SYNOPSIS

Name of Sponsor/Company: St James's Hospital, Dublin	Individual Study Table Referring to Part of the Dossier Volume: N/A Page: 5	*(For national Authority Use only)*
Name of Finished Product: Nivadil 8mg slow release (SR) capsules		
Name of Active Ingredient: Nilvadipine		

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

Investigators: Listed in appendix 14.1.4

Study centre(s):

The study took place across Europe. There were 23 clinical sites in total in Ireland, UK, France, Greece, Hungary, the Netherlands, Sweden, Germany, and Italy. There were 2 sites in Ireland, 1 in the UK, 7 in France, 4 in Italy, 1 in Hungary, 3 in Greece, 1 in Germany, 1 in Sweden and 3 in the Netherlands. The sites are listed below.

Country	Site
France	CHU Amiens
	CH Bethune
	CHU Caen
	CH Calais
	CH Saint-Philibert, GHICL
	CHRU Lille
	CH Lens
Greece	Pagageorgiou General Hospital
	Papanikolaou General Hospital of Thessaloniki
	AXEPA University General Hospital
Holland	Rijnstate Hospital, Arnhem
	Academic Hospital, Maastricht
	Radboud University Medical Centre, Nijmegen
Hungary	University of Szeged
Italy	IRCCS Centro san Giovanni di Dio-Fatebenefratelli Brescia
	IRCCS Multimedica Castellanza
	IRCSS AOU San Martino Genoa
	Fondazione Don Gnocchi Milan
Sweden	Goeteborgs Universitet Sahlgrenska
United Kingdom	Kings College London

	Ireland	St Finbarr's Hospital Cork	
		St James's Hospital Dublin	
	Germany	Bezirkskrankenhaus Günzburg (District Hospital Günzburg) Universität Ulm (UULM)	

Publication (reference):

1. Lawlor B, Kennelly S, O'Dwyer S, Cregg F, Walsh C, Coen R, Kenny RA, Howard R, Murphy C, Adams J, Daly L, Segurado R, Gaynor S, Crawford F, Mullan M, Lucca U, Banzi R, Pasquier F, Breuilh L, Riepe M, Kalman J, Wallin A, Borjesson A, Molloy W, Tsolaki M, Olde Rikkert M. 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, van Spijker G, Kennelly S, Cregg F, Olde Rikkert M, Abdullah L, Wallin A, Walsh C, Coen R, Kenny RA, Daly L, Segurado R, Borjesson-Hanson A, Crawford F, Mullan M, Lucca U, Banzi R, Pasquier F, Breuilh L, Riepe M, Kalman J, Molloy W, Tsolaki M, Howard R, Adams J, Gaynor S, Lawlor B. 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.
3. McCarthy, H, Kennelly, S, Crawford, F, Mullan, M, Cregg, F, Lawlor, BA. Repurposing nilvadipine for treatment of dementia: An overview. Drugs Fut 2017, 42(5): 281.

Studied period (years): 5.5 (2012 – 2017) **date of first enrolment:** 15/05/2013 **date of last completed:** 02/11/2016	**Phase of development:** Clinical development plan for repurposing nilvadipine for AD

Objectives:

• To investigate the efficacy of nilvadipine as a disease course modifying treatment for mild to moderate AD in a phase III double-blind placebo-controlled study

• To investigate the safety profile of nilvadipine in patients with mild to moderate AD

Methodology:

NILVAD is a multicentre, randomised, double-blind, placebo-controlled study group of nilvadipine compared with placebo. Qualifying patients are randomly assigned to receive 8mg of nilvadipine or placebo daily for 78 weeks. Patients undergo assessments at weeks 6, 13, 26, 39, 52, 65 +/- 7 days and week 78 + 7 days after beginning treatment.

Number of patients (planned and analysed): 500 patients was the target; 250 in the nilvadipine group and 250 in the placebo group. Between May 15th 2013 and April 13th 2015, 511 eligible participants were randomised to treatment (258 to control, 253 to nilvadipine).

Diagnosis and main criteria for inclusion: Subjects diagnosed with mild to moderate AD are suitable for treatment with nilvadipine.

Test product, dose and mode of administration, batch number: Orally-administered over-encapsulated 8 mg slow release nilvadipine taken once daily after breakfast.

Duration of treatment: The total study duration was 82 weeks. Patients received study medication for 78 weeks (18 months).

Reference therapy (placebo), dose and mode of administration, batch number: Matching over-encapsulated placebo consisting of sugar spheres (pharma-a spheres ™, starch and colour E100).

Criteria for evaluation: 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.

Efficacy: The primary efficacy outcome measures in this study is the change from baseline to week 78 in cognitive function, as assessed by the Alzheimer's Disease Assessment Scale (ADAS -Cog 12). The analysis will take account of the intermediate levels of this measure. There are two key secondary outcome measures, the Clinical Dementia Rating Scale Sum of Boxes (CDR-sb) and the Disability Assessment for Dementia (DAD). If a statistically significant effect is seen in the primary outcome, CDR-sb will be considered to be a co-primary endpoint and only the DAD will contribute to the secondary outcome analysis.

Safety: The safety set included all patients who took at least one dose of the trial treatment.

Statistical methods: The sample size of 250 patients in each group was calculated to allow detection of a 50% reduction in cognitive deterioration in the nilvadipine group over the 78 weeks of treatment. This resulted in 90% power to detect a 3.5 points reduction in decline on the ADAS-Cog 12 decline (SD=10), and 81% power to also 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.

Summary – Conclusions

Efficacy Results: The pre-specified primary analyses failed to show any treatment benefit for nilvadipine on the co-primary or secondary outcomes. The deterioration from baseline in ADAS-Cog 12 on placebo was 0.79 (95% CI: -0.07 to 1.64) at 13 weeks, 6.41 (5.33 to 7.49) at 52 weeks, and 9.63 (8.33 to 10.93) at 78 weeks, compared to changes in the nilvadipine arm of 0.88 (0.02 to 1.74) at 13 weeks, 5.75 (4.66 to 6.85) at 52 weeks, and 9.41 (8.09 to 10.73) at 78 weeks.

Safety Results: Nilvadipine was well tolerated.

Conclusion: The results do not suggest benefit of nilvadipine in a mixed group of mild to moderate Alzheimer's disease patients.