A Phase 1, Randomized, Double-Blind, Placebo- and Positive-Controlled, Parallel-Group Study to Evaluate the Effect of LMTM on the Response to an Oral Tyramine Challenge and to Determine the Multiple-Dose Pharmacokinetics of LMTM.

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Ethical review	Approved WMO
Status	Completed
Health condition type	Structural brain disorders
Study type	Interventional

Summary

ID

NL-OMON51826

Source
ToetsingOnline

Brief title
Tyramine challenge with LMTM

Condition

- Structural brain disorders

Synonym
Alzheimer□s Disease, thinking and behavior, type of dementia that affects memory

Research involving
Human

Sponsors and support

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

Intervention

Keyword: LMTM, Pharmacokinetics, Tyramine

Outcome measures

Primary outcome

To determine whether LMTM inhibits MAO as evidenced by a reduction in the dose

of tyramine required to produce a 30-mmHg increase in systolic blood pressure

(SBP), compared with placebo.

Secondary outcome

- To characterize the multiple-dose pharmacokinetics (PK) of LMTM.

- To assess the safety and tolerability of LMTM.

Study description

Background summary

LMTM is a new compound that may potentially be used for the treatment of Alzheimer*s disease. Alzheimer's disease is a slowly developing disease of the brain that affects memory and other brain functions. It is a disease in which misfolding of tau proteins occurs in the brain. Tau proteins are important for maintaining stability of certain parts of brain cells. When they are misfolded it causes damage to these brain cells. Therefore, treatment that helps to prevent or decrease the misfolding of tau proteins is being tested as possible treatment in Alzheimer*s disease. LMTM is thought to prevent the misfolding of tau proteins and to dissolve already misfolded tau proteins.

Study objective

Part 1:
The purpose of this study is to determine whether LMTM inhibits monoamine oxidase (MAO). MAO is an enzyme (protein involved in reactions in the body) which breaks down tyramine. By giving participants tyramine which raises the blood pressure we can indirectly measure MAO. If LMTM inhibits MAO, less tyramine is needed to reach a predefined rise in blood pressure, compared with placebo.

Large amounts of tyramine can be found in some specific foods (especially found in fermented food). The properties of some foods change through fermentation (breakdown of biological products in the absence of oxygen by bacteria for example) where tyramine is formed. This happens in particular in products such as aged cheese, aged meat, and soy products (soy sauce). More examples of tyramine rich foods and drinks are mentioned in Section 5 and Appendix E.

In this study we will also investigate how safe the new compound LMTM is and how well it is tolerated when it is used by healthy participants.

We compare the effects of LMTM with the effects of a placebo. A placebo is a compound without any active ingredient. We also compare the effects and safety of LMTM to the effects and safety of similar compounds, selegiline and phenelzine. Selegiline is already being used in the treatment of Parkinson*s disease and phenelzine in the treatment of depression. Please note that when the term *study compound* is used in this document, we mean LMTM, placebo, selegiline or phenelzine.

LMTM has been used before by healthy volunteers and patients. In addition, it has been extensively tested in the laboratory and on animals.

Part 2:
In this study we will investigate how safe the new compound LMTM is and how well it is tolerated when it is used by healthy participants.
We also investigate how quickly and to what extent LMTM is absorbed, transported, and eliminated from the body (this is called pharmacokinetics).

LMTM has been used before by healthy volunteers and patients. In addition, it has been extensively tested in the laboratory and on animals.

Study design

Part 1:
For the research it is necessary that the volunteer stays in the research center for a maximum of 1 period of 32 days (31 nights). After this there is

one more follow-up visit to the research center. This visit is between 6 and 8 days after leaving the research center.

Day 1 is the first day on which the volunteer receives tyramine. We expect the volunteer at the research center on the day prior to the first tyramine administration. The volunteer leaves the study center before or on Day 30 of the study depending on the tyramine response. The volunteer will leave the research center on Day 19 at the earliest.

Below is an overview of the days on which the volunteer stays in the research center or on which the volunteer visits the research center for both Group 1 and Group 2.

Examination:
Day -28 to Day 2

Entry:
Day 1

In-house stay:
Day -1 to Day 31*

Departure:
Day 31*

Follow-up:
Between 6 and 8 days after leaving the research center

* The length of stay may be shorter based on the tyramine response. The volunteer will leave the research center on Day 19 at the earliest.

In Group 1, the volunteer receives LMTM 60 mg/day, placebo or phenelzine 30 mg/day as capsules by mouth containing 240 milliliters (ml) of water.
In Group 2, the volunteer receives LMTM 16 mg/day, placebo or selegiline 10 mg/day as capsules by mouth containing 240 milliliters (ml) of water.

During the first 1.5 hours after taking the study drug, the volunteer should not lie down (unless asked by one of the investigators), as this may affect the absorption of the study drug.

Whether the volunteer receives LMTM, placebo, phenelzine (Group 1) or selegiline (Group 2) is determined by lottery. Per treatment group, 6 participants received LMTM, 6 participants placebo and 6 participants phenelzine (Group 1) or selegiline (Group 2). Neither the volunteer nor the investigators know whether the volunteer is receiving LMTM, placebo, selegiline, or phenelzine.

All volunteers also receive tyramine as capsules once daily in incremental doses (6.25 to 600 mg/day, see table below). Tyramine is not a medicine, but a substance that occurs naturally in several foods and drinks. This treatment will last until a certain predetermined rise in blood pressure is reached. The rise in blood pressure will probably occur between half an hour and 1 hour after taking tyramine and return to normal values **2 hours after taking tyramine. This will be closely monitored by the research team. You must lie down for the first 0.5 hour before tyramine administration and approximately 2 hours after this (unless otherwise instructed by one of the investigators), as this may affect the absorption of the study drug and the blood pressure being measured.

Part 2:
Day 1 is the first day on which the volunteer receives the research drug. We expect the volunteer at the study center on the day prior to the first administration of the study drug. The volunteer will leave the study center on Day 11 of the study.

Below is an overview of the days on which the volunteer stays in the research center or on which the volunteer visits the research center:

Examination:
Day -28 to Day 1

Intervention

Part 1:
For tyramine, the scheduled dosages are as follows:

- All treatment groups will receive Tyramine up to 100 mg to 600 mg once daily as oral capsules from Days 1 to 6.
- All treatment groups will receive a single dose of tyramine between 150 and 550 mg given as oral capsules on day 7 after a pre-determined increase in blood pressure has been achieved.
- The LMTM dose 1 and 2, placebo and selegiline group will receive Tyramine in ascending order from 25 mg to 600 mg, once daily as oral capsules from days 18 to 30.
-The Phenelzine group receives Tyramine in ascending order of 6.25mg to 350mg, once daily as oral capsules from day 18 to 30.
* The treatment stops when a predetermined increase in blood pressure is reached. It is important to note that the volunteer will be excluded from the study if they do not achieve the predetermined increase in blood pressure at the minimum and maximum dose of tyramine between Day 1 and Day 7.

Below are the planned treatment groups in this study:

- LMTM dose 1 group will receive LMTM 16 mg/day, oral capsules twice daily from day 8 to a maximum of 30.
- LMTM dose 2 group will receive LMTM 60 mg/day, oral capsules twice daily from day 8 to a maximum of 30.
- Placebo group will receive Placebo, oral capsules twice daily from day 8 to a maximum of 30.
- Selegiline will receive Selegiline 10 mg/day, oral capsules twice daily from day 8 to a maximum of 30.
- Phenelzine group will receive Phenelzine 30 mg/day, oral capsules twice daily from day 8 to a maximum of 30.
* The treatment stops when a predetermined increase in blood pressure is reached.

Part 2:
The planned treatment for the study are as follows:

LMTM 8 mg oral tablets (two tablets of 4 mg)
Twice daily on day 1-9
Once daily on day 10

Study burden and risks

Blood draw:
Drawing blood may be painful or cause some bruising. The use of the indwelling cannula can sometimes lead to inflammation, swelling, hardening of the vein, blood clotting, and bleeding in the environment of the puncture site. In some individuals, a blood draw can sometimes cause pallor, nausea, sweating, low heart rate, or drop in blood pressure with dizziness or fainting.

In total, we will take about Part 1: 53 ml ; Part 2: 213 ml of blood from screening to follow-up. This amount does not cause any problems in adults. To compare: a blood donation involves 500 mL of blood being taken at once each time. If the investigator thinks it is necessary for the safety of a participant, extra samples might be taken for possible additional testing. If this happens, the total amount of blood drawn may be more than the amount indicated above.

Heart tracing:
To make a heart tracing, electrodes will be placed on arms, chest and legs. Prolonged use of these electrodes can cause skin irritation.

Coronavirus test:
Samples for the coronavirus test will be taken from the back of the nose and throat using swabs. Taking the samples only takes a few seconds, but can cause discomfort and can give an unpleasant feeling. Taking a sample from the back of the throat may cause gagging. When the sample is taken from the back of the

nose, The volunteer may experience a stinging sensation and eyes may become watery.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Signature of an Independent Ethics Committee approved written informed consent prior to any clinical study-related procedures.
2. Male or female subjects
2.1. Aged 18 to 60 years, inclusive (Tyramine Challenge Parts 1 and 2);
2.1.1. The goal will be to enroll approximately 12 or more subjects aged >=50 years in each part.
2.2. Aged >=50 years (PK Substudy).
3. Weighing between 50 and 110 kg, inclusive such that the body mass index (BMI) is 18.5 to 32 kg/m2, inclusive.

4. In good health in the opinion of the PI as determined by:
4.1. Medical history;
4.2. Physical examination;
4.3. Vital signs assessment;
4.4. 12-lead electrocardiogram (ECG); and
4.5. Clinical laboratory evaluations.
5. If female, must meet one of the following:
5.1. Be permanently sterile, defined as at least 6 months following hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.
5.2. Have undergone bilateral tubal occlusion / ligation at least 6 months prior to screening.
5.3. Be postmenopausal, defined as at least 12 months post cessation of menses (without an alternative medical cause); postmenopausal status will be confirmed with a screening serum follicle stimulating hormone (FSH) level greater than 33.4 mIU/mL.
5.4. Using adequate contraception and agree to do so throughout study participation and for 90 days after the last dose of study drug; the following are considered effective forms of birth control:
5.4.1. Hormonal contraceptives started at least 90 days prior to study drug administration;
5.4.2. Intra-uterine contraceptive device (hormonal or non-hormonal) placed at least 4 weeks prior to study drug administration;
5.4.3. Male condom;
5.4.4. Sterile male partner (vasectomized for at least 6 months); and
5.4.5. True abstinence (when this is in line with the preferred and usual lifestyle of the subject).
6. If female, including those who have underwent hysterectomy, must agree to not donate ova starting from Day -1 and throughout the clinical study period, and for at least 28 days after the final study drug administration.
7. If male and sexually active with a female partner of childbearing potential (childbearing potential females are defined as women who are neither postmenopausal nor surgically sterile), must be willing to use one of the following acceptable contraceptive methods from the first study drug administration until at least 90 days after the last study drug administration:
7.1. Simultaneous use of a male condom and, for the female partner, hormonal contraceptives used since at least 4 weeks or intra-uterine contraceptive device placed since at least 4 weeks;
7.2. Simultaneous use of a male condom and, for the female partner, a diaphragm or cervical cap.
8. If male, must agree to not donate sperm from Day -1 until 90 days after the final study drug administration.

Exclusion criteria

1. If female, pregnant or lactating.

2. History of allergy/sensitivity to the following:
2.1. Phenelzine, selegiline, or other drugs of a similar class (Tyramine Challenge Parts 1 and 2 only).
2.2. Methylthioninium (methylene blue) or similar organic dyes, as determined by the PI.
2.3. Any of the excipients used in LMTM (which include mannitol, cellulose, crospovidone, and magnesium stearate).
3. Clinically significant history of allergic conditions (including severe hypersensitivity drug reactions, asthma, eczema or anaphylactic reactions, but excluding untreated, asymptomatic seasonal allergies at the time of dosing), as judged by the PI.
4. For Tyramine Challenge Parts 1 and 2 only, subject is unable to swallow the capsule sizes used in this study.
5. Febrile illness or symptomatic viral, bacterial (including upper respiratory infection), or fungal (noncutaneous) infection within 1 week prior to admission to the clinical unit.

Further criteria apply, see protocol.

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	15-03-2022
Enrollment:	120
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	Phenelzine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Selegiline
Generic name:	N/A
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	17-02-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-03-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-05-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2022-000192-40-NL
CCMO	NL80460.056.22

Study results

Date completed: 15-07-2022

Results posted: 13-05-2024

Summary results
Trial ended prematurely

First publication
14-07-2023