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A clinical trial to test amlodipine as a new treatment for vascular dementia

Submission date 07/03/2014	**Recruitment status** Stopped	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 15/04/2014	**Overall study status** Stopped	
Last Edited 21/07/2016	**Condition category** Mental and Behavioural Disorders	

Plain English summary of protocol

Background and study aims
Vascular dementia is the second most common form of dementia, affecting an estimated 20% of people with dementia and accounting for approximately 7 million people worldwide. It is caused by problems with the blood supply to the brain, for example following a stroke or due to damage to the tiny blood vessel network in the brain. The resulting damage causes cells to be lost, leading to the development of dementia. The most common form of vascular dementia is subcortical ischemic vascular dementia (SIVD), affecting up to 67% of people with vascular dementia. To date there has been minimal investment in treatments for people with vascular dementia despite the large number of people affected by the condition. As a result there are no drugs licensed for the treatment of vascular dementia and no ongoing clinical trials. The aim of this study is to investigate whether treatment with the calcium channel blocker medication amlodipine can improve outcomes for people with SIVD. The study will compare amlodipine treatment with a control to see if there is any difference compared to the care people usually receive.

Who can participate?
We aims to recruit 588 patients aged 50 years or over with SIVD.

What does the study involve?
Patients will be randomly allocated to one of two groups and neither the patients nor the clinicians will know which group someone has been allocated to: usual care + amlodipine or usual care + dummy drug (placebo). Patients will be required to take either amlodipine or placebo: 5 mg once daily for 2 weeks followed by 10 mg once daily for 50 weeks. Patients will be enrolled in the study for 2 years; 1 year on treatment and a follow up telephone call at the end of year 2. Patients will undergo an MRI brain scan at the screening stage of the study to confirm diagnosis and also after 1 year to monitor progress. During the study, patients with an informant (friend, relative or professional carer) will be asked to attend the clinic at various intervals and both will be asked to complete questionnaires with the help of an assessor. The study will measure changes in mental speed and executive function (overall cognition), detect changes in ability to perform everyday tasks, further symptoms of dementia and caregiver burden. Tools will also be used to measure the cost-effectiveness of the treatments.

What are the possible benefits and risks of participating?
Participants may see an improvement in their dementia symptoms.
This will be the first large scale treatment study in people with vascular dementia. There have been no study of this size and there are no studies currently registered. Amlodipine is already licensed for use in the UK; therefore if the results of this trial are successful amlodipine could quickly be made available as a treatment for vascular dementia. Amlodipine is a licensed drug but, as with all drugs, there are side effects associated. The most common side effects include headache, oedema, flushing, dizziness, ankle swelling, fatigue, nausea, and rash. Side effects will be monitored by the study team throughout the trial.

Where is the study run from?
The study will take place across sites in the UK. The trial co-ordinating centre is the Northern Ireland Clinical Trials Unit (NICTU) and the lead centre will be The Belfast Health and Social Care Trust (UK).

When is the study starting and how long is it expected to run for?
Recruitment is expected to start in October 2014 and will run for 2 years.

Who is funding the study?
Funding has been provided equally by the Alzheimer's Society and the British Heart Foundation (UK).

Who is the main contact?
Professor Peter Passmore
P.Passmore@qub.ac.uk

Study website
http://www.nictu.hscni.net/affect/

Contact information

Type(s)
Scientific

Contact name
Prof Peter Passmore

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Additional identifiers

EudraCT/CTIS number
2014-000926-39

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
13154PP-SP

Study information

Scientific Title
A randomised controlled trial of calcium channel blockade with Amlodipine For the treatment oF subcortical ischaEmic vasCular demenTia.

Acronym
AFFECT

Study objectives
1. To determine whether amlodipine will confer significant benefit with respect to change in cognitive outcome in people with subcortical ischaemic vascular dementia (SIVD) in comparison to placebo over 52 weeks.
2. To determine whether amlodipine will confer additional benefits on the following secondary outcomes; global impression, activities of daily living, neuropsychiatric symptoms and carer burden, in comparison to placebo.
3. To determine if amlodipine will be a cost effective treatment for SIVD compared to placebo.

On 07/10/2014 the anticipated end date was changed from to 13/01/2018 to 01/10/2018.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Office for Research Ethics Committees in Northern Ireland (ORECNI), 23/06/2014, Ref: 14/NI /0069

Study design
Multi-centre randomised double-blind placebo-controlled parallel arm phase IIb trial

Primary study design
Interventional

Secondary study design
Randomised parallel 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 patient information sheet

Health condition(s) or problem(s) studied
Subcortical ischaemic vascular dementia

Interventions
Patients will be randomised to either amlodipine or placebo: 5 mg once daily for 2 weeks followed by 10 mg once daily for 50 weeks

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Amlodipine

Primary outcome measure
Current primary outcome measures as of 09/11/2015:
A change from baseline to 12 months in Vascular Dementia Assessment Scale cognitive subscale (VADAS-cog) score. The VADAS-cog is a more detailed cognitive assessment designed to be more sensitive to the cognitive outcomes in people with vascular dementia. This assessment should be completed face to face by an assessor who will be blinded to the intervention.

Previous primary outcome measures:
An improvement of 2.5 points in mean Vascular Dementia Assessment Scale cognitive subscale (VADAS-cog) from baseline to 12 months. The VADAS-cog is a more detailed cognitive assessment designed to be more sensitive to the cognitive outcomes in people with vascular dementia. This assessment should be completed face to face by an assessor who will be blinded to the intervention.

Secondary outcome measures
Current secondary outcome measures as of 09/11/2015:
1. Change in cognitive function measured with the Standardised Mini-Mental State Examination (sMMSE) from baseline to 12 months.
2. Change in the Trail Making test B from baseline to 12 months. The Trail Making test B is a timed measure of executive function.
3. Change in cognitive function from baseline to 12 months with a follow up at 24 months measured by Modified Telephone Interview for Cognitive Status (TICS-M).
4. Change in Clinical Global Impression of Change (CGIC) from baseline to 12 months. CGIC is a simple standardised rating of overall clinical outcome, rated by a clinician blind to treatment allocation.
5. Change in blood pressure from baseline to 12 months.
6. Change in lesion accrual from baseline to 12 months. This will be based on quantitation of lacunar lesions and diffuse white matter lesions measured quantitatively by MRI.
7. Change in health-related quality of life from baseline to 12 months measured with the EuroQol Group EQ-5D Health Questionnaire (EQ-5D-5L) and the Dementia Quality of Life-Proxy (DEMQOL-Proxy), a carer-rated and disease-specific measure of quality of life in dementia.
8. Change in activities of daily living from baseline to 12 months measured using the Disability

Assessment in Dementia (DAD).
9. Change in non-cognitive dementia symptoms from baseline to 12 months measured with the Neuropsychiatric Inventory Caregiver Distress (NPI-D).
10. Change in care-giver burden from baseline to 12 months measured with the 12 item General Health Questionnaire (GHQ-12), and care-giver health-related quality of life measured with the EQ-5D-5L.
11. Cost-effectiveness measured as the combination of costs generated from the Client Service Receipt Inventory (CSRI).
12. Institutionalisation defined as permanent transition from living in an independent household to a care home, nursing home, NHS continuing care unit or hospital and measured with questions taken from the CSRI.

Previous secondary outcome measures:
1. Change in cognitive function measured with the Standardised Mini-Mental State Examination (sMMSE) from baseline to 12 months.
2. Change in the Trail Making test B from baseline to 12 months. The Trail Making test B is a timed measure of executive function.
3. Change in cognitive function from baseline to 12 months measured by Telephone Interview for Cognitive Status (TICS). There will also be a follow up at 24 months.
4. Clinical Global Impression of Change (CGIC) from baseline to 12 months. CGIC is a simple standardised rating of overall clinical outcome, rated by a clinician blind to treatment allocation.
5. Change in blood pressure from baseline to 12 months.
6. Change in lesion accrual from baseline to 12 months. This will be based on quantitation of lacunar lesions and diffuse white matter lesions measured quantitatively by MRI.
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9. Change in non-cognitive dementia symptoms from baseline to 12 months measured with the Neuropsychiatric Inventory (NPI).
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11. Cost-effectiveness measured as the combination of costs generated from the Client Service Receipt Inventory (CSRI).
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Overall study start date
01/10/2014

Completion date
01/10/2018

Reason abandoned (if study stopped)
Participant recruitment issue

Eligibility

Key inclusion criteria

Current inclusion criteria as of 09/11/2015:
1. Dementia syndrome according to the criteria a, b & d from code 290.4 of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).
2. Evidence of one or more clinical features in support of SIVD such as executive dysfunction, mood or gait disturbance or focal neurological signs
3. Multiple lacunae (>2) or diffuse lesions reaching a mean score of 2-3 across brain regions identified on baseline MRI scan.
4. sMMSE score between 15 and 26 (inclusive).
5. Age ≥ 50
6. If patients taking a cholinesterase inhibitor or memantine, dose stable for at least three months.
7. If patients taking antidepressants, dose stable for at least four weeks.
8. CT or MRI scan consistent with the probable diagnosis of SIVD providing there has been no significant clinical change since the scan.
9. Patient has resident family or professional carer or is visited at least twice a week by carer.
10. Fluency in English is essential as the study requires questionnaires to be completed.
11. Likely to be able to participate in all scheduled evaluations and complete all required tests.
12. Provision of appropriate consent.
13. Presence of an informant, aged 18 years or over who is willing to participate in the study.

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1. Dementia syndrome according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)
2. Evidence of one or more clinical features in support of SIVD such as executive dysfunction, mood or gait disturbance or focal neurological signs
3. Multiple lacunae (>2) or diffuse lesions reaching a mean score of 2-3 across brain regions identified on baseline MRI scan
4. sMMSE score between 20 and 26 (inclusive)
5. Age 50 years or older
6. If patients taking a cholinesterase inhibitor or memantine, dose stable for at least three months
7. If patients taking antidepressants, dose stable for at least four weeks
8. Diagnosis of probable SIVD with supportive imaging (CT or MRI) within last 24 months
9. Patient has resident family or professional carer or is visited at least twice a week by carer
10. Fluency in English and evidence of adequate premorbid intellectual functioning
11. Likely to be able to participate in all scheduled evaluations and complete all required tests
12. Provision of appropriate consent
13. Presence of an informant who is willing to participate in the study

Participant type(s)

Patient

Age group

Senior

Lower age limit

18 Years

Sex

Both

Target number of participants
588

Key exclusion criteria
Current exclusion criteria as of 09/11/2015:
1. Severe, unstable or poorly controlled medical conditions apparent from physical examination or clinical history.
2. Moderate/severe heart disease or severe hepatic disease.
3. Significant renal insufficiency; estimated glomerular filtration rate (eGFR) <30ml/min.
4. Blood pressure (sitting) exceeds 160 mmHg systolic and/or 110 mmHg diastolic.
5. Systolic blood pressure (sitting) is less than 110mmHg.
6. Infarction involving the cortex on MRI scan.
7. Cerebrovascular event within the last six months.
8. Myocardial infarction within the last three months.
9. Already taking any calcium channel blocker.
10. Contraindications to a calcium channel blocker as per Summary of Product Characteristics (SPC)
11. Patient is unable to take trial medications.
12. Pregnant women or women who may possibly become pregnant (pre-menopausal). Females must be postmenopausal (no menses for ≥ 12 months without an alternative medical cause) to participate in the study.
13. Female patients who are breastfeeding will be excluded.
14. AD is considered to be the primary diagnosis: i.e. a predominantly amnestic presentation or evidence of an amnestic (pre-dementia) phase or strong biomarker evidence to support a diagnosis of AD. Patients with severe hippocampal atrophy on MRI (Scheltens GR 3 and 4 on both sides (i.e. a total score (left plus right) of 6 or more) will be excluded.
15. Significant neurological disease that may affect cognition other than SIVD or AD as a concurrent pathology.
16. Current presence of a clinically significant major psychiatric disorder (e.g. Major Depressive Disorder) according to the criteria of the DSM-IV.
17. Current clinically significant systemic illness that is likely to result in deterioration of the patient’s condition or affect the patient’s safety during the study.
18. Treatment with immunosuppressive medications (e.g. systemic corticosteroids) within the last 90 days (topical and nasal corticosteroids and inhaled corticosteroids for asthma are permitted) or chemotherapeutic agents for malignancy within the last three years.
19. Other clinically significant abnormality on physical, neurological, laboratory, examination that could compromise the study or be significantly detrimental to the patient (e.g. postural hypotension diagnosed within the last year which in the opinion of the PI would exclude the patient).
20. Alcohol or drug dependence or abuse within the last two years.
21. Treated with any other investigational medication or device within 60 days.
22. Patient taking simvastatin 40 mg or greater. A patient may be switched to an alternative statin and on stable dose for three months to meet inclusion criteria. A reduction in simvastatin dose solely for the purposes of eligibility is not permitted.

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1. Severe, unstable or poorly controlled medical conditions apparent from physical examination or clinical history.
2. Moderate/severe heart disease or severe hepatic disease.
3. Significant renal insufficiency; estimated glomerular filtration rate (eGFR) <30ml/min.
4. Blood pressure exceeds 160 mmHg systolic and/or 110 mmHg diastolic.

5. Systolic blood pressure is less than 110mmHg.
6. Infarction involving the cortex on MRI scans.
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8. Myocardial infarction within the last three months.
9. Already taking any calcium channel blocker.
10. Contraindications to a calcium channel blocker as per Summary of Product Characteristics (SPC)
11. Patient is unable to take trial medications.
12. Pregnant women, women who have not yet reached the menopause (no menses for over 12 months without an alternative medical cause) who test positive for pregnancy, are unwilling to take a pregnancy test prior to trial entry or are unwilling to undertake adequate precautions to prevent pregnancy for the duration of the trial.
13. Female patients who are breastfeeding will be excluded.
14. AD is considered to be the primary diagnosis: i.e. a predominantly amnestic presentation or evidence of an amnestic (pre-dementia) phase or strong biomarker evidence to support a diagnosis of AD. Patients with severe hippocampal atrophy on MRI (Scheltens GR 3 and 4 on both sides (i.e. a total score (left plus right) of 6 or more) will be excluded.
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21. Treated with any other investigational medication or device within 60 days.

Date of first enrolment
01/10/2014

Date of final enrolment
30/09/2016

Locations

Countries of recruitment
Northern Ireland

United Kingdom

Study participating centre
Royal Victoria Hospital
NICTU
1st Floor
Elliott Dynes Building

Grosvenor Road
Belfast
United Kingdom
BT12 6BA

Sponsor information

Organisation
Belfast Health and Social Care Trust (UK)

Sponsor details
Research Office
2nd Floor King Edward Building
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Grosvenor Road
Belfast
Northern Ireland
United Kingdom
BT12 6BA
+44 (0)28 9063 6349
alison.murphy@belfasttrust.hscni.net

Sponsor type
Hospital/treatment centre

Website
http://www.belfasttrust.hscni.net/

ROR
https://ror.org/02tdmfk69

Funder(s)

Funder type
Charity

Funder Name
Alzheimer's Society (UK) - Grant Number: 184

Alternative Name(s)
alzheimerssoc

Funding Body Type
Private sector organisation

Funding Body Subtype
Associations and societies (private and public)

Location
United Kingdom

Funder Name
British Heart Foundation (UK)

Alternative Name(s)
the_bhf, The British Heart Foundation, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
To be confirmed at a later date.

Following any publication of the primary and secondary study outcomes, there may be scope for additional analyses on the data collected. In such instances, formal requests for data will need to be made in writing to the AFFECT CI upon which there will be agreement with TMG and TSC.

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	18/07/2016		Yes	No
HRA research summary			28/06/2023	No	No