a more detailed study is indicated of the effects of KH176 in various cognitive domains, using the confirmed safe and well-tolerated KH176 dose of 100 mg bid, as well as a lower dose of 50 mg bid. The primary objective is an evaluation of KH176 in the attention domain of cognitive functioning, as assessed by the visual identification test score of the Cogstate computerised cognitive testing battery.

Study objective

To evaluate the effect of KH176 during a 4 week treatment period on the attention domain score of cognitive functioning, as assessed by the visual identification test of the Cogstate computerised cognitive testing battery.

Study design

A Phase IIb double-blind, randomised, placebo-controlled, multi-centre, confirmative three-way cross-over study

This is a double-blind, randomised, placebo-controlled, multi-centre, confirmative three-way cross-over study in subjects with a genetically confirmed mitochondrial DNA tRNALeu(UUR) m.3243A>G mutation. Subjects will be receiving three courses of 28 days twice daily treatment with KH176 100 mg, KH176 50 mg and Placebo, in randomised sequences and separated by 2-week washout periods. A final follow-up visit is scheduled 4 weeks after the intake of the last dose of the third treatment period.

Intervention

Subjects will be receiving three courses of 28 days twice daily treatment with KH176 100 mg, KH176 50 mg and Placebo, in randomised sequences and separated by 2-week washout periods.

Study burden and risks

Risks associated with study participation are the potential for adverse reactions to study medication, concomitant medication, invasive study procedures like blood draws and risks related to the process of undergoing ECG/Holter registrations and testing of senses. There are no risks associated with the conduct of the tests/questionnaires, but the patients might feel frustrated during the tests and the tests might show progression of the disease, which may be upsetting.
The most common adverse events associated with KH176 seen in clinical studies are abnormal heart rate and in very high doses (20 times higher than used in this study) dizziness and a strange sensation around the mouth (e.g tingling sensation, numbness). Administration of the doses used in this study (50 mg KH176 BID and 100mg KH176 BID) have been generally safe and well tolerated in previous studies.
This study is expected to benefit the patient population with this mitochondrial disease by furthering the development of a new therapy and providing more information to those studying potential treatments for mitochondrial diseases.

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 provide written Informed Consent prior to screening evaluations.
3. Confirmed mitochondrial DNA tRNALeu(UUR) m.3243A>G mutation (heteroplasmy >= 20%, urinary epithelial cells).
4. Positive NMDAS score >10 at Screening.
5. Three or more clinical features, with no other causative unifying diagnosis, found to commonly occur in subjects with a m.3243A>G mutation:
- Deafness
- Developmental delay
- Diabetes Mellitus
- Epilepsy
- Gastrointestinal complaints
- Progressive External Ophtalmoplegia (PEO) and retinopathy
- Ataxia
- Exercise intolerance
- Fatigue
- Migraine (with or without aura), specified by at least five attacks fulfilling diagnostic criteria B-D:
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics:
1. unilateral location
2. pulsating quality
3. moderate or severe pain intensity
4. aggravation or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache at least one of the following:
1. nausea and/or vomiting
2. photophobia and phonophobia
6. Attentional dysfunction score (Cogstate Identification test) >= 0.2 standard deviations poorer than healthy controls at Screening.
7. Disease appropriate physical and mental health as established at Screening by medical history, physical examination, ECG and vital signs recording, and results of clinical chemistry and haematology testing as judged by the investigator.
8. Objectified Left Ventricular Ejection Fraction (LVEF) >=45% (echocardiography, or otherwise).

9. Left Ventricular (LV) wall thickness <=15 mm.
10. Left atrium dilatation <= 40 mL/m2.
Note: No need to test LV parameters (criteria #8, #9, #10) if favorable echocardiography (or otherwise) results dated less than 6 months prior to Screening are available.
11. Women of childbearing potential must be willing to use adequate contraceptive methods during the entire study, i.e., a hormonal contraceptive method (pill, vaginal ring, patch, implant, injectable, hormone-medicated intrauterine device) or an intrauterine device. Sexual abstinence is an acceptable contraceptive method only as true abstinence: when this is in line with the preferred and usual lifestyle of the patient. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].
Note 1: Natural family planning methods, female condom, cervical cap or diaphragm are not considered adequate contraceptive methods in the context of this study.
Note 2: To be considered not of childbearing potential, potential female subjects must be post-menopausal for at least two years, or have been surgically sterilised (bilateral tubal ligation, hysterectomy or bilateral oophorectomy) for at least 6 months prior to Screening.
Note 3: KH176 has been shown non-genotoxic judged from the Ames test, Chromosomal Aberration test and in vivo Micronucleus test. Moreover, appreciable systemic exposure from the exposure to (~2.5 mL) semen is extremely unlikely. However, until reproductive toxicology studies have confirmed that KH176 does not adversely affect normal reproduction in adult males and females, as well as causing developmental toxicity in the offspring, the following contraceptive precautions must be adhered to:
• male subjects with female partners of childbearing potential must be willing to use condoms during the entire study.
• female partners of childbearing potential of male subjects must be willing to use adequate contraceptive methods during the entire study, i.e., a hormonal contraceptive method (pill, vaginal ring, patch, implant, injectable, hormone-medicated intrauterine device) or an intrauterine device.
12. Able to comply with the study requirements, including swallowing study medication.

Exclusion criteria

1. Surgery of gastro-intestinal tract that might interfere with absorption.
2. Treatment with an investigational product within 3 months or 5 times the half-life of the investigational product (whichever is longer) prior to the first dose of the study medication.
3. Documented history of ventricular tachycardia (HR>110 beats/min).
4. History of acute heart failure, (family) history of unexplained syncope or congenital long and short QT syndrome or sudden death.

5. Clinically relevant abnormal laboratory, vital signs or physical or mental health:
a) Aspartate aminotransferase (ASAT) or alanine aminotransferase (ALAT) > 3 x upper limit of normal (ULN), or bilirubin > 3 x ULN at screening. If a patient has ASAT or ALAT > 3 x ULN but < 3.5 x ULN, re-assessment is allowed at the investigator*s discretion.
b) Estimated glomerular filtration rate <= 60 mL/min according to the CKD-EPI formula at screening.
c) Systolic Bloodpressure > 150 mmHg at screening or baseline.
d) All other clinically relevant parameters at screening or baseline as judged by the Investigator.
6. Clinically relevant abnormal ECG or cardiac functioning, defined as ST-segment elevation >1 mm in I, II, III, aVL, aVF ,V3 ,V4 ,V5 ,V6; >2 mm in V1, V2; QTc >450 ms for male subjects; QTc > 470ms for female subjects (local, machine read), T-top inversion in >1 consecutive lead.
7. Serum Hyper-potassium (> 5.0 mEq/L).
8. Serum Hypo-potassium (< 3.5 mEq/L).
9. History of ischemic heart disease.
10. Symptomatic heart failure.
11. Clinically relevant aorta and/or mitralis valvular defect as judged by the investigator.
12. Pregnancy or breast feeding (females).
13. Poor nutritional state as judged by the investigator.
14. History of hypersensitivity or idiosyncrasy to any of the components of the investigational drug.
15. Medical history of drug abuse (illegal drugs such as cannabinoids, amphetamines, cocaine, opiates or problematic use of prescription drugs such as benzodiazepines, opiates).
16. The use of any of the following medication and/or supplements within 4 weeks or 5 times the half-life (whichever is longer) prior to the first dosing of the study medication:
a. (multi)vitamins, co-enzyme Q10, Vitamine E, riboflavin, and anti-oxidant supplements (including, but not limited to idebenone/EPI-743, mitoQ); unless stable for at least one month before first dosing and remaining stable throughout the study.
b. any medication negatively influencing mitochondrial functioning (including but not limited to valproic acid, glitazones, statins, anti-virals, amiodarone, and non-steroidal anti-inflammatory drugs (NSAIDs)), unless stable for at least one month before first dosing and remaining stable throughout the study. Note: thus, mitoQ and any medication negatively influencing mitochondrial functioning are allowed as long as the dose has been stable for at least one month prior to first dosing and remains stable throughout the study.
c. any strong Cytochrome P450 (CYP)3A4 inhibitors (all *conazoles-anti-fungals*, HIV antivirals, grapefruit).
d. strong CYP3A4 inducers (including HIV antivirals, carbamazepine, phenobarbital, phenytoin, rifampicine, St Johns wort, pioglitazone, troglitazone).

e. any medication known to affect cardiac repolarisation, unless the QTc interval at screening is normal during stable treatment (all anti-psychotics, several anti-depressants, e.g. nor/amytriptiline, fluoxetine, anti-emetics: domperidone (motilium) granisetron, ondansetron). For a complete list see https://crediblemeds.org.
f. any medication metabolised by CYP with a narrow therapeutical width.
For reference (Germany and United Kingdom): drug interaction table of Indiana University (http://medicine.iupui.edu/clinpharm/ddis/clinical-table/). For reference (The Netherlands): KNMP Kennisbank (https://www.knmp.nl/producten/knmp-kennisbank/inloggen-knmp-kennisbank.

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:	Recruitment stopped
Start date (anticipated):	02-01-2020
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine

Ethics review

Approved WMO

Date:	31-07-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-10-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-12-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-04-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-05-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-10-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-12-2020
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	EUCTR2019-000599-40-NL
CCMO	NL68866.091.19

Study results

Date completed: 17-12-2020

Actual enrolment: 9

Summary results
Trial is onging in other countries