A Double-Blind, Placebo-Controlled, Randomized, Parallel Group, 12-Month Safety and Efficacy Trial of Leuco-methylthioninium bis(hydromethanesulfonate) in Subjects with Behavioral Variant Frontotemporal Dementia (bvFTD)

Published: 09-08-2012
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Primary:To demonstrate the efficacy of LMTM as assessed by the change from Baseline on:* Addenbrooke*s Cognitive Examination Revised (ACE-R)* Symptomatic effect as reflected by the Functional Activities Questionnaire (FAQ)* Disease-modifying effect...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Mental impairment disorders
Study type	Interventional

Summary

ID

NL-OMON41446

Source
ToetsingOnline

Brief title
TRx-237-007

Condition

- Mental impairment disorders
- Dementia and amnestic conditions

Synonym

Dementia, Picks disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Behavioral symtoms, Frontotemporal dementia

Outcome measures

Primary outcome

Primary Efficacy endpoints:

* Change from Baseline to Week 52 in the ACE-R

* Either of two co-primary endpoints:

o Change from Baseline to Week 52 in FAQ

o Reduction in decline in whole brain volume at Week 52 using change from

Baseline as measured by the Brain Boundary Shift Integral (BBSI)

by MRI imaging

Secondary outcome

Secondary clinical endpoints include the following:

* Modified CGIC

* FRS

* UPDRS Parts II and III

Study description

Background summary

Onset of bvFTD typically occurs sometime in the 50s, though it can occur as early as age 20 or as late as age 80. Diagnosis of bvFTD is primarily on the basis of clinical signs and symptoms, informed by imaging of selected regions of the brain. Character change and disordered social conduct are the dominant features initially and throughout the disease course. Instrumental functions of perception, spatial skills, praxis and memory are intact or relatively well preserved. LMTM delivers the active moiety, MT, following dissociation of the counter ions. The proposed primary mechanism through which MT acts to ameliorate and prevent the pathology which underlies bvFTD is through the dissolution of tau aggregates and prevention of tau aggregation through dissolution of early tau oligomers in the brain and by inhibition of TDP-43 protein aggregation, most likely by binding to and disrupting TDP-43 dimers and oligomers and thereby inhibiting fibril formation. Nonclinical and clinical evidence supports the further study of LMTM in subjects with bvFTD.

Study objective

Primary:
To demonstrate the efficacy of LMTM as assessed by the change from Baseline on:
* Addenbrooke*s Cognitive Examination Revised (ACE-R)
* Symptomatic effect as reflected by the Functional Activities Questionnaire (FAQ)
* Disease-modifying effect based on reduction in decline in whole brain volume (WBV), using change from Baseline as measured by the Brain Boundary Shift Integral (BBSI) by MRI imaging

Secondary:
To evaluate the effect of LMTM as measured by the following additional global, disease severity, and motor impairment scales:
* Modified Alzheimer's Disease Cooperative Study * Clinical Global Impression of Change (Modified ADCS-CGIC) * independently rated
* Frontotemporal Dementia Rating Scale (FRS)
* Unified Parkinson's Disease Rating Scale (UPDRS Parts II and III)
- To evaluate the safety and tolerability of LMTM

Exploratory:
4. To evaluate an early effect on ADCS-CGIC (after 8 weeks of treatment)
5. To evaluate the effect of LMTM on the Mini-Mental Status Examination (MMSE)
6. To determine the effect of LMTM on bvFTD by showing retardation of the expected decline in whole brain volume

Study design

Multinational, randomized, placebo-controlled, double-blind, parallel-group, 52-week, outpatient study with seven post-baseline on-treatment visits planned and an off-treatment follow-up visit for subjects who either discontinue early or complete treatment but chose not to enter a separate open-label extension study. Unscheduled visits and housing may be occur as needed for assessment.

Intervention

Subjects will be randomized 1:1 (stratified by country) 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=90]
* 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=90]
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

We hope that the treatments will improve the patient's symptoms and that he will feel better. However this cannot be guaranteed. He will be helping to test a treatment that could help people suffering from bvFTD in the future.

The patients will have to give up some of their time and will need to visit the clinic a total of 10 times over a period of approximately 62 weeks (15 months). Study visits could last for several hours up to an entire day. The study staff will also communicate with the patient and carer via telephone several times throughout the study. This may be inconvenient. The patient and his carer will also have to answer some personal questions.
The trial medication will cause urine and/or bowel movements to turn blue. This can be an inconvenience and may become a problem if the patient is unable to control when he goes to the toilet. In this case, his/her clothes may become stained. If this happens, the study doctor or nurse will tell the patient and his/her carer the best way to remove the stains. The patient will also be provided with an information leaflet to describe this. Also, the inside of the patient*s mouth or teeth will become stained if the tablets are bitten or chewed. This should not happen if the trial medication is taken as directed.
The patient may feel some discomfort and have some bruising as a result of giving blood samples during the trial.
Patients who are covered by private medical insurance should check with their company whether participation in this trial will affect their medical insurance.
Patients may have side effects while on the trial. Everyone taking part in the trial will be watched carefully for any side effects. To find out about any side effects, trial team will need to ask the patient and his/her carer some personal questions. Some of these questions may be uncomfortable for him to answer but it is important that he answers these as honestly as possible.

Patients will need to have 4 MRI scans. This means that they will have to lie still in an enclosed space for up to 20 minutes. Some people with claustrophobia may not be able to tolerate this. Some MRI scanners make a loud noise when they are working. This test will use a Gadolinium contrast agent to help detect any problems in the brain. The patient will be injected with this agent before the test starts. The study doctor may also decide this agent is not right for the patient. Gadolinium contrast agent must not be used in people who are hypersensitive (allergic) to medicines containing gadolinium. It must not be used in patients who have poor kidney function due to a risk of a condition called nephrogenic systemic fibrosis (NSF). NSF causes thickening of the skin and connective tissues. If the patient is allergic or it is not right for him, the MRI scan may be done without contrast. The contrast agent used in this study is approved by the European Medicines Agency and the United States Food and Drug Administration. There is a chance that the study doctor will find something abnormal on the brain scan that is not related to this research. If this happens, the study doctor will inform the patient of these findings.

Risks and side effects for LMTM include those which are:
Likely:
* Stomach irritation and upsets that can include loose stools or diarrhoea, nausea, retching, or vomiting
* Urinary problems that can include discomfort and pain when urinating, and the need to urinate more frequently or more urgently
Less Likely:
* Dizziness and falls
* Skin rashes
* Anaemia: this can cause tiredness, weakness, and shortness of breath. The patient*s blood will be checked for this side effect when blood samples are taken at trial visits.
* Other changes in the patient*s blood cells may be seen, for example, changes in the number of white blood cells.
The patient*s blood will be checked for this when blood samples are taken at trial visits.
Rare but serious:
* There is a small risk that the trial medication LMTM may cause methaemoglobinaemia. MetHb levels will be measured at each visit during the course of the trial. Other changes to the blood may also occur and these will be checked for when blood samples are taken at trial visits.
* There is a small risk that taking LMTM may cause a change in the way the patient*s liver works. The patient*s blood will be checked for this side effect when blood samples are taken at trial visits to catch early signs.
* Anaphylaxis has been reported for treatment with a similar medication.
* There is some information to suggest that LMTM may cause serotonin toxicity. This could happen when LMTM is taken at the same time as medicines used to treat depression or with some other medicines. Common symptoms of serotonin syndrome include increased temperature and heart rate, shivering, sweating and dilated pupils. The trial doctor will tell the patient if he/she is taking one

of these medicines and he/she will be monitored for signs of serotonin toxicity
* There is some information from studies in animals to suggest that LMTM may cause heart damage. Although the risk of damage to the heart is very small, and is not expected to be seen, it is a possibility. The heart will be checked for any damage with an ECG at each visit.
* Certain drugs that work in the brain can increase the risk of suicidal thoughts or actions. Because LMTM falls into this category of drug, the trial doctor will watch for new or sudden changes in mood, behaviour, actions, and will ask about feelings and thoughts at each trial visit, including thoughts about killing oneself.
Other possible side effects may include: headaches, traces of blood and protein in urine samples (this finding will be investigated if it is found, urine samples will be checked for this), pain around the chest area (however in cases where this has been found it has been described as muscular pain and not in relation to any pain connected with the heart), weakness, itching, slight change in sense of taste, or the patient may become flushed.
There is some information to suggest that LMTM may cause increased photosensitivity (or sun sensitivity) of the patient*s skin, however this has only been reported when MT has been delivered to the body through the veins using a needle rather than taken by mouth.
In laboratory studies on cells, a drug similar to LMTM damaged genetic material in these cells. In studies with living animals, the same damage was not seen. Based on these studies, there may be a risk of damage to genetic material in cells in the body when LMTM is given to humans. Some mice and rats developed cancers after receiving a drug similar to LMTM for a long period of time. Some of these were in numbers that are higher than expected. Based on these studies, there may also be a higher risk of cancer when LMTM is given to humans.
There may also be side effects of the medicine that are as yet unknown:
* In a small number of patients who took part in other studies for Alzheimer's disease, a small amount of bleeding and/or swelling of the brain was seen. This bleeding or swelling was temporary. There is a chance that this might happen to the patient while he is in this study. If this happens, he 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. The study doctor will look at the MRI scans for any signs of any bleeding or swelling in the brain. If the study doctor sees any bleeding or swelling in the brain, the patient will be taken out of the study.
* Laboratory studies of cells showed that LMTM may damage genetic material. This type of damage was not seen in studies with living animals. Based on these studies, there may be a risk of damage to genetic material in cells in the body when LMTM is given to humans.
* Some types of cancers were seen more often in mice and rats after they received doses of the study medicine for a long time. Based on these studies, LMTM might increase the chance of getting certain types of cancer when given to humans.

There is not enough information available about whether the trial medication

causes harm to the unborn child.
Therefore:
A female patient will be excluded from the trial if she is pregnant, breastfeeding or if she plans to become pregnant during the trial. If she could become pregnant, she will be asked to have a pregnancy test before taking part in the trial and again at every other visit. This will involve providing a blood sample. If she could become pregnant she must also agree to use a reliable form of contraception during the trial, e.g. combined oral contraceptive pill, injectables, intrauterine device (IUD), foams, jellies, diaphragm not having sexual intercourse or having a vasectomised partner. The trial doctor will discuss with her what methods of contraception are appropriate and acceptable to use while she is in the trial. If she becomes pregnant during the course of the trial, she should tell the trial doctor immediately so he/she can help her decide what to do. The trial doctor would discuss referral for specialist counselling on the possible risks.
A male patient should use condoms during the trial and for an additional 4 days after treatment has finished.

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 of probable bvFTD according to the International Consensus Criteria for bvFTD;2. Centrally rated frontotemporal atrophy score of 2 or greater, taken as the maximum of right or left frontal or anterior temporal lobes on brain MRI of sufficient quality obtained at Screening or within a maximum of 42 days before Baseline, irrespective of pre-existing structural or functional imaging evidence supporting a diagnosis of bvFTD;3. MMSE *20 at the Screening visit;4. Age <80 years at the Screening visit;5. Modified Hachinski ischemic score of *4 at the Screening visit;6. Females must meet one of the following:;* Surgically sterile (hysterectomy, bilateral salpingectomy / oophorectomy) for at least 6 months minimum;* Have undergone bilateral tubal occlusion / ligation at least 6 months prior;* Post-menopausal for at least 1 year;* Using adequate contraception (a barrier method [such as condom, diaphragm, or cervical/vault cap] with spermicidal foam, gel, film, cream, or suppository; intrauterine device [IUD] or system, or 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 be competent to use adequate contraception and to agree to continue to maintain adequate contraception throughout participation in the study;7. 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;8.Has one or more identified adult caregivers who meets the following criteria:
* Either lives with the subject or sees the subject on average for * 2 hours/day * 3 days/week, or 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;9. If currently taking an AChEI (i.e., donepezil, galantamine, or rivastigmine) and/or memantine, at the time of Screening:;* 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;* 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 Screening) 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;10. Able to comply with the study procedures in the view of the investigator

Exclusion criteria

1.Significant CNS disorder other than bvFTD;2.Other significant intracranial pathology seen on brain MRI scan that would lead to a diagnosis other than probable bvFTD or that puts the subject at risk of Amyloid Related Imaging Abnormalities including: large confluent white matter hyperintense lesions, other focal brain lesion(s), a single area of superficial siderosis, >4 cerebral microhemorrhages, evidence of a prior macrohemorrhage.;3.Biomarker evidence of underlying AD pathology as etiology of dementia;4.Expressive language deficits such that the subject is too severely impaired to allow testing at Baseline;5.Meets research criteria for Amyotrophic Lateral Sclerosis or motor; evidence of mild motor neuron disease on examination is allowed if not expected to interfere with subject's completion of study but prominent bulbar symptoms would be exclusionary;6.Meets diagnostic criteria for probable bvFTD but has a proven mutation producing non-tau, non-TDP-43 pathology;7.Clinical evidence or history of:;*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);8.Epilepsy (a single prior seizure is considered acceptable);9.Rapid eye movement sleep behavior disorder;10.DSM IV-TR criteria met for the following within specified period:;*Major depressive disorder (current);*Schizophrenia (lifetime);*Other psychotic disorders, bipolar disorder (within the past 5 years), or substance related disorders (within the past 2 years);11.Metal implants in the head (except dental), pacemaker, any other non-removable items that are contraindications to MR imaging; any device proven to be MR compatible will be allowed.;12.Resides in hospital or moderate to high dependency continuous care facility;13.History of swallowing difficulties;14.Pregnant or breastfeeding;15.G6PD deficiency;16.History of significant hematological abnormality or current acute or chronic clinically significant abnormality, including:;*Hereditary or acquired methemoglobinemia or Baseline measurement of MetHb >2.0%;*Hemoglobinopathy, myelodysplastic syndrome, hemolytic anemia, or splenectomy;*Screening value below normal range for hemoglobin and vitamin B12 or folate;17.Abnormal serum chemistry laboratory value at Screening clinically relevant. In addition, subjects with the following abnormalities must be excluded:;*Creatinine clearance: <50 mL/min at Screening;*Thyroid stimulating hormone above laboratory normal range;18.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 uncontrolled atrial fibrillation on Screening ECG or history of atrial fibrillation that is not currently controlled or where the QT interval cannot be assessed by triplicate ECGs;*QTcF at Screening > 460 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;*Hypotension;*Heart rate <48 bpm or >96 bpm by measurement of vital signs or by ECG at Screening;19.Preexisting or current signs or symptoms of respiratory failure.;Subjects with previously diagnosed moderate to severe sleep apnea not adequately controlled should be excluded;20.Concurrent acute or chronic clinically significant immunologic, hepatic, or endocrine disease and/or other unstable or major disease other than bvFTD.
*Subjects with hepatitis or primary biliary cirrhosis should be excluded

*HTLV-III, LAV (incl.any mutants/derivatives),any condition associated with Acquired Immunodeficiency Syndrome;21.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;22.Prior intolerance or hypersensitivity to MT-containing drug, similar organic dyes, or any of the excipients;23.Treatment currently or within 3 months before Baseline with the following medications:;*Tacrine;*Amphetamine or dexamphetamine;*Antipsychotics: clozapine, olanzapine (other antipsychotics are allowable if they have not been initiated within 3 months before Baseline and are used in a stable dose and regimen);*Carbamazepine, primidone;*Other mood stabilizers;*Drugs associated with methemoglobinemia;24.Current or prior participation in a clinical trial:;*Clinical triall of a product for cognition within the 3 months prior to Screening (unless randomized to placebo);*A clinical trial of a drug, biologic, device, or medical food 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):	13-05-2014
Enrollment:	20
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	09-08-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-02-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-04-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-06-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-06-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-10-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-10-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	24-04-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-05-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-10-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-10-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-06-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-10-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-01-2016
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	EUCTR2011-005529-34-NL
ClinicalTrials.gov	NCT01626378
CCMO	NL41019.078.12