An Open-Label, Extension Study of the Effects of Leuco-methylthioninium bis(hydromethanesulfonate) in Subjects with Alzheimer's Disease or Behavioral Variant Frontotemporal Dementia

Published: 13-07-2015
Last updated: 13-04-2024

To provide subjects who have completed participation in a Phase 2 or Phase 3 trial continued access to therapy and to evaluate the long-term safety and tolerability of leuco-methylthioninium bis(hydromethanesulfonate) given in flexible doses of up...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Central nervous system vascular disorders
Study type	Interventional

Summary

ID

NL-OMON41951

Source
ToetsingOnline

Brief title
TRx-237-020

Condition

- Central nervous system vascular disorders

Synonym
Alzheimer's Disease or a rare form of dementia (Behavioral Variant Frontotemporal Dementia)

Research involving
Human

Sponsors and support

Primary sponsor: TauRx Therapeutics Ltd
Source(s) of monetary or material Support: Sponsor: TauRx Therapeutics Ltd

Intervention

Keyword: - Alzheimer's Disease, - Behavioral Variant Frontotemporal Dementia, - Leuco-methylthioninium bis(hydromethanesulfonate), - Open-Label Extension Study

Outcome measures

Primary outcome

The primary objectives of this study are to provide subjects who have completed

participation in a Phase 2 or Phase 3 trial continued access to

therapy and to evaluate the long-term safety and tolerability of LMTM given in

flexible doses of up to 300 mg/day.

Secondary outcome

Not applicable

Study description

Background summary

Alzheimer's disease is the most common form of dementia for which there is no cure which worsens as it progresses eventually leading to death. Treatments commonly used to treat this illness, only predominantly address certain aspects, but do not directly affect the core pathology of the disease.
Behavioral variant frontotemporal dementia (bvFTD) is a rare, progressive neurodegenerative disease characterized by progressive deterioration of behavior and language, associated with atrophy of the frontal and temporal lobes. It typically occurs sometime in the 50s, though it can occur as early as age 20 or as late as age 80. There are currently no licensed treatments for any form of FTD.
As there is a need to develop new medications for these diseases, the investigational product for this trial (TRx0237), is believed to have the potential to offer benefits over current treatments.
There are currently a few studies ongoing to assess the efficacy, safety and

tolerability of TRx0237 and this study is an open-label extension to provide subjects who have completed participation in a Phase 2 or Phase 3 trial continued access to therapy and to evaluate the longterm safety and tolerability of leucomethylthioninium dihydromesylate (LMTM) in subjects with AD or a rare form of dementia (Behavioral Variant Frontotemporal Dementia). Appropriateness of continued treatment will be reevaluated every 12 months on the basis of benefit and safety/tolerability* informed consent must be obtained for each subsequent extension. A 4-week posttreatment follow-up visit will be scheduled for all subjects if they discontinue prematurely or do not re-enroll for a subsequent extension phase. The study will continue until alternate options for access to treatment are available, i.e., commercialization or, depending on country, on a Named Patient or compassionate basis or via a Managed Access Program.

Please refer to section "2 Background" of the study protocol, version 1.1 dated 11 June 2014

Study objective

To provide subjects who have completed participation in a Phase 2 or Phase 3 trial continued access to therapy and to evaluate the long-term safety and tolerability of leuco-methylthioninium bis(hydromethanesulfonate) given in flexible doses of up to 300 mg/day.

Study design

This is a multicenter, flexible dose, open-label extension study. Appropriateness of continued treatment will be re-evaluated every 12 months on the basis of benefit and safety/tolerability; informed consent must be obtained for each subsequent extension. A 4-week post-treatment follow-up visit should be scheduled for all subjects if they discontinue prematurely or do not re-enroll for a subsequent extension phase.

The trial will be monitored for safety by a Data Safety Monitoring Board (DSMB) throughout its duration.

Intervention

Assessments:

Baseline:
Following the signing of informed consent, the following Baseline assessments are to be performed in order to confirm continued eligibility for study:
• If the Baseline visit does not coincide with the final double-blind study visit, intervening medical history, adverse events, and concomitant medication use are to be recorded; serum pregnancy testing in women of childbearing

potential is to be performed.
• If the final double-blind study visit occurred more than 42 days prior, safety assessments are to be repeated, including seated vital signs, clinical laboratory tests, and if indicated, targeted physical and neurological examinations.

Safety and Tolerability:
At each post-Baseline visit (unless otherwise noted), whether or not subjects are on study medication, all adverse events (AEs), concomitant medications, vital signs, and clinical laboratory findings will be assessed (unless otherwise noted) according to the following:
• Adverse events recording.
• Concomitant medication use.
• Seated blood pressure and pulse (after the subject has been at rest in a seated position for approximately 5 minutes, with pulse recorded over 60 seconds).
• Body weight.
• Standard clinical laboratory testing, including hematology and serum chemistry.
• A serum pregnancy test (women of childbearing potential).
• Targeted physical and neurological assessments (as needed in response to an AE or to changes in the subject*s physical condition or medical history).

Resource Utilization and Quality of Life:
The following scales will be evaluated at Baseline (if not available from within the prior 42 days in the previous study of participation) and approximately every 6 months:
• RUD-Lite.
• EQ-5D-5L.

Study burden and risks

This is a clinical study to find out what effects, LMTM has on patients. It is not known if it will help patient*s symptoms improve or make patient feel better. Subejcts will be helping to test a treatment that could help people suffering from Alzheimer*s disease or bvFTD in the future. At the moment, there are no treatments that prevent or cure Alzheimer*s disease or bvFTD.
The intent of this extension study is to provide LMTM treatment to those subjects in whom the benefit is judged to outweigh the risk.

LMTM will likely cause urine and maybe bowel movements to turn blue-green. This can be an inconvenience and may become a problem if subject is unable to control faeces. In this case, clothes or other items that urine or faeces come in contact with may become stained. Leather items, some fabrics and furniture may be difficult or impossible to clean. Subjects should therefore take

precautions such as wearing only clothing that they do not mind becoming stained blue and protecting items of furniture or carpets with a protective covering or avoiding using them.

The inside mouth or teeth will become stained if subjects bite or chew the tablet or if subejcts dissolve the tablet in liquid prior to taking them. If LMTM is taking as directed, mouth or teeth should not be stained blue. If subjects have difficulty swallowing the tablet which keeps them from taking the LMTM as instructed, subjects are instruct to tell the study doctor right away.

Subjects may feel some discomfort and have some bruising from giving blood samples during the study.

Risks and side effects for LMTM include those which are:

Likely:
• Stomach or intestinal problems: loose stools or diarrhoea; nausea, retching, or vomiting
• Urinary problems: discomfort or pain when you urinate, the need to urinate more often, strong or urgent need to urinate
• Change in colour or staining when you go to the toilet: blue-green colour of urine or stool

Less likely:
• Anaemia: Red blood cells carry oxygen in your body. Haemoglobin is a molecule in red blood cells. A low number of red blood cells or a low level of haemoglobin can make you feel tired or weak. Your doctor will check for this condition with a blood test.
• Dizziness
• Falls
• Headache
• Skin rashes

Rare but serious:
• Methaemoglobinaemia: In methaemoglobinaemia, your blood contains too much methaemoglobin (an abnormal form of haemoglobin that is not able to transport oxygen around your body effectively). The levels of normal haemoglobin may also decrease (anaemia). Most of the time if you have a small increase in methaemoglobin level and decrease in haemoglobin level, your body will adjust. Rarely, if the levels change too much, you may have symptoms, which include: bluish colour of the skin and lips, headache, anxiety, fatigue, shortness of breath, confusion, and dizziness. In severe cases, this condition can cause irregular heartbeat, seizures, coma, and death.
• Changes in the number of white blood cells, which can make infections occur more often: Your doctor will check for this change with a blood test at study visits.
• Changes in the liver: In other studies, subjects taking a similar medicine

had changes in blood tests for the liver. These test results returned to normal after stopping LMTM. If your liver is not working properly, your skin and eyes may turn yellow. Your doctor will check your liver function with blood tests at study visits to catch possible early signs of problems.
• Sudden and severe allergic reaction: Some subejcts had a bad reaction, including breathing problems, fast heartbeat, and low blood pressure, after they were treated with a similar medicine.
• Sensitivity to light: LMTM may cause sensitivity to sunlight or sensitivity to strong lights that a doctor may use. This may cause redness of the skin, similar to sunburn.

There may also be other possible side effects of the medicine or interactions with other medicines or food based on the way that LMTM works in the body that have not happened yet:
• Bleeding: In a small number of subjects who took part in studies of other medicines for Alzheimer's disease, a small amount of bleeding and/or swelling of the brain was seen (called ARIA). This bleeding or swelling was temporary. There is a possible risk that this might happen to you while you are in this study. If this happens, you may become confused or think less clearly, see or hear things that are not there, have a headache, have trouble walking, vomit, or have an upset stomach.
• Serotonin syndrome: Serotonin is a chemical that helps nerve cells in your brain and your body talk to each other. Some medicines can make the levels of this chemical too high. LMTM may be linked to serotonin syndrome. Your study nurse or doctor will teach you and your caregiver about the symptoms to look out for. This condition can be life-threatening and may include:
o feeling anxious and restless, seeing things that are not there, coma or other changes in mental state
o coordination problems or muscle twitching (overactive reflexes)
o racing heartbeat, high or low blood pressure
o sweating or fever
o nausea, vomiting, or diarrhoea
o stiff muscles
• Heart damage: In studies in animals, high doses of LMTM (higher than those used in this study) caused heart damage. This side effect has not been seen in humans, but must be looked out for.
• Laboratory studies of cells showed that LMTM may damage genetic material. This type of damage was not seen in studies with living animals. However, because of the laboratory studies' findings, the risk of damage to genetic material must be considered when LMTM is given.
• Some types of cancers were seen more often than expected in mice and rats after they received doses of a similar medicine for a long time. Based on these studies, LMTM might increase the risk of getting certain types of cancer when given to humans.
• There may also be interactions between LMTM and certain other medicines. Your study doctor will review your medications with you.
o Some medicines may cause serotonin syndrome when taken with LMTM. Your study

nurse or doctor will discuss this with you and teach you and your caregiver about the symptoms to look out for (they are listed in the section above).
• Interaction with foods containing tyramine: Some drinks which are fermented and foods that are fermented, aged, or spoiled naturally contain high amounts of tyramine, a natural substance. Consuming tyramine-rich foods and drinks while taking LMTM could possibly lead to a sudden, large increase in blood pressure called hypertensive crisis or tyramine reaction. This is a serious medical condition that may be life threatening. Hypertensive crisis has not been reported in studies with LMTM or related experimental medicines and subje

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. Subjects with a diagnosis according to NIA/AA criteria of all cause dementia and probable

Alzheimer*s disease (AD) at enrollment and who completed participation in one of the following three TauRx studies (inclusive of the 4-week post-treatment follow-up visit):
TRx-237-005,
TRx-237-008, or TRx-237-015
(Subjects who participated in Study TRx-237-015 and did not consent to extended treatment for up to 15 months as per Protocol Version 3.0 (extended from 12 months as per the original study protocol) may be enrolled into this open-label extension study following completion of the 12-month double-blind treatment period and 4-week post-treatment follow-up visit for Study TRx-237-015.);OR ;Subjects with a diagnosis of probable bvFTD according to the International Consensus Criteria for behavioral variant frontotemporal dementia (bvFTD) at enrollment and who completed participation in TauRx study TRx-237-007 through Visit 9 (Week 52). ;Treatment will not be made available to subjects who have withdrawn from the double-blind study of prior participation prior to completion.;2. Females of child-bearing potential must continue to use adequate contraception (or, if in Italy, agree to avoid pregnancy) defined as follows:
• barrier method (such as condom, diaphragm or cervical/vault cap) with spermicidal foam, gel, film, cream, or suppository; intrauterine device (IUD) or system; oral or long-acting injected or implanted hormonal contraceptives for at least 3 months prior to Baseline; or vasectomized partner (with the appropriate post-vasectomy documentation of the absence of spermatozoa in the ejaculate); or true abstinence (when this is in line with the preferred and usual lifestyle of the subject)
• subjects must agree to continue to maintain adequate contraception throughout participation in the study;3. Subject and/or, in the case of reduced decision-making capacity, legally acceptable representative(s) consistent with national law and IRB/EC approval, is/are able to read, understand, and provide written informed consent in the designated language of the study site;4. Has an identified adult caregiver who meets the following criteria:
• Either lives with the subject or sees the subject on average for >= 1 hour/day >= 3 days/week, and in the investigator*s opinion, the extent of contact is sufficient to provide meaningful assessment of changes in subject behavior and function over time and provide information on safety and tolerability
• Is willing to provide written informed consent for his/her own participation
• Is able to read, understand, and speak the designated language at the study site
• Agrees to accompany the subject to each study visit
• Is able to verify daily compliance with study drug;5. Able to comply with the study procedures in the view of the investigator

Exclusion criteria

1. History of swallowing difficulties (note: study drug should be swallowed whole and MUST NOT be broken crushed, chewed or dissolved in fluids prior to ingestion);2. Pregnant or breastfeeding;3. Clinically significant laboratory, pulse co-oximetry, electrocardiogram, or imaging abnormality (in original study) or emergent intercurrent illness that, in the judgment of the principal investigator, could result in the risk of participation outweighing the potential benefit;4. Current participation in, or intent to enroll in, a clinical trial of a drug, biologic, device, or medical food

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	28-06-2016
Enrollment:	11
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Leuco-methylthioninium bis(hydromethanesulfonate)
Generic name:	N/A

Ethics review

Approved WMO

Date:	13-07-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	24-03-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	19-05-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-07-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2014□002013□37-NL
ClinicalTrials.gov	NCT02245568
CCMO	NL52155.078.15