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Roflumilast and cognition in memory-impaired elderly

Submission date
08/05/2017

Recruitment status
No longer recruiting

Registration date
23/05/2017

Overall study status
Completed

Last Edited
18/02/2019

Condition category
Mental and Behavioural Disorders

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[X] Results
[ ] Individual participant data

Plain English summary of protocol

Background and study aims
With increasing age, more and more people are having problems with their memory, attention, planning and learning ability. This can often be a sign of a common condition called dementia, which describes the decline of the brain and its functioning. The ability to treat people with these complaints is currently limited. For this reason, new medications are being investigated that can help to reduce these complaints. Roflumilast, which is current being used to treat certain serious lung diseases, may have a positive impact on memory and could be used to treat memory problems. However, this requires more research. The aim of this study is determine whether aging associated cognitive (mental) impairment can be helped by roflumilast administration as assessed by cognitive tests.

Who can participate?
Elderly between 60 and 80 years of age.

What does the study involve?
Participants are randomly allocated as to which order they receive four different treatments. Participants attend four test days, where they are given either a placebo (dummy), 100 mcg, 250 mcg or 1000 mcg dose of roflumilast. By the end of the study, they will have had one of each of the doses. Participants receive the treatment (taken by mouth as a tablet) and then wait one hour to complete tests on the computer that tests their memory. Participants then complete two more delayed tests, one 110 minutes after they take the medication and another 24 hours to test their recalled memory. Participants also provide blood samples. In addition to measuring performance during a number of computer tests, the brain activity using an electroencephalogram (EEG) device to determine how the research tool affects memory.

What are the possible benefits and risks of participating?
There are no notable benefits with participating. Participants may experience discomfort when providing blood samples and while using electrodes. They may also feel tired due to the time commitment required from the study. It is possible that multiple tasks are performed in succession, this can be exhausting. Furthermore, it is possible that during the study it is

observed that you have a particular condition. The participant and GP are informed of any accidental findings. This applies especially to the examinations that are being done during the medical examination and also to the questions about participants psychological condition.

Where is the study run from?
Maastricht University (The Netherlands)

When is the study starting and how long is it expected to run for?
October 2013 till July 2015

Who is funding the study?
Takeda Pharma A/S (Denmark)

Who is the main contact?
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Contact information

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Public

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Scientific

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Additional identifiers

EudraCT/CTIS number
2013-001223-39

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
ROF-ALZ_103

Study information

Scientific Title
A randomized, double-blind, placebo controlled, four-period, cross-over study to evaluate the cognitive effects of single oral administration of roflumilast in age-associated memory impairment

Study objectives
The aim of this study is determine whether aging associated cognitive impairment can be attenuated by roflumilast administration as assessed by cognitive battery tests.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics Committee of Maastricht University and the Academic Hospital Maastricht (The Netherlands), 23/09/2013, ref: METC 13-3-033.5/pl

Study design
Randomized double-blind placebo controlled four-period cross-over study

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Dementia

Interventions
Participants are asked to attend four study visits in which each participant receives four treatments (one at each of the study visits). The order in which they receive each dose is

randomly allocated. Personnel not otherwise involved in the study generates the randomisation schedule, which is provided to the contract packaging facility prior to the start of the study. All randomization information is stored in a secured area, accessible only by authorized personnel. The four different doses are:

A) Placebo
B) Roflumilast 100 mcg
C) Roflumilast 250 mcg
D) Roflumilast 1000mcg

Participants receive the treatment at each of the four tests days consisting of a single capsule containing either placebo, 100, 250 or 1000 µg roflumilast. Participants received every dose only once.

Participants are instructed to wait one hour before they underwent a battery of tests measuring their cognitive functioning including the verbal learning test as well as electroencephalogram (EEG) measurements.

Participants also complete two delayed tests at two different time points. The first one is done 110 minutes after taking the medication and participants are asked to return to the study centre 24 hours later to complete the second delayed task. The entire study occurs over three months. In the study, the effects of the drug (roflumilast) will be compared to those of a placebo.

Intervention Type
Drug

Primary outcome measure
Number of recalled items in the immediate and two delayed tests as well as correct answers in recognition part is measured using the verbal learning test (VLT) at 60 minutes (immediate recall), 110 minutes (delayed recall and recognition) and 1140 minutes (delayed recall and recognition 24 hours later).

Secondary outcome measures
1. Amplitude and latency of ERP's are assessed during memorization phase of the VLT (ie, P300, N400, and P600) at 60 and 110 minutes
2. SMT outcome scores captured as the number of correctly localized items in the immediate and in the 2 delayed recalls and the recognition test at 75 (immediate recall), 20 (delayed recall) and 1450 minutes (delayed recall 24 hours later)
3. EEG measurements captured as the amplitude and latency of ERP's (ie, P300, N400, and P600) during the SMT at 75 and 110 minutes.
4. Stroop task outcome scores captured as both the number of errors and reaction time and the amplitude and latency of ERP's (ie, N200 and P300) at 85 and 1460 minutes (24 hours later)
5. EEG measurements captured as Mismatch Negativity (MMN) and P3a amplitude and latency during the Novelty oddball task at 125 minutes
6. EEG measurements captured as S2/S1 ratio and S1-S2 difference score of the P50 amplitude at sensory gating paradigm at 95 minutes
7. Cognitive improvement is measured by BL-VAS at baseline, 105, and 1435 minutes
8. Cmax and AUC of roflumilast and roflumilast N-oxide is measured by venipuncture at 70, 140, 1470 minutes (24 hours later). Blood samplesa re collected by certified study personnel by means of venipuncture. Blood samples are collected for measurement of roflumilast and roflumilast N-oxide concentrations at time points specified above. Plasma concentrations of

roflumilast and roflumilast N-oxide were determined using a validated assay using high-performance liquid chromatography with tandem mass spectrometry.

Overall study start date
01/04/2013

Completion date
01/07/2015

Eligibility

Key inclusion criteria
1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements
2. Signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures
3. Healthy adult as judged by Medical Supervisor
4. Aged 60 to 80 years, inclusive, at the time of informed consent
5. Memory performance between 1 to 2 SD below (for Impaired Elderly) and between 0.5 SD below and 0.5 SD above (for Healthy Elderly) age, gender, and education level corrected normative values assessed using the VLT
6. The subject has normal hearing demonstrated by average audiometric hearing thresholds of 20 dB hearing level (HL) and relatively symmetric hearing (left/right ear asymmetry of 15 dB)
7. Body mass index (BMI) between 18 and 30 kg/m2 inclusive at Screening
8. A male subject who is nonsterilized and sexually active with a female partner of childbearing potential agrees to use adequate contraception from signing of informed consent throughout the duration of the study and for 12 weeks after last dose
9. A female subject of childbearing potential who is sexually active with a nonsterilized male partner agrees to use acceptable methods of contraception from signing of informed consent throughout the duration of the study and for 12 weeks after last dose
10. Clinical laboratory evaluations (including clinical chemistry, hematology and complete urinalysis) within the reference range for the testing laboratory, unless the results are deemed not to be clinically significant (CS) by the investigator or sponsor at screening and Day 1 of Period 1

Participant type(s)
Healthy volunteer

Age group
Senior

Sex
Both

Target number of participants
80

Key exclusion criteria
1. Received any investigational compound within 30 days prior to the first dose of study medication

2. Received roflumilast in a previous clinical study or as a therapeutic agent
3. Immediate family member, study site employee, or in a dependant relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress
4. Uncontrolled, clinically significant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, or endocrine disease or other abnormality which may impact the ability of the subject to participate or potentially confound the study results
5. Previous or existing major psychiatric symptoms (evaluated through semi- Structured Clinical Interview for DSM MINI for the assessment of lifetime DSM-IV Axis -II diagnoses)
6. Known hypersensitivity to any component of the formulation of roflumilast or related compounds
7. Positive urine drug result for drugs of abuse at Screening Visit 2
8. History of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to the screening visit or is unwilling to agree to abstain from alcohol from 72 hrs prior to Day 1 through Day 2 of each Period and/or drugs throughout the study
9. Taken any excluded medication, supplements, or food products listed in the Excluded Medications and Dietary Products table listed in Section 7.3
10. Evidence of uncontrolled cardiovascular, central nervous system, hepatic, hematopoietic disease, renal dysfunction, metabolic or endocrine dysfunction, serious allergy, asthma hypoxemia, hypertension, seizures, or allergic skin rash. There is any finding in the subject's medical history, physical examination, or safety laboratory tests giving reasonable suspicion of a disease that would contraindicate taking roflumilast or a similar drug in the same class, or that might interfere with the conduct of the study as judged by Medical Supervisor. This includes, but is not limited to, peptic ulcer disease, seizure disorders, and cardiac arrhythmias.
11. Current or recent (within 6 months) gastrointestinal disease that would be expected to influence the absorption of drugs (ie, a history of malabsorption, esophageal reflux, peptic ulcer disease, erosive esophagitis frequent [more than once per week] occurrence of heartburn, or any surgical intervention [eg, cholecystectomy, bariatric surgery])
12. History of cancer within the past 5 years prior to the first dose of study medication. This criterion does not include those subjects with basal cell or stage I squamous cell carcinoma of the skin who are eligible.
13. Has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCV), human immunodeficiency virus (HIV) antibody/antigen at Screening
14. Used nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patch or nicotine gum) greater than the equivalent of 10 cigarettes per day during the one month prior to study start
15. Ppoor peripheral venous/arterial access
16. Donated or lost 450 mL or more of his or her blood volume (including plasmapheresis), or had a transfusion of any blood product within 3 months prior to Day 1
17. Abnormal Screening laboratory values that suggest a clinically significant underlying disease or subject with the following lab abnormalities: Alanine Aminotransferase (ALT) and/or Aspartate Aminotransferase (AST) >1.5 the upper limits of normal
18. Risk of suicide according to the Investigator's clinical judgment or has made a suicide attempt

Date of first enrolment
27/10/2013

Date of final enrolment
09/03/2015

Locations

Countries of recruitment
Netherlands

Study participating centre
The Department of Psychiatry and Neuropsychology
The Department of Psychiatry and Neuropsychology (Lead)
Faculty of Medicine, Heath and Life Sciences
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Study participating centre
The Department of Neuropsychology and Psychopharmacology
Faculty of Psychology and Neuroscience
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Sponsor information

Organisation
Takeda Pharma A/S

Sponsor details
Langebjerg 1
Roskilde
Denmark
DK-4000

Sponsor type
Industry

ROR
https://ror.org/03bsswy66

Funder(s)

Funder type

Industry

Funder Name
Takeda Pharma A/S

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal

Intention to publish date
31/12/2017

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study is not expected to be made available due to data being stored according to university policy on protected university servers and eventually by means of hardcopy at the university library protected storage facilities and will remain stored for a minimum of 15 years. Storage facilities are only accessible by authorized personnel. Data will be made available on request if needed, e.g. for a publication.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/05/2019		Yes	No