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Geriatric medicine

Protocol

NILVAD protocol: a European multicentre double-blind placebo-controlled trial of nilvadipine in mild-to-moderate Alzheimer's disease

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Abstract

Introduction This study is a European multicentre, randomised, double-blind, placebo-controlled trial investigating the efficacy and safety of nilvadipine as a disease course modifying treatment for mild-to-moderate Alzheimer's disease (AD) in a phase III study that will run for a period of 82 weeks with a treatment period of 78 weeks.

Methods and analysis Adult patients, males and females over 50 years with mild-to-moderate AD as defined by the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA) criteria, will be included in the study. It aims to recruit a total of 500 patients with AD; 250 in the nilvadipine group and 250 in the placebo group. Participants will be randomised to receive nilvadipine, an 8 mg overencapsulated, sustained release capsule, or a matching overencapsulated placebo (sugar pill) for a period of 78 weeks of treatment. The primary efficacy outcome measure in this study is the change in cognitive function as assessed by the Alzheimer's disease Assessment Scale (ADAS-Cog 12) from baseline to the end of treatment duration (78 weeks). 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 coprimary end point and only the DAD will contribute to the secondary outcome analysis.

Ethics and dissemination The study and all subsequent amendments have received ethical approval within each participating country according to national regulations. Each participant will provide written consent to participate in the study. All participants will remain anonymised throughout and the results of the study will be published in an international peer-reviewed journal.

Trial registration number EUDRACT Reference Number: 2012-002764-27.

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Strengths and limitations of this study

Large European multicentre double-blind, randomised placebo-controlled trial.

Investigator driven.

Testing a repositioned medication with a proven safety profile and approved for the treatment of hypertension.

Does not test the disease modifying efficacy and safety of nilvadipine at the predementia stage.

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Introduction

The current disappointing state of clinical trials aimed at advancing therapeutic interventions for Alzheimer's disease (AD) has necessitated the need for development of novel strategies that target multiple aspects of the pathogenic process in this neurodegenerative condition. Furthermore, ideally, any novel drugs or compounds tested would have a demonstrated safety profile in order to expedite the path to clinical application.

Calcium antagonists or calcium channel blockers (CCBs) were first introduced over 25 years ago as coronary vasodilators for the treatment of coronary heart disease, and have since achieved notable recognition in the treatment of arterial hypertension.¹ Nilvadipine (trade name: Nivadil), a dihydropyridine (DHP) calcium channel antagonist, is currently licensed to treat patients with hypertension.² However, recent research has highlighted other properties of certain CCBs, including

nilvadipine, suggesting that they are protective not just against stroke-related dementia, but also independently against AD.³

Research to date has suggested that the AD preventive effect of DHP CCBs, may not be mediated through their antihypertensive effects, but rather via an anti- β -amyloid ($A\beta$) mechanism where the accumulation of $A\beta$ in the brain is reduced by altering $A\beta$ production in the brain and $A\beta$ clearance across the blood–brain barrier (BBB). Paris et al investigated the effects of a number of commonly used antihypertensive DHPs and non-DHPs on $A\beta$ production both in vitro and in vivo and found that not all DHPs are equal. Nilvadipine and amlodipine were found to significantly lower $A\beta_{40}$ as well as $A\beta_{42}$ production in vitro, however, other DHPs and non-DHPs had little effect or even increased $A\beta_{40}$ and $A\beta_{42}$ production in vitro. The in vivo studies using transgenic mouse models of AD (Tg PS1/APPsw) highlighted nilvadipine reduced levels of $A\beta$ in the brain and, furthermore, nilvadipine enhanced $A\beta$ clearance across the BBB. In addition to these properties, nilvadipine has shown efficacy against a broad range of AD pathological mechanisms, including τ -phosphorylation, reduced cerebral blood flow and neuroinflammation.³

Studies have found that nilvadipine is distributed extensively throughout the body, including the brain and has been shown to have a cerebrocirculatory enhancing effect.⁴ Nilvadipine has also been shown to protect low-density lipoprotein cholesterol from in vivo oxidation in patients with hypertension with high risk of atherosclerosis and to inhibit the generation of cytokines derived from activated T lymphocytes in collagen disease complicated with essential hypertension.^{5,6}

Several epidemiological studies with different calcium channel antagonists have been conducted to determine their potential usefulness in the management of AD. In the Systolic Hypertension in Europe (Syst-Eur) trial, which involved active treatment with the DHP CCB nitrendipine in over 2400 patients, there was a 55% reduction in the incidence of AD.⁷ The Baltimore Longitudinal Study of Ageing also found a strong trend towards reduced relative risk of AD in patients treated with DHP CCBs, with no lowered risk observed in the non-DHP CCB treatment group.⁸

Furthermore, nilvadipine has been shown to have favourable effects on cognitive function with stabilisation of cognitive decline and reduced conversion to AD in patients with hypertension with mild cognitive impairment.⁹ A study by Kennelly et al¹⁰ provided preliminary evidence suggesting the potential efficacy in the treatment of AD. A 6-week open label study demonstrated that nilvadipine was well tolerated in patients with AD.¹¹ A nilvadipine slow release 8 mg formulation did not reduce blood pressure (BP) in non-hypertensive patients with AD, but appropriately lowered BP in hypertensive cases. No patient started on nilvadipine requested or required discontinuation of the medication throughout this study, highlighting that nilvadipine is well tolerated in patients with AD and has demonstrated safety as a licensed antihypertensive treatment.

In summary, this study will investigate the safety and efficacy of nilvadipine as a disease-modifying treatment in patients with mild-to-moderate AD over a period of 18 months across nine countries in Europe including Ireland, Germany, Greece, France, Holland, Hungary, Italy, Sweden and the UK.

Overall, the aim is to build on the initial studies of nilvadipine as a treatment for AD by investigating its efficacy and establish its safety profile in a phase III double-blind, randomised, placebo-controlled trial.

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Methods and analysis

Trial design

This is a multicentre, randomised, double-blind, placebo-controlled study of nilvadipine compared with placebo. Eligible patients will be randomly assigned to receive 8 mg of nilvadipine or placebo daily for 78 weeks of treatment. Patients will initially undergo a screening assessment to confirm eligibility. This will be followed by a baseline visit (week 0), when each patient is randomised and will receive the first dose of study medication. Patients will then undergo assessments at weeks 6, 13, 26, 39, 52, 65 and 78 (± 7 days) after beginning treatment. A final follow-up assessment will be undertaken at 82 weeks (study end point).

Inclusion/exclusion criteria

Patients diagnosed with mild-to-moderate AD based on the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's disease and Related Disorders Association, Inc (NINCDS-ADRDA) criteria are suitable for treatment with nilvadipine.¹² See box 1 for details of study inclusion and exclusion criteria.

Box 1 Inclusion and exclusion criteria

Inclusion criteria

Males and females over age 50.

Diagnosis of probable Alzheimer's disease.

Standardised Mini-Mental State Examination (SMMSE; Standish & Molloy, 1997) score of greater than or equal to 12 and less than 27.

Patients on a stable dose (>3 months) of cholinesterase inhibitor or memantine.

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

Patients with blood pressure (BP) values greater than 100/65 mm Hg but less than 159/99 mm Hg using an office-based BP measurement, or patients with BP values greater than 105/70 mm Hg but less than 140/90 mm Hg using an ambulatory BP measurement.¹⁹

Patients who retain capacity will provide written informed consent for participation.

Patients 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.

Exclusion criteria

Patients with comorbid 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 tumour, progressive supranuclear palsy, seizure disorder, subdural haematoma or multiple sclerosis, as well as patients 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.

Patients currently taking a calcium channel blockers (CCB) or β -blocker.

Patients who, in the opinion of the investigator, have a medical condition that would preclude them from participating in the study, for example, chronic heart failure, syncope within the past year, significant valvular heart disease, that is, severe aortic and mitral stenosis, or symptomatic orthostatic hypotension within the last year.

Patients with significant cardiovascular disease including recent history of acute myocardial infarction or unstable angina pectoris.

Patients who in the opinion of the investigator are unlikely to complete the protocol due to care issues, etc.

Current Axis I (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM IV)) diagnosis of schizophrenia, bipolar disorder or major depression.

Patients who are currently or who have within the past year met criteria for drug or alcohol abuse or dependence.

Pregnant women or women who may possibly become pregnant (premenopausal). Female patients must be postmenopausal (no menses for ≥ 12 months without an alternative medical cause) to participate in the study.

Female patients who are breast feeding.

Patients with a history of hypersensitivity to nilvadipine (Nivadil).

Patients who have taken an investigational or other unapproved drug during the 30 days or 5 half-lives, whichever is longer, prior to baseline.

Patients who are taking any excluded medications. Specific groups of medications are excluded in the trial, including CCB, β -blocker, α -agonist and nitrates.

Abnormal ECG results that, in the opinion of the clinician, prevent participation in the study.

SMMSE score of less than 12 or greater than 26.

Patients who are participating in other clinical research studies.

Clinically significant laboratory blood test abnormality on his/her screening test.

Significant renal impairment (estimated glomerular filtration rate: < 30 mL/min).

Severe hepatic impairment (liver cirrhosis).

BP values less than 100/65 mm Hg or greater than 159/99 mm Hg using an office-based BP measurement or patients with BP values less than 105/70 mm Hg or greater than 140/90 mm Hg using an ambulatory BP measurement.

Patients with clinically significant abnormalities in their CT/MRI results, which would prevent inclusion in the study.

The medical food stuff Souvenaid is under exclusion from the study.

Randomisation and blinding

To prevent the introduction of bias, randomisation will be via an online system, accessed via <http://www.ctu.co.uk>, hosted by the Clinical Trials Unit (CTU), King's College London (KCL). Eligible participants will be randomised to either the nilvadipine or placebo treatment group. The nilvadipine capsules and placebo capsules will be packaged and labelled identically. Randomisation will be at the level of the individual patient, using block randomisation with randomly varying block sizes and stratified by country site. Once the patient has been randomised, the online system will automatically recognise which treatment packs are located in each study pharmacy at the recruiting study site and will randomly select a pack in the appropriate trial arm to be dispensed to the patient. All study staff at all sites will be blinded to treatment allocation and will remain blind until the end of the trial.

Unblinding

Medtox, an Emergency Scientific and Medical Service, (<http://www.medtox.co.uk>), will provide a 24 h emergency unblinding service across all participating countries. Unblinding requests will only be granted in a medical emergency and when requested by a physician. This system will be available to any physician treating a patient in the study, including out of hours general practitioner (GP) services and hospital emergency departments. Details of the emergency service will be provided to all participants at the baseline visit.

Recruitment

There are a total of 23 study sites in nine participating European countries. Recruitment for the study will be undertaken locally at each study site according to local guidelines and procedures relevant to that site.

Screening

Once a patient has been identified and has expressed an interest in participation, a screening assessment will be arranged to determine eligibility. The screening assessment consists of: (1) medical history and physical examination including neurological examination; (2) confirmation of diagnosis of AD; (3) Standardised Mini-Mental State Examination (SMMSE); (4) confirmation that the patient is not on any excluded medications for the trial; (5) BP readings standing as well as sitting; (6) ECG; (7) clinical laboratory tests including full blood count, renal and liver function and (8) review of CT/MRI report if undertaken in the past 4 years and if available.

Once the screening assessment has been completed and the patient is deemed eligible for trial participation, the baseline visitation will be arranged and will take place within 6 weeks of the screening assessment. The patient's GP will be notified in writing regarding the patient's participation and will also be provided with a list of excluded trial medications (table 1).

Table 1

Excluded medications for NILVAD trial

CCB	β -Blocker	Nitrates	α -Antagonists
Nifedipine	Bisoprolol	Amyl nitrate	Prazosin
Nimodipine	Atenolol	Isosorbide dinitrate	Doxazosin
Diltiazem	Metoprolol	Nitroglycerin	Tamsulosin
Verapamil	All other β -blockers	Pentaerythritol tetranitrate	All other α -antagonists
Isradipine			
All other CCB			

Other agents/excluded agents

Warfarin

Dantrolene

Aprepitant

Erythromycin

Fluconazole

Anticonvulsants: phenytoin, carbamazepine

Medications that are *not excluded* but drug interactions are noted for:

Other vasodilators: nitroprusside and hydralazine. Monitor for risk of antihypertensive effect

Tricyclic Antidepressants: monitor for risk of antihypertensive effect.

Antiarrhythmics: amiodarone, quinidine and disopyramide. Monitor levels of quinidine

Digoxin: nilvadipine may increase plasma digoxin levels. Monitor digoxin levels

Ciclosporin: monitor ciclosporin levels with concomitant use with nilvadipine

Cytochrome P450 3A4 inhibitors: indinavir, nelfinavir, ritonavir, itraconazole, ketoconazole, voriconazole, posaconazole, nefazodone, saquinavir, telithromycin and cimetidine. Nilvadipine is metabolised by CYP450 3 A4 and thus any agent that inhibits this enzyme system may potentially cause elevated levels of nilvadipine in the plasma. All patients will be monitored throughout, as per the study protocol, for any possible adverse drug interactions

Cytochrome P450 3A4 inducers: rifampicin, gemfibrozil and some antihyperglycaemics such as troglitazone. CPY450 3A4 inducers may potentially decrease the bioavailability of nilvadipine

Patients will be advised of the possible interaction with grapefruit juice (CPY450 3A4 inhibitor) and requested to avoid taking the trial medication with it

CCB

β -Blocker

Nitrates

α -Antagonists

This list is not exhaustive and therefore investigators should contact the sponsor's medical advisor for clarification regarding the acceptability and safety of these and other agents. All participants will be advised of potential interactions with other medications and the GP will also be provided with the list of exclusionary and precautionary medications. Any patient prescribed any of the above medications will be monitored closely throughout the study

CCB, calcium channel blockers; GP, general practitioner.

Excluded medications for NILVAD trial

Consenting process

Written consent for trial participation will be sought from all potential participants following a full explanation of the trial and its objectives, risks and potential benefits. A patient information leaflet (PIL) and carer's information leaflet (CIL) will be provided at least 7 days prior to obtaining written consent to allow participants time to consider enrolling in the trial. Written consent will be obtained from the patient as well as the carer at the screening visit prior to the undertaking of any interventions or assessments. The carer will consent to accompany the patient to assessments, supervise administration of the study drug and participate in certain assessments requiring caregiver input.

The procedure for obtaining informed consent when the participant has reduced decision-making capacity will follow national law and will be assessed by the relevant bodies in each of the participating countries.

Study medication

Trial drug dose and treatment duration

There is little published data regarding the efficacy of nilvadipine to reduce the risk or improve the symptoms of dementia in humans. As such, the dosage selection for this study is based on the findings of Kennelly et al, 2011, and on findings from reports indicating benefit, including increased cerebral blood flow, from standard dosage antihypertensive medication.^{8,10,13–15} An 8 mg enteric coated capsule will be used in the trial. The matching placebo will consist of sugar pellets. The active trial drug and placebo will both be overencapsulated with a gelatin capsule.

Treatment with the trial drug will be for a duration of 78 weeks, based on statistical and power calculations using the Alzheimer's disease Assessment Scale–cognitive subscale (ADAS-Cog 12) as the primary efficacy outcome measure. This is the minimum duration of treatment necessary to demonstrate a disease modifying effect.

Dispensing of study medication

A treatment pack with a unique batch number, patient identification number (PIN) and expiry date, containing either the nilvadipine or placebo capsules, will be dispensed to each participant at the

baseline assessment (week 0) and subsequently at weeks 13, 26, 39, 52 and 65. Each pack will contain 98 capsules (a 13-week supply with 7 extra capsules). The first dose will be taken at the baseline visit under observation. Thereafter, patients will take one capsule daily after breakfast. The timing of the medication is to reduce the risk of orthostatic hypotension.

Medication adherence will be monitored at each dispensing time point. At each assessment participants will be requested to return the used treatment packs and any leftover capsules. Any excess capsules returned will be recorded and patients will be counselled regarding compliance when necessary. If a patient returns more than 20 capsules the reasons for this must be recorded and the site investigator informed.

Excluded medications

Specific medications have been excluded from use during the trial to reduce the risk of adverse effects. Namely, all other CCBs, β -blockers, α -blockers and nitrates. Other specific medications excluded from use during the trial include warfarin, dantrolene, anticonvulsants such as phenytoin, carbamazepine, phenobarbital and all moderate-to-potent cytochrome P450 3A4 inhibitors.

The GP for each patient will be provided with a detailed list of the excluded medications and requested not to prescribe any, if possible, for the duration of the trial (table 1). If treatment with an excluded medication is indicated and prescribed during the trial, the participant will become ineligible and trial participation will be terminated.

Trial assessment schedule

Following the screening assessment to determine eligibility, all participants will have a total of nine assessments throughout the trial, a baseline assessment (week 0) followed by assessments at weeks 6, 13, 26, 39, 52, 65 and 78 (± 7 days), with a study end point assessment at week 82.

The baseline assessment will consist of: (1) concomitant medications check; (2) weight and height check; (3) ADAS-Cog; (4) Clinical Dementia Rating Scale Sum of Boxes (CDR-sb); (5) Disability Assessment for Dementia (DAD) and (6) BP measurements (sitting and standing).

At all subsequent visits, the following assessments will be carried out: (1) concomitant medications check; (2) adverse events check; (3) BP measurements (sitting and standing) and (4) medication compliance check.

In addition, at weeks 13, 52 and 78, cognitive assessments will be undertaken, the ADAS-Cog CDR-sb and DAD.

Furthermore, at week 78 participants will undergo repeat weight and height check, physical examination and clinical laboratory blood test. The study medication will also terminate at this point.

At week 82, participants will undergo their final assessment where they will be asked if they experienced any adverse events after finishing the trial medication (figure 1 and table 2).

Table 2

Trial assessment schedule

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
Procedures	Screen	Week 0	Week 6	Week 13	Week 26	Week 39	Week 52	Week 65	Week 78	Week 82
Informed consent	X									
SMMSE	X									
NINCDS/ADRDA	X									
Medical history	X									
Neurological examination	X									
Physical examination	X								X	
ECG	X									
Sitting & standing blood pressure	X	X	X	X	X	X	X	X	X	
Clinical laboratory blood test	X								X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	
Adverse events			X	X	X	X	X	X	X	X
Weight/height		X							X	
ADAS-Cog 12; CDR-sb, DAD		X		X			X		X	
Dispense drug		X		X	X	X	X	X		
Med compliance			X	X	X	X	X	X	X	
Terminate treatment									X	

ADAS-Cog 12, Alzheimer's disease Assessment Scale–cognitive subscale; CDR-sb, Clinical Dementia Rating Scale Sum of Boxes; DAD, Disability Assessment for Dementia; NINCDS/ADRDA, National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's disease and Related Disorders Association; SMMSE, Standardised Mini-Mental State Examination.

Figure 1 : NILVAD trial flow chart: The requested URL /bmjopen/4/10/e006364/F1.large.jpg was not found on this server.

Termination of trial participation

Scheduled termination of participation in the trial will occur once a patient has completed the week 82 assessment (study end point assessment).

Unscheduled terminations may occur if a participant chooses to withdraw from the study at any time. Each participant has the right to withdraw at any time without providing a reason. Participants may also be removed from the study based on treatment discontinuation criteria: see box 2. All such cases will be discussed with the trial physician and may result in patient withdrawal from the study, if this is deemed necessary on patient safety grounds. If a site is considering removing a participant from the study, this must be discussed with the Principal Investigator (PI) and the Project Coordinator before the participant is withdrawn.

Box 2 Study discontinuation criteria

Adverse experience related to the trial drug.

Intercurrent illness.

The request of the participant, his/her legal representative, investigator or sponsor, whether for administrative or other reasons.

Non-compliance with medication, protocol violation or unreliable behaviour.

Patients who develop symptomatic elevated blood pressure (BP; greater than 159/99 mm Hg using office-based BP measurements or greater than 140/90 mm Hg using ambulatory blood pressure monitoring (ABPM)) or symptomatic lowered BP (less than 100/65 mm Hg with office-based BP measurements or less than 105/70 mm Hg with ABPM), which fails to be controlled with medication.

Patients who develop symptomatic orthostatic hypotension with symptoms including a syncopal episode (but not a seizure), recurrent unexplained falls, intolerant orthostatic hypotensive symptoms, defined as recurrent presyncopal symptoms interfering with daily functioning.

Patients who develop persistent or severe symptoms possibly related to treatment with nilvadipine, such as a persistent headache interfering with daily functioning, severe peripheral oedema or any other symptoms considered to be related to treatment with nilvadipine.

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Statistics

Sample size calculation

The total number of participants is based on the power calculation computed on the primary efficacy parameter, ADAS-Cog 12, as follows: the primary variable of the study is a continuous response variable—the ADAS-Cog 12 score—from independent control (ie, placebo) and experimental participants (ie, treatment) with one control per experimental participant. In previous studies the

change in ADAS-Cog score was normally distributed with a mean score of 7 and SD of 11 for the placebo group and with a mean score of 3.5 and SD of 9 for the experimental group.¹⁶ To observe such a difference between the two groups, 175 experimental participants and 175 control participants must be recruited to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with a probability (power) of 0.9. The type I error probability associated with this test of this null hypothesis is a two sided 0.05. To account for an attrition rate of 30%, the total sample size per group is 250. Since the power calculation assumes a 50% smaller decline in the experimental group compared with the placebo group for the ADAS-Cog, we could make the same assumption for the CDR-sb. If used as a single primary end point, the CDR-sb has similar power to the ADAS-Cog, because, historically, the mean to SD ratio is very similar between these two outcomes, and because we are assuming a fixed percentage effect relative to placebo. So if we assume independence of the two outcomes, which each have a 90% probability of success, then the probability of succeeding on both primary outcomes is $0.9 \times 0.9 = 0.81$, indicating that the power for achieving both outcomes simultaneously is more than 80%. As the change from baseline on the ADAS-Cog and CDR-sb are somewhat correlated, this is a conservative estimate of the power for this study to be pivotal.

The primary and key secondary efficacy analyses will use a mixed-model repeated measures analysis for the change from baseline, including data from all postbaseline visits, with terms for baseline score, site and treatment group. The linear contrasts on the LS-Means of the treatment effects will be used to perform the between-group comparisons. The primary and key secondary statistical analyses will be performed once, after data collection has been halted and the database has been finalised. No interim analyses will be performed.

Primary analysis

The primary analyses will consist of a gatekeeper approach with the following stages:

First, the p value for between-group comparison of the ADAS-Cog outcome will be compared with 0.05. If significance is achieved, then the study will be considered a successful proof of concept study for efficacy. If significance is not achieved the secondary analyses will proceed.

Second, if significance is achieved in step 1, then the p value for the between-group comparison of the CDR-sb outcome will be compared with 0.05. If significance is achieved, then the study will be considered a successful pivotal study for efficacy. If significance is not achieved the secondary analyses will proceed.

Third, if significance is achieved in steps 1 and 2, then an analysis will be undertaken using time as a continuous numerical variable, on ADAS-Cog. The same analysis will be undertaken on CDR-sb. The between-group comparison of slopes will be evaluated for statistical significance at $\alpha=0.05$. If significance is achieved in both of these measures, then the study will have provided evidence of a delay of disability. If significance is achieved in neither the secondary analyses will proceed.

In the case of step 1 of the primary analysis not achieving statistical significance, steps 2 and 3 will still be performed, but any significant outcomes will be for discussion purposes only.

The primary statistical analysis will be carried out on the intent-to-treat population, which will include all randomised patients. For the intention-to-treat secondary analyses, all data from patients

who are terminated or withdrawn from the study will be held and analysed. Where possible, even if patients are withdrawn from the study medication, follow-up data collection will continue as scheduled.

Secondary analysis

The above analysis will be conducted on the DAD measure to assess change in functional capacity between groups in the intention-to-treat population. Patients will be classified as 'responders' if a change in an outcome score is observed from baseline to 78 weeks, which is less than half of the expected decline in the placebo group over that time span. For example, on the ADAS-Cog measure this corresponds to a change of -3.5 or higher for classification as 'responder'. A Cochran-Mantel-Haenszel (CMH) χ^2 test will be used to compare the proportions of responders between the treatment groups, stratified by country.

The above analyses will be repeated on the 'per protocol population' (those participants who have no violations to the protocol for the duration of the study).

Safety analysis

Safety analysis will include descriptive statistics for all randomised participants.

Outcome measures

The primary outcome measure is the change from baseline to week 78 in cognitive function, as assessed by the ADAS-Cog 12. There are two secondary outcome measures, the CDR-sb and the DAD. If a statistically significant effect is seen in the primary outcome, CDR-sb will be considered to be a coprimary end point and only the DAD will contribute to the secondary outcome analysis.

Trial data management system

All the patient data generated from the trial will be recorded online via an electronic case report form (eCRF), on an online Macro System, prepared and run by the CTU, KCL, and will be accessible to all study sites via <http://www.ctu.co.uk>. A unique PIN will be generated for each patient once they are registered on the system at the time of screening and this will be used to identify them throughout the trial.

In addition, the CTU will send each study site 'source data worksheets', to be printed by the study sites and used to record all patient data, from screening through to the end of the trial. A paper file containing the hard copies of all the relevant patient documentation and 'source data worksheets' will be opened for each participant at each study site.

Study site staff will be given unique usernames and passwords to access this system for data entry. Data must be entered, where possible, on the system within 7 days of data collection.

Study monitors in each country will be issued with unique usernames and passwords to access the system for monitoring. Each participating country will have a study monitor who will be responsible for overview and monitoring of trial activities at each study site within each country, including maintenance of the trial master file, site pharmacy files and site investigator file. Site PIs will be given unique usernames and passwords to access the online system with particular PI privileges,

specifically the ability to place an eSignature on each patient's eCRF at the end of the trial to confirm the data set for the patient is complete.

Trial management

The day-to-day management of the trial will be coordinated through the scientific project manager at St James's Hospital, Dublin, the sponsor site. An investigators' meeting will be held once a year and key PI from each of the partner countries will be in attendance.

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Ethics and dissemination

The study will be conducted according to Good Clinical Practice (GCP) guidelines and in accordance with the Declaration of Helsinki.

Regarding safety considerations, the risk associated with the trial is low. Nilvadipine is a licensed medication for high BP in several European countries including Ireland, Germany, France, Spain, Portugal and the UK and it has a reliable safety profile. A successful short-term safety study was carried out on patients with AD in 2008, which showed very good tolerability in this patient population over the 6-week trial period.¹¹

Patient safety monitoring will be assessed by physical examination, clinical laboratory tests and serial BP measurements. Physical examination and routine laboratory blood tests will be undertaken at the screening visit. A routine evaluation of general health and well-being will be conducted at baseline and at all subsequent visits also.

BP measurements will be carried out at each visit. For any patient who develops elevated BP during the study or who presents with elevated BP at screening, add on therapy with a non-centrally acting ACE inhibitor will be considered in consultation with the trial clinician and the patient's GP.

All adverse events will be assessed and reported, including: Adverse Events or Adverse Experiences (AE); Adverse Drug Reactions (ADR); Unexpected Adverse Drug Reactions (UAR); Serious Adverse Events (SAE) or Serious Adverse Reactions (SAR); and Suspected Unexpected SAR (SUSAR).

Additional safety measurements may be conducted more frequently if clinically indicated or at the discretion of the site investigator. The reason for any additional safety measurements will be recorded in the eCRF.

A Data Management and Safety Monitoring Board (DMSB) has been established to which all SAE will be reported. The DMSB consists of a statistician and three clinicians, one of whom will act as the chair of the DMSB. The DMSB will meet on a 6 monthly basis and will review and monitor blinded data exported from the eCRF system and the randomisation system (KCL), these data will be sent to the trial statistician who will prepare reports on data and safety monitoring.

Dissemination

It is intended that all positive, neutral or negative results from the trial will be published in international peer reviewed journals. Authorship and publication will be as per the agreed study publication policy.

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Discussion

AD is an ever-increasing public health concern among the ageing 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.¹⁷ 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 such as cholinesterase inhibitors and glutamate antagonists available for AD, these medications do not stop the disease process or prevent neuronal degeneration. Therefore there is a clear unmet medical and public health need for the development of new treatments and it is imperative that the scientific community strive to discover disease modifying treatments that can be introduced at the earliest possible stage of neurodegeneration.¹⁸

There is convincing scientific evidence for an anti-amyloid effect of nilvadipine, with reduced A β production, enhanced A β clearance from the brain and improved cortical perfusion in mouse models of AD, highlighting potential disease modifying benefits.³ This study will help to establish if such disease modifying effects will be evident in human subjects also.

Research to date has shown that nilvadipine has a good safety profile and is well tolerated in patients with AD, facilitating the inclusion of older adults with a range of comorbidities in this study and the results from this study will provide further information about the efficacy and safety of Nilvadipine in patients with AD.

If this trial is successful, nilvadipine would represent a significant advance in the treatment and management of patients with AD and would have a major impact on the health and social care costs incurred in Europe by this neurodegenerative disorder.

Trial status

Enrollment for the trial began in May 2013 and the recruitment period will continue until December 2014.

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Footnotes

Collaborators Dr Suzanne Hendrix, Prof. Robin Jacoby and Dr Paul Aisen.

Contributors BL, SK, Fiona Crawford, and MM made substantial contributions to the initial study conception and study design. BL, SK, SOD, Fiona Cregg, CW, RC, RAK, RH, CM, JA, LD, RS, SG, Fiona Crawford, MM, UL, RB, FP, LB, MR, JK, AW, AB, WM, MT and MOR made substantial contributions to the design and content of the study protocol, to the initial drafting of this manuscript and the critical revision of the submitted manuscript; and have approved the final article for submission. BL, SK, SOD, Fiona Cregg, RC, RH, UL, RB, FP, AW, AB, WM, MT and MOR are responsible for recruitment and monitoring of study participants. BL, SK, SOD, Fiona Cregg, RC, JA, CM and SG have responsibility for overseeing the study as it progresses and for provision of both verbal and written guidance to each study site.

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Competing interests AW is a member of the speaker bureau for Esai and a member of the advisory board for Nutricia. Fiona Crawford and MM are officers in Archer Pharmaceuticals, which has licensed the technology for use of Nilvadipine in Alzheimer's disease.

Ethics approval The study has been submitted for approval to the relevant independent ethics committees in each country. The trial has also been reviewed and will be monitored by a NILVAD Ethics Advisory Board throughout the study duration.

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

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