ISRCTN43372293 https://doi.org/10.1186/ISRCTN43372293

A dose-escalating clinical trial with KH176

Submission date	Recruitment status	[_] Prospectively registered
23/06/2017	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
27/06/2017	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
31/07/2018	Genetic Diseases	

Plain English summary of protocol

Background and study aims
Mitochondrial diseases are rare progressive, multi-system, often early fatal disorders affecting both children and adults. KH176 is a new drug currently under development for the treatment of inherited mitochondrial diseases, including MELAS (Mitochondrial Encephalomyopathy, Lactic acidosis, and Stroke-like episodes), Leigh's Disease and LHON (Leber's Hereditary Optic Neuropathy). Having been found to be safe in pre-clinical tests, the aim of this study is to assess the safety, tolerability (side effects) and pharmacokinetic and pharmacodynamic characteristics of KH176 in healthy male volunteers. Pharmacodynamics is the study of how a drug affects the body, whereas pharmacokinetics is the study of how the body affects the drug.

Who can participate?
Healthy adult male volunteers

What does the study involve?
The study involves two parts. For the first part, participants are randomly allocated to receive either KH176 (at six different doses) or placebo (dummy drug), with one week in between each dose. Pharmacokinetic, pharmacodynamic and safety tests take place before dosing and on the day of dosing up to 24 hours after dosing and at follow-up one week later. For the second part participants are randomly allocated to receive either KH176 (at three different doses) or placebo twice a day for 7 days. Pharmacokinetic, pharmacodynamic and safety tests take place before dosing and at multiple days after dosing, and at follow-up one week after the last dose is given.

What are the possible benefits and risks of participating?
Not provided at time of registration

Where is the study run from?
Drug Research Unit Genth (Belgium)

When is the study starting and how long is it expected to run for?
April 2015 to October 2015

Who is funding the study?
Khondrion (Netherlands)

Who is the main contact?
Dr Edwin Spaans

Contact information

Type(s)
Public

Contact name
Dr Edwin Spaans

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT02544217

Protocol serial number
KH176-101

Study information

Scientific Title
A Phase I, randomized, double-blind, placebo-controlled, dose-escalating clinical trial with KH176

Study objectives
Mitochondrial diseases are rare progressive, multi-system, often early fatal disorders affecting both children and adults. KH176 is a novel chemical entity currently under development for the treatment of inherited mitochondrial diseases, including Mitochondrial Encephalomyopathy, Lactic acidosis, and Stroke-like episodes (MELAS), Leigh's Disease and Leber's Hereditary Optic Neuropathy (LHON). KH176 is a potent intracellular redox modulating agent targeting the reactive oxygen species which are important in the pathogenesis of disorders of mitochondrial oxidative phosphorylation. After demonstrating a favourable safety profile in the pre-clinical testing, the safety, tolerability and pharmacokinetic and pharmacodynamic characteristics of the compound will now be evaluated in healthy male subjects in this trial.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Comité voor Medische Ethiek (Committee for Medical Ethics), 05/06/2015, ref: 2015/0508

Study design
Randomized crossover double-blind placebo-controlled single-center trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Mitochondrial disease

Interventions
For the single-ascending dose (SAD) part, a partial alternating crossover design was applied. The effects of 6 single orally administered ascending doses of KH176 of 10, 30, 100, 300, 800 and 2000 mg or placebo were investigated alternately dosed to two groups of 6 healthy male subjects. For each dose, 4 subjects received active treatment and 2 subjects received placebo, with one week in between dosing (thus resulting in a 2-week washout period for each subject in an alternating cross-over design). Pharmacokinetic, pharmacodynamic and safety evaluations took place prior to dosing and on the day of dosing up to 24 hours post dosing and at follow-up one week later.

For the multiple-ascending dose (MAD) part a sequential group design was applied. In the MAD part 3 multiple ascending doses of KH176 of 100, 200 and 400 mg b.i.d. were administered for 7 days to 3 sequential groups of 6 healthy male subjects each. For each dose 4 subjects received active treatment and 2 subjects received placebo. In the MAD part, pharmacokinetic, pharmacodynamic and safety evaluations took place prior to dosing and at multiple days post-dosing, and at follow-up one week after the last dose was administered.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
KH176

Primary outcome(s)
1. Pharmacokinetic parameters (peak plasma concentration, time to reach peak plasma concentration, area under the plasma concentration versus time curve [AUC], half life), non-compartmentally derived from measurement of plasma concentrations of KH176 and its metabolite at pre-dose and 0.5, 1, 1.5, 2, 3, 6, 8, 12, and 24 hours post-dose in the SAD part and at pre-dose at Day 1, 2, 4, 7, and post-dose at Day 1 and Day 7 at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 hours in the MAD part
2. Safety and tolerability:
2.1. In the SAD part vital signs recorded pre-dose and 1, 2, 4, 6, 8, 12 and 24 hours post-dosing. In the MAD part vital signs recorded pre-dose on Day 1, and 1, 2, 4, 6, 8, 12 hours post dosing on Day 1, pre-dose on Day 2, 3, 4, 5, 6 and 7 and 1, 2, 4, 6 and 12 hours post dosing on Day 7
2.2. ECG recordings obtained at pre-dose (triplicate recording) and 1, 2, 4, 6, 8, 12 and 24 hours post-dosing in the SAD part, and at pre-dose (triplicate recording) and 1, 2, 4, 6, 8, 12 hours post dosing on Day 1 and pre-dose on Day 2, 3, 4, 5, 6 and 7 and 1, 2, 4, 6, 8 and 12 hours post dosing on Day 7
2.3. Adverse events evaluated continuously for the entire dosing period

Key secondary outcome(s))
Pharmacodynamic parameters of KH176: changes in biochemistry related to OXPHOS (glutathione, lactate) from baseline to Day 7

Completion date
10/10/2015

Eligibility

Key inclusion criteria
1. Healthy as assessed by medical history, physical examination, vital signs, clinical laboratory, ECG
2. Adult males

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Sex
Male

Key exclusion criteria
1. Allergies
2. Concomitant medication
3. Concomitant disease
4. Relevant surgery
5. Recent blood donation

Date of first enrolment
01/04/2015

Date of final enrolment
30/04/2015

Locations

Countries of recruitment
Belgium

Study participating centre
Drug Research Unit Genth
De Pintelaan 185

Gent
Belgium
9000

Sponsor information

Organisation
Khondrion

ROR
https://ror.org/02a1g6f69

Funder(s)

Funder type
Industry

Funder Name
Khondrion

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	16/10/2017		Yes	No