# A randomized, double-blind, placebo controlled, four-period, cross-over study to evaluate the cognitive effects of single oral administration of roflumilast in aging-related memory impairment

Published: 29-08-2013
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Primary Objective(s):1. To determine whether aging associated cognitive impairment can be attenuated by roflumilast administration as assessed by cognitive battery tests.Secondary Objective(s):1. To determine whether brain electrical activity (ie,...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Other condition |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON40236

**Source**
ToetsingOnline

**Brief title**
ROF-ALZ_103

### Condition

- Other condition

**Synonym**
mild memory impairment, sub-clinical cognitive deficits

**Health condition**

memory impairment

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Takeda
**Source(s) of monetary or material Support:** the pharmaceutical industry

## Intervention

**Keyword:** cognitive effects, eldery, phase 1, phospodiesterase

## Outcome measures

### Primary outcome

Primary endpoints:

1. VLT outcome scores captured as number of recalled items both in the immediate (ie, first, second, third, and total) and in the two delayed tests as well as captured as correct answers in the recognition part of the VLT.

### Secondary outcome

Secondary endpoints:

1. Amplitude and latency of ERP*s assessed during memorization phase of the VLT (ie, P300, N400, and P600).

2. SMT (Spatial memory task) outcome scores captured as the number of correctly localized items in the immediate and in the 2 delayed recalls and the recognition test.

3. EEG measurements captured as the amplitude and latency of ERP*s (ie, P300, N400, and P600) during the SMT.

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).

5. EEG measurements captured as Mismatch Negativity (MMN) and P3a amplitude and

latency during the Novelty oddball task.

6. EEG measurements captured as S2/S1 ratio and S1-S2 difference score of the

P50 amplitude at sensory gating paradigm.

7. Cognitive improvement as captured by BL-VAS (Bond-Lader Visual Analogue

Scales).

8. Cmax and AUC of roflumilast and roflumilast N-oxide.

Safety assessments:

1. Physical examination findings.

2. Vital signs.

3. 12-lead electrocardiogram (ECG) findings.

4. Clinical laboratory evaluations including hematology, chemistry and

urinalysis.

5. Treatment emergent adverse events (TEAEs).

# Study description

**Background summary**

Aging is known to be accompanied by cognitive deficits including learning and retention of new information. Several community based studies have estimated the prevalence rates of memory complaints varying from approximately 25% to over 50% (Jonker et al., 2000). It is important to note that people with memory complaints may have an increased risk of progressing towards dementia, including Alzheimer*s Disease (AD) (Dartigues et al., 1997; Elias et al., 2000; Stephan et al., 2010). Currently there are few drugs available to attenuate cognitive impairment in AD: four acetylcholinesterase inhibitors and one N-Methyl-D-aspartate antagonist (Loveman et al., 2006). Even though AD constitutes more than half of all dementias (Qiu et al., 2007), there is a significant and growing number of non-demented people with cognitive impairment having no claim to any form of pharmaceutical intervention.

In case the development of effective prevention strategies or treatments fail, it is predicted that the number of dementia cases will rise to 42.3 million in 2020 and 81,1 million by 2040 (Ferri et al., 2005). The development of goal-directed treatment is hampered by limited insight in the molecular groundwork of memory and in the mechanisms of ageing-related impairment. Recently, Phosphodiesterase-4 inhibitors (PDE-4i) gained more attention as a potential goal for cognitive improvement (Prickaerts et al., 2004; Blokland et al., 2006; Reneerkens et al., 2009).PDE-4i*s exert their actions by the selective inhibition of PDE-4, an enzyme which degrades the second messenger cyclic adenosine monophosphate (cAMP) (Bender and Beavo, 2006). Second messengers translate an extracellular signal, such as the binding of a neurotransmitter to its receptor, into structural (receptor and/or synapse formation) and non-structural (increased neurotransmitter release) cellular responses (Wei et al., 1998; Lu and Hawkins, 2002). Both responses increase the efficacy of signal transduction. Counteracting the function of PDE-4 prolongs the activity of cAMP which facilitates the transition from short-term to long-term memory (Barad, 2003). In contrast to the existing pro cognitive drugs, PDE-4i*s do not target a single neurotransmitter system, but exert their effects on the level of intracellular second messenger cascades. As a result, multiple neurotransmitter systems are affected, which might be preferable since optimal memory function relies on the action of different neurotransmitters (Myhrer, 2003; Rose et al., 2005).

The current study will include a battery that enables assessment of different domains of cognition including memory, attention, and response inhibition. In addition, electroencephalography (EEG) recordings including event-related potential (ERP) measurements will be included. The study aims at providing proof-of-mechanism for the pro-cognitive effects of roflumilast using cognitive deficits associated with aging as a model in certain subject populations in which cognitive deficits (ie, learning/memory) are well defined with screening.

**Study objective**

Primary Objective(s):
1. To determine whether aging associated cognitive impairment can be attenuated by roflumilast administration as assessed by cognitive battery tests.
Secondary Objective(s):
1. To determine whether brain electrical activity (ie, EEG) changes due to cognitive impairment can be normalized by roflumilast administration as assessed by EEG recordings.
2. To evaluate safety, tolerability, and pharmacokinetics of roflumilast and roflumilast N-oxide.
Exploratory objectives:
1. To explore the relationship between exposure of roflumilast and the pharmacodynamic endpoints observed on specific cognitive domains (eg, learning and memory, executive function, attention).

### Study design

The study will be a randomized, double-blind, placebo-controlled, four-period cross-over study designed to evaluate the effect of single-dose roflumilast in attenuating the cognitive deficits associated with aging.
The study will consist of 11 visits: (1) First screening visit (Day -28 to -7; prior to first dose, Day 1) covering memory screening (Verbal Learning Task, VLT) and psychiatric examination by qualified personnel (semi-structured clinical interview, Mini International Neuropsychiatric Interview [MINI] for the assessment of lifetime Diagnostic & Statistical Manual of Mental Disorders, 4th Edition [DSMI-V] Axis -II diagnoses), (2) Second screening visit covering full medical and neurological examination for the subjects met VLT criteria (Day -28 to -1), (3) Familiarization visit for cognitive testing (Day -7 to -1), (4) Four treatment/testing visits on Day 1 of each Treatment Period (each separated by 14 days; 2 days of testing and 12 days wash-out), and (5) Four postdose, 24-hour testing on Day 2 of each Treatment Period. A poststudy telephone call 12±3 days after the last treatment visit (Day 52). There is no subject confinement in this study.

### Intervention

Subjects will be treated 4 times with Roflumilast 100µg, 250µg, 1000µg and a placebo. The treatment order will be established by counterbalancing.

### Study burden and risks

The burden related to the actual testing is considered light. EEG measurements can be slightly inconvenient, but are not painful and do not limit normal functioning within the laboratory conditions. Test days take 2.5 hr in total, during which the subjects will actively perform cognitive tasks for 45 minutes. A short break is foreseen after 30 minutes of active testing. It is possible subjects will feel somewhat tired due to the test procedures.

## Contacts

**Public**
Takeda

Aldwych 61
London WC2B 4AE
GB
**Scientific**
Takeda

Aldwych 61
London WC2B 4AE
GB

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

1. Healthy subject, aged 60 to 80 years, inclusive, at the time of informed consent.
2. 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) aged, gender, and education level corrected normative values assessed using the VLT.;For a complete list of all inclusion criteria, please see protocol page 34.

## Exclusion criteria

1. Subjects with previous or existing major psychiatric symptoms.
2. Subjects received any investigational compound within 30 days prior to the study.
3 Subjects received Roflumilast in a previous study or as therapeutic agent.
For a complete list of all exclusion criteria, please see protocol page 34/35.

# Study design

## Design

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|---|---|
| Study type: | Interventional |
| Intervention model: | Crossover |

| | |
|---|---|
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

### Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 25-11-2013 |
| Enrollment: | 40 |
| Type: | Actual |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Daxas |
| Generic name: | Roflumilast |
| Registration: | Yes - NL outside intended use |

## Ethics review

Approved WMO

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|---|---|
| Date: | 29-08-2013 |
| Application type: | First submission |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |

Approved WMO

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|---|---|
| Date: | 23-09-2013 |
| Application type: | First submission |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |

Approved WMO

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|---|---|
| Date: | 18-11-2013 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |

Approved WMO

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|---|---|
| Date: | 20-11-2013 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |

Approved WMO

| | |
|---|---|
| Date: | 13-01-2014 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |

Approved WMO

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|---|---|
| Date: | 16-01-2014 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |

Approved WMO

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|---|---|
| Date: | 17-03-2014 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |

Approved WMO

| | |
|---|---|
| Date: | 16-05-2014 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |

Approved WMO

| | |
|---|---|
| Date: | 04-07-2014 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |

Approved WMO

| | |
|---|---|
| Date: | 18-07-2014 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |

Approved WMO

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|---|---|
| Date: | 24-10-2014 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit |

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|---|---|
| | Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 19-12-2014 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |

# 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 | EUCTR2013-001223-39-NL |
| CCMO | NL44887.068.13 |