A randomized placebo controlled, double-blind phase II study to explore the safety, efficacy and pharmacokinetics of sonlicromanol in children with genetically confirmed mitochondrial disease.

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Primary Objective:To evaluate the effect of sonlicromanol on motor symptom severity in children with genetically confirmed mitochondrial disease affecting oxidative phosphorylation during a 6 month treatment period (GMFM).

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

Summary

ID

NL-OMON54867

Source
ToetsingOnline

Brief title
KHENERGYC (KH176-204)

Condition

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

Synonym
MELAS spectrum diseases, Metabolic diseases

Health condition

Mitochondriële aandoeningen

Research involving
Human

Sponsors and support

Primary sponsor: Khondrion B.V.
Source(s) of monetary or material Support: Europees Fonds voor Regionale Ontwikkeling (EFRO); Khondrion B.V. (Sponsor)

Intervention

Keyword: Mitochondrial Disease, Pediatric study, Randomized double blind study, Sonlicromanol

Outcome measures

Primary outcome

Change from baseline (measured at pre-dose Day 1) to end of treatment in the

Gross Motor Function Measure (GMFM).

Secondary outcome

Secondary endpoints:

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

1. 9 Hole Peg Test

2. 10 meters walk and run test

3. Modified Tardieu Scale for spasticity

4. Barry-Albright Dystonia scale (BAD)

5. Scale for the Assessment and Rating of Ataxia (SARA)

6. Paediatric Evaluation of Disability Inventory Computer Adaptive Test

(PEDI-CAT)

7. International Paediatric Mitochondrial Disease Scale (IPMDS) (total and for

each domain and individual item).

8. Zarit-12 Burden scale

9. NeuroQL-SF

10. Clinician-scored global impression of change (7-point Likert scale)

11. Patient/Caregiver scored global impression of change (7-point Likert scale)

12. Patient/Caregiver scored impression of change on patient-identified 3 most bothersome symptoms caused by mitochondrial disease (7-point Likert scale)

13. Growth and Weight

Other endpoints:

14. Proportion of responders on Clinician-scored and Patient/Caregiver scored global impression of change (defined as patients with any improvement from baseline)

15. Pharmacokinetic endpoints (Tmax, Cmax, Ctrough, AUCinf, AUCtau, T1/2, and CL/F)

16. Safety / tolerability endpoints (TEAEs, change from baseline in vital signs (SBP, DBP, PR), ECG and laboratory parameters)

17. Metabolomics and biomarkers in plasma and urine

18. Overall survival

19. Palatability / acceptability endpoints: children self-report scales; parent report

20. EQ-5D-Y (proxy version 1), Health Utilities Index (HUI)

Study description

Background summary

Mitochondrial Diseases (MD) are rare progressive, multi-system, often early onset and fatal disorders affecting both children and adults. 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. Sonlicromanol (KH176) is an orally bio-available small molecule under development for the treatment of these disorders. The current study will explore the pharmacokinetics, safety and efficacy of sonlicromanol in children (from birth to 17 years) with genetically confirmed mitochondrial disease of which the gene defect is known to decrease one or more oxidative phosphorylation system enzymes and who suffer from motor symptoms.

Study objective

Primary Objective:
To evaluate the effect of sonlicromanol on motor symptom severity in children with genetically confirmed mitochondrial disease affecting oxidative phosphorylation during a 6 month treatment period (GMFM).

Study design

The trial consists of 2 phases, with the main phase being a randomized placebo controlled, double-blind, phase II parallel group study to explore the efficacy and safety of sonlicromanol in twenty-four (24) children with mitochondrial disease and motor symptoms,.

The first phase is an adaptive PK study with 4 days treatment (to expected steady state in most subjects) in the following age-groups: birth - 1 year, 1-2 years, 2- 6 years, 6-12 years, and 12 - 17 years. An age group should have at least 3 subjects before being analysed. Subjects will take 4 days of open-label sonlicromanol orally at the anticipated adult-equivalent dose. After completion of enrolment in an age group, the PK data from that age group will be analysed to confirm the adult-equivalent dose that will be used thereafter in the second phase of the trial. Older age groups will be studied before younger age groups.

In the second phase subjects will be randomized (by age group) over 2 groups. Group 1 will receive an adult-equivalent dose of sonlicromanol twice daily orally for 26 weeks. Group 2 will receive matching placebo twice daily for 26 weeks. A final follow-up visit is scheduled 2 weeks after the intake of the last dose of the treatment period.

Duration of Subject Participation:
The overall study duration of the trial for a eligible subject is estimated to be approximately 7 months, consisting of up to 4 weeks screening, 26 weeks (6

months) of treatment and 2 week post-treatment follow-up. At the end of the study treatment all participants will be offered to continue treatment with sonlicromanol during a open label extension (OLE) trial for 12 months.

Intervention

Sonlicromanol in paediatric-equivalent oral dose (4 days) and subsequently sonlicromanol in paediatric-equivalent oral dose or placebo b.i.d. (for 26 weeks). According to Physiologically Based Pharmaciokinetics Modelling (PBPK modelling), the following fixed doses per age group are expected to result in similar exposures to adults with a mitochondrial disease dosed at 100 mg BID (i.e. the PED):

Population Dose (mg)
Neonates (0-28 days) 2
Infants (1-2.5 months) 4
Infants (2.5-12 months) 12
Toddlers (1-2 years) 23
Young Children (2-6 years) 33
Middle-Aged Children (6-12 Years) 55
Adolescents (12-17 years) 80

The dose may be changed in each age group as appropriate based on the results of the adaptive PK period.

Study burden and risks

Risks associated with participating in this study include the possibility of adverse reactions to the study medication, concomitant medication, invasive examination procedures such as blood draws, and the risks associated with undergoing various study procedures such as the ECG registrations and sensory testing, the risks of the latter being considered very low. There are no risks associated with the execution of the various tests / questionnaires. However, the participant may feel frustrated during the tests and the tests may show progression (worsening) of the disease, which can be disturbing. The most common adverse events associated with KH176 observed in clinical studies are abnormal heart rate and at very high doses exposures (approximately 10-20 times higher than used intended in this study), dizziness and strange feeling around the mouth (e.g. tingling, numbness) and QTc interval prolongation. Administration of the dose used in this study (max. 100mg KH176 twice daily) was generally safe and well tolerated in previous studies. This study is expected to benefit the patient population of these mitochondrial disorders by promoting the development of a new therapy and providing more information to people investigating potential treatments for mitochondrial diseases.

Contacts

Public
Khondrion B.V.

Philips van Leydenlaan 15
Nijmegen 6525EX
NL
Scientific
Khondrion B.V.

Philips van Leydenlaan 15
Nijmegen 6525EX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Age between birth and 17 years
2. Genetically confirmed mitochondrial disease, of which the gene defect is known to decrease one or more oxidative phosphorylation system enzymes and who suffer from motor symptoms, based on investigator judgement.
3. Abnormal gross motor function and/or presence of at least one clinically significant motor symptom (ataxia, dystonia, chorea and/or spasticity) based on investigator judgement
4. Before enrollment in the adaptive PK phase and before randomization into the double-blind placebo-controlled phase: GMFM-88 Total Score <=96%
5. Before enrollment in the adaptive PK phase and before randomization into the double-blind placebo-controlled phase: IMPDS Score >=10

6. Stable disease symptoms since the previous routine control visit (consistent with a score of *stable* on the item *disease course since previous IPMDS* of the IPMDS) in the opinion of the investigator.
7. Written informed (patient/parental/caregiver) assent/consent, able and willing to comply with the study requirements of the study protocol.
8. Women of childbearing potential must be willing to use highly effective contraceptive methods during the entire study, i.e. combined (estrogen and progestogen containing) oral, intravaginal or transdermal hormonal contraception associated with inhibition of ovulation; oral, injectable, or or implantable progestogen-only hormonal contraception associated with inhibition of ovulation; use of an intrauterine device; an intrauterine hormone releasing system, bilateral tubal occlusion and vasectomy of the partner. Any hormonal contraception method must be supplemented with a barrier method (preferably male condom). Vasectomised partner is considered a highly effective birth control method provided that partner is the sole sexual partner of the subject and that the vasectomised partner has received medical assessment of the surgical success. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. Reliability of sexual abstinence needs to be evaluated in in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. 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 have been surgically sterilized (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.

Exclusion criteria

1. Surgery of the gastro-intestinal tract with removal of piece(s) of stomach, duodenum or jejunum that might interfere with absorption. Feeding through gastrostomy tube is however allowed.
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. Clinically relevant cardiovascular disease or risk factors for arrythmia:
a. Abnormal ECG (including QTcF exceeding the 95th percentile for the age- and sex-dependent QTc interval (https://www.qtcalculator.org) and/or abnormal structural of functional 2D ECHO
b. Systolic Blood Pressure (SBP) above the 95th percentile for the sex, age group and height percentile at screening or baseline on single measurement (see appendix 1)
c. History of acute or chronic heart failure, (family history of unexplained syncope or congenital long and short QT syndrome or sudden death
d. Hyperkalemia or hypokalemia; hypomagnesemia or hypermagnesemia; hypocalcemia or hypercalcemia (local laboratory normal values; to be judged by investgator)
4. Clinically relevant abnormal laboratory results:
a. Aspartate aminotransferase (ASAT) or alanine aminotransferase (ALAT) > 3 times upper limit of normal (ULN), or bilirubin > 3 x ULN. 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 below age-appropriate limits (according to the formula: 40.9* ((1.8 / Cystatine C)0.93):
< 2 months: < 25 ml/min/1.73 m2
2 months to 1 year: < 35 ml/min/1.73 m2
> 1 year: < 60 ml/min/1.73 m2
c. All other clinically relevant parameters at screening or baseline as judged by the investigator.
5. History of hypersensitivity or idiosyncrasy to any of the components of the investigational product.
6. Medical history of drug abuse (illegal drugs such as cannabinoids, amphetamines, cocaine, opiates or problematic use of prescription drugs such as benzodiazepines, opiates).
7. 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, Vitamin E, riboflavin, and antioxidant 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, rifampicin, St. John*s wort, pioglitazone, troglitazone).
e. any medication known to affect cardiac repolarisation, unless the QTc interval at screening is normal during stable treatment for a period of two weeks, or 5 half-lives of the medication and its major metabolite(s), whichever period is the shortest (all anti-psychotics, several anti-depressants: nor/amytriptyline, fluoxetine, anti-emetics: domperidone (Motilium®), granisetron, ondansetron).
f. any medication metabolised by CYP3A4 with a narrow therapeutic width.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	26-03-2021
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Sonlicromanol
Generic name:	Sonlicromanol

Ethics review

Approved WMO Date:	20-10-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-01-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-05-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-06-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-07-2021
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	EUCTR2020-003124-16-NL
CCMO	NL75221.091.20