A proof of concept phase II study with the PDE-4 inhibitor roflumilast in patients with mild cognitive impairment (MCI)

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON24630

Source
Nationaal Trial Register

Brief title
ROMEMA

Health condition

MCI due to AD

Sponsors and support

Primary sponsor: ZonMw
Source(s) of monetary or material Support: ZonMw
University of Maastricht

Intervention

Outcome measures

Primary outcome

The main study parameter is cognitive performance using a test battery in which episodic memory is the primary outcome measure as assessed with the VLT (15 words), 5 times immediate recall, and a 20 min delayed recall.

Secondary outcome

Secondary tests include the ADAS-Cog scale (global cognition), MMSE (global cognition), Pattern Separation Memory Task (spatial memory), Letter Digit Substitution Test (information processing speed), Trail Making Test (information processing speed and executive functioning), as well as VLT recognition (verbal episodic memory). Other study parameters include assessment of clinically relevant effects including determination of anxiety and depression by the use of the Hospital Anxiety and Depression Scale (HADS), as well as the Neuropsychiatric Inventory (NPI) to determine neuropsychiatric symptoms. The EuroQoL scale and the Qol_AD will be included to measure quality of life. The Alzheimer's Disease Cooperative Study Activities of Daily Living Scale MCI (ADCS ADL-MCI) scale assesses the competence of the patients in basic and instrumental activities of daily living. The possible conversion to AD dementia (yes/no) will be considered as well, as will tau amount measurement in tears.

Study description

Background summary

Rationale: The current failure of drug trials in Alzheimer's disease (AD) treatment has shifted the focus toward delaying progression from mild cognitive impairment (MCI) to dementia, which would reduce the prevalence and costs of dementia profoundly. MCI represents a transitional stage between healthy aging and dementia, and it affects 10-15% of the population over the age 65. Research on the neurobiological foundations of learning and memory has shown the cognitive enhancing effects of different types of phosphodiesterase (PDE) inhibitors. Specific PDE inhibitors are known to improve communication between neurons by selectively inhibiting the activity of PDEs, enzymes that inactivate the intracellular second messengers. In 2010, roflumilast, a PDE-4 inhibitor, was approved as an anti-inflammatory drug under the name of Daxas (European Union) for the treatment of chronic obstructive pulmonary disease exacerbations (COPD). Its favorable side effect profile allowed the first studies in healthy adults and healthy elderly. Roflumilast has been shown to improve memory in healthy adults, as well as elderly subjects with pronounced memory impairment, indicative of amnestic MCI. Accordingly, the following protocol aims to provide a proof of concept phase II of the potential of roflumilast to aid mild cognitive impairment. Its chronic effect in clinical MCI patients above 50 years of age will be assessed using behavioral tasks, questionnaires and their informal caregiver's input.

Objective: The objective is to validate the chronic treatment effect of roflumilast on cognitive function i.e. episodic memory in MCI patients by means of behavioral tasks. Secondary, we will assess the effects of roflumilast on other cognitive domains and its resulting possible

interrelationship effect on mood.

Study design: The study will be conducted according to a double-blind, randomized placebo-controlled, between-subjects design.

Study population: 81, female and male, clinical patients with MCI due to AD (50-90 years old) will be recruited from our memory clinic at the Maastricht University Medical Center (MUMC+) and the Bio Bank-Alzheimer Center Limburg (BB-ACL) study (METC 15-4-100). Zuyderland MC will be included as a recruiting center i.e. only to draw attention to the study, not as a participating center. MCI due to AD diagnosis is characterized by a 1-2 standard deviation (SD) below the average memory performance on the delayed recall in the clinically relevant 15 words verbal learning test (VLT), and a decreased cerebrospinal fluid (CSF) A marker and/or a positive biomarker of neuronal injury i.e. magnetic resonance imaging (MRI) scan including measurements of decreased hippocampal volume or medial temporal atrophy by volumetric measures or visual rating).

Intervention: The study will consist of 3 arms (N = 27 per arm): placebo, 50 µg roflumilast and 100 µg roflumilast. The duration of treatment is 24 weeks and participants will be tested at baseline, acute intake, after 12 weeks, after completion of the treatment at 24 weeks, and two weeks thereafter (follow-up) to test if positive effects last.

Main study parameters/endpoints: Main study parameter includes the assessment of cognitive performance using a test battery in which episodic memory is the primary outcome measure, as assessed with the VLT (15 words, 5 times immediate recall, 20 min delayed recall and recognition). Secondary cognitive tests are the Alzheimer's Disease Assessment Scale-Cognitive Subscale (global cognition), Mini Mental State Examination (global cognition), Pattern Separation Memory Task (spatial memory), Letter Digit Substitution Test (information processing speed), and Trail Making Test (information processing speed and attention). Questionnaires used to assess clinically relevant effects are the Hospital Anxiety and Depression Scale, Neuropsychiatric Inventory, EuroQoL scale and QoL-AD (quality of life assessment), and the Alzheimer’s disease co-operative study activities of daily living scale (to measure instrumental and basic activities of daily living). Tau measurements in tear samples and lastly, the possible conversion to AD (yes/no), will be considered as well.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Time invested by the patient will be approximately 12 hours in total distributed over the time of 7 months (28 weeks), comprised of: filling in a medical questionnaire (30 minutes), explanation and filling in the informed consent (30 minutes), an assessment for eligibility (medical evaluation) (1 and a half hours), baseline test session (2 hours), acute test session after first single dose (3 hours), test session after 12 week chronic intake (2 hours), test session after completion of 24 week chronic intake (2 hours) and a test session two weeks post-completion for follow up (2 hours). Medical screening and test sessions are performed at the University of Maastricht. Additionally, the informal caregiver of the participant will accompany them to fill in the informed consent (30 minutes) and 2 questionnaires (per test day 30 minutes, total of 3 hours) related to daily living of the participant for each test day. The most common side-effects described for roflumilast are: weight loss, headache, nausea, diarrhoea, abdominal pain, insomnia, and dizziness. The

intensity has been described as mild. Measurement that could be perceived as uncomfortable are blood samples at each test session and tear samples at baseline and the 24-week mark test session. MCI has been described as the prodromal state of AD and as of now, no treatment has been made available for MCI. Intervention at an early stage could potentially slow down or even prevent the conversion to AD because of the possible neuroprotective and anti-inflammatory effects of roflumilast.

Study objective

1. Chronic treatment of 24 weeks with 50 µg roflumilast, compared to placebo, will improve episodic memory in MCI patients
2. Chronic treatment of 24 weeks with 100 µg roflumilast, compared to placebo, will improve episodic memory in MCI patients.

Study design

1. Medical screening (SCR)
2. Baseline test day (no intervention) (T0)
3. Acute intake intervention test day (T1)
4. 12-weeks of chronic intake test day (T2)
5. 24-weeks of chronic intake test day (T3)
6. Follow-up 2 weeks thereafter (T4)

Intervention

Participants will be instructed to take one capsule every day for 24 weeks. The capsule can be taken with or without food.

The following dose levels will be used, as well as a placebo that only contains principal constituent lactose monohydrate.

• Roflumilast (Daxas®), 50 µg orally (N = 27)
• Roflumilast (Daxas®), 100 µg orally (N = 27)
• Placebo, orally (N = 27)

Contacts

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Eligibility criteria

Inclusion criteria

- MCI due to AD diagnosis (diagnosis not older than 1 year), which includes either increased cerebrospinal fluid (CSF) Abeta marker and/or a positive biomarker of neuronal injury i.e. magnetic resonance imaging (MRI) scan including measurements of decreased hippocampal volume or medial temporal atrophy by volumetric measures or visual rating),
and a memory performance on the delayed recall in the 15 words VLT of 1-2 standard deviation(s) (SD) below the average.
- BMI between 18.5 and 30
- Age between 50 and 90 years
- (The same) informal caregiver for each test day
- MMSE of 20 or higher
- Willingness (both the participant and informal caregiver) to sign an informed consent

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participating in this study:
- Participants positive for human immunodeficiency virus (HIV) and Hepatitis B & C
- Normal Pressure Hydrocephalus (NPH)
- Morbus Huntington
- Parkinson's disease
- Recent Transient Ischemic Attack (TIA)
- Cerebrovascular Accident (CVA) (< 2 years)
- TIA/CVA followed by cognitive decline (within 3 months)
- COPD, asthma
- History of schizophrenia, bipolar disorder or psychotic symptoms not otherwise specified or previous treatment for these diseases (lifetime),
- Current affective disorder (i.e. anxiety or major depression)
- Cognitive problems due to alcohol abuse
- Brain tumor, epilepsy, encephalitis or lack of capacity to consent to participation
- Current treatment with (or illicit use of) centrally acting beta-blockers, cannabis, opiates, benzodiazepines, Methylenedioxymethamphetamine (MDMA) and cocaine.
- Use of medication showing strong inhibition of either CYP3A4 (e.g. clarithromycin, erythromycin and other antibiotics) or CYP1A2 (e.g. fluvoxamine, ciprofloxacin and other fluoroquinolones) is also an exclusion criterion because of interference with roflumilast

metabolism resulting in reduced therapeutic effectiveness of roflumilast.
- Individuals with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption will be excluded, as both the placebo and roflumilast contain lactose monohydrate.
- Additionally, during the period of the present study, participants are not allowed to participate in other drug trials.
- Lastly, if a participant does not have the possibility to be accompanied at every test session by the same informal caregiver (i.e. retraction informed consent) they will be excluded.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-01-2021
Enrollment:	81
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	16-12-2020
Application type:	First submission

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
NTR-new	NL9129
Other	METC azM/UM : METC 20-021

Study results