

A trial of Nilvadipine in mild to moderate Alzheimer's disease

Submission date 22/07/2013	Recruitment status No longer recruiting	<input type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
Registration date 22/07/2013	Overall study status Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
Last Edited 19/08/2019	Condition category Nervous System Diseases	<input type="checkbox"/> Individual participant data

Plain English summary of protocol

Background and study aims

Alzheimer's disease (AD) is the most common form of dementia for which currently there is no cure available. Early symptoms include memory loss and mild cognitive impairment, often related to stress or aging. As the disease progresses, symptoms worsen to affect all areas of brain function, such as memory, behaviour, language and motor skills. In the final stages of Alzheimer's disease, the patient is completely dependent upon caregivers.

With more than 15 million people affected worldwide (5 million in Europe), Alzheimer's disease is an ever-increasing public health concern among the aging population, causing a great burden to patients and their caregivers. The economic costs of Alzheimer's disease and other dementias are estimated at more than 180 billion in Europe each year.

Even small advances in treatment that delay the start of disease (onset) or its progression could significantly reduce the global burden of the disease and the level of care required by patients. While there are drug therapies available for AD that treat symptoms, these medications do not delay onset, slow progression or prevent the disease process itself. Therefore it is necessary to develop new treatments for AD that have disease-modifying effects.

The aim of this study is to investigate the effectiveness and safety of the drug nilvadipine in Alzheimer's disease. Nilvadipine is a licensed blood pressure medication with a proven safety record in people with high blood pressure and more recently has been shown to be well tolerated and safe in older people with Alzheimer's disease. There is preliminary evidence for clinical benefit in individuals with cognitive impairment and strong scientific evidence based on animal model studies of Alzheimer's disease.

Who can participate?

The study will recruit 500 people over 50 with mild to moderate Alzheimer's disease.

What does the study involve?

Participants will be randomly allocated to receive either nilvadipine or placebo (dummy) for 78 weeks.

What are the possible benefits and risks of participating?

This study tests whether nilvadipine has a disease-modifying effect in mild to moderate Alzheimer's disease. If this is found to be correct, patients may benefit from this treatment.

In routine treatment, effects of medication are not monitored as regularly as in this study, so patients may benefit from the routine examinations during study participation. Subjects administered the nilvadipine drug may experience adverse events, adverse drug reactions or other clinically significant complaints, symptoms or other abnormalities. However, the risk associated with the trial is low. Nilvadipine is a licensed medication for high blood pressure in certain European countries with a reliable safety profile. A successful short-term safety study was carried out on Alzheimers patients in 2008 which showed very good tolerability in this patient population over the 6-week trial period.

Where is the study run from?

The study will be conducted across 23 study sites in nine partner countries (Ireland, UK, Netherlands, Sweden, Greece, Hungary, France, Italy, Germany) and is being coordinated by Prof Brian Lawlor from Trinity College Dublin, Ireland.

When is the study starting and how long is it expected to run for?

The study started in May 2013 and will be recruiting patients until December 2014. The study is expected to complete in July 2016.

Who is funding the study?

The study is funded by the European Commission's Framework 7 programme.

Who is the main contact?

Fiona Cregg
creggf@tcd.ie

Study website

<https://www.nilvad.eu/#>

Contact information

Type(s)

Scientific

Contact name

Ms Jessica Adams

Contact details

Institute Of Psychiatry
16 De Crespigny Park
London
United Kingdom
SE5 8AF
+44 (0)207 848 0549
Jessica.adams@kcl.ac.uk

Additional identifiers

EudraCT/CTIS number

2012-002764-27

IRAS number**ClinicalTrials.gov number**

NCT02017340

Secondary identifying numbers

14541

Study information

Scientific Title

A European multicentre double-blind placebo controlled phase III trial of nilvadipine in mild to moderate Alzheimer's disease

Acronym

NILVAD

Study objectives

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

More details can be found at: http://www.nilvad.eu/fileadmin/websites/nilvad/media/NILVAD_Brochure.pdf

Ethics approval required

Old ethics approval format

Ethics approval(s)

NRES Committee- North London Harrow, 06/02/2013, ref 12/LO/1903

Study design

Randomized double-blind placebo controlled parallel; Design type: Treatment

Primary study design

Interventional

Secondary study design

Randomised controlled trial

Study setting(s)

Hospital

Study type(s)

Treatment

Participant information sheet

https://www.nilvad.eu/fileadmin/websites/nilvad/media/NILVAD_Brochure.pdf

Health condition(s) or problem(s) studied

Topic: Dementias and Neurodegenerative Diseases Research Network; Subtopic: Dementia;
Disease: Alzheimer's Disease

Interventions

A total of 500 subjects with Alzheimers disease; 250 in the nilvadipine group and 250 in the placebo group recruited from 31 European centres.

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.

The total study duration will be 82 weeks. Patients will receive study medication for 78 weeks.

Intervention Type

Drug

Phase

Phase III

Drug/device/biological/vaccine name(s)

Nilvadipine

Primary outcome measure

Cognitive and non-cognitive symptoms of Alzheimer's disease are measured using the Alzheimer's Disease Assessment Scale (ADAS) at baseline, 13, 52 and 78 weeks

Secondary outcome measures

1. Involvement in activities of daily living are measured using the Disability Assessment for Dementia (DAD) at baseline, 13, 52 and 78 weeks
2. Severity of symptoms is measured using the Clinical Dementia Rating Scale (CDR) Assessments at baseline, 13, 52 and 78 weeks

Overall study start date

01/01/2012

Completion date

19/12/2016

Eligibility

Key inclusion criteria

1. Age range: Adult subjects, males and females over age 50 years.
2. Subjects with a diagnosis of probable Alzheimers disease based on the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimers disease and Related Disorders Association, Inc (NINCDS-ADRDA) criteria (McKhann et al, 1984)
3. Subjects with a Standardised Mini-Mental State Examination (SMMSE) (Standish & Molloy, 1991) score of greater than or equal to 12 and less than 27.
4. Subjects on a stable dose (>3 months) of cholinesterase inhibitor or memantine. The dose must be stabilised prior to randomisation. Patients due to begin these medications must not be enrolled until the dose is stabilised. 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.

5. Subjects who retain capacity will provide written informed consent for participation. The procedure for obtaining informed consent when the subject has reduced decision making capacity will follow national law and will be assessed by the relevant bodies in each of the participating countries.

6. Fluency in relevant language sufficient to reliably complete all study assessments.

7. Subjects with blood pressure values greater than 100/65 mmHg but less than 159/99 mmHg (Grade 1 hypertension, ECS guidelines 2007; escardio.org/guidelines) using an office based BP measurement will be included.

Subjects with blood pressure values greater than 105/70mmHg but less than 140/90 mmHg using an Ambulatory BP measurement will be included.

Participant type(s)

Patient

Age group

Adult

Sex

Both

Target number of participants

Planned Sample Size: 500; UK Sample Size: 60

Key exclusion criteria

1. Subjects with co-morbid dementia due to other neurological disorders such as Parkinson's disease, vascular dementia, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, brain dementia, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, brain tumour, progressive supranuclear palsy, seizure disorder, subdural hematoma, or multiple sclerosis, as well as subjects with HIV disease, neurosyphilis, history of significant head trauma with loss of consciousness followed by persistent neurological deficits, known structural brain abnormalities, or any other condition known to interfere with cognitive function.
2. Subjects currently taking any calcium channel blocker or beta-blocker
3. 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.
4. 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.
5. Pregnant women or women who may possibly become pregnant.
6. Female subjects who are breastfeeding will be excluded from the study
7. Subjects with a history of hypersensitivity to nilvadipine (Nivadil).
8. Subjects who have taken an investigational or other unapproved drug during the 30 days or five half-lives, whichever is longer, prior to baseline.
9. Subjects who are taking any medication listed in the list of exclusion medication for the study.
10. Subjects with abnormal ECG results which prevent participation in the study.
11. Standardised Mini-Mental State Examination (SMMSE) score of less than 12 or greater than 26.

12. Subjects who are participating in other clinical research studies.
13. Subjects with any clinically significant laboratory blood test abnormality on his/her screening test.
14. Subjects with blood pressure values less than 100/65 mmHg but greater than 159/99 mmHg (Grade 1 hypertension, ECS guidelines 2007; escardio.org/guidelines) using an office based BP measurement will be excluded. Subjects with blood pressure values less than 105/70mmHg but greater than 140/90 mmHg using an Ambulatory BP measurement will be excluded.
15. Subjects with clinically significant abnormalities in their CT/MRI results which would prevent inclusion in the study.
16. Patients with significant renal insufficiency (estimated glomerular filtration rate: eGFR <30ml/min) will be excluded .
17. Subjects with severely impaired hepatic function (liver cirrhosis) will be excluded.
18. The medical food stuff Souvenaid® is under exclusion from the study.

Date of first enrolment

23/04/2013

Date of final enrolment

10/04/2015

Locations

Countries of recruitment

England

France

Germany

Greece

Hungary

Ireland

Italy

Netherlands

Sweden

United Kingdom

Study participating centre

St. James's Hospital

James Street

Dublin

Ireland

Study participating centre

St Finbarrs Hospital

Douglas Road

Ballinlough

Cork

Ireland

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Study participating centre

Centre Hospitalier Regionale et Universitaire de Lille

Avenue Oscar Lambret, 2

Lille

France

59037

Study participating centre

Centre Hospitalier de Béthune

27 Rue Delbecque

Verquigneul

France

62131

Study participating centre

Centre Hospitalier Universitaire de Caen

Avenue de la Côte de Nacre

Caen

France

14033

Study participating centre

Hospital Center De Lens

99 Route de la Bassée

Lens

France

62300

Study participating centre

CHU Amiens-Picardie

1 Place Victor Pauchet

Amiens
United Kingdom
80000

Study participating centre
Centre Hospitalier de Calais
1601 Boulevard des Justes
Calais
France
62107

Study participating centre
Centre de Recherche Clinique - DRM
53-55 rue Jean Jaurès
Lille
France
59000

Study participating centre
Universität Ulm
Helmholtzstraße
Ulm
Germany
89081

Study participating centre
AHEPA University Hospital
Kiriakidi 1
Thessaloniki
Greece
546 21

Study participating centre
Papageorgiou General Hospital
Pavlos Melas
Papageorgiou
Greece
564 29

Study participating centre
Papanikolaou Peripheral General Hospital
Epar.Od. Asvestochoriou
Chortiatis
Greece
570 10

Study participating centre
University of Szeged
Dugonics square 13
Szeged
Hungary
H-6720

Study participating centre
Ospedale MultiMedica Castellanza
Viale Piemonte, 70
Castellanza
Italy
21053

Study participating centre
University of Genova
Department of Neuroscience, Ophthalmology and Genetics (DiNOG)
Via Balbi, 5
Genova
Italy
16126

Study participating centre
Fondazione Don Gnocchi - Centro IRCCS S. Maria Nascente
Via Alfonso Capecelatro, 66
Milan
Italy
20148

Study participating centre
IRCSS-San Giovanni di Dio-Fatebenefratelli
Via Corsica, 339

Brescia
Italy
25125

Study participating centre
Radboudumc
Geert Grooteplein Zuid 10
Nijmegen
Netherlands
6525 GA

Study participating centre
Academisch Ziekenhuis Maastricht
Ziekenhuisapotheek
P. Debyelaan 25
Maastricht
Netherlands
6229 HX

Study participating centre
Ziekenhuisapotheek Rijnstate
Wagnerlaan 55
Arnhem
Netherlands
6815 AD

Study participating centre
Saghlgrenska Academy
Dept. of Psychiatry and Neurochemistry
Wallinsgatan 6
Mölndal
Sweden
SE-43141

Study participating centre
Maudsley Hospital
King's College London
Denmark Hill
Camberwell

London
United Kingdom
SE5 8AZ

Sponsor information

Organisation

St James Hospital (Ireland)

Sponsor details

James Street
Dublin
Ireland
Dublin 8
+353 1 896 1000
creggf@tcd.ie

Sponsor type

Hospital/treatment centre

Website

<http://www.stjames.ie/>

ROR

<https://ror.org/04c6bry31>

Funder(s)

Funder type

Government

Funder Name

European Commission Framework 7 programme; Grant Codes: 279093

Results and Publications

Publication and dissemination plan

Planned publication in a high-impact peer reviewed journal in mid 2017.

Intention to publish date

31/07/2017

Individual participant data (IPD) sharing plan

The current data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	09/10/2014		Yes	No
Results article	results	24/09/2018		Yes	No
Results article	results	21/05/2019	19/08/2019	Yes	No
Results article	results	01/08/2019	19/08/2019	Yes	No
HRA research summary			28/06/2023	No	No