Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, 18-Month Safety and Efficacy Study of Leuco-methylthioninium bis(hydromethanesulfonate) in Subjects with Mild Alzheimer*s Disease

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1. To demonstrate the clinical efficacy of leuco-methylthioninium bis(hydromethanesulfonate) (also known as LMTM,TRx0237) in mild Alzheimer*s disease as assessed by change from baseline on:• Alzheimer*s Disease Assessment Scale - Cognitive Subscale...

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

Summary

ID

NL-OMON40577

Source
ToetsingOnline

Brief title
TRx-237-005

Condition

- Central nervous system vascular disorders
- Dementia and amnestic conditions

Synonym
memory trouble, Mild Alzheimer's disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Mild Alzheimer's disease

Outcome measures

Primary outcome

The co-primary efficacy endpoints for the clinical demonstration of efficacy

are the following:

• ADAS-cog11

• ADCS-CGIC

To further demonstrate disease modification, the following is the primary

endpoint:

• Reduction in glucose uptake decline by FDG-PET/CT of the temporal lobes

Secondary outcome

• MMSE

• ADCS-ADL23

• NPI

• MADRS

Study description

Background summary

Leuco-methylthioninium bis(hydromethanesulfonate) is a new drug that is called LMTM for short. LMTM is a drug that
is being studied for the treatment of Alzheimer*s disease.
Alzheimer's disease (AD) 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.
In AD, the microtubule associated protein
tau is redistributed exponentially into paired helical filaments forming neurofibrillary tangles which correlate with
pyramidal cell destruction. There is a robust clinico-pathological correlation between tau pathology, tau aggregation,
and clinical measures of dementia. These relationships are maintained from the earliest detectable stages of dementia
and progress in parallel with clinical deterioration.
Drugs currently available to treat AD, such as acetylcholinesterase inhibitors (AChEIs) and memantine, are
symptomatic treatments which address certain central neuronal dysfunctions associated with AD, but are not known to
directly affect the neurofibrillary tangles in the brain that represent a core pathological component of AD.Controlled
studies with the AChEIs have demonstrated small improvements in cognitive tests and global measures of change in
selected subjects with mild to moderate Alzheimer*s disease over 3-12 months. However, improvements in function
and behavior have been demonstrated less reliably with AChEIs. Furthermore, although these medications provide
benefits for some subjects, their effectiveness often is limited in duration and they do not affect the rate of progression
of the disease.
Therefore, an unmet need exists to develop new medications for AD that more directly modify the underlying disease
pathology and offer longer term greater efficacy. Leuco-methylthioninium bis(hydromethanesulfonate) (LMTM), the
investigational product, is believed to have the potential to confer benefits over existing treatments for AD due to its
ability to affect the process of tau aggregation responsible for the underlying neurofibrillary pathology of Alzheimer*s
disease. Available nonclinical and clinical evidence supports the clinical evaluation of LMTM in Alzheimer*s disease.

Study objective

1. To demonstrate the clinical efficacy of leuco-methylthioninium bis(hydromethanesulfonate) (also known as LMTM,
TRx0237) in mild Alzheimer*s disease as assessed by change from baseline on:

• Alzheimer*s Disease Assessment Scale - Cognitive Subscale (ADAS-cog11)
• Alzheimer*s Disease Cooperative Study - Clinical Global Impression of Change (ADCS-CGIC) - independently rated
2. To evaluate the effect of LMTM on Alzheimer*s disease modification as evidenced by reduction in decline in glucose
uptake in the temporal lobe on 18F-flurodeoxyglucose positron emission tomography (FDG-PET) / computerized
tomography (CT) imaging
3. To assess the safety and tolerability of LMTM 200 mg/day given for up to 78 weeks
Secondary:
4. To evaluate the effect of LMTM on functional activities of daily living using the Alzheimer*s Disease Cooperative
Study - Activities of Daily Living (ADCS-ADL23)
5. To evaluate the effects of LMTM on other aspects of Alzheimer*s disease including cognition (Mini-Mental Status
Examination, MMSE), behavior (Neuropsychiatric Inventory, NPI), and mood (Montgomery-Asberg Depression Rating
Scale, MADRS)

Exploratory:
6. To determine the effects of LMTM on Alzheimer*s disease modification by showing retardation of the expected
decline in whole brain volume as evaluated by brain magnetic resonance imaging (MRI)
7. To determine the effects of LMTM on resource utilization using the Resource Utilization in Dementia (RUD) Lite
8. To explore changes in certain cerebrospinal fluid (CSF) biomarkers of Alzheimer*s disease (total tau, p-tau-181, and
Aβ42) in subjects who consent to lumbar puncture
9. To explore the influence of the Apolipoprotein E genotype on the primary and selected secondary outcomes (in
subjects who provide separate consent)

Study design

Multinational, randomized, placebo-controlled, double-blind, parallel-group, 78-week, outpatient study with eight postbaseline
on-treatment visits planned (Visits 3 - 10), followed by an off-treatment follow-up visit for all subjects to occur 4
weeks after completion of randomized treatment (Visit 11). Unscheduled visits and housing may occur as needed for
assessment.

Intervention

Subjects will be randomized 1:1 (stratified by geographic region [North America, Europe, and Rest of World]), use of an AChEI and/or memantine (never used, used but stopped, ongoing use), and baseline severity (CDR 0.5 or 1) to one of the following oral treatment groups:
• LMTM 200 mg/day group: LMTM 100 mg twice daily (b.i.d.) (one 100-mg tablet in the morning and one 100-mg tablet in the evening) [n=250]
• Placebo group: Placebo twice daily (b.i.d.) (one LMTM 4-mg tablet in the morning and one LMTM 4-mg tablet in the evening) [n=250]
A 75-mg tablet is also provided to allow for dose reduction. The placebo group will receive low dose LMTM as a urinary and fecal colorant to maintain blinding. All tablets are of matching appearance.

Study burden and risks

If you take part in this study, you will have to give up some of your time. From the time you begin having tests to see if you qualify, until the last study visit, you will need to attend 11 clinic visits over a period of up to 86 weeks, at times set by the clinic. One of these visits (Visit 2) may take 2 days to complete all of the exams, tests, and procedures. You will also have tests (PET/CT scans and MRI scans) that require additional visits. This may be inconvenient.
The study medicine (both the LMTM tablets and the placebo or dummy tablets) will likely cause your urine and maybe your bowel movements to turn blue-green. This can be an inconvenience and may become a problem if you are unable to control when you go to the toilet. In this case, your clothes may become stained. Your study doctor or nurse will tell you and your caregiver the best way to remove the stains if this happens. We will also give you an information leaflet that describes what to do. Also, the inside of your mouth or teeth will become stained if you bite or chew the tablets; if you take the study medicine as directed, this should not happen.
You may feel some discomfort and have some bruising from giving blood samples during the study.
Reproductive risks: There is not enough information available about whether the study medicine causes harm to the unborn child. Women will not be allowed to participate in the study if they are pregnant or breast-feeding. Women of childbearing potential will be required to have a pregnancy test before being enrolled in the study and at each visit to the clinic throughout the study. While taking part in this study, women should not become pregnant or breastfeed a

baby and men should not father a baby. You must use birth control while in this study. Talk with your study doctor
about what kind of birth control methods to use and how long to use them. If, during the course of the study, you think
that you might be pregnant, you must notify study staff right away. Should you become pregnant during the study, you
will stop using the study drug and you will be removed from the study.
You may have side effects from taking the study medicine. Everyone taking part in the study will be watched carefully
for any side effects. To find out about any side effects, your healthcare team will ask you and your caregiver some
personal questions. Some of these questions may be uncomfortable for you to answer, but it is important that you
answer these as honestly as possible.

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. Diagnosis according to the National Institute on Aging (NIA) and Alzheimer*s Association (AA) criteria of:;• All cause dementia;and;• Probable Alzheimer*s disease;2. Clinical Dementia Rating (CDR) total score of 0.5 or 1 (mild) and MMSE score of 22-26 (inclusive) at Screening;3. Age <=90 years at Screening;4. Modified Hachinski ischemic score of <=4 at Screening;5. Females must meet one of the following: ;• Surgically sterile (hysterectomy, bilateral oophorectomy) for at least 6 months minimum;• Have undergone bilateral tubal ligation at least 6 months prior ;• Post-menopausal for at least 1 year ;• Using adequate contraception (such as condoms, foams, jellies, diaphragm, intrauterine device [IUD], oral or long-acting injected contraceptives for at least 3 months prior to Baseline or vasectomized partner) or true abstinence (when this is in line with 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); subjects must agree to continue to maintain adequate contraception throughout participation in the study;6. Subject and/or, in the case of reduced decision-making capacity, legally acceptable representative(s) consistent with national law, is/are able to read, understand, and provide written informed consent in the designated language of the study site ;7. Has an identified caregiver who meets the following criteria:;• Either lives with the subject or sees the subject on average for >= 2 hours/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;8. If currently taking an acetylcholinesterase inhibitor (AChEI), i.e., donepezil, galantamine, or rivastigmine, and/or memantine:;• The subject must have been taking such medication(s) for >= 3 months ;• The current dosage regimen and dosage form must be within the locally approved dose range and must have remained stable for >= 6 weeks before Baseline (Visit 2) ;• It must be planned that the dosage regimen will remain stable throughout participation in the study;Subjects not being treated with an AChEI or memantine (for >= 6 weeks before Baseline) may also be enrolled if initiation of an AChEI or memantine is not planned for the time period during which the subject will be participating in this study;9. Able to comply with the study procedures in the view of the investigator

Exclusion criteria

1.Significant CNS disorder other than Alzheimer*s disease;2.Significant intracranial focal or vascular pathology seen on brain MRI scan within a maximum of 28 days before Baseline that would lead to a diagnosis other than probable Alzheimer*s disease or that puts the subject at risk of ARIA, including: other focal brain lesions, a single area of superficial siderosis, > 4 cerebral microhemorrhages, evidence of a prior macrohemorrhage;3.Clinical evidence or history of any of the following within specified period prior to Baseline:;•Cerebrovascular

accident (2 years);•Transient ischemic attack (6 months);•Significant head injury with associated loss of consciousness, skull fracture or persisting cognitive impairment (2 years);•Other unexplained or recurrent loss of consciousness >=15 minutes (2 years);4.Epilepsy (a single prior seizure is considered acceptable);5.DSM IV-TR criteria met for any of the following within specified period:;•Major depressive disorder (current) ;•Schizophrenia (lifetime);•Other psychotic disorders, bipolar disorder, substance (including alcohol) related disorders (within the past 5 years);6.Metal implants in the head (except dental), pacemaker, cochlear implants, or any other non-removable items that are contraindications to MR imaging; MR compatible prosthetics, clips, stents, or any other device proven to be compatible will be allowed. ;7.Resides in hospital or moderate to high dependency continuous care facility;8.History of swallowing difficulties;9.Pregnant or breastfeeding;10.History of significant hematological abnormality or current acute or chronic clinically significant abnormality, including: ;•History of hereditary or acquired methemoglobinemia or baseline measurement of MetHb >2.0%;•History of hemoglobinopathy, myelodysplastic syndrome, hemolytic anemia, or splenectomy;•G6PD deficiency ;•Baseline value below age/sex appropriate lower limit of the central laboratory normal range for any of the following:;oHemoglobin (subject may be treated and re-screened after 3 months);oVitamin B12 or folate (subject may be treated and re-screened after 3 months);11.Abnormal serum chemistry laboratory value at Screening. In addition, subjects with either of the following abnormalities must be excluded: creatinine clearance <30 mL/min at Screening, TSH above laboratory normal range (subject may be treated and re-screened after 3 months);12.Clinically significant cardiovascular disease or abnormal assessments such as:;•Hospitalization for acute coronary syndrome or symptoms consistent with angina pectoris, within the 12 months preceding Baseline;•Signs or symptoms of clinical heart failure within the 12 months preceding Baseline;•Evidence of atrial fibrillation on ECG or history of atrial fibrillation that is not currently controlled;•QTcB at Screening or Baseline >450 msec in males or >470 msec in females, or low or flat T waves making measurement of QT interval unreliable;•Recent history of poorly controlled hypertension, systolic blood pressure >160 mmHg, or diastolic blood pressure >100 mmHg, at Screening or at Baseline;•Hypotension: systolic blood pressure <100 mmHg at Screening or at Baseline;•Heart rate <48 bpm or >96 bpm by measurement of vital signs or by ECG at Screening or at Baseline;13.Preexisting or current signs or symptoms of respiratory failure; in addition, subjects should be excluded if they have: previously diagnosed moderate to severe sleep apnea not adequately controlled;14.Concurrent acute or chronic clinically significant immunologic, hepatic, or endocrine disease (not adequately treated) and/or other unstable or major disease other than Alzheimer*s disease. Subjects with primary biliary cirrhosis should be excluded.;15.Diagnosis of cancer within the past 2 years prior to Baseline (other than basal cell or squamous cell skin cancer or Stage 1 prostate cancer) unless treatment has resulted in complete freedom from disease for at least 2 years;16.Prior intolerance or hypersensitivity to MT-containing drug, similar organic dyes, or any of the excipients;17.Treatment currently or within 3 months before Baseline with any of the following medications:;•Moderate to strong inhibitors of CYP1A2 (e.g., ciprofloxacin, fluvoxamine) ;•Tacrine ;•Anxiolytics and/or sedatives/hypnotics before cognitive testing (exceptions: sedation for MRI or short-acting benzodiazepines, chloral hydrate, or zolpidem as needed at bedtime);•Antipsychotics: clozapine, olanzapine. Other antipsychotics are allowable, preferably at a stable dose and regimen.;•Carbamazepine, primidone;•Drugs associated with methemoglobinemia;18.Prior participation in a clinical trial as follows:;•Phase 3 clinical trial of a product for cognition

within the 3 months prior to Screening (unless confirmed to have been randomized to placebo);•A clinical trial of a drug, biologic, or device in which the last dose was received within 28 days prior to Baseline

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-12-2013
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	n/a
Generic name:	Leuco-methylthioninium bis(hydromethanesulfonate)

Ethics review

Approved WMO

Date:	16-12-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	16-05-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-08-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-09-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-06-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-06-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-10-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-12-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-02-2016
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-03-2016
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	EUCTR2012-002847-28-NL
ClinicalTrials.gov	NCT01689233
CCMO	NL47146.078.13