A European Multicentre Double-Blind Placebo Controlled trial of Nilvadipine in Mild to Moderate Alzheimer*s disease

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neurological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON37208

Source
ToetsingOnline

Brief title
NILVAD study

Condition

- Neurological disorders NEC

Synonym
Alzheimer disease, dementia

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Europese Unie (hoofdstudie+substudie 1&2);voor substudie 3 (CBF) wordt geld aangevraagd

Intervention

Keyword: Alzheimer disease, calcium channel blocker, elderly, nilvadipine

Outcome measures

Primary outcome

The primary efficacy outcome measures in this study is the change from baseline to week 78 in cognitive function, as assessed by the Alzheimer*s -Disease Assessment Scale (ADAS -Cog 12). The analysis will take account of the intermediate levels of this measure.

Substudy 1 (frailty): the change from baseline to week 78 in the frailty index (if a statistically significant effect is seen the change to week 13 and 52 will be considered as co-primary)

Substudy 2 (research bloods): the change from baseline to week 78 in measured biomarkers

Substudy 3 (CBF): the change from baseline to week 26 (with change to week 78 as a co-primary, when the change to week 26 is significant) in cerebral blood flow, as assessed by pulsed Arterial Spin Labeling MRI

Secondary outcome

There are two key secondary outcome measures, the Clinical Dementia Rating Scale Sum of Boxes (CDR-sb) and the Disability Assessment for Dementia (DAD). If a statistically significant effect is seen in the primary outcome, CDR-sb

will be considered to be a co-primary endpoint and only the DAD will contribute to the secondary outcome analysis.

Substudy 3 (CBF): the change from baseline to week 26 and to week 78 in:

-Blood pressure

-Blood pressure variability

-Cerebral autoregulation as measured by the dynamic relationship between: 1) Blood pressure changes (Finapres), 2) Cerebral blood flow velocity, measured in the middle cerebral artery (TCD), 3) Oxy/deoxy hemoglobin concentration in the frontal cortex (NIRS)

-Orthostatic hypotension

-Vasomotor reactivity

-White matter integrity (MD/FA, measured with DTI)

-Regional CBF (ASL): frontal, temporal lobes and insula

Study description

Background summary

Alzheimer*s disease (AD) is an ever-increasing public health concern among the aging population and is the most common form of dementia affecting more than 15 million individuals worldwide and around 5 million Europeans. The direct and indirect costs of AD and other dementias amount to more than ¤440,000 million each year (www.alz.org, 2010). It is estimated that by 2050, 1 in 85 of the population worldwide will have AD and that approximately 40% of these cases will need the level of care equivalent to a nursing home. Even modest therapeutic advances that lead to small delays in Alzheimer*s onset and progression could significantly reduce the global and European burden of the disease and the level of care required by patients. While there are

symptomatic-based drug therapies available for AD, these medications do not stop the disease process or prevent neuronal degeneration. There is therefore a clear unmet medical and public health need for the development of new treatments for AD that have disease modifying effects.

Study objective

The objectives of this study are to investigate the efficacy and safety of Nilvadipine as a disease course modifying treatment for mild to moderate AD in a phase III double-blind placebo-controlled study.

substudy1 (frailty): the objectives of this study is to investigate the efficacy of Nilvadipine on the frailty index in patients who participate in this NILVAD substudy.

substudy 2 (research bloods): the objectives of this study is to investigate the genetic influences on the effect of Nilvadipine (through APOE4) and to better understand the biological effects of Nilvadipine in humans by measuring changes in biomarkers (amyloid, tau and inflammatory markers) in patients who participate in this NILVAD substudy.

substudy 3 (CBF): the objectives of this study is to investigate the efficacy of Nilvadipine on blood pressure, cerebral autoregulation, cerebral blood flow, and -damage in patients who participate in this NILVAD substudy.

Study design

randomized double-blind placebo controlled parallel design

Intervention

Over encapsulated nilvadipine 8 mg, sustained release capsule, for the treatment group, taken once a day at lunchtime or, matching over encapsulated placebo for the control group, taken once a day at lunchtime.

Study burden and risks

Risk: Previous research showed that Nilvadipine is well tolerated by patients with AD. Considering this finding and the low dosis of the medication we do not expect a risk for the patient.

Burden: the study comprises 10 visits spread over 1,5 year. The visits are well distributed over this period of time. We experience that patients find it pleasant to regularly visit their doctor.

NOTE: the burden may increase if the patient chooses to participates in one or more of the substudies. Further we will apply for an extra substudy for the patients in Nijmegen, which results in more measurements.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

-prior diagnosis of mild to moderate AD based on NINCDS-ADRDA criteria
-age range: males and females over age 50 years.
-SMMSE score greather than or equal to 12, and less than 27
-stable dose (>3 months of cholinesterase inhibitor and or memantine). Subjects who are not on cholinesterase inhibitors or memantine due to poor tolerability and/or who will not require treatment with these medications during the course of the study can be included.
-Collateral informants such as a spouse, family member, close friend. The informant must

have close contact with the subject and agree to monitor/manage study drug adherence, observe for possible adverse events, assist with psychometric measures requiring informant information, and accompany the subject to all evaluation visits.
-Fluency in relevant language sufficient to reliably complete all study assessments.
-Systolic BP between 100 mmHg and 159 mmHg, and diastolic BP between 65 mmHg and 99 mmHg on resting office based BP measurements, or a Systolic BP between 105 mmHg and 140 mmHg, and diastolic BP between 70 mmHg and 90 mmHg on ABPM measurement.
-written informed consent of patient and collateral informant

Exclusion criteria

-Diagnosis of significant neurological disease other than AD
-Subjects currently taking any calcium channel blocker or betablocker
-Subjects who in the opinion of the investigator, have a medical condition that would preclude them from participating in the study (e.g.hemodynamically significant coronary artery disease., chronic heart failure, syncope within the past year, significant valvular heart disease i.e. severe aortic and mitral stenosis.. symptomatic orthostatic hypotension within the last year, subjects requiring more than one agent to control BP.), or subjects who in the opinion of the investigator are unlikely to complete per protocol due to care issues etc.
-Current Axis I diagnosis of schizophrenia, bipolar disorder, major depression. Subjects who are currently or who have within the past year met criteria for drug or alcohol abuse or dependence.
-Subjects with a history of hypersensitivity to nilvadipine (Nivadil).
-Subjects who have taken an investigational or other unapproved drug during the 30 days or five half-lives, whichever is longer, prior to baseline.
(remaining, see protocol 4.3);substudy 3 (CBF): MRI-contra indication (metal implants, claustrophobia)

Study design

Design

Study phase:	3
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):	20-06-2013
Enrollment:	100
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nivadil
Generic name:	Nilvadipine

Ethics review

Approved WMO Date:	21-12-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-04-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-09-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-03-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-04-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	27-10-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2012-002764-27-NL
CCMO	NL40980.091.12

Study results

Date completed:	31-10-2016
Actual enrolment:	77

Summary results
Trial is onging in other countries