



Project Final Report

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Controlled phase III trial of nilvadipine in mild to moderate Alzheimer's disease

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Section 1 – Final publishable summary report

NILVAD

Logo:



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

Website: <http://www.nilvad.eu/>

Contractors involved (NILVAD consortium):

The project is coordinated by Prof. Brian Lawlor [Partner 01] TCD, The Provost, Fellows, Foundation Scholars and the other members of Board, of the College of the Holy and Undivided Trinity of Queen Elizabeth near Dublin, College Green, Dublin 2, Ireland

Other partners and team leaders:

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[Partner 03]	AE	Alzheimer Europe
[Partner 04]	ARCHER	ARCHER Pharmaceuticals Inc. Corp.
[Partner 05]	NEWS	E-Search Limited
[Partner 06]	NUID UCD	University College Dublin, National University of Ireland, Dublin
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1.1 Executive summary

Alzheimer's disease (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. It is estimated that by 2050, 1 in 85 of the population worldwide will have AD. While there are symptomatic-based drug therapies available for AD, these medications do not stop the disease process or prevent neuronal degeneration and there is a need for the development of new treatments for AD that have disease modifying effects. In late onset AD, the contribution of vascular disease, either by lowering the threshold for AD pathology to be expressed clinically or by accelerating or triggering the amyloid cascade in the ageing brain may have been underestimated. Alternative strategies for treating AD, particularly those assessing the potential benefits of repurposed medications, are particularly attractive. Such approaches could speed up the drug development process, utilising medications of known safety profile thereby accelerating the pathway to clinical application. One such repurposed medication for which there is clinical and scientific rationale for a multimodal action through amyloid, vascular and inflammatory mechanisms is nilvadipine.

Nilvadipine, a dihydropyridine (DHP) calcium channel blocker (CCB) or antagonist, is currently licensed to treat patients with hypertension. Recent research has highlighted other properties of CCBs, including nilvadipine, suggesting that they may be protective not just against stroke-related dementia, but also for AD. The NILVAD trial was established in 2012 to determine if nilvadipine was effective at slowing cognitive decline in mild to moderate AD patients.

NILVAD is an 18-month, randomised, placebo-controlled, double blind trial of 8mg SR nilvadipine and matched placebo in participants with mild to moderate AD. The trial was conducted at 23 centres in nine European countries. Participants, caregivers and assessors were masked to treatment assignment. The co-primary outcomes were progression on the Alzheimer's disease Assessment Scale Cognitive-12 (ADAS-Cog 12) and Clinical Dementia Rating Scale sum of boxes (CDR-sb) in the intention-to-treat population. The Disability Assessment for Dementia (DAD) was a key secondary efficacy outcome measure.

This phase III clinical trial to test the efficacy of nilvadipine in a combined population of mild to moderate AD was successfully completed on time and within budget. Between May 15th 2013 and April 13th 2015, 511 eligible participants were randomised to treatment (258 to control, 253 to nilvadipine). Nilvadipine was well tolerated. Analysis has been completed on the primary and secondary efficacy outcomes and a manuscript detailing the results is being prepared for submission to a high impact peer-reviewed journal. Due to a publication embargo, details of the results will not be made publicly available until this peer-reviewed publication is published. This is anticipated in late 2017. Analysis is ongoing on population subgroups and for each of the substudies. There is also work underway on the analysis of a blood pressure variability study and a report on NILVAD patient and caregivers' experiences of participating in a clinical trial. The report below contains only information that is currently publicly available and details of the main efficacy findings will be announced on the trial website <http://www.nilvad.eu> as soon as the paper is published.

1.2 Summary description of project context and objectives:

Background and Aims

Nilvadipine is a dihydropyridine (DHP) calcium channel blocker (CCB) or antagonist which is currently licensed to treat patients with hypertension. There is good clinical and scientific rationale for a multimodal action of nilvadipine in the treatment of AD through amyloid, vascular and inflammatory mechanisms. Nilvadipine significantly lowers A β 40 and A β 42 production *in vitro*. *In vivo* transgenic mouse models of AD (Tg PS1/APPsw) have shown that nilvadipine can reduce A β in the brain as well as increase A β clearance across the BBB. In addition to these properties, nilvadipine has shown efficacy against a broad range of putative AD pathological mechanisms, including τ -phosphorylation, reduced cerebral blood flow and neuroinflammation. Nilvadipine stabilised cognitive decline and reduced conversion to AD in a small study of patients with hypertension and mild cognitive impairment. A six-week open label study demonstrated that nilvadipine was safe and well tolerated in patients with AD and did not reduce blood pressure (BP) in non-hypertensive patients with AD, but appropriately lowered BP in hypertensive cases. Based on this research, the NILVAD trial was established in 2012 to determine whether treatment with nilvadipine SR 8mg, once a day, was safe and could slow the rate of cognitive decline in patients with mild to moderate AD. NILVAD is an 18 month phase III, randomised, placebo-controlled, double-blind, parallel-group study carried out at 23 academic centres in nine European countries. The specific objectives of the NILVAD trial were:

- To augment the initial studies of nilvadipine as a treatment for AD by investigating its efficacy in a phase III double blind placebo-controlled study
- To demonstrate the feasibility of a multi-site European clinical trial of a potential AD treatment with a demonstrated safety profile
- To promote a European clinical trial network of AD clinicians and researchers
- To expedite the availability of effective treatment to AD patients by advancing a promising, safe, anti-Alzheimer drug through Phase III clinical trials
- To financially support the larger scale investigation of nilvadipine in AD patients which the existing preclinical and clinical data strongly mandate
- To investigate biomarkers of AD progression and response to nilvadipine and
- Ultimately, to improve treatment options and quality of life for people with AD in Europe

There are four substudies to NILVAD, namely the Blood & Genetic Biomarker substudy, the Cerebrospinal Fluid Substudy (CSF), the Cerebral Blood Flow (CBF) substudy and the Frailty substudy. The four substudies protocol was published in an article in *BMJ Open* in 2016 (Meulenbroek O, O'Dwyer S, de Jong D, *et al*. European multicentre double-blind placebo-controlled trial of Nilvadipine in mild-to-moderate Alzheimer's disease-the substudy protocols: NILVAD frailty; NILVAD blood and genetic biomarkers; NILVAD cerebrospinal fluid biomarkers; NILVAD cerebral blood flow. *BMJ Open*. 2016 Jul 19;6(7):e011584). The aims of each of the four substudies (as per the published protocol) are:

1. The aim of the Blood & Genetic Biomarker substudy is to determine whether genetic influences can modify the effect of Nilvadipine on AD pathogenesis and whether changes in plasma A β , τ and inflammatory markers from study baseline to end point are altered by nilvadipine treatment.
2. The aim of the CSF is to explore the biomarker status of NILVAD participants at baseline as a predictor of response to nilvadipine and investigate biomarker changes over time, with nilvadipine treatment, possibly enhancing our understanding of the *in vivo* effect of nilvadipine.

3. The aim of the CBF substudy is to investigate the effects of nilvadipine on CBF, blood pressure (BP) and BP variability in study participants. It is expected that Nilvadipine treatment, through direct systemic and cerebral vascular effects, will beneficially modulate these characteristics.
4. The aim of the Frailty substudy is to demonstrate that if nilvadipine has a positive effect on cognition, it will also do so on frailty, with less deterioration or with possible stabilisation.

Since commencement of the trial two additional substudies have been undertaken, both of which are independently funded from NILVAD but have arisen from the trial. The first is a post-hoc study which aims to expand on the CBF substudy and investigate the effects of nilvadipine on mean BP, BP instability (orthostatic changes) and BP variability (visit to visit changes in BP). The Dutch team are conducting this extra BP study. The second additional study is a non-interventional study to investigate the experience of patients and caregivers of participating in the NILVAD clinical trial which is being coordinated by the French team. Work on all substudies is underway and the first set of publications should be available in late 2017 or early 2018.

Work strategy and general description

The NILVAD trial is a multicentre, randomised, double-blind, placebo-controlled study of 8mg slow release nilvadipine compared with placebo. The NILVAD trial consists of 23 recruiting sites across nine European countries; Ireland (2 sites), United Kingdom (1 site), Italy (4 sites), Netherlands (3 sites), France (7 sites), Greece (3 sites), Sweden (1 site), Germany (1 site) and Hungary (1 site). The coordinating centre is Trinity College Dublin (TCD) and the Sponsor is St. James's Hospital (SJH) in Dublin which is also a recruiting site. The Coordinator is Professor Brian Lawlor, Connolly Norman Professor of Old Age Psychiatry at TCD and consultant psychiatrist at St. James's Hospital.

The NILVAD trial consists of eight workpackages:

1. Project Management
2. Set up framework
3. Education and Training
4. Ethics & Ethical Issues
5. Clinical Platform-Nilvadipine Clinical Trial
6. Outcome Analysis
7. Dissemination & Communication
8. Exploitation and Scientific Direction

Management structure and procedures

The Project Coordinator, Prof Brian Lawlor, ensured the smooth operation of the project and guaranteed that all efforts were focused towards the objectives. He submitted all required progress reports, deliverables, financial statements to the European Commission, and he was responsible for the proper use of funds and their transfers to

participants. The NILVAD office was established by the coordinator and based at TCD in Dublin. The Project Office under the Coordinator was concerned with the scientific management and the co-ordination of all research activities. From 2012 until their termination as a project partner in mid-2016 GABO:mi was responsible for administrative, financial and contractual management and the organisational co-ordination of the project activities. After approval of an amendment to the grant agreement by the European Commission in late 2016, the Project Office at TCD became responsible for the final administrative, financial and contractual aspects of the trial in addition to the scientific aspects.

Governance and management of the NILVAD trial consists of the General Assembly, the Steering Committee, the Data Safety Monitoring Board, a Scientific Advisory Board and an Ethics Advisory Board.

General Assembly (GA):

The GA consists of one representative of each Participant with authority to vote. All other nonvoting researchers working for this project were permitted to join the meetings and discussions. The GA met once a year and the main tasks were to:

- Grant proper implementation of the Participants' respective rights and obligations in accordance with the contractual framework of the project and the Consortium Agreement;
- Decide upon withdrawal, inclusion and exclusion of Participants to the project;
- Take preliminary decisions on the amendment of the Consortium Agreement (subject to ratification by the authorised legal representatives);
- Agree on standard operation procedures within NILVAD, in relation to reporting procedures;
- Agree on procedures and policies in accordance with the Grant Agreement, Annex II, Article 30 for dissemination of foreground and IPR;
- Approve the provisional budgets, discuss and approve the annual executive budget and cost claims prepared by the Steering Committee including the reimbursements to the Participants.

Steering Committee (STC):

The STC met once a year and was in charge of monitoring all activities towards the objective of the project in order to deliver as promised, in due time and within budget. The STC consisted of the lead of each of the 8 NILVAD workpackages and the coordinator. The STC thus:

- Controlled the execution of the project with regards to the project schedule and the description of work annexed to the Grant Agreement and to monitor corrective actions;
- Proposed all significant modifications of the work plan, the Grant Agreement, the Consortium Agreement to the GA for approval;
- Proposed changes in work sharing and membership to the Work packages to the GA;
- Proposed the global and detailed provisional budget to the GA for approval;
- Reported to and was accountable to the GA.

Data Safety Monitoring Board (DSMB):

The DSMB members were all independent of the trial and their tasks during the NILVAD trial were to:

- Review all significant and unexpected adverse events on a regular basis to ensure that no unexpected safety trends were emerging

- Review study enrolment on a regular basis
- Carry out a planned unblinded interim analysis during the course of the study to ensure the overall objectives were being met and that there were no safety and/or ethical reasons to terminate the study
- Communicate on a regular basis with the chair of the Trial Management Committee who remained blind to all study outcomes, and offer advice on the conduct of the trial if necessary

Scientific Advisory Board (SAB):

The SAB ensured a high standard of research and monitored progress of the project by attending GA meetings and STC meetings and regular teleconferences. The SAB consists of an Old Age Psychiatrist, an Internist, a statistician and a lay person with knowledge of AD.

Ethics Advisory Board (EAB):

The EAB were engaged with on an ongoing basis as and when the need arose. The role of the EAB is to oversee all activities relating to the study ethics. The board consists of a geriatrician, a palliative care physician, a senior lecturer in law and the regional manager of the Alzheimer's Society of Ireland.

Objectives of NILVAD:

- To augment the initial studies of Nilvadipine as a treatment for AD by investigating its efficacy in a phase III double-blind placebo-controlled study
- To demonstrate the feasibility of a multi-site European clinical trial of a potential AD treatment with a demonstrated safety profile
- To promote a European clinical trial network of AD clinicians and researchers
- To expedite the availability of effective treatment to AD patients by advancing a promising, safe, anti-Alzheimer drug through Phase III clinical trials
- To financially support the larger scale investigation of Nilvadipine in AD patients which the existing preclinical and clinical data strongly mandate
- To investigate biomarkers of AD progression and response to nilvadipine
- Ultimately, to improve treatment options and quality of life for people with AD in Europe

1.3 Description of the main S&T results/foregrounds of NILVAD

Following the work programme of NILVAD, significant progress in the field of Alzheimer's disease (AD) research has been achieved. This is highlighted by the detailed progress reports of work packages (WP) 2, 3, 5, 6 and 7, which are summarised below. Due to publication embargoes, details of the trial results have been withheld at this point. Details on the results will be publicly available through the peer-reviewed publication which is anticipated to be published in late 2017. An announcement on the publication of the results will be made on the trial website, <http://www.nilvad.eu/>.

WP 02: Set up framework

The objectives of WP02 were to:

- develop an effective scientific management framework (coordination, managerial and administrative tasks to facilitate the clinical trial)
- facilitate the foundation for study participation at each individual centre (protocol, safety, legal, ethical issues & pharmacy issues).

Essential Documents

An essential aspect of WP02 was the development and finalisation of the trial protocol and standard operating procedures (SOPs). The trial protocol integrates the protocols for both the main study and the four substudies, namely the Blood and Genetic substudy, the CSF substudy, the CBF substudy and the Frailty substudy. The complete protocol, which is currently in use and approved is Complete Protocol Version 8. A number of substantial amendments were made to the protocol since the commencement of recruitment these include:

- Exclusion of the medical food stuff, Souvenaid
- Extending the time allowed between screening and baseline from 28 days to 6 weeks
- Allowing patients to be included in the study who are already on up to two blood pressure agents

The main study protocol and the substudy protocols were published in BMJ Open in 2014 and 2016, respectively:

1. Brian Lawlor, Sean Kennelly, Sarah O'Dwyer, *et al.* NILVAD protocol: a European multicentre double-blind placebo-controlled trial of nilvadipine in mild-to-moderate Alzheimer's disease. *BMJ Open*. 2014 Oct 9;4(10):e006364.
2. Meulenbroek O, O'Dwyer S, de Jong D, *et al.* European multicentre double-blind placebo-controlled trial of Nilvadipine in mild-to-moderate Alzheimer's disease-the substudy protocols: NILVAD frailty; NILVAD blood and genetic biomarkers; NILVAD cerebrospinal fluid biomarkers; NILVAD cerebral blood flow. *BMJ Open*. 2016 Jul 19;6(7):e011584.

There were eight Standard Operating Procedures (SOPs) in operation during the trial and a Study Site Guidance Document. The following is the list of the SOPs which were in place for duration of the trial:

- Version Control SOP – describes how documents are named, numbered and controlled for the NILVAD study
- Protocol Deviation and Violation SOP – describes how to deal with protocol deviations and violations
- Study Site Guidance – includes notes on all of the NILVAD study processes
- Safety Reporting SOP – provides detailed information on the NILVAD pharmacovigilance policy and procedures
- Unblinding SOP – provides a guide for the use of the NILVAD unblinding service
- Filing and Archiving SOP – provides a guide on how the TMF and ISFs should be organised and maintained
- IMP Management SOP – provides a guide on ordering, transporting and returning IMP
- Close-Out SOP – provides detail on how sites should be closed out and how files should be archived at the end of the study
- Monitoring SOP – provides a guide on the monitoring process for the trial duration

All of the relevant NILVAD study documents and all essential study documents are stored on the central, password-protected, document repository on the NILVAD website. This allows study staff to access the current approved version of the documents online. All study documents are controlled by the Project Office in Dublin. Changes to documents are communicated via email alerts when the updated version of the document is added to the online repository. The country monitors check the sites investigator site file (ISF) during their monitoring visits as per the Monitoring SOP to ensure that the correct versions of the study documents are on file.

The Trial Master File (TMF) was established at the Project Office in Dublin and contains essential study documents including:

- Investigators Brochure
- Signed Complete Protocol
- Patient Information Leaflet and Consent forms for the main study and the substudies (for each of the partner countries)
- Insurance and Indemnity statement for every country for the main study and substudies
- Consortium Agreement
- Description of Work and the Grant Agreement
- Ethics Approval letters for each of the partner countries
- Regulatory Approval letters for each of the partner countries
- Contracts with sub-contractors
- CVs for all of the study staff across all sites
- Training records for all of the study staff (GCP, ADAS, CDR, DAD, Webinar Training records)
- Important correspondence
- Meeting minutes

Establishment of Clinical, Pharmacovigilance and Safety Procedures

A number of documents relating to the clinical aspects of the trial have been developed or obtained and they include:

- A source data workbook (SDW) which is a paper case report form (CRF) for each of the study visits.
- A matching electronic CRF (eCRF) database (Macro) built by our partners in KCL (partner 08)
- Documents relating to the study drug include; Investigators Medicinal Product Dossier (IMPD), batch files for the production of the IMP, purchase records, drug ordering system, QP Release documentation, SmPC (Summary of Medicinal Product Characteristics)
- A Safety Reporting SOP is in place which includes instructions on how to report adverse events (AEs), Serious Adverse Events or Reactions (SAEs/SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs).

Trial Initiation and training

Site Initiation visits were conducted at each of the study sites by the country monitors prior to commencement of recruitment. The site initiation visits were attended by the study staff at the site and included essential trial training, confirmation that IMP was in stock and that all essential documents were in place in the investigator site file (ISF). The Sponsor oversaw by paper review the site initiation activities. Following completion of the review of the site

initiation activities by the Sponsor, sites were allowed to commence recruitment. Training was given on ICH-GCP, the protocol and the outcome measures specific to the trial:

1. The Alzheimer's Disease Assessment Scale (Cognitive) ADAS-Cog 12
2. The Clinical Dementia Rating Scale Sum of Boxes (CDR-sb)
3. The Disability Assessment for Dementia (DAD)

As a result of NILVAD and the activity conducted as part of the set-up framework, there is now a network of highly-trained AD researchers in key study outcome measures who are well equipped to continue working in the field of AD trials.

Final selection of centres for the study

In total, 23 study sites were selected for recruiting to the NILVAD study across 9 EU countries, see below.

Final List of Study Sites for the NILVAD Clinical Trial		
Country	Site	Site Code
France (P1)	Amiens	11
	Bethune	12
	Caen	13
	Calais	14
	GHICL	15
	LILLE	16
	LENS	17
Greece (P3)	Pagag	31
	Papan	32
	AXEPA	33
Holland (P4)	Arnhem	41
	Maastricht	42
	Nijmegen	43
Hungary (P5)	Szeged	51
Italy (P6)	Brescia	61
	Castellanza	62
	Genoa	63
	Milan	64
Sweden (P7)	Sahlgrenska	71
United Kingdom (P8)	Kings College	81
Ireland (P8)	Cork	82
	Dublin	83
Germany (P9)	UULM	91

Development of monitoring network for NILVAD in Europe

Each site had an assigned monitor for the study. In total there were nine monitors for the study (UK and Ireland shared the same monitor and the Netherlands had 2 monitors shared across the 3 sites). The Project Office held regular teleconferences with the NILVAD Monitors to share information and discuss ongoing study management issues. A monitoring plan, SOP and monitoring report templates were in place which specified how the monitoring visits should be conducted and reported on. The completed monitoring visit reports were sent to the Project Office for review and follow up and filing. Monitoring visits were performed at regular intervals for each of the study sites with oversight from the Project Office.

Coordination of regulatory and ethical approvals in different European countries

The submission of the regulatory and ethical applications was coordinated centrally by the Sponsor/Project Office. The Voluntary Harmonisation Procedure (VHP) was availed of for the regulatory submissions for 7 out of the 9 partner countries. Italy and Greece did not take part in the VHP process. Once central conditional approval was granted by the VHP the approved documents were circulated to the partners for submission to their National Competent Authorities (NCA). Submission for Ethics approval commenced following receipt of regulatory approval through the VHP process. The first Ethics submission was made to the Sponsor's Ethics Committee (St. James's Hospital). Following receipt of approval from the Sponsor's Ethics Committee, the approved documents were circulated to the key representatives in the partner countries for submission to their respective Ethics Committees. The partner countries informed the Project Office of the granting of ethical approval and all approval documentation was provided prior to recruitment commencing at any of the partner sites. Regulatory and ethical approvals were subsequently applied for and granted for each of the substantial amendments across each of the partner sites/countries.

Drug Procurement, packaging & distribution

The study drug nilvadipine (Nivadil 8mg SR capsules) was purchased from Astellas Pharma Ireland. The nilvadipine was shipped to the IMP manufacturer (LC2) in France where it was overencapsulated and a matched overencapsulated placebo was manufactured. In total, three batches of IMP were produced. Please see the report on WP02 in the body of the periodic report for details of the three batches. The Sponsor/Project Office reviewed stock levels across the study sites on an ongoing basis to ensure adequate stock was maintained. A final return of IMP to the manufacturer at LC2 was organised at the end of the study for all remaining used and unused IMP and all expired and returned IMP was destroyed by LC2.

Establishment of the NILVAD boards

As outlined above, the SAB, EAB and DSMB were established early in the study to provide the consortium with support, guidance and advice. The boards ensured that the trial adhered to international regulations and the principles of ICH-GCP. The boards also aided in the smooth running of the trial and were an important factor in ensuring the trial was completed on time and within budget.

WP03: Education and Training

This WP involved the establishment of trial-specific training procedures which was done by the coordinator and the Project Office in Dublin. A number of training webinars were developed by the coordinator's team and were available to all study staff through the private log-in area of the NILVAD website. Examples of training material available to staff through the private log-in area of the NILVAD website were hands on role play training, demonstrations regarding all standardised tests including administration and scoring conventions and common problems encountered. Training was provided to each monitor by the Project Office who was then able to conduct training during site initiation visits. Training included knowledge of the Protocol and project timeframe, Good Clinical Practice, Ethics, and administration of tests and rating instruments. The three outcome measures specific to the trial were:

1. The Alzheimer's Disease Assessment Scale (Cognitive) ADAS-Cog 12
2. The Clinical Dementia Rating Scale Sum of Boxes (CDR-sb)
3. The Disability Assessment for Dementia (DAD)

The ADAS-Cog 12 includes 12 items of cognitive evaluation, namely immediate word recall, naming objects and fingers, commands, constructional praxis, ideational praxis, orientation, word recognition, remembering test instructions, spoken language ability, word-finding difficulty in spontaneous speech, comprehension & delayed recall. CDR-sb is the secondary efficacy outcome measure. This is a semi-structured interview and the patient's performance in the domains of memory, orientation, judgment, problem solving, community affairs, home and hobbies and personal care are assessed. The DAD evaluates the basic and instrumental activities in daily activities of elderly people with dementia. This 40-item scale addresses a range of functional domains: eating, meal preparation, telephoning, hygienic, dressing, medication, corresponding, finance, leisure, and housework.

The Project Office also maintained oversight of all the tests and rating instruments that were being used in the study, which are key clinical end points, through reviewing monitoring reports. DVDs were created by staff at SJH (partner 17) to demonstrate the rating instruments and these DVDs and accompanying training material were circulated to all recruiting sites. This ensured that all rating instruments were administered in a harmonised fashion at all the clinical trial sites.

There was ongoing assessment of training for people involved in the study. Monitors were responsible for checking that all new site staff were trained according to the study requirements and the tasks that they performed as part of the study. In addition, the Sponsor assessed training records filed at sites during Sponsor site inspection visits and enquired about training records of staff after review of monitoring reports. The NILVAD network now consists of an array of clinicians and research workers who are trained to a high standard in AD-specific outcome assessments and are equipped to work on future dementia-related research studies to ICH-GCP standards. Additionally, there is established expertise in SJH (partner 17) where the training material, in collaboration with colleagues at KCL (partner 08), was developed. This expertise and collaboration will be invaluable for designing appropriate training material for future similar investigator-led studies in the field of AD research.

WP05: Clinical Platform-Nilvadipine Clinical Trial

This WP was established to ensure a smooth running of the clinical phase of the NILVAD trial. This WP involved activities at all 23 recruiting sites with oversight and management of all activities by the Project Office at TCD. The main achievements of this WP were:

- Successful completion of the investigator initiated European multi-centre clinical trial according to ICH-GCP guidelines and in accordance with the regulatory and ethical frameworks of each participating country
- Recruitment of 511 subjects to the study and maintenance of a low attrition rate of 12.3%
- Assessment of the symptomatic and disease modifying benefit of nilvadipine using cognitive and global efficacy endpoints in a mixed population of mild to moderate AD patients
- Assessment of the safety of nilvadipine in mild to moderate AD and concluding that nilvadipine was safe and well tolerated in the study population

- Collection of and transport of biosamples to a long-term biobank facility to facilitate future analysis for the NILVAD substudies and future projects
- Examination of the modifying effects of potential multimodal therapeutic interventions such as frailty, exercise level, nutritional status and social connection on treatment outcome through substudies

Successful completion of the investigator-initiated European multi-centre clinical trial according to ICH-GCP guidelines and in accordance with the regulatory and ethical frameworks of each participating country:

The Sponsor/Project Office at TCD/SJH with guidance from the Coordinator oversaw the activities in WP05 to ensure the clinical phase of the study was completed on time and within budget. Activities at all 23 recruiting sites were closely monitored by local monitors and the Sponsor to ensure adherence to ICH-GCP standards and all applicable regulations as well as the trial protocol. Key to this was maintaining central oversight of training of the study staff across the sites at the Project Office throughout the duration of the trial. An SOP on protocol violations was developed to assist with central oversight of adherence at sites. In total 77 violations were recorded centrally by the Project Office – 22 GCP violations and 55 protocol violations.

Another critical aspect of ensuring adherence to ICH-GCP and all other applicable standards was maintaining oversight of pharmacovigilance at all clinical sites. To facilitate this, a Safety Reporting SOP was written and a dedicated email account was set up at the Project Office to which all Serious Adverse Events/Reactions (SAE/SAR) were reported to the Sponsor. In total, 119 SAEs were recorded during the trial, 5 of which were SUSARs and were all reported to the relevant authorities. To further ensure compliance with regulations and ICH-GCP, a member of the Sponsor office was trained in EudraVigilance reporting.

The Sponsor at SJH was responsible for ensuring that insurance was in place for the duration of the trial and successfully met this requirement with all insurance documents filed in the TMF.

The establishment of robust monitoring procedures was important for ensuring adherence of the trial activities to all applicable standards and regulations. As discussed, a monitoring SOP was established and a schedule for monitoring for each clinical site based on recruited numbers was agreed upon with the local monitors. The Project Office maintained regular communication with monitors to ensure monitoring was on target and was being conducted in line with the SOP. To augment the activities of the local monitors the Sponsor/Project Office also conducted Sponsor site inspections to the study sites, during which the ISF and Pharmacy file and 20% of the patient files were inspected. In total 22 of the 23 clinical sites were inspected by the Sponsor. The site at GHICL in France (site 15) was not inspected by the Sponsor. As only one patient is recruited at this site it was decided due to time and financial constraints to focus on inspections at the larger French sites.

Establishment of the TMF at the Sponsor/Project Office and the ISFs at recruiting sites was vital for ensuring all essential documents were in place for the duration of the trial. Any updates to the trial documents made by the Sponsor were added to the private log-in area of the NILVAD website. This document repository was used by study staff as a reliable source of the current version of each of the trial documents.

In order to comply with regulations, the Project Office produced four Development Safety Update Reports (DSURs) which were submitted to each of the relevant regulatory authorities and ethics committees.

The Project Office coordinated the successful close-out of the study with datalock occurring on the 19th December 2016 after the final last patient last visit (LPLV) occurred at the Dublin site on 2nd November 2016. Analysis of the locked dataset commenced immediately and an independent validation of the results was conducted in February 2017 which verified the analysis completed by the trial statistician. To ensure compliance with all applicable regulations and ICH-GCP, a close-out SOP and filing and archiving SOP were developed to ensure close-out and archiving activities at the 23 clinical sites were appropriate. Close out reports were produced by the country monitors and sent to the Project Office for review as per the close-out SOP. Arrangements for archiving the ISF and patient files were made locally at each of the study sites and key contacts at each site were established who can be contacted if the files need to be accessed at a later date. This information is contained on archiving forms which are part of SOP004 Filing and Archiving. All ethics committees and regulatory authorities were sent the end of trial notification within the required 90 day timeframe. The project office invited an external audit of the trial master file (TMF) in April 2017 to ensure that all required documents were in place prior to archiving. Work is underway on finalising the paper on the detailed trial results for publication in a high impact peer-reviewed scientific journal. In addition, preparation of the clinical study report for the applicable regulatory bodies is underway and will be ready for submission well ahead of the 12-month required timeframe.

Recruitment of 511 subjects to the study and maintenance of a low attrition rate of 12.3%:

The EC agreed target across the study sites of 510 patients was reached by the end of March 2015 when 511 patients were enrolled to the study. Please see figure 1 for recruitment progress during the clinical phase of the study. In order to achieve the recruitment targets, the Project Office arranged for the transfer of patients from low recruiting sites to strong recruiters. Additional patients were recruited in KCL (partner 08), SJH (partner 17), SFH (partner 14), Sweden (partner 13) and the Italian sites (partner 09). This compensated for lower than expected recruitment in Hungary (partner 12) and Germany (partner 11). Early in the clinical phase, the Sponsor monitored the recruitment numbers on a weekly basis and held regular calls with the study sites/coordinating centres to see how recruitment was progressing and what the recruitment projections were for the coming month. The Sponsor maintained recruitment tables and charts of actual versus target which were reviewed weekly (figure 1).

The planned recruitment window was to run from July 2013 until the end of December 2014 representing a recruitment period of 18 months. Recruitment was slow to start across a number of the sites due to delays in the sites starting up and completing their site initiation and also the speed of patient enrolment in the active trial sites was slightly lower than expected. The Project Office then worked out recruitment projections based on the level of recruitment achieved per site between January and August 2014 and projected that if recruitment progressed at the same rate it would need three more months in order to reach the target of 510 patients. The request for the extension of the recruitment phase by three months was part of the 2nd Amendment. The corrective measures taken by our side together with the extended recruitment phase led to an achievement of our target of 511 patients enrolled by March 2015. Please see Figure 1 below detailing the targeted and actual recruitment from July 2013 through to March 2015. Between May 15th 2013 and April 13th 2015, 511 eligible participants were randomised to treatment (258 to control, 253 to nilvadipine). A sample size of 250 patients in each treatment group was calculated to allow detection of a 50% reduction in cognitive deterioration in the nilvadipine group over the 78 weeks of follow-up. This gave 90% power to detect a 3.5 points reduction in the ADAS-Cog 12 decline (standard deviation=10), and 81% power to detect a

significant effect on the CDR-sb as a gated co-primary endpoint. This sample size still allowed for a 30% loss to follow-up. A low attrition rate of 12.3% was maintained throughout the study.

The three month extended recruitment phase had a knock-on effect on the scheduling of the follow-up phase which continued until Week 82 for the last patient last visit (LPLV) which took place at the Dublin site on 2nd November 2016. The study team requested and were granted a six-month no-cost extension by the EC in a 4th Amendment. This facilitated cleaning, verification and close-out of the data set in November 2016 and allowed for the data analysis to commence in December 2016. This six-month no-cost extension also allowed time for sites to be closed, end of trial notifications to be sent to all relevant bodies, the main study publication to be written and for an audit of the TMF to be conducted.

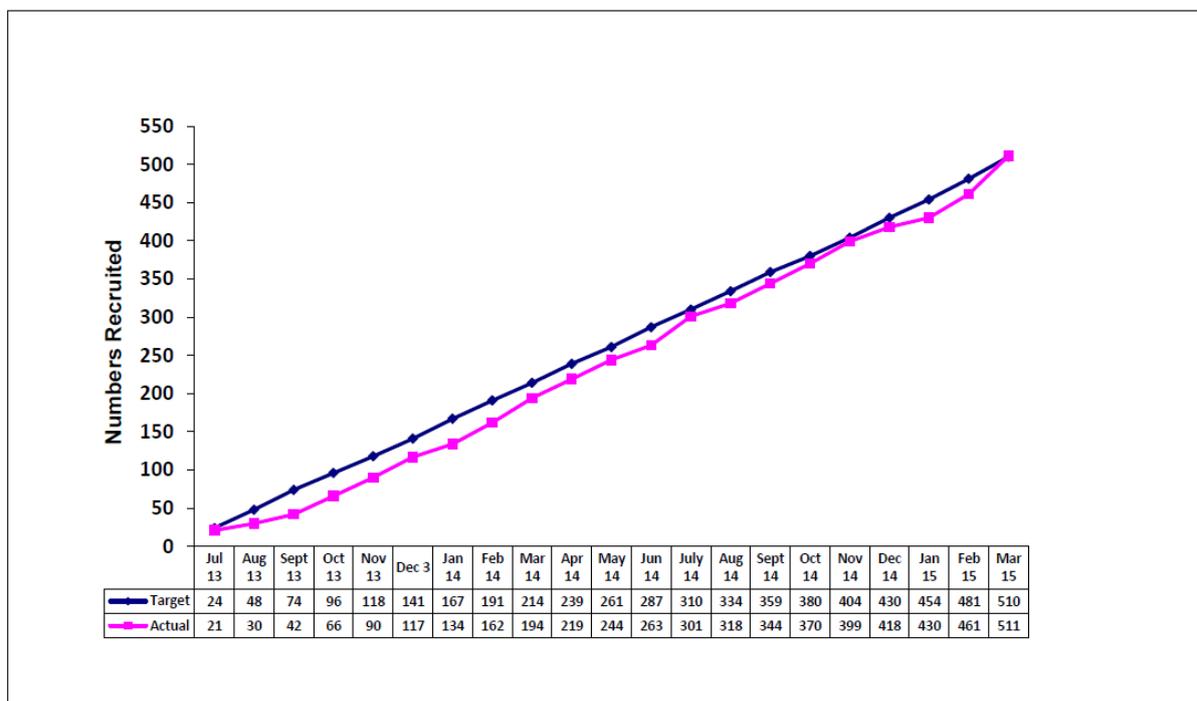


Figure 1. Progress of recruitment to the NILVAD study

Assessment of the symptomatic and disease modifying benefit of nilvadipine using cognitive and global efficacy endpoints in a mixed population of mild to moderate AD patients:

The clinical phase of the NILVAD trial ended on 16th December 2016 which was the last date that changes were made to the trial database. On the 19th December the database was locked for analysis and sent to the trial

statistician at University College Dublin (UCD) (partner 6). A working instructions document was produced by the project office to facilitate a smooth process for datalock. The working instructions contain a checklist which needed to be ticked off before datalock could commence. The checklist is presented in figure 2. As per the datalock checklist in figure 2, a database pre-lock meeting was held on 14th December 2016. In the days following the meeting the final items on the datalock checklist were marked as complete and instructions were issued to the Clinical Trials Unit at KCL (partner 08) on 19th December 2016 to lock the database and send the unblinded extract to the trial statistician at UCD (partner 06). The analysis phase of the study commenced immediately as per the statistical analysis plan (SAP) and secondary and exploratory analysis plans. Both of these analysis plans were reviewed and sign off on by the coordinator, the trial statisticians and members of the DSMB prior to database lock. The signed SAP and secondary analysis plans are filed in the archived TMF. Copies of the unblinded dataset containing treatment allocation and the accompanying decoding information were sent to the trial statistician at UCD and copies are filed in the archived TMF.

Detailed discussion on the analysis of the results is presented in the main trial publication, which is anticipated to be published in a high impact peer-reviewed scientific journal in late 2017. An announcement of the publication will be made on the NILVAD website.



Appendix 1: Study Lock Checklist

This document lists the items to be checked prior to final lock of a study database. It should be used at the pre-lock meeting to ensure all items have been completed before the database is locked.

	Item	Comments	Complete
1	All active clinical research participants have completed their final visit, including the follow up visits		
2	All Serious Adverse Events (SAEs) have been reconciled with the eCRF		
3	All outstanding queries are resolved and database updated		
4	Unblinding requests have been reconciled with the eCRF		
5	Central Protocol Violation Log up to date and ready to be sent to the statistician		
6	Statistical Analysis Plan signed off by the DSMB		
7	Secondary and Exploratory Analysis Document signed by the DSMB		

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Figure 2. Checklist from database lock working instructions

Assessment of the safety of nilvadipine in mild to moderate AD and concluding that nilvadipine was safe and well tolerated in the study population:

A key activity for WP05 was monitoring pharmacovigilance at the clinical sites. This was managed by the Project Office and was done according to the pharmacovigilance SOP. In total 2,156 adverse events (AEs) were reported throughout the study, of which 119 were reported as serious adverse events (SAEs). Nilvadipine was well tolerated. There were 18 suspected serious adverse reactions (SARs) and five confirmed suspected unexpected serious

adverse events (SUSARs). All SUSARs were reported to the relevant authorities. For the whole study duration, there were 9 syncope-related SAEs from a total of 119 SAEs. Of these 9, 5 were unblinded and 2 were found to be on study drug and 3 on placebo. Four remained blinded. There were 17 falls reported (1 relating to nilvadipine, 2 to placebo and 14 blinded) and 15 fractures reported (all blinded) for the whole study duration. A number of measures were taken in the protocol to protect patients with a risk of reduction in blood pressure. The risk of syncope is apparent in NILVAD patients on nilvadipine and the IB was updated to reflect this.

In total ten patients died since recruitment commenced (7 patients died during the study duration and a further 3 died during the longer-term follow-up of serious adverse events). None of the deaths were thought to be related to the study drug and the events were classified as not related under causality in the SAE reports. The causes of death were; sepsis, heart failure, myocardial infarction, cardiac arrest, pneumonia, respiratory infection, hip fracture and surgery, cerebrovascular accident, fatal fall and bone cancer.

In order to monitor the safety of the study drug the following tools were used:

1. All Adverse Events/Reactions are recorded: All adverse events are reported and logged on the paper and electronic source data worksheets. A review of the AEs was conducted by study clinicians and the data manager prior to datalock to ensure that no SAEs were missed and that the correct body coding systems had been used.
2. SAEs/SARs are reported to the Project Office through a dedicated email account: SAEs/SARs are reported to the Project Office in SJH within 24 hours of the study staff becoming aware of the event. The incidents are assessed by the coordination team in SJH to decide if they are a SAE, SAR or SUSAR and report as appropriate following the instructions in the pharmacovigilance SOP.
3. Regular DSMB meetings held: The Data Safety Monitoring Board (DSMB) meet approximately every 6 months during the recruitment and follow up phase to review the safety data which is presented in DSMB reports. Seven DSMB meetings/teleconferences have taken place throughout the study. On each occasion that they met, the DSMB recommended that the trial continue. During their final meeting which was held after datalock, the DSMB agreed that the AEs experienced by the study cohort during the trial were standard for the study population and were unlikely to be related to the study drug.
4. Country Monitor Visits: One of the tasks of the country monitor was to assess whether adverse events and serious adverse events were being recorded and reported correctly. This is reported on in each of the monitoring visit reports which were reviewed by the Project Office. In addition, the Sponsor conducted spot checks of AEs/SAEs during the Sponsor site inspections conducted in 2016.
5. 24HR unblinding phone service: To ensure safety of the trial subjects, a 24HR unblinding emergency service was made available to participants, their caregivers and clinicians for the duration of the trial.

Further detailed discussion of the safety analysis is discussed in the main trial publication which is anticipated to be published in a high-impact peer-reviewed scientific journal in late 2017.

Collection of and transport of bio-samples to a long-term biobank facility to facilitate future analysis for the NILVAD substudies and future projects:

There are four substudies of the NILVAD project, two of which required collection of bio-samples from participants.

For the Blood and Genetic Biomarker substudy, blood and plasma samples were collected. For the CSF substudy CSF and paired albumin samples were collected. A total of 17,999 biosamples were collected during the trial and were sent for storage in the biobank facility in Lille, France. This biobank is an invaluable resource for both the blood and CSF substudies and future studies arising from NILVAD and from future collaborations. In June 2017 the Project Office coordinated shipment of blood biosamples to Archer in Florida, USA (partner 04) for the analysis phase of the Blood Substudy to commence. Alongside this, CSF samples were shipped from the biobank to the neurochemical laboratory of Prof Kaj Blennow at Gothenburg University (partner 13) for the analysis phase of the CSF substudy to commence. As of August 2017 there are 14,962 biosamples (combination of blood and CSF samples) remaining at the biobank. Further requests for biosamples may be made by the Blood and CSF substudy leads as analysis progresses on both substudies. Where permission is in place, the other remaining biosamples will be used by future research groups as part of ongoing collaborations the NILVAD consortium has formed.

Through the NILVAD study collaborative links have been forged between the NILVAD consortium and other projects. The NILVAD consortium will provide biosamples to the following collaborators:

- The Fair Park II project (Conservative Iron Chelation as a disease modifying strategy in Parkinson's disease: A multicentre, parallel group, placebo controlled, randomised control clinical trial of Deferiprone) which was funded under H2020. NILVAD will provide biobanked biosamples to Fair Park II which will be used to analyse the efficacy of Biomarkers for Parkinson's disease
- The EADB (A European DNA bank for deciphering the missing heritability of Alzheimer's Disease) consortium. EADB is a JPND funded study and NILVAD will provide DNA extracts from the patients who participated in the Blood Biomarker substudy
- Cellular Neuroscience at Trinity College Institute of Neuroscience in Trinity College Dublin (Prof. Marina Lynch) will be provided biosamples for research on cellular markers to distinguish between mild cognitive impairment and Alzheimer's disease patients.
- Prof Kaj Blennow's Clinical Neurochemistry lab at Gothenburg University has also been agreed via the NILVAD PI Dr Anders Wallin, the lead PI on the CSF substudy. As part of this collaboration, analysis of NILVAD CSF biomarkers is being performed at the laboratory of Prof Kaj Blennow for the substudy. CSF samples and paired albumin were sent to the laboratory of Prof Blennow in June 2017 and analysis is underway.

A NILVAD Review Group will be established to review requests for access to biosamples remaining at the biobank and to facilitate future collaborations arising from the NILVAD trial. This Review Group will include the coordinator and nominated key members from the consortium.

Examination of the modifying effects of potential multimodal therapeutic interventions such as frailty, exercise level, nutritional status and social connection on treatment outcome through substudies:

There are four substudies to the NILVAD trial which are incorporated into the main protocol;

1. Frailty substudy,
2. Cerebrospinal Fluid (CSF) substudy,
3. Blood and Genetic Biomarker substudy
4. Cerebral Blood Flow (CBF) substudy.

The following have been the recruitment rates into the various studies:

- 468 patients were recruited to the Frailty Substudy from a cohort of 495 giving a recruitment rate of 95%

- 335 patients were to the Blood and Genetic substudy from a cohort of 368 giving a recruitment rate of 91%
- 58 out of 78 available patients recruited to the Cerebral blood flow (CBF) substudy giving a recruitment rate of 74%
- 93 from 264 available patients were recruited to the Cerebrospinal (CSF) substudy giving a recruitment rate of 36%.

As discussed, analysis of the biosamples for the Blood and Genetic Biomarker substudy and the CSF substudy is underway. As part of the other substudies, lifestyle factors, frailty, blood pressure (BP) and cerebral blood flow (CBF) are currently being analysed. The first results from the NILVAD substudies are planned to be published in late 2017 or early 2018, after the main findings of the NILVAD trial have been published.

Our Dutch partners at Radboud University (SKU partner 16) were granted funding from the Dutch Alzheimer's Society to fund the CBF substudy. SKU were also granted funding from the ADDF (Alzheimer's Drug Discovery Foundation) for the CBF substudy but as they were also awarded funding from the Dutch Alzheimers Society for this work, the ADDF agreed that the funds can be used to fund the Blood and Genetic Biomarker substudy for which analysis is underway. For the CBF substudy, CBF was assessed at 3 stages during the NILVAD trial in the RUNMC (partner 16) subgroup of 58 subjects using transcranial Doppler and innovative MRI-based arterial spin labelling sequences. The aim of the substudy is to investigate the effect of nilvadipine on CBF. This data is currently being analysed and publication is planned in 2018.

The Dutch team are also conducting a post-hoc study which aims to investigate the effects of nilvadipine on mean BP, BP instability (orthostatic changes) and BP variability (visit to visit changes in BP). Analyses will mainly focus on the effects of treatment with nilvadipine on prevalence of orthostatic hypotension and BP variability. Data of all patients that participated in NILVAD will be used. Orthostatic changes will be investigated and follow-up and off-IMP patients will be included. These analyses will be extended using the subgroup of patients of the Radboud University Medical Centre Alzheimer Centre (58 patients) that had measurements of beat-to-beat and home BP measurements at 3 moments during the study. It is expected that this will lead to a publication in 2018. This study arose out of the NILVAD trial and is being conducted independently of the budgetary resources of the NILVAD project.

An additional study to report the experience of patients and caregivers of participating in the NILVAD clinical trial is currently being conducted in CHRU-Lille (Partner 10), SJH (Partner 17) and AUTH (Partner 15). The study is being led by CHRU-Lille and is comprised of a patient questionnaire and a face to face interview. As with the post-hoc BP study, this study also arose out of the NILVAD trial and is being conducted independently of the budgetary resources of the NILVAD project.

WP06: Outcome Analysis

The key achievements of WP06 has been:

- The development of the statistical analysis plan and the secondary and exploratory analysis plan
- Production of safety monitoring reports for the DSMB meetings
- Development of Bayesian statistical methodology in order to estimate disease modification effect of treatment
- Performance of the final data analysis and production of the statistical section of clinical study report

The development of the statistical analysis plan and the secondary and exploratory analysis plan:

The statistical analysis plan (SAP) and secondary and exploratory analysis plan were finalised and approved by the coordinator, the statistician team at UCD and the DSMB prior to datalock. The co-primary outcome measures were the change from baseline in the 12-item Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-Cog 12) and the Clinical Dementia Rating scale sum of boxes (CDR-sb). The key secondary outcome measure was the Disability Assessment for Dementia (DAD). Data on all primary and secondary outcome measures were collected at baseline, and at 13, 52 and 78 weeks.

As detailed in the SAP, the primary outcomes of NILVAD are to achieve less cognitive decline in treated patients, using the ADAS-Cog 12 and the CDR-sb, measured at baseline and three subsequent time points. As a multicentre trial, the SAP allows for adjustments for potential differences in baseline cognitive function using a random Country effect. The main endpoint is to show that the change in cognitive function from baseline is different in the treated than the placebo arm.

In order to demonstrate change in the primary outcome measures, while controlling the false positive rate at 5%, a strategy of three analyses is adopted which is conducted in a specific order. Firstly the differences in change in ADAS-Cog 12 at the 3 follow-up visits are compared between arms, using an omnibus (F) test for a Time x Group interaction. If this result is significant, it is demonstrated at a proof-of-concept level that nilvadipine alters cognitive decline, and this will permit examination of CDR-sb as a co-primary endpoint. In an identical model, the Time x Group effect on CDR-sb is tested, and if this is significant it can be concluded that this is a successful pivotal study from two strands of evidence. Having achieved significance on both of the above, it is permissible to proceed to a third step, where the aim is to show that the alterations in cognitive decline are linear and persistent, which will be done with two further models: using a slope for linear change over time (rather than an ANOVA-style categorical time), the difference in slope between arms is examined; this is done for both ADAS-Cog 12 and CDR-sb. In the case that the Time x Group interaction terms for both instruments are statistically significant, it can be concluded that there is evidence for a delay of disability.

Irrespective of the results of the primary analysis, secondary and exploratory analysis was conducted as per the secondary and exploratory analysis plan to explore factors which may influence a treatment effect of nilvadipine. Factors included in the secondary and exploratory analysis plan include the sample size calculation, within-person variability and country or site-specific effects. Key secondary analysis is change in CDR-sb and the DAD scales using identical methods as the primary analysis with categorical time. The analysis of the CDR-sb replicates some of the analysis in the SAP and in the case that the primary analysis strategy terminates early due to non-significance these will proceed as the key secondary analyses. The DAD stands alone as a separate key secondary outcome. The secondary analysis plan also contains descriptions of how sensitivity analysis, responder analysis, subgroup analysis illness severity and blood pressure analysis will be conducted following completion of the primary analysis. Both analysis plans are located in the archived TMF.

Production of safety monitoring reports for the DSMB meetings:

Seven safety monitoring reports were produced throughout the trial for the each of the seven DSMB meetings. The following steps were followed in preparation for the DSMB meetings:

1. seven weeks prior to the meeting the data manager contacts the country monitors with data cleaning tasks. Three weeks is allowed for data cleaning.
2. four weeks prior to the meeting the designated Statistician submits the request for the data extract from the Clinical Trials Unit (CTU) in KCL (partner 8). The data is sent in a blinded manner (grouped only by Arm A and Arm B).
3. one week prior to the meeting the report is circulated to the DSMB members and the coordination team (open report only).

The DSMB meeting consists of two sessions; an open session which is attended by the coordination team, trial statisticians, data manager and DSMB members and a closed session which is only attended by the DSMB members. The chair of the DSMB passes on the recommendations to the coordination team following the meeting and sends a letter to the Scientific Advisory Board chair to recommend whether the trial should continue. A total of seven DSMB meetings were held during the project. All safety monitoring reports and minutes of the meetings are archived in the TMF. At all meetings the DSMB were satisfied with the safety on the trial and recommended continuation of the trial.

Development of Bayesian statistical methodology in order to estimate disease modification effect of treatment:

This task was completed during the third reporting period on the project and details are presented in Deliverable 6.4. The work in this task builds on the validation of trial design, review and verification of the statistical and data management protocols albeit using a Bayesian approach and additional analyses. A post doctorate fellow commenced work on this deliverable in June 2015 and a first draft was completed in March 2016. The aim of this work was to investigate and document alternative statistical approaches in the analysis of data from the NILVAD trial. The primary output was the development of code to fit and compare the modelling approaches and the statistical code used for the fitting of the models is included in the appendix of D6.4. However, for the analysis it was decided by the DSMB statistician that, given the low variation between timepoints and groups, application of the Bayesian methodology would not add anything to the findings.

Performance of the final data analysis and production of the statistical section of the clinical study report:

After the locked dataset was sent to the trial statistician at UCD, analysis commenced as per the SAP and secondary and exploratory analysis plans. Due to publication embargoes at the time of writing this report discussion of the results is not included here. Detailed discussion on the analysis of the results is presented in the main trial publication which is anticipated to be published in a high impact peer-reviewed scientific journal in late 2017.

WP07: Dissemination and Communication

The main results from this WP are:

1. Publication of the trial protocol, the substudy protocols and a review article repurposing Nilvadipine for AD
2. Progress towards publishing the main trial results
3. Preparation of a key learnings paper on the NILVAD trial

Publication of the trial protocol, the substudy protocols and a review article repurposing Nilvadipine for AD:

The NILVAD trial protocol was published in BMJ Open in 2014 (Lawlor B, *et al.* NILVAD protocol: a European multicentre double-blind placebo-controlled trial of nilvadipine in mild-to-moderate Alzheimer's disease. BMJ Open 2014;4:e006364. doi: 10.1136/bmjopen-2014-006364).

The substudies protocol describing the protocols for the Frailty, CSF, CBF and Blood and Genetic Biomarkers substudies was published in BMJ Open in 2016 (Meulenbroek O, *et al.* BMJ Open 2016;6:e011584. doi:10.1136/bmjopen-2016-011584).

A review article describing how nilvadipine is being repurposed for AD through the NILVAD trial was published in 2017 in Drugs of the Future Thomson Reuters (McCarthy, H. *et al.*, Repurposing nilvadipine for treatment of dementia: an overview. *Drugs Fut* 2017, 42(5): 281).

Progress towards publishing the main trial results:

Work is underway with the final preparations of the manuscript on the main trial results and it is anticipated that the paper will be published in a high impact peer-reviewed journal before the end of 2017.

Preparation of a key learnings paper on the NILVAD trial:

The Coordinator is writing a manuscript on the key learnings from running the NILVAD trial. This manuscript is anticipated to be submitted later in 2017 and will be a key reference document for future investigator-led trials. The manuscript will discuss the challenges and successes of NILVAD and aims to help standardise how investigator-led studies on the scale of NILVAD are run in the future.

1.4 The potential impact

Socio-economic impact and the wider societal implications of the project

Contribution to Community and social objectives

The objective of NILVAD was to determine whether treatment with nilvadipine SR 8mg, once a day, was safe and could slow the rate of cognitive decline in patients with mild to moderate Alzheimer's disease (AD). The co-primary outcomes were progression on the Alzheimer's Disease Assessment Scale Cognitive-12 (ADAS-Cog 12) and Clinical Dementia Rating Scale sum of boxes (CDR-sb) in the intention-to-treat population. The Disability Assessment for Dementia (DAD) was a key secondary efficacy outcome measure. The results are presented in detail in the main trial publication, which is anticipated to be published in a high impact peer-reviewed scientific journal in late 2017. Nilvadipine was well tolerated within the study population.

When published, the results of NILVAD will add to the existing body of information about AD and will be another step forward towards informing the development of effective treatments for the disease. The strengths of this investigator-driven clinical trial include the successful recruitment and retention of subjects and the conduct of the study to a high standard. A key success of the NILVAD trial has been the development of the NILVAD consortium, a network of 17 academic and clinical institutions based in ten different EU member states as well as one partner in the USA. Within the network are world-leading experts on AD who have gained valuable experience of working on a phase III trial with AD patients and are well positioned to build on the work of NILVAD and progress the field of AD research. The first examples of the strengths of the network are in the collaborations that have already been established with the following groups:

- The Fair Park II project (Dr. David Devos, Lille)
- The EADB consortium (A European DNA bank for deciphering the missing heritability of Alzheimer's disease)
- Cellular Neuroscience at Trinity College Institute of Neuroscience in Trinity College Dublin (Prof Marina A Lynch)
- Clinical Neurochemistry lab at Gothenburg University (Prof Kaj Blennow)

The establishment of the NILVAD Review Group will ensure the remaining biosamples stored at the biobank in Lille are utilised and will ensure that the NILVAD trial has a lasting legacy in the field of AD research and beyond.

In addition, the planned publication of a key learnings paper of the NILVAD study will be a valuable asset for future researchers planning and conducting an investigator-led study on the scale of NILVAD. This paper discusses the challenges and accomplishments related to the key management aspects of the trial. As part of the preparation for this manuscript, a key learnings of NILVAD workshop was held during the final GA meeting held in St. James's Hospital in Dublin on 9th June 2017. This workshop involved a brainstorming session on the key learnings from the study and a group discussion of the learnings amongst members of the consortium. It is anticipated that this paper will be submitted in late 2017.

Main dissemination activities and exploitation of results

Dissemination through publications:

During the NILVAD trial, three key papers have already been published:

1. The NILVAD trial protocol was published in BMJ Open in 2014 (Lawlor B, *et al.* NILVAD protocol: a European multicentre double-blind placebo-controlled trial of nilvadipine in mild-to-moderate Alzheimer's disease. BMJ Open 2014;4:e006364. doi: 10.1136/bmjopen-2014-006364)
2. A paper describing the protocols for the Frailty, CSF, CBF and Blood and Genetic Biomarkers substudies was published in BMJ Open in 2016 (Meulenbroek O, *et al.* European multicentre double-blind placebo-controlled trial of Nilvadipine in mild-to-moderate Alzheimer's disease-the substudy protocols: NILVAD frailty; NILVAD blood and genetic biomarkers; NILVAD cerebrospinal fluid biomarkers; NILVAD cerebral blood flow. BMJ Open 2016;6:e011584. doi:10.1136/bmjopen-2016-011584)
3. A review article describing how nilvadipine is being repurposed for AD through the NILVAD trial was published in 2017 in Drugs of the Future Thomson Reuters (McCarthy, H. *et al.* Repurposing nilvadipine for treatment of dementia: an overview. Drugs Fut 2017, 42(5): 281).

Work is underway to prepare the main trial results for publication and it is anticipated that the manuscript will be published in a high impact peer-reviewed journal by the end of 2017. A key learnings paper on the successes and challenges of NILVAD is also anticipated to be submitted in late 2017.

There are a number of substudies that arose from the NILVAD trial and publications will follow completion of these substudies in due course:

1. Results of the Frailty substudy examining whether baseline frailty status could predict relevant events during a drug trial in Alzheimer's disease are planned to be published in late 2017
2. Publication is planned in 2018 of the CBF substudy results. This substudy is investigating the effect of nilvadipine on CBF using transcranial Doppler and innovative MRI-based arterial spin labelling sequences
3. Analysis is underway on the CSF biosamples collected from NILVAD participants for the CSF substudy and publication of this work will follow in due course. The aim of this study is to investigate the biomarker status of NILVAD participants at baseline as a predictor of response to nilvadipine and to investigate biomarker changes over time, with nilvadipine treatment, possibly enhancing our understanding of the *in vivo* effect of nilvadipine.

4. Analysis is underway on the biosamples collected from NILVAD participants for the Blood and Genetic Biomarker substudy and publication of this work will follow in due course. This study aims to determine whether genetic influences can modify the effect of Nilvadipine on AD pathogenesis and whether changes in plasma amyloid (A β 40 and A β 42), τ and inflammatory markers from study baseline to end point are altered by nilvadipine treatment.
5. An additional post-hoc study which aims to investigate the effects of nilvadipine on mean BP, BP instability (orthostatic changes) and BP variability (visit to visit changes in BP) is underway and publication is anticipated in 2018. This study arose out of the NILVAD trial and is being conducted independently of the budgetary resources of the NILVAD project.
6. A publication is also anticipated from an additional non-interventional study investigating the experience of patients and caregivers of participating in the NILVAD clinical trial, which is currently being conducted in CHRU-Lille (Partner 10), SJH (Partner 17) and AUTH (Partner 15). The study is being led by CHRU-Lille and is comprised of a patient questionnaire and a face to face interview. This study arose out of the NILVAD trial and is being conducted independently of the budgetary resources of the NILVAD project.

Dissemination through conference proceedings:

Members from across the NILVAD consortium have attended multiple conferences during the trial to present information arising from NILVAD. Information on NILVAD has been presented to a wide variety of audiences, including fellow AD researchers, clinical trial personnel and members of the public. The following conferences have been attended by NILVAD staff:

- A poster on the key learnings of NILVAD was presented by Prof Brian Lawlor at the Alzheimer's Association International Conference in London in 16th – 20th July 2017
- On 15th May 2017, a poster on the NILVAD study was presented at the International Clinical Trials Day in Mansion House, Dublin entitled "Nilvad: An Irish-led European clinical study for a new treatment in Alzheimer's disease". The poster discussed the concept, set-up and management aspects of the trial
- The NILVAD project was represented through an oral presentation at the Clinical Trials in Alzheimer's Disease conference (CTAD) in San Diego in December 2016. The title of the presentation was "NILVAD: A European multicentre double-blind controlled phase III trial of Nilvadipine in mild to moderate Alzheimer's disease"
- In July 2016, a poster on the NILVAD study was presented at the Alzheimer's Association International Conference in Toronto. This poster contained information on patient status data, recruitment to the four substudies and information on serious adverse events.
- In the period Jan 2015 – June 2016, the team at SKU presented baseline data of the CBF substudy during two conferences:

The 5th International Meeting on Cerebral Haemodynamic Regulation (CARNet), 13-15 July 2015:

- Poster presentation: "The relationship between BP variability, White Matter Lesions and frailty in Alzheimer's Disease patients" Gerrita J. van Spijker, Olga V. Meulenbroek; Maarten J.T. van Els, Daan. L.K. de Jong, Marcel G.M. Olde Rikkert; Jurgen A.H.R. Claassen.

The 16th International Symposium on Intracranial Pressure and Neuromonitoring, in conjunction with the 6th Annual Meeting of the Cerebral Autoregulation Research Network, 28 June - 2 July 2016:

- Poster presentation: “Cerebral autoregulation and baroreflex sensitivity are not related to cerebrovascular damage in an Alzheimer’s disease population” DLK de Jong, RAA de Heus, OV Meulenbroek, GJ van Spijker MGM Olde Rikkert, JAHR Claassen
- Oral presentation: “Changes in blood pressure and cerebral blood flow after standing are related to cerebrovascular damage in Alzheimer’s disease” RAA de Heus, DLK de Jong, GJ van Spijker, OV Meulenbroek, MGM Olde Rikkert, JAHR Claassen.

Dissemination through a dedicated website:

The NILVAD website (<https://www.nilvad.eu/>) has been a critical dissemination point for the study. Newsletters on the study progress are regularly posted on the website to provide participants, caregivers and members of the public with updates. Publications produced during the trial are also available to the public via the website. Now that the clinical phase has finished, plans have been put in place to keep the website live for two years until 2019. This will allow for the main results to be announced on the website and for the main publication to be posted to the site. Announcements will also be made as publications are produced for each of the NILVAD substudies.

Dissemination through Alzheimer’s Europe and social media:

Between May 2015 – June 2016, Alzheimer Europe (partner 03) have published three articles in their newsletter and one on their website about progress on the NILVAD study:
Newsletters published in this reporting period:

1. 13 May 2015: NILVAD partners hold 4th General Assembly
2. 24 May 2016: NILVAD project nears completion as partners hold 5th General Assembly
3. 14 June 2016: NILVAD releases latest issue of participant and carer newsletter

Website article: 24 May 2016: NILVAD project nears completion as partners hold 5th General Assembly.

These articles are also mentioned in the @AlzheimerEurope twitter feed and Facebook account. During the 5th General Assembly meeting in Dublin, @AlexTeligadas wrote several #NILVAD tweets which were re-tweeted by @AlzheimerEurope.

In the past 12 months (July 2016 – June 2017), Alzheimer Europe (partner 03) has published three articles in its newsletter and on its website about progress on the NILVAD study:

Articles published in this reporting period:

1. [http://alzheimer-europe.org/News/EU-projects/Wednesday-20-July-2016-NILVAD-sub-study-protocols-are-published-in-BMJ-Open-journal/\(language\)/eng-GB](http://alzheimer-europe.org/News/EU-projects/Wednesday-20-July-2016-NILVAD-sub-study-protocols-are-published-in-BMJ-Open-journal/(language)/eng-GB)
2. [http://alzheimer-europe.org/News/EU-projects/Friday-09-June-2017-NILVAD-project-nears-completion-as-partners-hold-6th-General-Assembly/\(language\)/eng-GB](http://alzheimer-europe.org/News/EU-projects/Friday-09-June-2017-NILVAD-project-nears-completion-as-partners-hold-6th-General-Assembly/(language)/eng-GB)

3. [http://alzheimer-europe.org/News/EU-projects/Tuesday-13-June-2017-NILVAD-review-article-published-in-Drugs-of-the-Future/\(language\)/eng-GB](http://alzheimer-europe.org/News/EU-projects/Tuesday-13-June-2017-NILVAD-review-article-published-in-Drugs-of-the-Future/(language)/eng-GB)

These articles have also been mentioned on its social media

accounts: <https://twitter.com/AlzheimerEurope> and <https://www.facebook.com/alzheimer.europe/>.

There are plans to disseminate the results of NILVAD through an article scheduled to be included in Alzheimer's Europe's newsletter in early in 2018.

Please refer to Appendix 1 for Summary of the dissemination activity related to NILVAD during the lifetime of the NILVAD project.

Outlook and future research

Through the NILVAD study, collaborative links have been forged between the NILVAD consortium and other projects:

- NILVAD are collaborating with the Fair Park II project (Conservative Iron Chelation as a disease modifying strategy in Parkinson's disease: A multicentre, parallel group, placebo controlled, randomised control clinical trial of Deferiprone) which was funded under H2020. NILVAD will provide biobanked biosamples to Fair Park II which will be used to analyse the efficacy of Biomarkers for Parkinson's disease.
- The NILVAD consortium will collaborate with the EADB (A European DNA bank for deciphering the missing heritability of Alzheimer's disease) consortium. EADB is a JPND funded study and NILVAD will provide DNA extracts from the patients who participated in the Blood Biomarker substudy.
- The consortium is collaborating with Kaj Blennow's Clinical Neurochemistry lab at Gothenburg University who is analyzing the CSF samples for the CSF substudy.
- The NILVAD consortium is collaborating with the Cellular Neuroscience Group (Professor Marina Lynch) at Trinity College Institute of Neuroscience in Trinity College Dublin, who are exploring cellular markers to distinguish between mild cognitive impairment and Alzheimer's disease patients.
- Discussions are underway regarding potential links between the US, Ireland and Europe in terms of developing cooperative clinical trials networks, expanding on NILVAD.

Establishment of a biobank resource and the NILVAD Review Group:

A total of 17,999 blood and CSF biosamples were collected during the NILVAD trial and are stored in a biobank in Lille, France. This biobank is an invaluable resource and is currently being used for the blood and CSF substudies. A NILVAD Review Group is being established which will consist of the coordinator and nominated key members of the consortium who will ensure that this valuable resource of biosamples is utilised to advance AD and related research. The Review Group will work to a charter which ensures that the group upholds the values of the NILVAD trial when deciding to what projects samples should be used and the group will be in place for five years beyond the end of the project. This will help to keep connections within the NILVAD network and has the potential to enable members of the network to make submissions for future funding calls or explore opportunities as they arise.

Section 2 – Use and dissemination of foreground

Please see PARTICIPANT PORTAL.

Section 3 – Report on societal implications

Please see PARTICIPANT PORTAL.

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/ Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
1	Medical Press	Fukuoka University	Biol.Pharm.Bull Author: Katsunori Iwasaki	Nilvadipine Prevents the Impairment of Spatial memory Induced by Cerebral Ischemia Combined with B-Amyloid in Rats	23-Jul-07	International	Medical industry	not available	International	No
2	Articles published in the popular press	Roskamp Institute	Michael Mullan http://www.heraldtribune.com/news/20120301/guest-roskamp-institute-focuses-on-alzheimers	Roskamp Institute focuses on Alzheimer's	1-Mar-12	USA	Public	not available	International	No
3	Articles published in the popular press	Alzheimer Europe	Newsletter February 2012	NILVAD project team holds first meeting in Dublin	3/9/2012	Luxembourg	Scientific Community, Industry, Civil Society, Policy makers, Media	4000	International	No
4	Articles published in the popular press	Alzheimer Europe	Newsletter February 2012	Maurice O'Connell is on the NILVAD Scientific Advisory Board	3/9/2012	Luxembourg	Scientific Community, Industry, Civil Society, Policy makers, Media	4000	International	No

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
5	Articles published in the popular press	Alzheimer Europe	Newsletter March 2012	NILVAD project website is launched	4/13/2012	Luxembourg	Scientific Community, Industry, Civil Society, Policy makers, Media	4000	International	No
6	Articles published in the popular press	Alzheimer Europe	Newsletter May 2012	Fiona Cregg joins the NILVAD team	6/8/2012	Luxembourg	Scientific Community, Industry, Civil Society, Policy makers, Media	4000	International	No
7	Articles published in the popular press	Alzheimer Europe	Dementia in Europe Magazine, issue 11, June 2012	NILVAD: a European project to test the efficacy of new drug for Alzheimer's disease	6/26/2012	Luxembourg	Scientific Community, Industry, Civil Society, Policy makers, Media	3000	International	No

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
8	Articles published in the popular press	Alzheimer Europe	Newsletter September 2012	NILVAD project holds pre-trial meeting	10/5/2012	Luxembourg	Scientific Community, Industry, Civil Society, Policy makers, Media	4000	International	No
9	Web	TCD	Trinity Engage E-zine www.tcd.ie/research/engage/news/ezone-2012.pdf	NILVAD	1-Nov-12	Ireland	Public	not available	International	No
10	Articles published in the popular press		Corbett A et Al	Drug repositioning for Alzheimer's disease	2012	Ireland	Public	not available	International	Yes

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
11	Articles published in the popular press	Alzheimer Europe	Newsletter December 2012	NILVAD partner secures funding for sub-study	1/8/2013	Luxembourg	Scientific Community, Industry, Civil Society, Policy makers, Media	4000	International	No
12	Articles published in the popular press	Alzheimer Europe	Newsletter December 2012	NILVAD welcomes new Scientific Medical Advisor	1/8/2013	Luxembourg	Scientific Community, Industry, Civil Society, Policy makers, Media	4000	International	No
13	Web	Cleveland Clinic Lou Ruvo Center for Brain Health, Cleveland, OH, USA.	S. Karger AG Authors: Brian S. Appleby Dimitrios Nacopoulos Nicholas Milano Kate Zhong Jeffrey L. Cummings Cleveland Clinic	Dement Geriatr Cogn Disord 2013;35:1–22 A Review: Treatment of Alzheimer's Disease Discovered in Repurposed Agents (References Nilvadipine)	9-Jan-13	USA	Dementia Research	not available	International	No

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
			Lou Ruvo Center for Brain Health, Cleveland, Ohio, USA							
14	Interviews	Newsweaver	Irish Times Health (interview with Prof. Brian Lawlor)	Alzheimer's drug trial begins this week	4/30/2013	Ireland	General Public	265068	Ireland	PR
15	Press releases	Newsweaver	Daily Mail	Irish spearhead tests into pill which may help slow down progression of disease	5/6/2013	Ireland	General Public	150159	Ireland	PR

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
16	Press releases	Newsweaver	Silicon Republic	Irish researchers to lead Alzheimer's drug trials	5/7/2013	Ireland	General public, Technology	250,000	International	PR
17	Web	TCD	Silicon Republic http://www.siliconrepublic.com/innovation/item/32546-irish-researchers-to-lead-a-07.05.2013-11:32	Irish researchers to lead Alzheimer's drug trials	7-May-13	Ireland	Public	not available	Ireland	No
18	Press releases	Newsweaver	Irish Medical News	Preserving cognitive health	5/13/2013	Ireland	Medical industry	22464	Ireland	PR

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
19	Web	Archer	http://www.archerpharma.com/NILVAD.html	NILVAD	29-May-13	USA	Public	not available	International	No
20	Web		http://www.naukowsy.pl/medycyna/trwaja-szeroko-zakrojone-testy-kliniczne-lekow-na-chorobe-alzheimera/	Trwają szeroko zakrojone testy kliniczne leków na chorobę Alzheimer	31-May-13	Poland	Public	not available	Poland	No
21	Web		http://www.choroby.senior.pl/80,0,Skuteczne-leki-na-chorobe-Alzheimera-juz-niedlugo,16743.html	Skuteczne leki na chorobę Alzheimer już niedługo?	31-May-13	Poland	Public	not available	Poland	No

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
22	Web	Archer	http://www.michaelmullan.us/blog/dr-michael-mullan-participates-in-the-nilvad-project-five-year-project-will-conduct-phase-iii-clinical-trials-of-the-drug-nilvadipine/	Dr. Michael Mullan participates in the NILVAD project - five year project will conduct Phase III clinical trials of the drug Nilvadipine	5-Jun-13	USA	Public	not available	International	No
23	Web	Roskamp Institute	http://www.rfdn.org/newsletter/newsletter-2013-06.html	Drs. Michael Mullan and Fiona Crawford recently attended the NILVAD General Assembly Meeting in Schloss Hohenkammer, Munich, Germany	6-Jun-13	USA	Research	not available	International	No
24	Articles published in the popular press	Alzheimer Europe	Newsletter May 2013	NILVAD project team holds General Assembly	6/7/2013	Luxembourg	Scientific Community, Industry, Civil Society, Policy makers, Media	4000	International	No

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
25	Articles published in the popular press	Alzheimer Europe	Newsletter June 2013	NILVAD project is featured on EU research website	7/5/2013	Luxembourg	Scientific Community, Industry, Civil Society, Policy makers, Media	4000	International	No
26	Web	TCD	Current Controlled Trials http://www.controlled-trials.com/ISRCTN14485052/ 22/7/2013	A trial of Nilvadipine in mild to moderate Alzheimer's disease	22-Jul-13	Web	Research	not available	International	No
27	NILVAD Study Newsletter – Sep 2013	Newsweaver	WP7	Study Newsletter	8/22/2013	Ireland	Study members & Interested others	186	International	Yes

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
28	Web	Alzheimer Europe	http://www.alzheimer-europe.org/News/Alzheimer-Europe/Sunday-01-September-2013-NILVAD-reports-on-successful-first-period-of-project-work	NILVAD reports on successful first period of project work	1-Sep-13	Luxembourg	Public	not available	International	No
29	Web	TCD	http://irishamerica.com/2013/08/dublin-researchers-lead-promising-alzheimers-study	Dublin Researchers Lead Promising Alzheimer's Study	1-Sep-13	USA	Public	not available	International	No

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
30	Web	TCD	http://www.tcd.ie/Neuroscience/neil/research/nilvad.php	NILVAD	6-Sep-13	Ireland	Public	not available	International	No
31	Web	Goteborgs Universitet	http://www.sahlgrenska.gu.se/aktuellt/nyheter/Nyheter+Detalj/?contentId=1190129	Lovande alzheimerläkemedel undersöks i omfattande EU-studie	8-Nov-13	Sweden	Medical industry	not available	Sweden	No
32	Web	Alzheimer Europe	http://alzheimerportugal.org/pt/news_text-77-15-181-reuniao-de-direcao-da-alzheimer-europe-05-12-2013	Projects Alzheimer Europe are participating in	5-Dec-13	Portugal	Alzheimer stakeholders	not available	Portugal	No

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
33	Web	Goteborgs Universitet	Science Daily http://www.sciencedaily.com/releases/2013/12/131209105022.htm	Promising Alzheimer's drug trialled in large EU study	9-Dec-13	Sweden	Research	not available	International	No
34	Web	Goteborgs Universitet	Medical Xpress http://medicalxpress.com/news/2013-12-alzheimer-drug-trialled-large-eu.html December 9, 2013	Promising Alzheimer's drug trialled in a large EU study	9-Dec-13	Web	Medical industry	not available	International	No
35	Web		L'Associazione Alzheimer di Riese Pio X° http://www.alzheimer-riese.it/index.php?option=com_content&view=arti	Farmaco promettente per l'Alzheimer in fase sperimentale in Europa	10-Dec-13	Italy	Alzheimer stakeholders	not available	International	No

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/ Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
			cle&id=3426:far maco- promettente- per-lalzheimer- in-fase- sperimentale-in- europa&catid=1 8:annunci&Itemid=235							
36	Web	Goteborgs Universitet	http://www.neuromedia.ca/un-antihypertenseur-teste-dans-la-maladie-dalzheimer/	Un antihypertenseur sera testé dans la maladie d'Alzheimer	13-Dec-13	Web	Public	not available	International	No
37	NILVAD Study Newsletter – Dec 2013	Newsweaver	WP7	Study Newsletter	16-Dec-13	Ireland	Study members & Interested others	186	International	Yes

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
38	Articles published in the popular press		O'Caoimh R et al.	Effects of Centrally Acting Angiotensin Converting	2014	Ireland	Public	not available	International	Yes
39	Articles published in the popular press	Alzheimer Europe	Newsletter Feruary 2013	11 December: NILVAD holds 3rd Steering Committee meeting	2/2/2014	Luxembourg	Scientific Community, Industry, Civil Society, Policy makers, Media	4000	International	No
40	Medical Press		Nature medicine	Plasma phospholipids identify antecedent memory impairment in older adults	9-Mar-14	USA	Medical industry	not available	International	No

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
41	Newsletter	Newsweaver	WP7	NILVAD Study Newsletter – Apr 2014	21-Mar-14	Ireland	Study members & Interested others	203	International	Yes
42	Exhibitions	St James	St James	Brain Health Awareness Day at St James's Hospital	27-May-14	Ireland	General Public	not available	Ireland	No
43	Advertisement	UMC St Radboud	UMC St Radboud	Web Ads: http://www.alzheimer-nederland.nl/actueel/onderzoek/2014/februari/deelnemers-gezocht-voor-medicijnstudie-alzheimer.aspx https://www.radboudumc.nl/Zorg/Meedoenaanwetenschappelijkonderzoek/Pages/PersonenmetAlzheimer.aspx	29-May-14	The Netherlands	Alzheimer Nederland Alzheimer patients/careers in Netherlands	Unknown	The Netherlands	No

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
				http://www.radboudalzheimercentrum.nl/wetenschappelijk-onderzoek/deelname-aan-wetenschappelijk-onderzoek/nilvad-onderzoek						
44	Articles published in the popular press	Alzheimer Europe	AE Newsletter May 2014	12 May: NILVAD hosts 3rd General Assembly	5/31/2014	Luxembourg	Scientific Community, Industry, Civil Society, Policy makers, Media	4000	International	No
45	Newsletter	Newsweaver	WP7	NILVAD Patient and Caregiver's Newsletter - July 2014	1-Jul-14	Ireland	NILVAD Patient and Caregiver's	300	International	Yes

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
46	Newsletter	Newsweaver	WP7	NILVAD Study Newsletter – June 2014	4-Jul-14	Ireland	Study members & Interested others	221	International	Yes
47	Newsletter	Newsweaver	WP7	NILVAD Study Newsletter – Sep 2014	2-Oct-14	Ireland	Study members & Interested others	225	International	Yes
48	Peer review publication	TCD	BMG Open Authors: Brian Lawlor, Sean Kennelly, Sarah O'Dwyer, Fiona Cregg, Cathal Walsh, Robert Coen, Rose Anne	NILVAD protocol: a European multicentre double-blind placebo-controlled trial of nilvadipine in mild-to-moderate Alzheimer's disease http://bmjopen.bmj.com/content/4/10/e006364.full?keytype=ref&ijkey=y53W6GcCiPI93zL	9-Oct-14	UK	Medical industry	BMJ Print approx 120K BMJ Online avg monthly hits approx 1.2m	International	Yes

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/ Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
			Kenny, Robert Howard, Caroline Murphy, Jessica Adams, Leslie Daly, Ricardo Segurado, Siobhan Gaynor, Fiona Crawford, Michael Mullan, Ugo Lucca, Rita Banzi, Florence Pasquier, Laetitia Breuilh, Matthias Riepe, Janos Kalman, Anders							

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
			Wallin, Anne Borjesson, William Molloy, Magda Tsolaki, Marcel Olde Rikkert							
49	Tweet	Alzheimer Europe	Alex Teligadis	NILVAD protocol published	14-Oct-14	Luxembourg	Scientific Community, Industry, Civil Society, Policy makers, Media	not available	International	No
50	Peer review publication	Roskamp Institute	Journal of Biological Chemistry Author: Daniel Paris*, Ghania Ait-Ghezala, Corbin Bachmeier,	The Spleen Tyrosine Kinase (syk) Regulates Alzheimer's A β Production and Tau Hyperphosphorylation	20-Oct-14	USA	Medical industry	JBC Online unique monthly visitors approx 442K	International	No

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
			Gary Laco, David Beaulieu-Abdelahad, Yong Lin, Chao Jin, Fiona Crawford and Michael Mullan							
51	Articles published in the popular press	Alzheimer Europe	AE Newsletter Oct 2014	13 October: NILVAD protocol appears in BMJ	10/31/2014	Luxembourg	Scientific Community, Industry, Civil Society, Policy makers, Media	4000	International	No
52	Web	St James	http://clinicaltrials.gov/show/NCT02017340	A Phase III Trial of Nilvadipine to Treat Alzheimer's Disease (NILVAD)	16-Dec-14	USA	Patients, their families and caregivers, health care professionals, clinical researchers, and study record managers	57,000 unique visitors daily (as of July 2014)	International	No

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
53	Interviews	Newsweaver	Evening Echo (interview with Prof. Brian Lawlor)	Patients sought for trial of potential breakthrough drug	16.07/2013	Ireland	General Public	16,560	Ireland	PR
54	Interviews	TCD	The European Commission Representation in Ireland	Short radio interview clip with Prof. Brian Lawlor for distribution to Irish radio stations	31/06/2013	Ireland	General Public	not available	Ireland	PR
55	Web	TCD	ASAPS http://www.hellobrain.eu/en/research/researcher?id=nilvad-can-an-old-drug-learn-a-new-trick-to-help-alzheimers	Nilvad: Can an old drug learn a new trick to help Alzheimer's?	Web search Sep 2014	Europe	Public	not available	International	No

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
56	Web	KCL	http://www.kcl.ac.uk/ioppn/depts/oldage/research/Pharmacological-Studies/Clinical-Trials/nilvadipine-in-mild-to-moderate-alzheimers-disease-.aspx	Nilvadipine in mild to moderate Alzheimer's Disease (NILVAD)	Web search Sep 2014	UK	Public	not available	International	No
57	Web		Irish Times http://www.irishtimes.com/premium/loginpage?destination=http://www.irishtimes.com/news/health/alzheimer-s-drug-trial-begins-this-week-1.1376779	alzheimer-s-drug-trial-begins-this-week	Web search Sep 2014	Ireland	Public	not available	International	No

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/ Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
58	Web	KCL	UK Clinical Research Network http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=14541	NILVAD A European multicentre double-blind placebo controlled phase III trial of nilvadipine in mild to moderate Alzheimer's disease.	Web search Sep 2014	UK	Research	not available	International	No
59	Web		Alzforum http://www.alzforum.org/therapeutics/nilvadipine	Nilvadipine	Web search Sep 2014	Italy	Alzheimer stakeholders	not available	International	No
60	Web		Centro Alzheimer http://www.centroalzheimer.org/site/Nilvadipidina.php	Studio Europeo multicentrico in doppio cieco per valutare l'efficacia di nilvadipina versus placebo nella malattia di Alzheimer da lieve a moderata	Web search Sep 2014	Italy	Alzheimer stakeholders	not available	International	No

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
61	Web	Archer	BILAT USA 2.0 Project http://www.euusciencetechnology.eu/content/european-multicentre-double-blind-placebo-controlled-phase-iii-trial-nilvadipine-mild	A European multicentre double-blind placebo-controlled phase III trial of nilvadipine in mild to moderate Alzheimers disease	Web search Sep 2014	USA	Research	not available	International	No
62	Web	TCD	Health Research Board http://www.hrb.ie/research-strategy-funding/external-relations/eu-funding-opportunities/successful-fp7-projects/professor-brian-lawlor/	Clinical trial in Alzheimer's disease	Web search Sep 2014	Ireland	Medical industry	not available	Ireland	No

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
63	Web	Mario Negri	http://www.marionegri.it/mn/it/sezioni/dipartimento/labInfo35/attRicerca.html	A European Multicentre Double-Blind Placebo Controlled trial of Nilvadipine in Mild to Moderate Alzheimer's disease (NILVAD Project - European Union FP7 Program) -	Web search Sep 2014	Italy	Medical industry	not available	Italy	No
64	Web	Radboud UMC	http://www.radboudalzheimercentrum.nl/wetenschappelijk-onderzoek/deeln-ame-aan-wetenschappelijk-onderzoek/nilvad-onderzoek	NILVAD onderzoek	Web search Sep 2014	The Netherlands	Alzheimer stakeholders	not available	The Netherlands	No
65	Articles published in the popular press		Cherian J and Gohil K	Cautious Optimism for Growth In Alzheimer's Disease Treatments	2015	Ireland	Public	not available	International	Yes

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
66	Articles published in the popular press	Alzheimer Europe	AE Newsletter May 2015	13 May: NILVAD partners hold 4th General Assembly	5/31/2015	Luxembourg	Scientific Community, Industry, Civil Society, Policy makers, Media	4000	International	No
67	Report	Gabo:mi	http://cordis.europa.eu/result/rcn/171004_en.html	Periodic Report Summary 2 - NILVAD (A European multicentre double-blind placebo-controlled phase III trial of nilvadpine in mild to moderate Alzheimer's disease)	25-Sep-15	Brussels	Public	not available	International	Yes
68	Other	TCD	http://www.universityvacancies.com/trinity-college-dublin/research-assistant-clinical-trials-administrator-nilvad-3562	Research Assistant (Clinical Trials Administrator): NILVAD - See more at: http://www.universityvacancies.com/trinity-college-dublin/research-assistant-clinical-trials-administrator-nilvad-3562#sthash.CaphOzql.dpuf	11/1/2015	Dublin	Public	not available	International	No

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69	Other	TCD	http://jobs.sciencecareers.org/job/387118/research-assistant-clinical-trials-administrator-nilvad/	http://jobs.sciencecareers.org/job/387118/research-assistant-clinical-trials-administrator-nilvad/	11/4/2015	Dublin	Public - research recruitment	not available	International	No
70	Newsletter	Newsweaver	WP7	NILVAD Study Newsletter – Dec 2015	2-Dec-15	Ireland	Study members & Interested others	211	International	Yes
71	Articles published in the popular press		Ruthirakuhan M et al.	Beyond immunotherapy: new approaches for disease modifying treatments for early Alzheimer's disease	2016	Ireland	Public	not available	International	Yes

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72	Articles published in the popular press		Dacks P et al	A call for comparative effectiveness research to learn whether routine clinical care decisions can protect from dementia and cognitive decline	2016	Ireland	Public	not available	International	Yes
73	Articles published in the popular press		Khan A et al	Emerging amyloid and tau targeting treatments for Alzheimer's disease	2017	Ireland	Public	not available	International	Yes
74	Articles published in the popular press	Alzheimer Europe	AE Newsletter May 2016	24 May: NILVAD partners hold 5th General Assembly	5/24/2016	Luxembourg	Scientific Community, Industry, Civil Society, Policy makers, Media	4000	International	No

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/ Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
75	Web	Alzheimer Europe	http://alzheimer-europe.org/News/EU-projects/Wednesday-20-July-2016-NILVAD-sub-study-protocols-are-published-in-BMJ-Open-journal/(language)/eng-GB	Nilvad sub Study protocols are published in BMJ Open Journal	20-07-16	Luxembourg	Scientific Community, Industry, Civil Society, Policy makers, Media	4000	International	No
76	Web	Alzheimer Europe	http://alzheimer-europe.org/News/EU-projects/Friday-09-June-2017-NILVAD-project-nears-completion-as-partners-hold-6th-General-Assembly/(language)/eng-GB	Nilvad project nears completion as partners hold 6th General Assembly	9/6/2017	Luxembourg	Scientific Community, Industry, Civil Society, Policy makers, Media	4000	International	No

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77	Web	Alzheimer Europe	http://alzheimer-europe.org/News/EU-projects/Tuesday-13-June-2017-NILVAD-review-article-published-in-Drugs-of-the-Future/(language)/eng-GB	Review article published in Drugs of the Future	9/6/2017	Luxembourg	Scientific Community, Industry, Civil Society, Policy makers, Media	4000	International	No
78	Newsletter	Newsweaver	WP7	NILVAD Patient and Caregiver's Newsletter - July 2016	31-Jul-16	Ireland	NILVAD Patient and Caregiver's	300	International	Yes
79	Peer review publication	TCD	Olga Meulenbroek , Sarah O'Dwyer , Daan de Jong , Gerrita van Spijker , Sean Kennelly , Fiona Cregg , Marcel	European multicentre double-blind placebo-controlled trial of Nilvadipine in mild-to-moderate Alzheimer's disease—the substudy protocols: NILVAD frailty; NILVAD blood and genetic biomarkers; NILVAD	7/1/2016	United Kingdom	Scientific Community, Industry, Civil Society, Policy makers, Media	Unknown	International	Yes

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/ Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
			Olde Rikkert , Laila Abdullah , Anders Wallin , Cathal Walsh , Robert Coen , Rose Anne Kenny , Leslie Daly , Ricardo Segurado , Anne Borjesson-Hanson , Fiona Crawford , Michael Mullan , Ugo Lucca , Rita Banzi , Florence Pasquier , Laetitia Breuilh , Matthias Riepe , Janos Kalman , William Molloy , Magda Tsolaki , Robert Howard , Jessica Adams , Siobhan Gaynor , Brian Lawlor	cerebrospinal fluid biomarkers; NILVAD cerebral blood flow						

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80	Newsletter	Newsweaver	WP7	NILVAD Study Newsletter – December 2016	18/12/2016	Ireland	Study members & Interested others	211	International	Yes
81	Conferences	TCD	http://www.ctad-alzheimer.com/files/files/PROGRAMfinal_CTAD2016_1dec.pdf	NILVAD: A European multicentre double-blind controlled phase III trial of Nilvadipine in mild to moderate Alzheimer's disease	09 - Dec - 16	San Diego	Scientific Community, Industry, Civil Society, Policy makers, Media	not available	International	No
82	Tweet	Alzheimer Europe	Jean Geoges	6th Steering Committee	1-Feb-17	London	Scientific Community, Industry, Civil Society, Policy makers, Media	not available	International	No

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
83	Tweet	Newsweaver	WP7	Group Photo 6th Steering Committee @NilvadEU	1-Feb-17	London	Scientific Community, Industry, Civil Society, Policy makers, Media	not available	International	No
84	Articles published in the popular press		Khan A et al	Emerging amyloid and tau targeting treatments for Alzheimer's disease	2017	Ireland	Public	not available	International	Yes
85	Newsletter	Newsweaver	WP7	NILVAD Patient and Caregiver's Newsletter - March 2017	4-Apr-17	Ireland	NILVAD Patient and Caregiver's	511	International	Yes

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/ Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
86	Poster	Rianne deHeus	de Heus R., Witjes B., Sanders M., Oudegeest-Sander M., de Jong D., Claassen J	Intact cerebral autoregulation in clinical Alzheimer's disease during spontaneous oscillations in blood pressure	1 - 4 April 17	Berlin	Scientific Community, Industry, Civil Society, Policy makers, Media	not available	International	Yes
87	Poster	TCD	Hannah McCarthy	International Clinical Trials Day . "NILVAD: An Irish-led European clinical study for a new treatment in Alzheimer's disease"	15 May 17	Dublin	Scientific Community, Industry, Civil Society, Policy makers, Media	not available	Ireland	Yes
88	Peer review publication	TCD	McCarthy, H., Kennelly, S., Crawford, F., Mullan, M., Cregg, F., Lawlor, B.A.	Repurposing nilvadipine for treatment of dementia: An overview	13-06-17	United Kingdom	Scientific Community, Industry, Civil Society, Policy makers, Media	not available	International	Yes

No.	Type of activities	Main leader (Institution) ¹	Author of dissemination activity ¹	Title ²	Date/Period	Place	Type of audience ³	Size of audience	Countries addressed	Project Publication
89	Newsletter	Newsweaver	WP7	NILVAD Study Newsletter – June 2017	29-06-17	Ireland	Study members & Interested others	211	International	Yes
90	Poster	TCD	Prof. Brian Lawlor	Alzheimers Association International Conference (AAIC). "Design and Execution of the Nilvad Study"	19-07-17	London	Scientific Community, Industry, Civil Society, Policy makers, Media	not available	International	Yes
91	Conferences	Rianne deHeus	A. Santoso, M. Olde Rikkert.	Abstract for the EUGMS "Frailty, study dropouts, and adverse events: findings from a drug study in mild to moderate Alzheimer's Disease".	20 - 22 Sept 17	Nice	Scientific Community	not available	International	Yes