A Phase 2 multi-center, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of T 817MA in patients with mild cognitive impairment due to Alzheimer*s Disease or mild Alzheimer*s Disease.

Published: 18-12-2018
Last updated: 12-04-2024

To evaluate the efficacy and safety of T-817MA in patients with mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Dementia and amnestic conditions
Study type	Interventional

Summary

ID

NL-OMON52556

Source
ToetsingOnline

Brief title
T817MAEU201

Condition

- Dementia and amnestic conditions

Synonym
Alzheimer's disease, Dementia

Research involving
Human

Sponsors and support

Primary sponsor: FUJIFILM Toyama Chemical Co., Ltd.
Source(s) of monetary or material Support: Fujifilm Toyama Chemical Co.;Ltd.

Intervention

Keyword: Alzheimer, Dementia, Neurology, T-817MA

Outcome measures

Primary outcome

Primary objective:

To evaluate the neuroprotective effect of T 817MA on Tau protein phosphorylated

at threonine 181 (p-tau181) in cerebrospinal fluid (CSF) compared with placebo

in patients with a diagnosis of MCI due to AD or mild AD.

Primary endpoint:

The change in the CSF p-tau181 from Baseline to Week 78.

Secondary outcome

Secondary objectives:

To evaluate in patients on T-817MA and placebo:

• cognitive function measured by the Clinical Dementia Rating Scale Sum of

Boxes (CDR-sb) and the Cognitive Functional Composite (CFC).

• AD-related biomarkers in CSF and plasma

• imaging analysis using volumetric magnetic resonance imaging (vMRI)

• alpha/theta ratio of the electroencephalogram (EEG)

To evaluate the safety of T 817MA by clinical laboratory tests and adverse

events (AEs).

To evaluate the pharmacokinetics of T 817MA in plasma and CSF.

Secundairy endpoints:

• The change in the CSF p-tau181 from Baseline to Week 52

• The change in AD-related biomarkers in CSF (p-tau217, total tau, Aβ1-42, Aβ1-40, neurofilament light [NFL], neurogranin, YKL-40 and Aβ1-42/Aβ1-40 ratio) from Baseline to Weeks 52 and 78

• The change in AD-related biomarkers in plasma (Aβ1-42, Aβ1-40, NFL, glial fibrillary acidic protein [GFAP], p-tau181, p-tau217 and Aβ1-42/Aβ1-40 ratio) from Baseline to Weeks 52 and 78

• The change in cognitive function assessed by CDR-sb and the CFC from Baseline to Weeks 28, 52 and 78

• The change in brain volume (total brain volume (TBV), ventricular volume and hippocampal volume) and cortical thickness measured by vMRI from Baseline to Weeks 52 and 78

• The change in alpha/theta ratio measured by the EEG from Baseline to Weeks 52 and 78

• Safety as assessed by the occurrence of AEs, clinical laboratory tests, vital signs, physical examinations, ECGs

• Population pharmacokinetics (PPK) analysis of T 817MA with assessment of maximum plasma concentration (Cmax), minimum plasma concentration (Cmin), and area under the plasma concentration-time curve during a dosage interval (AUCtau) at steady-state.

• The ratio of T-817 levels in CSF to plasma (CSF/plasma)

Study description

Background summary

Alzheimer's Disease (AD) is a progressive, incurable disease. It is characterized by degeneration of large portions of the brains, resulting in a progressive decline in cognitive functions and behavior with the typical symptoms of memory loss in patients. The therapeutic options for AD are limited and only reduce the symptoms. There is a need for treatments that address the underlying pathological process of the disease.

T-817MA is a low molecular weight compound, which shows neuroprotection and preservation of neural network by acting on both neurons and glial cells. In the previous phase 2 study targeting mild to moderate AD patients, dose-dependent decreases in both p-tau and total tau in CSF were observed and the differences between 448 mg of T-817MA and placebo were statistically significant. The data may suggest a neuroprotective effect of T-817MA against tau-related AD pathology. T-817MA may show benefit by modifying pathology of tau-related diseases (tauopathies) such as mild cognitive impairment (MCI) due to AD or early AD, because tau-related pathological changes of AD are known to precede memory and functional impairment.

Study objective

To evaluate the efficacy and safety of T-817MA in patients with mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease.

Study design

A Phase 2 multi-center, randomized, double-blind, placebo-controlled, parallel group study.

Intervention

During the first 4 weeks of treatment, two tablets per day will be administered (a daily dose of 224 mg T-817MA and placebo or placebo only); from Day 29 onwards two tablets per day will be administered (a daily dose of 448 mg or placebo).

Study burden and risks

Risks associated with study participation are the potential for adverse reactions to the study medication, concomitant medications, invasive study assessments like blood draws and lumbar puncture, and risks related to the process of undergoing brain MRI scans, and neuropsychological testing.

The most common adverse events associated with T-817MA seen in clinical studies conducted thus far are similar in study populations of healthy adults and patients with AD. They are headache, diarrhea, nausea, and dizziness. The adverse reaction most often deemed related to T-817MA is diarrhea.
Administration of one daily dose of 448 mg T-817MA, as will be done in this study, has been generally safe and well-tolerated.
Patients participating in this study may experience an improvement in their AD symptoms, even though such improvement cannot be predicted with any surety.
This study is expected to benefit the AD community by furthering the development of a new therapy and providing more information to those studying potential treatments for AD.

Contacts

Public
FUJIFILM Toyama Chemical Co., Ltd.

Kyobashi 2-chome 14-1
Chuo-ku, Tok 104-0031
JP
Scientific
FUJIFILM Toyama Chemical Co., Ltd.

Kyobashi 2-chome 14-1
Chuo-ku, Tok 104-0031
JP

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for enrolment:
1. Male or female, age 50 to 80 inclusive at date of ICF signature.
2. Diagnosis by the investigator of a clinical syndrome of cognitive impairment consistent with either MCI due to AD or mild AD per NIA-AA diagnostic criteria (Jack et al., 2018), with MMSE 24 to 30 (inclusive).
3. CSF results at screening consistent with the presence of Aß1-42 and p-tau181 abnormality (<=1000 pg/ml for Aß1-42, >=19 pg/ml for p-tau181) or (p-tau181/Aβ1-42 ratio >0.020 for patients with p-tau181 >=19 pg/ml and 10004. A brain MRI not-inconsistent with the clinical diagnosis of MCI due to AD or mild AD
5. Receiving an AChE inhibitor (donepezil, galantamine or rivastigmine) at a stable dose for more than 3 months prior to randomization, or not receiving any AChE inhibitors.
6. Weight of <= 100 kg (220 pounds) at Screening
7. Ability (patients and their study partners) to read, speak and understand local language to ensure compliance with cognitive testing and study visit procedures
8. Living in the community (includes assisted living facilities, but excludes long-term care nursing facilities)
9. Ambulatory, or able to walk with an assistive device, such as a cane or walker
10. If male, patients must:
a. agree he will not donate sperm during the study and until 104 days after the last dose, AND b. be required to use the following highly effective methods of contraception during the study and
until 104 days after the last dose:
i. Abstain from sexual intercourse OR
ii. Use a condom during sexual intercourse with
pregnant or non-pregnant women of childbearing potential (WOCBP) partner even if he is
vasectomized. In addition, WOCBP partner of the male patient (except a vasectomized male)
must use one of the following highly effective methods of contraception.
• Combined (estrogen and progestogen containing) hormonal contraception associated with
inhibition of ovulation: - oral - intravaginal - transdermal • Progestogen-only hormonal
contraception associated with inhibition of ovulation: - oral - injectable - implantable
• Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
11. If female, patients must:
a. be post-menopausal (i.e. no menses for 12 months without an alternative

medical cause) OR b. be permanently sterilized with methods including hysterectomy, bilateral salpingectomy and bilateral oophorectomy
12. A study partner who has regular contact with the patient for at least 10 hours per week and is able to participate in the patient*s clinical assessment and complete the questionnaire about the patient*s daily life at Screening, Baseline and Weeks 28, 52 and 78
13. Patient is clearly able to understand the nature, meaning and consequences of the clinical trial and its interventions and conveys his/her will to participate by personally signing the informed consent form
14. Written informed consent obtained from study partner

Exclusion criteria

Patients meeting any of the following criteria must not be included in the study:
1. Has had an MRI of the brain within the previous 2 years that showed pathology that would be inconsistent with a diagnosis of AD
2. Use of prohibited medications, including memantine
3. Has any contraindications for MRI including claustrophobia, the presence of metal (ferromagnetic) implants, or a cardiac pacemaker that is not compatible with MRI
4. Has any contraindications to lumbar puncture
5. Pregnant or breastfeeding woman
6. Psychiatric disorder such as schizophrenia or dementia not of the Alzheimer*s type according to the criteria of DSM-5
7. Other neurodegenerative diseases, including Parkinson*s disease and Huntington*s disease, or cerebral tumor
8. Dementia other than AD
9. History of untreated thyroid disorder, Type I diabetes, and insulin-dependent or uncontrolled Type II diabetes, as determined by the investigator (except non-insulincontrolled Type II diabetes, whose HbA1c value must be below 8.0 %). The HbA1c value should not be older than 6 months prior to screening. If no recent HbA1c value is available, then HbA1c should be assessed locally.
10. History of a seizure disorder or stroke, unless >5 years ago
11. History of alcohol abuse or dependence or drug abuse in the past 5 years
12. Uncorrected impairment of vision or hearing that would preclude the patient from taking tests or patients lacking the ability to communicate
13. Clinically significant abnormal laboratory values in the opinion of the investigator
14. Severe hepatic or severe renal impairment (e.g. bilirubin > 3 x ULN, AST/ALT > 5 x ULN, eGFR < 30 ml/min/1.73m2 or CrCl <30 ml/min)
15. Clinically significant B12 deficiency (i.e., no macrocytosis) in the opinion of the investigator
16. Severe heart disease (history of myocardial infarction, congestive heart

disease, history of unstable angina pectoris, clinically significant ECG abnormality) within 6 months prior to screening. Patients with arterial thrombosis will not be excluded if they are stable for at least 6 months prior to Screening
17. Cancer or a malignant tumor within the past 3 years, except patients who underwent potentially curative therapy with no evidence of recurrence.
18. Participation in another clinical trial for an investigational agent and having taken at least one dose of study medication, unless confirmed as having been on placebo, within 12 weeks prior to screening. (The end of a previous investigational trial is defined as the date of the last dose of an investigational agent.)
19. Participation in a previous clinical trial with T-817MA
20. Patients whom the investigator deems to be otherwise ineligible
21. Has an MRI of the brain at screening indicative of significant abnormality, including, but not limited to, prior hemorrhage or infarct, large (>1 cm) infarct, >2 lacunar infarcts outside the brain stem, severe white matter changes (Fazekas grade 3), >4 microbleeds, superficial hemosiderosis >1 cm, aneurysm, vascular malformation, subdural hematoma, hydrocephalus, space-occupying lesion (e.g, abscess or brain tumor such as meningioma).

Study design

Design

Study phase:	2
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):	15-11-2019
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Not applicable
Generic name:	edonerpic

Ethics review

Approved WMO Date:	18-12-2018
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-05-2019
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-05-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-06-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-06-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-06-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	07-10-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-10-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-11-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-11-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-06-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-06-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-09-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-09-2020
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-10-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-10-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-05-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-05-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-02-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-02-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-11-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	15-11-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2018-003567-66-NL
CCMO	NL67180.100.18

Study results