DOMINO-AD

Donepezil and Memantine in Moderate to Severe Alzheimer's Disease

Trial Identifier: ISRCTN49545035
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Final Trial Report

17th November 2011

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First patient randomisation:	**11th February 2008**
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CONFIDENTIAL

The trial was conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including, but not limited to, the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

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Abbreviations & Definitions of Terms

AD	Alzheimer's disease
AIC	Akaike information Ccriterion
BADLS	Bristol activities of daily living scale
BPSD	Behavioural and psychiatric symptoms of dementia
ChEIs	Cholinesterase inhibitors
CI	Confidence interval
CSRI	Client service receipt inventory
GHQ-12	12-item General Health Questionnaire
HRQoL	Health related quality of life
IDMC	Independent data monitoring committee
IEC	Independent ethics committee
IRB	Institutional review board
IQR	Interquartile range
ITT	Intention to treat
MCID	Minimum clinically important differences
MMRM	Multilevel modelling repeated measures
NICE	National institute for health and clinical excellence
NPI	Neuropsychiatric inventory
PP	Per-protocol
SAE	Serious adverse events
SAR	Serious adverse reaciton
SD	Standard deviation
sMMSE	Standardised mini-mental state examination
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial management group
TSC	Trial steering committee

Introduction

Synopsis

Currently the evidence is unclear on what clinicians should prescribe to patients with Alzheimer's disease (AD) once they reach the moderate to severe transition point. The trial planned to look at whether pharmacological **NINCDS-ADRDA** treatment with Donepezil alone or Memantine alone is better than placebo at maintaining cognitive function and activities of daily living in the patients described above. It also considered whether there are synergistic effects of the two drugs combined, compared with each drug alone.

It was a pragmatic, multi-centre, double-blind, randomised, placebo-controlled (double dummy), parallel group, 2X2 factorial clinical trial. Patients recruited to this trial had been diagnosed with Alzheimer's disease which had reached a moderate to severe diagnosis (SMMSE score 5 – 13) and who were currently taking Donepezil.

Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The study and all amendments were reviewed by Scotland A Research Ethics Committee. The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

Patient Information & Consent

Patients and carers were consented by the principal investigator or delegate at each site. Carers signed a 'Carer Consent Form' and a 'Consent Form-to consent on behalf of a non-competent patient' if the patient was deemed to not have the capacity to consent themselves. Competent patients with the capacity to consent signed a 'Patient Informed Consent Form'. Patients and carers were consented during the screening visit, after having been sent the patient and carer information sheets in advance, and before randomisation. See Appendix I for current information sheets and consent forms.

Investigators & Study Administrative Structure

The co-ordinating chief investigator of the study is Professor Robert Howard (Institute of Psychiatry, King's College London) and the study was conducted at 15 centres in the UK.

An Independent Data Monitoring Committee (IDMC) was responsible for monitoring the progress of the trial including: recruitment, protocol adherence, serious adverse events and side effects of treatment as well as the difference between the trial treatments on the primary outcome measures. The Trial Management Group (TMG) oversaw the running of the trial, monitored and maintained recruitment rates, and advised participants on any necessary changes in the running of the trial or analysis of the data. It also resolved any problems that arose in patient management or conduct of the trial. The Trial Steering Committee (TSC) was responsible for the independent oversight of the progress of the trial, investigation of serious adverse events and determining the future progress of the trial in light of regular reports from the IDMC and TMG. The study statistician was Patrick Phillips (Medical Statistician, Medical Research Council Clinical Trials Unit). See Appendix II for details of principal investigators and committee memberships.

The study was funded by the UK Medical Research Council and the Alzheimer's Society. Pfizer-Eisai and Lundbeck donated supplied of drug and placebo. Catalent Pharma Solutions provided packaging, storage and distribution services.

This study was monitored by the Joint Clinical Trials Office (who have been delegated sponsor responsibilities by King's College London) and the trial manager. This included the

initiation and close out of sites, review of patient eligibility and consent, IMP accountability and Source Data Verification. Central data management was performed and data centrally monitored.

Trial Summary

Introduction

The impact of cholinesterase inhibitors (ChEIs) in AD has been most investigated in mild to moderate patients where, despite questions about trial methodology[1] and whether reported benefits have clinical significance[1,2], guidelines advocate treatment, although some recommend discontinuation when AD becomes severe.[3] Evidence for efficacy of memantine is mostly in moderate and severe AD[4], but additional benefits of combination with a cholinesterase inhibitor[5] have not been replicated.[6] Randomised controlled trials with ChEIs in moderate to severe[7,8] and severe[9-12] AD suggest modest improvements in cognition, function and clinical global impression and these drugs are licensed for severe AD in the United States . The severe AD trials have, however, all involved nursing home residents and, critically, none of the moderate to severe or severe trials has investigated continuing treatment in patients already taking ChEIs. There is very limited evidence to guide the difficult decision regarding treatment continuation or discontinuation when disease severity progresses, but continued treatment increases adverse outcomes including syncope, permanent pacemaker insertion and hip fractures.[13]

We investigated whether community-living AD patients, already prescribed donepezil, benefit from continuing treatment once they have progressed to severe dementia, and whether commencing memantine at this point is beneficial.

Objectives

The trial tested a number of hypotheses in memory clinic patients who had declined in terms of cognitive function to reach the transition point to moderate-to-severe AD.

Primary objectives:

a) Patients with AD who continue Donepezil beyond the moderate to severe transition point will show a significantly smaller decline on ratings of cognitive function and activities of daily living over the following 12 months than those discontinuing Donepezil.
b) Patients with AD who commence Memantine therapy at the moderate to severe transition point will show a significantly smaller decline on ratings of cognitive function and activities of daily living over the following 12 months than those who do not.
c) Patients given the combination of Memantine and Donepezil at the moderate to severe transition point will show additive or synergistic significant benefits on measures of activities of daily living and cognitive function after 12 months compared to those patients continuing on either monotherapy.

Secondary objectives:

a) Patients with AD who continue Donepezil beyond the moderate to severe transition point will show a significantly smaller deterioration on ratings of non-cognitive symptoms and health related quality of life over the following 12 months than those discontinuing Donepezil. Analysis at the margins using 100% of trial patients
b) Patients with AD who commence Memantine therapy at the moderate to severe transition point will show a significantly smaller deterioration on ratings of non-cognitive symptoms and health related quality of life over the following 12 months than those who do not.
c) Patients given the combination of Memantine and Donepezil at the moderate to severe transition point will show additive or synergistic significant benefits on measures of non-cognitive symptoms and health related quality of life after 12 months compared to those patients continuing on either monotherapy.

d) Treatment of patients with Donepezil beyond the moderate to severe transition point will be more cost-effective than discontinuing Donepezil. Memantine therapy will be more cost-effective than placebo. The combination of Memantine and Donepezil will be more cost-effective than monotherapy.
e) Patients who continue on Donepezil beyond the moderate to severe transition point will be institutionalised later than those who do not. Patients who commence Memantine therapy will be institutionalised later than those taking placebo. Patients who commence combination of Memantine and Donepezil will be institutionalised later than those on monotherapy. For carers, parallel secondary objectives will be changes in psychological morbidity and health related quality life.

Outcome measures

1) **Primary outcome measures**:
   a) Cognitive function (measured using the SMMSE)
   b) Activities of daily living (measured using the BADLS)
2) **Secondary outcome measures**:
   a) Non-cognitive dementia symptoms (measured using the NPI[19])
   b) Health related quality of life (measured using EQ-5D[23] and DEMQOL-proxy[20])
   c) Care giver burden (measured using the GHQ-12[21])
   d) Cost effectiveness (assessed through consideration of the combination of the CSRI[22] and assessments of function and quality of life)
   e) Institutionalisation (defined as permanent transition to a care home, continuing care unit or hospital)

Trial interventions

The trial consisted of 4 arms with equal allocation to each of:

1) 10mg Donepezil plus 20mg Memantine (continue donepezil 10 mg and immediately commence memantine 5 mg, increasing in 5 mg increments weekly until 20 mg from Week 4)
2) Donepezil placebo plus 20mg Memantine (donepezil 5 mg in Weeks 1 to 4 and placebo donepezil from Week 5. Immediately commence memantine 5 mg, increasing in 5 mg increments weekly until 20 mg from Week 4)
3) 10mg Donepezil plus Memantine placebo (from week 1)
4) Donepezil placebo plus Memantine placebo (donepezil 5 mg in Weeks 1 to 4 and placebo donepezil from Week 5 plus placebo memantine from Week 1)

Planned inclusion and exclusion criteria

Inclusion criteria:

1. Must meet standardized clinical (NINCDS-ADRDA) criteria[15] for probable or possible Alzheimer's disease
2. Must have been continuously prescribed Donepezil for at least 3 months and continuously prescribed 10mg Donepezil in previous 6 weeks
3. Must have had no changes in prescription of drugs for other psychiatric symptoms (e.g. antipsychotic, antidepressant, benzodiazepine) in previous 6 weeks
4. Must have deteriorated to the point where there is uncertainty that the person is receiving benefit from Donepezil and their prescribing physician was considering a change of drug treatment
5. sMMSE[16] score is between 5 and 13 on testing with a standardized assessment of cognitive function
6. Must be community based with a resident family or professional carer or visited on at least a daily basis by a carer

7. Must have given consent if considered capable and the main carer (informal or institutional) must also give consent to their own involvement and to the patient's involvement.

Exclusion criteria:

1. Must not have severe, unstable or poorly controlled medical conditions
2. Must not have a current prescription of Memantine
3. Must not have contra-indications or previous adverse or allergic reactions to the trial drugs
4. Must not be involved in another trial
5. There should be no concerns over the patient's compliance

Duration

The duration of the treatment period was 52 weeks post randomisation. All study measures were to be assessed at randomisation, at 6 weeks (except DEMQOL-proxy) to address the acute effects of withdrawal of Donepezil, and at 18 weeks (except CSRI and GHQ-12), 30 weeks (except DEMQOL-proxy) and at 52 weeks. Patients are then followed up every 26 weeks for 3 years by telephone interview to establish whether and on what date they have entered a care institution.

Risks and benefits

As both Donepezil and Memantine are well tolerated drugs the main risk for patients was withdrawal of their existing prescription of Donepezil. There was also a risk of minor distress or inconvenience. This is balanced by the fact that although neither Donepezil nor Memantine are recommended by NICE for the treatment of patients with low MMSE scores on the basis of cost effectiveness, both drugs have shown advantages over placebo on important clinical outcomes in this patient group.

Design & Study Procedures

The original sample size was 800, adjusted to 430, based on reduced standard deviations of outcomes from a blinded analysis of accrued data. Allowing for an expected 20% missing visits, 430 would give 95% power, at a two-sided significance level of 5%, to detect a 1.0 point sMMSE difference and 90% power to detect a 2.0 point Bristol Activities of Daily Living Scale (BADLS)[17] difference between donepezil and placebo, or between memantine and placebo, at any one assessment point (primary objectives a and b). It would also give 96% power to detect a 1.5 point sMMSE difference, and 80% power to detect a 2.5 point BADLS difference between combination treatment and monotherapy at any one assessment point (primary objective c). Details of the design have been published.[14]

Participants were allocated to one of the four arms by the UK Medical Research Council Clinical Trials Unit by telephone. Patients were allocated using minimisation balancing across four factors: centre (15), duration of donepezil treatment prior to randomisation (3-6 months, more than 6 months), baseline sMMSE score (5-9, 10-13), and age (less than 60, 60-74, 75 years or greater). To maintain allocation concealment, the first 80 participants were allocated using a prepared list of simple randomised allocations.[18] Matched placebo tablets for donepezil 5 mg and memantine 5 mg and 10 mg were provided by the manufacturers; patients, caregivers, clinicians, outcome assessors, and investigators were blinded to allocation.

Statistical Analysis

Unless otherwise specified, analyses were conducted on all patients randomised who received at least one dose of trial medication, applying the principle of intention to treat as far as was practically possible, given any missing data. Participants were analysed in the groups to which they were randomised irrespective of treatment discontinuations or open-label

treatment. The primary analysis of the primary outcomes and the continuous secondary outcomes was conducted using multilevel modelling repeated measures regression[24] adjusted for baseline scores and the four minimisation factors. All non-missing scores at every visit, irrespective of whether the patient was still on trial medication or had switched to open-label treatment, were included in the primary analysis and there was no imputation of missing scores. Scheduled, rather than actual, visit week was used in the model. For each outcome, two models were fitted: (i) with the donepezil by memantine interaction to estimate the additional benefit of combination therapy (primary objective c) and to test for the interaction, and (ii) without the interaction to estimate the difference between active drug and placebo for each of donepezil and memantine (primary objectives a and b). Different random effects structures were compared using the Akaike Information Criterion (AIC).[25] The chosen model included random effects for each visit with an unstructured covariance matrix. Time on trial medication was compared between treatment arms using the log-rank test for equality of survivor functions. The incidence of serious adverse events was compared between groups using Poisson regression. To explore the impact of missing data and treatment discontinuation, sensitivity analyses were conducted; details in the Supplementary Appendix. Analysis was conducted using Stata 11.2.[26] Since the primary objectives were well-defined and ordered, adjustment for multiplicity was not indicated in the analysis.[27] For secondary outcome measures and outcomes at assessment points other than over 52 weeks we defined statistical significance at the 99% confidence interval (CI) level to compensate for multiple comparisons.

Before commencing data analysis, we published values for minimum clinically important differences (MCID) on the sMMSE (1.4 points), BADLS (3.5 points) and the NPI (8 points), based upon 0.4 standard deviations (SD) of the change from baseline of the first 127 participants to complete DOMINO.[28]

Results

From February 2008 to March 2010, 295 participants were entered. Recruitment was less than anticipated and it was not possible to extend the recruitment period as the study's public funder considered that the disadvantages of a delay in reporting results outweighed benefits of increasing power. Baseline characteristics of participants in each treatment arm were broadly comparable. The Consort Flow Chart is Figure 1.6. of trial treatment differed by treatment arm (p=0.0001).

Primary outcome measures

Patients allocated continuing donepezil averaged 1.9[95% CI 1.3 to 2.5;p<0.001] sMMSE points and 3.0[95% CI 1.8 to 4.3;p<0.001] BADLS points better than those discontinuing. For both these outcomes there were strong (donepezil x visit) interactions (p=0.002 and 0.004). Patients starting memantine averaged 1.2[95% CI 0.6 to 1.8;p<0.001] sMMSE points and 1.5[95% CI 0.3 to 2.8;p=0.016] BADLS points better than those on placebo, and the memantine x visit interactions were unimportant. The benefits from both donepezil and memantine appeared larger in the absence than in the presence of the other agent for sMMSE and BADLS but these differences were not statistically significant (tests for interaction p=0.14 and p=0.093 respectively). Benefits of adding memantine to donepezil continuation did not reach statistical significance on sMMSE 0.8[95% CI -0.1 to 1.6;p=0.07] points or BADLS 0.5[95% CI -2.2 to 1.2;p=0.57] points. Dementia severity at randomisation significantly affected the effect of donepezil on sMMSE. Moderate (sMMSE 10-13) patients showed an average difference of 2.6[95% CI 1.5 to 3.7;p<0.001], and severe (sMMSE) patients 1.3[95% CI 0.2 to 2.4;p=0.024], points. Dementia severity had no significant effect on BADLS difference with donepezil or on the sMMSE or BADLS differences seen with memantine.

See sections 7 and 8 for further detail.

Secondary outcome measures

Memantine compared with memantine placebo showed an average benefit of 4.0[99% CI 0.6 to 7.4;p=0.002] NPI points. There was a suggestion that continuing donepezil was associated with a small benefit on the NPI, although this was not statistically significant (2.3[95% CI 5.7 to -1.1;p=0.081] points. Adding memantine to donepezil continuation showed NPI benefit of 5.1[99% CI 0.3 to 9.8;p=0.006] points. In contrast with the sMMSE and BADLS, the benefits from both donepezil and memantine on the NPI appeared larger in the presence than in the absence of the other agent but these differences were not statistically significant (p=0.42). Both donepezil continuation compared with discontinuation and memantine compared with placebo showed average benefits across trial visits on caregiver GHQ-12 which marginally failed to reach statistical significance (continuing donepezil 05[99% CI -1.0 to 0.01;p=0.01], memantine versus placebo 0.5[95% CI -0.9 to 0.1;p=0.03] points.
See sections 7 and 10 for further detail.

Sensitivity Analyses

Patients who withdrew from treatment after the 18 Week visit or after the 30 Week visit had a lower sMMSE score and a higher BADLS score at their last visit before discontinuing as compared to those who continued treatment. Patients who withdrew at any point in the study had lower sMMSE scores and higher BADLS scores after withdrawal as compared to those that stayed on treatment. Of the 137 patients who withdrew from treatment before the end of the trial, 64 (47%) attended the 52 week visit (with one missing the sMMSE assessment). A number of sensitivity analyses were conducted to assess the effect of treatment discontinuation on the results. The results of the sensitivity analyses were broadly similar to the primary analysis.
See section 9 for further detail.

Safety

A total of 187 serious adverse events (SAEs) were reported of which 6 (2 placebo, 2 memantine only, 2 donepezil and memantine) were considered possibly related to trial medications. None were considered to be suspected unexpected serious adverse reactions. There was no evidence that the incidence of SAEs or deaths differed by treatment arm (p=0.77). Only 1 death occurring during the trial was considered to be related to trial medications and this occurred in the arm where donepezil was discontinued and placebo memantine started.
See section 5 for futher detail.

Discussion

DOMINO provides the first controlled trial data from community-living patients to support continuation of ChEIs beyond mild to moderate AD and shows significant cognition and function benefits over 52 weeks. Starting memantine was associated with better cognition and function although the magnitude of benefit was smaller than for donepezil. Memantine was associated with emergence of fewer behavioural symptoms. There was no evidence for an interaction between continuing donepezil and adding memantine on any of the primary or secondary outcomes.

Differences seen with treatment were modest in the context of deterioration on outcomes during the trial. Although the cognitive benefit of donepezil exceeded a distribution-based MCID[28,29], cognitive benefits of memantine treatment were smaller and did not reach the MCID. Cognitive benefits of continuing donepezil were equivalent to 32%, and of starting memantine to 20%, of the 12 months deterioration[30,31] (5.8 sMMSE points) seen in the group discontinuing donepezil and starting placebo memantine. Functional benefits of continuing donepezil were equivalent to 23%, and of starting memantine to 11%, of the 12.8 BADLS points deterioration seen in the group discontinuing donepezil and starting placebo memantine over 12 months. Memantine treatment was associated with a significantly smaller

worsening of NPI scores, as reported by others[32], that represented a benefit that was equivalent to 83% of the 12 months deterioration (4.8 NPI points) seen in the group discontinuing donepezil and starting placebo memantine.

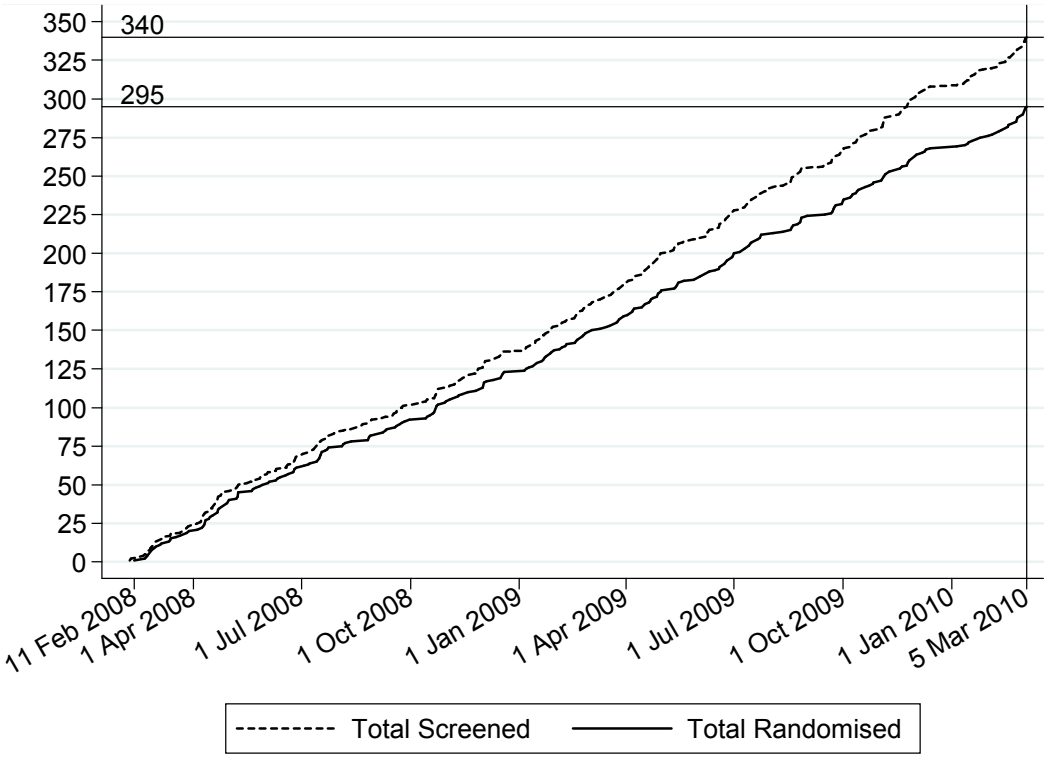
DOMINO provides the first double-blind, placebo-controlled data for withdrawal of a cholinesterase inhibitor. We did not find abrupt withdrawal phenomena[33] but discontinuation of trial medication was significantly more common in participants randomised to discontinue donepezil with the majority of withdrawals occurring between weeks 6 and 18. Modest reductions in caregiver psychological morbidity seen with donepezil or memantine marginally failed to achieve statistical significance, and, taken together with lower rates of withdrawal, argue for treatment effects apparent to those who live with patients as well as those captured by formal outcome measures.

Participants were recruited from National Health Service clinics across England and Scotland and were representative of AD patients treated with ChEIs. Difficulties arose with trial recruitment because of caregiver reluctance to consent to withdrawal of treatment and because many prescribers did not follow NICE Guidance. Despite recruitment difficulties, moderate cognitive and functional treatment effects of donepezil meant that we successfully demonstrated the benefit of continuing donepezil (our first objective), even at the 99% level. For testing the benefit of starting memantine (objective two), although the size of cognitive and functional differences were smaller than for donepezil, they were still significant at the 95% CI level and the reduction in emergence of neuropsychiatric symptoms was significant at the 99% CI level. For our third objective, testing whether the combination of donepezil and memantine treatment showed additive benefits, efficacy of each on cognition and function was non-significantly reduced in the presence of the other agent. The marginal size of p values for interaction suggest that recruitment of more participants might have permitted demonstration of statistically significant antagonism, but lack of trial power cannot be said to have missed a potentially important positive I nteraction on the primary outcomes, although there was a possible synergy on the NPI that greater participant numbers might have demonstrated.

Moderate cognitive and functional benefits are obtained by continuation of donepezil treatment beyond the transition from moderate to severe AD. Memantine treatment also conveys modest cognitive and functional benefits at this point and may be useful in the reduction of emergence of neuropsychiatric symptoms as dementia progresses.

1. Screening and Enrolment

Figure 1.1: Total patients screened and randomised



The first patient was randomised on 11th February 2008 and the last on 5th March 2010. The original planned sample size was 800 which was adjusted to 430 in April 2009 based on smaller than expected standard deviations of data accrued. No analyses by treatment arm were done for the sample size re-estimation.

Table 1.2: Randomisation by centre

Centre	Total Randomised	Date of First Randomisation	Date of Last Randomisation
Bath	16	20/02/2008	25/01/2010
Belfast	0	-	-
Birmingham	36	22/02/2008	04/03/2010
Cambridge	19	12/03/2008	05/03/2010
Dundee	11	30/09/2008	02/03/2010
Glasgow	8	01/05/2008	08/10/2009
Leicester	34	21/02/2008	04/03/2010
Maudsley	13	15/04/2008	20/10/2009
Imperial	28	29/02/2008	24/02/2010
Manchester	14	07/01/2009	04/03/2010
Newcastle	24	13/03/2008	14/12/2009
Nottingham	17	05/03/2008	17/02/2010
Oxford	35	11/02/2008	02/03/2010
Southampton	18	26/02/2008	01/12/2009
Warwick	22	10/04/2008	04/03/2010
Total	**295**	**11/02/2008**	**05/03/2010**

Table 1.3: Monthly enrolment by centre

Cumulative Enrolment from 11th Feb 2008 to 5th March 2010 (*Monthly total in brackets*)

	Bath	Belfast	Birmingham	Cambridge	Dundee	Glasgow	Leicester	Maudsley	Imperial	Manchester	Newcastle	Nottingham	Oxford	Southampton	Warwick	Overall
Feb 2008	2 (2)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	2 (2)	3 (3)	0 (0)	**10 (10)**
Mar 2008	2 (0)	0 (0)	1 (0)	1 (1)	0 (0)	0 (0)	4 (3)	0 (0)	4 (3)	0 (0)	1 (1)	1 (1)	3 (1)	3 (0)	0 (0)	**20 (10)**
Apr 2008	2 (0)	0 (0)	5 (4)	1 (0)	0 (0)	0 (0)	5 (1)	1 (1)	7 (3)	0 (0)	3 (2)	3 (2)	4 (1)	4 (1)	3 (3)	**38 (18)**
May 2008	2 (0)	0 (0)	5 (0)	1 (0)	0 (0)	1 (1)	5 (0)	1 (0)	10 (3)	0 (0)	4 (1)	4 (1)	8 (4)	5 (1)	4 (1)	**50 (12)**
Jun 2008	3 (1)	0 (0)	7 (2)	1 (0)	0 (0)	2 (1)	5 (0)	2 (1)	11 (1)	0 (0)	5 (1)	6 (2)	9 (1)	5 (0)	5 (1)	**61 (11)**
Jul 2008	3 (0)	0 (0)	8 (1)	1 (0)	0 (0)	2 (0)	9 (4)	3 (1)	11 (0)	0 (0)	7 (2)	7 (1)	11 (2)	7 (2)	5 (0)	**74 (13)**
Aug 2008	3 (0)	0 (0)	9 (1)	1 (0)	0 (0)	2 (0)	13 (4)	3 (0)	12 (1)	0 (0)	8 (1)	7 (0)	11 (0)	8 (1)	5 (0)	**82 (8)**
Sep 2008	3 (0)	0 (0)	10 (1)	1 (0)	1 (1)	4 (2)	16 (3)	3 (0)	12 (0)	0 (0)	9 (1)	7 (0)	12 (1)	8 (0)	6 (1)	**92 (10)**
Oct 2008	3 (0)	0 (0)	10 (0)	1 (0)	3 (2)	4 (0)	19 (3)	4 (1)	13 (1)	0 (0)	9 (0)	7 (0)	16 (4)	8 (0)	7 (1)	**104 (12)**
Nov 2008	5 (2)	0 (0)	11 (1)	1 (0)	3 (0)	4 (0)	19 (0)	5 (1)	13 (0)	0 (0)	10 (1)	8 (1)	17 (1)	8 (0)	7 (0)	**111 (7)**
Dec 2008	6 (1)	0 (0)	12 (1)	1 (0)	4 (1)	4 (0)	22 (3)	5 (0)	13 (0)	0 (0)	12 (2)	8 (0)	18 (1)	8 (0)	10 (3)	**123 (12)**
Jan 2009	6 (0)	0 (0)	14 (2)	3 (2)	4 (0)	4 (0)	24 (2)	5 (0)	13 (0)	1 (1)	14 (2)	10 (2)	18 (0)	9 (1)	12 (2)	**137 (14)**
Feb 2009	8 (2)	0 (0)	16 (2)	3 (0)	6 (2)	5 (1)	24 (0)	5 (0)	13 (0)	2 (1)	14 (0)	10 (0)	20 (2)	10 (1)	12 (0)	**148 (11)**
Mar 2009	8 (0)	0 (0)	17 (1)	3 (0)	6 (0)	5 (0)	26 (2)	6 (1)	13 (0)	4 (2)	16 (2)	10 (0)	21 (1)	11 (1)	13 (1)	**159 (11)**
Apr 2009	9 (1)	0 (0)	20 (3)	3 (0)	6 (0)	5 (0)	26 (0)	8 (2)	16 (3)	4 (0)	18 (2)	11 (1)	24 (3)	12 (1)	13 (0)	**175 (16)**
May 2009	9 (0)	0 (0)	21 (1)	3 (0)	6 (0)	6 (1)	26 (0)	8 (0)	17 (1)	5 (1)	18 (0)	11 (0)	25 (1)	13 (1)	15 (2)	**183 (8)**
Jun 2009	9 (0)	0 (0)	22 (1)	7 (4)	6 (0)	6 (0)	27 (1)	8 (0)	18 (1)	6 (1)	19 (1)	12 (1)	28 (3)	13 (0)	17 (2)	**198 (15)**
Jul 2009	10 (1)	0 (0)	23 (1)	8 (1)	7 (1)	6 (0)	29 (2)	8 (0)	21 (3)	7 (1)	20 (1)	12 (0)	30 (2)	14 (1)	17 (0)	**212 (14)**
Aug 2009	11 (1)	0 (0)	25 (2)	10 (2)	9 (2)	6 (0)	30 (1)	10 (2)	21 (0)	8 (1)	20 (0)	12 (0)	30 (0)	14 (0)	17 (0)	**223 (11)**
Sep 2009	12 (1)	0 (0)	25 (0)	13 (3)	9 (0)	6 (0)	30 (0)	11 (1)	22 (1)	8 (0)	20 (0)	12 (0)	31 (1)	15 (1)	18 (1)	**232 (9)**
Oct 2009	13 (1)	0 (0)	27 (2)	15 (2)	9 (0)	8 (2)	30 (0)	13 (2)	22 (0)	8 (0)	21 (1)	14 (2)	32 (1)	16 (1)	18 (0)	**246 (14)**
Nov 2009	15 (2)	0 (0)	30 (3)	16 (1)	9 (0)	8 (0)	30 (0)	13 (0)	24 (2)	9 (1)	22 (1)	14 (0)	33 (1)	16 (0)	21 (3)	**260 (14)**
Dec 2009	15 (0)	0 (0)	31 (1)	17 (1)	9 (0)	8 (0)	30 (0)	13 (0)	24 (0)	10 (1)	24 (2)	15 (1)	33 (0)	18 (2)	21 (0)	**268 (8)**
Jan 2010	16 (1)	0 (0)	34 (3)	18 (1)	9 (0)	8 (0)	31 (1)	13 (0)	25 (1)	10 (0)	24 (0)	15 (0)	33 (0)	18 (0)	21 (0)	**275 (7)**
Feb 2010	16 (0)	0 (0)	35 (1)	18 (0)	10 (1)	8 (0)	33 (2)	13 (0)	28 (3)	13 (3)	24 (0)	17 (2)	34 (1)	18 (0)	21 (0)	**288 (13)**
Mar 2010	16 (0)	0 (0)	36 (1)	19 (1)	11 (1)	8 (0)	34 (1)	13 (0)	28 (0)	14 (1)	24 (0)	17 (0)	35 (1)	18 (0)	22 (1)	**295 (7)**

Table 1.4: Screening by centre

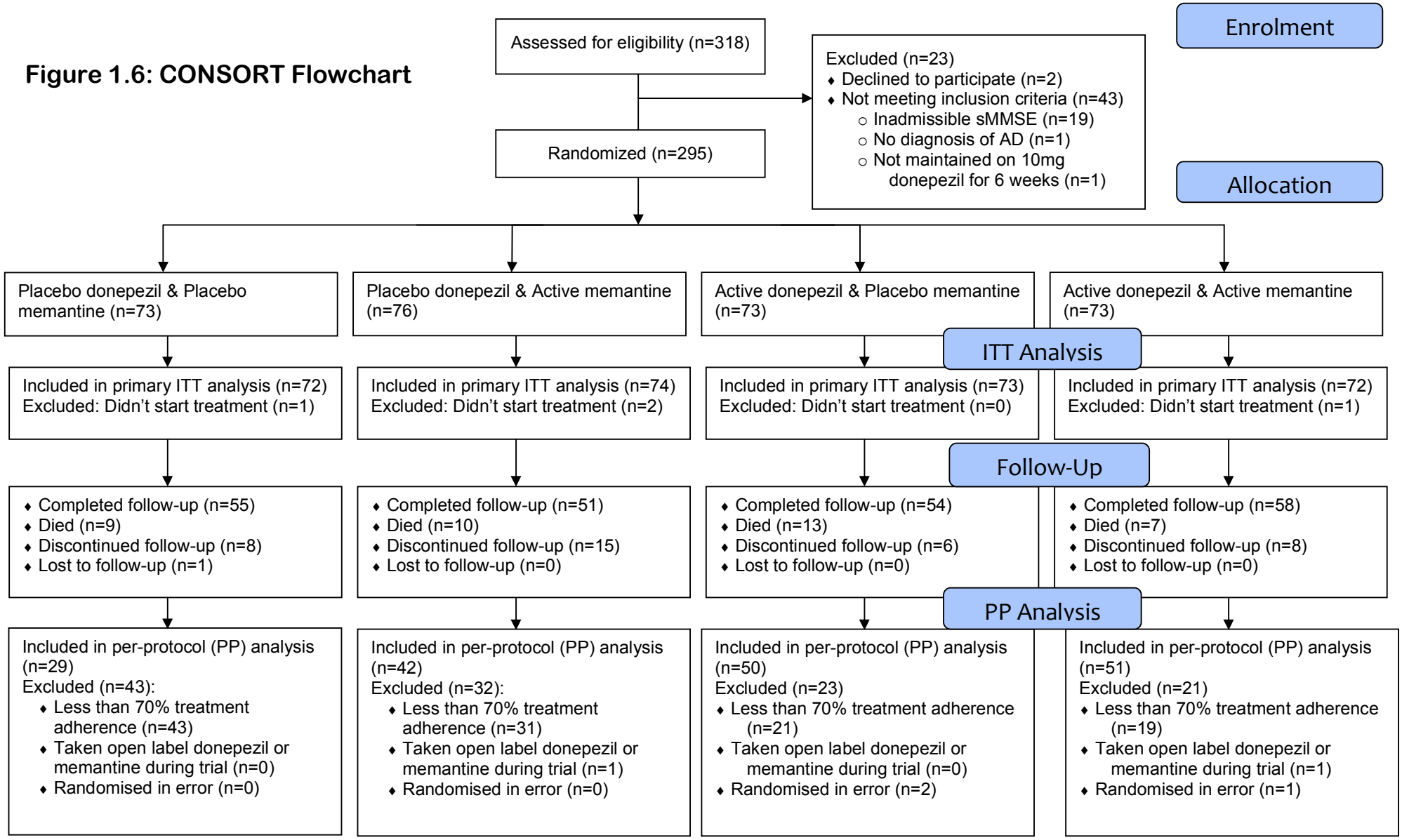
Centre	Total Screening Visits	Total Patients Screened*	Total Patients Excluded from Randomisation	Date of First Patient Registration	Date of Last Patient Registration
Bath	18	16	0	20/02/2008	22/01/2010
Belfast	0	0	0	-	-
Birmingham	36	36	0	22/02/2008	04/03/2010
Cambridge	26	24	5	19/02/2008	05/03/2010
Dundee	11	11	0	25/09/2008	02/03/2010
Glasgow	9	9	1	07/04/2008	08/10/2009
Leicester	45	37	3	14/02/2008	04/03/2010
Maudsley	14	13	0	14/04/2008	20/10/2009
Imperial	30	29	1	27/02/2008	23/02/2010
Manchester	19	17	3	24/07/2008	03/03/2010
Newcastle	25	25	1	07/02/2008	14/12/2009
Nottingham	21	19	2	05/03/2008	01/03/2010
Oxford	40	37	2	08/02/2008	01/03/2010
Southampton	20	20	2	24/02/2008	01/12/2009
Warwick	26	25	3	10/04/2008	03/03/2010
Total	**340**	**318**	**23**	**07/02/2008**	**05/03/2010**

* Several patients were screened for eligibility into the trial on more than one occasion.

Table 1.5: Reasons for exclusion from randomisation

Reason	N (%)
sMMSE score outside range 5-13	19 (83%)
Consent to participate in trial withdrawn	2 (9%)
Patient not maintained on 10mg donepezil daily for 6 weeks prior to randomisation	1 (4%)
No clinical diagnosis of probable or possible Alzheimer's disease	1 (4%)
Total	**23**

Figure 1.6: CONSORT Flowchart



2. Baseline Characteristics

Randomisation is by minimisation to ensure balanced allocation of patients across the four treatment groups for the following four factors:

(i) Centre (15 centres),
(ii) Duration of donepezil treatment prior to enrolment to study (3-6 months, 6 months or more),
(iii) Baseline sMMSE score (5-9, 10-13),
(iv) Age (less than 60 years, 60-74 years, 75 years or more).

The minimisation algorithm will be applied with an allocation ratio that is not fully deterministic.

The first 80 patients were allocated using simple randomisation.

Table 2.1: Allocated treatment arm by centre

Centre	Allocated Treatment Arm N (%)				
	Placebo Donepezil		Donepezil		Total
	Placebo Memantine	Memantine	Placebo Memantine	Memantine	
Bath	3 (4%)	6 (8%)	4 (5%)	3 (4%)	16 (5%)
Belfast	0	0	0	0	0
Birmingham	9 (12%)	8 (11%)	9 (12%)	10 (14%)	36 (12%)
Cambridge	5 (7%)	5 (7%)	4 (5%)	5 (7%)	19 (6%)
Dundee	3 (4%)	3 (4%)	3 (4%)	2 (3%)	11 (4%)
Glasgow	1 (1%)	4 (5%)	. (.%)	3 (4%)	8 (3%)
Leicester	7 (10%)	8 (11%)	10 (14%)	9 (12%)	34 (12%)
Maudsley	3 (4%)	3 (4%)	3 (4%)	4 (5%)	13 (4%)
Imperial	8 (11%)	7 (9%)	7 (10%)	6 (8%)	28 (9%)
Manchester	4 (5%)	5 (7%)	2 (3%)	3 (4%)	14 (5%)
Newcastle	7 (10%)	6 (8%)	6 (8%)	5 (7%)	24 (8%)
Nottingham	3 (4%)	3 (4%)	6 (8%)	5 (7%)	17 (6%)
Oxford	10 (14%)	7 (9%)	10 (14%)	8 (11%)	35 (12%)
Southampton	4 (5%)	6 (8%)	4 (5%)	4 (5%)	18 (6%)
Warwick	6 (8%)	5 (7%)	5 (7%)	6 (8%)	22 (7%)
Total	**73**	**76**	**73**	**73**	**295**

Table 2.2: Patient and carer characteristics by treatment arm

			Placebo Donepezil		Donepezil		Total
			Placebo Memantine	Memantine	Placebo Memantine	Memantine	
Total Randomised			**73**	**76**	**73**	**73**	**295**
Patient Characteristics	**Age in years / Median (IQR)**		78.8 (73.4-83.4)	79.0 (71.6-82.0)	77.9 (72.4-81.7)	79.6 (71.7-84.0)	**78.5 (72.3-83.1)**
	Age in years	**50-**	7 (10%)	11 (14%)	5 (7%)	10 (14%)	**33 (11%)**
		65-	17 (23%)	16 (21%)	18 (25%)	16 (22%)	**67 (23%)**
		75-	19 (26%)	20 (26%)	25 (34%)	11 (15%)	**75 (25%)**
		80-	18 (25%)	16 (21%)	13 (18%)	22 (30%)	**69 (23%)**
		85-95	12 (16%)	13 (17%)	12 (16%)	14 (19%)	**51 (17%)**
	Gender N (%)	**Male**	26 (36%)	30 (39%)	22 (30%)	24 (33%)	**102 (35%)**
		Female	47 (64%)	46 (61%)	51 (70%)	49 (67%)	**193 (65%)**
	Ethnicity N (%)	**White**	71 (97%)	73 (96%)	69 (95%)	67 (92%)	**280 (95%)**
		Mixed	0	0	1 (1%)	0	**1 (0%)**
		Asian	0	0	1 (1%)	1 (1%)	**2 (1%)**
		Black	2 (3%)	2 (3%)	1 (1%)	4 (5%)	**9 (3%)**
		Chinese	0	1 (1%)	0	0	**1 (0%)**
		Other	0	0	1 (1%)	1 (1%)	**2 (1%)**
	Previous duration of donepezil	**3-6 Months**	3 (4%)	4 (5%)	3 (4%)	4 (5%)	**14 (5%)**
		6 Months or more	70 (96%)	72 (95%)	70 (96%)	69 (95%)	**281 (95%)**
Carer Characteristics	**Gender N (%)**	**Male**	36 (49%)	31 (41%)	36 (49%)	34 (47%)	**137 (46%)**
		Female	37 (51%)	45 (59%)	37 (51%)	39 (53%)	**158 (54%)**
	Relationship to Patient N (%)	**Spouse / Partner**	56 (77%)	49 (64%)	41 (56%)	43 (59%)	**189 (64%)**
		Son / Daughter	15 (21%)	18 (24%)	30 (41%)	28 (38%)	**91 (31%)**
		Sibling	0	3 (4%)	0	0	**3 (1%)**
		Other Relative	0	4 (5%)	1 (1%)	1 (1%)	**6 (2%)**
		Friend / Neighbour	0	2 (3%)	0	0	**2 (1%)**
		Paid Carer	2 (3%)	0	1 (1%)	1 (1%)	**4 (1%)**

Table 2.3: Efficacy measures at baseline

		Placebo Donepezil		Donepezil		Total
		Placebo Memantine	Memantine	Placebo Memantine	Memantine	
Total Randomised		**73**	**76**	**73**	**73**	**295**
Standardised Mini-Mental State Examination (sMMSE)	**Mean (SD)**	9.1 (2.4)	9.2 (2.5)	9.0 (2.8)	9.1 (2.6)	**9.1 (2.6)**
	Missing / N	0	0	0	0	**0**
Bristol Activities of Daily Living Scale (BADLS)	**Mean (SD)**	28.6 (8.9)	27.1 (9.0)	28.2 (9.0)	26.9 (9.8)	**27.7 (9.2)**
	Missing / N	0	0	0	0	**0**
Neuropsychiatric Inventory (NPI)	**Mean (SD)**	22.9 (17.0)	23.1 (16.2)	22.3 (16.7)	20.3 (14.4)	**22.2 (16.1)**
	Missing / N	0	0	0	0	**0**
DEMQOL-Proxy	**Mean (SD)**	101.4 (11.7)	96.5 (15.3)	98.3 (13.5)	100.9 (12.9)	**99.3 (13.5)**
	Missing / N	0	0	0	0	**0**
General Health Questionnaire (GHQ-12)	**Mean (SD)**	2.8 (3.1)	3.1 (3.1)	2.3 (2.3)	1.8 (2.3)	**2.5 (2.8)**
	Missing / N	1	1	0	0	**2**

1. The sMMSE is a measure of cognitive function in elderly people. Scores range from 30 (unimpaired) to 0 (impaired).
2. The BADLS is an assessment of activities of daily living in dementia. Scores range from 0 (unimpaired) to 60 (impaired).
3. The NPI is used to measure the caregiver's assessment of frequency and severity of behavioural and psychiatric symptoms of dementia (BPSD). Scores range from 0 (no disturbance) to 144 (maximum disturbance).
4. DEMQOL–Proxy is a disease specific instrument for evaluating health-related quality of life (HRQoL) in dementia completed by the carer. Scores range from 31 (minimum HRQoL) to 124 (maximum HRQoL).
5. The GHQ-12 is used to measure levels of psychological distress in the carers of study patients. Scores range from 0 (not distressed) to 12 (distressed).

3. Discontinuations and Patient Retention

Multiple reasons for discontinuation can be given, but reasons are given an order of priority. Tables 3.1 and 3.2 therefore only capture the main reason for the discontinuation.

Table 3.1: Permanent discontinuations from follow-up

Reason for discontinuation N (%)	Placebo Donepezil		Donepezil		Total
	Placebo Memantine	Memantine	Placebo Memantine	Memantine	
Total Randomised	**73**	**76**	**73**	**73**	**295**
Death of Patient	9 (50%)	10 (40%)	13 (68%)	7 (47%)	**39 (51%)**
Withdrew consent to treatment	5 (28%)	8 (32%)	4 (21%)	6 (40%)	**23 (30%)**
Deterioration of pre-existing medical condition	2 (11%)	3 (12%)	1 (5%)	0	**6 (8%)**
Adverse event	1 (6%)	2 (8%)	1 (5%)	1 (7%)	**5 (6%)**
Deterioration of emergent medical condition	0	2 (8%)	0	0	**2 (3%)**
Unable to Locate Patient	1 (6%)	0	0	1 (7%)	**2 (3%)**
Total	**18**	**25**	**19**	**15**	**77**

Table 3.2: Permanent discontinuations of trial medication (but not follow-up)

	Placebo Donepezil		Donepezil		Total
	Placebo Memantine	Memantine	Placebo Memantine	Memantine	
Total Randomised	**73**	**76**	**73**	**73**	**295**
Perceived lack of efficacy of trial medication	17 (44%)	6 (22%)	8 (32%)	5 (33%)	**36 (34%)**
Deterioration of pre-existing medical condition	6 (15%)	4 (15%)	7 (28%)	1 (7%)	**18 (17%)**
Adverse event	2 (5%)	7 (26%)	5 (20%)	3 (20%)	**17 (16%)**
Withdrew consent to treatment	4 (10%)	3 (11%)	3 (12%)	2 (13%)	**12 (11%)**
Deterioration of emergent medical condition	3 (8%)	2 (7%)	2 (8%)	3 (20%)	**10 (9%)**
Other	3[a] (8%)	3[b] (11%)	0	1[c] (7%)	**7 (7%)**
Patient not adhering to treatment	4 (10%)	2 (7%)	0	0	**6 (6%)**
Total	**39**	**27**	**25**	**15**	**106**

[a]Family decisions following deterioration of medical condition (2); visual hallucinations (1).
[b]Ran out of medication (1); Grand Mal seizure (1); GP stopped medications following faecal incontinence (1). [c]Carer finding it difficult to give medications (1).

Table 3.3: Overall patient retention

Total Patients (% of total randomised)			Placebo Donepezil		Donepezil		Total
			Placebo Memantine	Memantine	Placebo Memantine	Memantine	
Total Randomised			**73**	**76**	**73**	**73**	**295**
Baseline	**Seen**	**Total seen**	**73 (100%)**	**76 (100%)**	**73 (100%)**	**73 (100%)**	**295 (100%)**
	Missed	Following death	0	0	0	0	**0**
		Following discontinuation	0	0	0	0	**0**
		Other reason*	0	0	0	0	**0**
6 Week Visit	**Seen**	**Total seen**	**71 (97%)**	**73 (96%)**	**72 (99%)**	**68 (93%)**	**284 (96%)**
		Still on trial medications	67 (92%)	67 (88%)	69 (95%)	67 (92%)	270 (92%)
	Missed	Following death	0	1 (1%)	0	0	**1 (<0.5%)**
		Following discontinuation	2 (3%)	2 (3%)	1 (1%)	3 (4%)	**8 (3%)**
		Other reason*	0	0	0	2 (3%)	**2 (1%)**
18 Week Visit	**Seen**	**Total seen**	**65 (89%)**	**64 (84%)**	**67 (92%)**	**67 (92%)**	**263 (89%)**
		Still on trial medications	41 (56%)	54 (71%)	62 (85%)	62 (85%)	219 (74%)
	Missed	Following death	1 (1%)	3 (4%)	2 (3%)	0	**6 (2%)**
		Following discontinuation	7 (10%)	8 (11%)	3 (4%)	5 (7%)	**23 (8%)**
		Other reason*	0	1 (1%)	1 (1%)	1 (1%)	**3 (1%)**
30 Week Visit	**Seen**	**Total seen**	**60 (82%)**	**60 (79%)**	**63 (86%)**	**63 (86%)**	**246 (83%)**
		Still on trial medications	32 (44%)	45 (59%)	53 (73%)	56 (77%)	186 (63%)
	Missed	Following death	5 (7%)	3 (4%)	5 (7%)	3 (4%)	**16 (5%)**
		Following discontinuation	7 (10%)	12 (16%)	4 (5%)	6 (8%)	**29 (10%)**
		Other reason*	1 (1%)	1 (1%)	1 (1%)	1 (1%)	**4 (1%)**
52 Week Visit	**Seen**	**Total seen**	**55 (75%)**	**51 (67%)**	**54 (74%)**	**58 (79%)**	**218 (74%)**
		Still on trial medications	26 (36%)	37 (49%)	41 (56%)	50 (68%)	154 (52%)
	Missed	Following death	9 (12%)	10 (13%)	13 (18%)	7 (10%)	**39 (13%)**
		Following discontinuation	8 (11%)	15 (20%)	6 (8%)	8 (11%)	**37 (13%)**
		Other reason*	1 (1%)	0	0	0	**1 (<0.5%)**

* See Table 3.4 for listing of reasons for missed visits.

Table 3.4: Listing of missed visits for patients in follow-up

Patient	Centre	Treatment arm	Date of randomisation	Visits	Reason for missed visit
P03029	Birmingham	Donepezil + Memantine	09/11/2009	6	Patient was away in Ireland
P08005	Maudsley	Donepezil + Memantine	14/11/2008	6, 18, 30	Patient withdrew from trial medications and agreed to return only for final 52 week visit
P11020	Newcastle	Donepezil	29/06/2009	18	The patient was in a care home, the carer was not available
P14003	Southampton	Memantine	26/02/2008	18	Error by research worker
P13028	Oxford	Memantine	20/05/2009	30	The carer was not available
P08009	Maudsley	Donepezil	27/04/2009	30	The carer was not available
P13027	Oxford	Placebo	17/04/2009	30, 52	The site staff were unable to locate the patient. After the end of the trial, the patient was found to have gone into a care home 13/11/2009

Table 3.5: Listing of patients randomised but not starting trial medications

Patient	Centre	Treatment arm	Date of randomisation	Reason for not starting trial medications
P13008	Oxford	Memantine	23/05/2008	Discontinued from follow-up 24/05/2008 due to adverse event. Patient had a fall, moved to general hospital and unable to continue.
P04016	Cambridge	Memantine	01/10/2009	Discontinued from follow-up 05/10/2009. Patient suffered angina attack and carer withdrew consent.
P03027	Birmingham	Donepezil + Memantine	26/10/2009	Discontinued from follow-up 16/11/2009 due to adverse event. Fracture to the hip due to cancerous deposits.
P04022	Cambridge	Placebo	05/03/2010	Discontinued from follow-up 09/03/2010. Family withdrew consent.

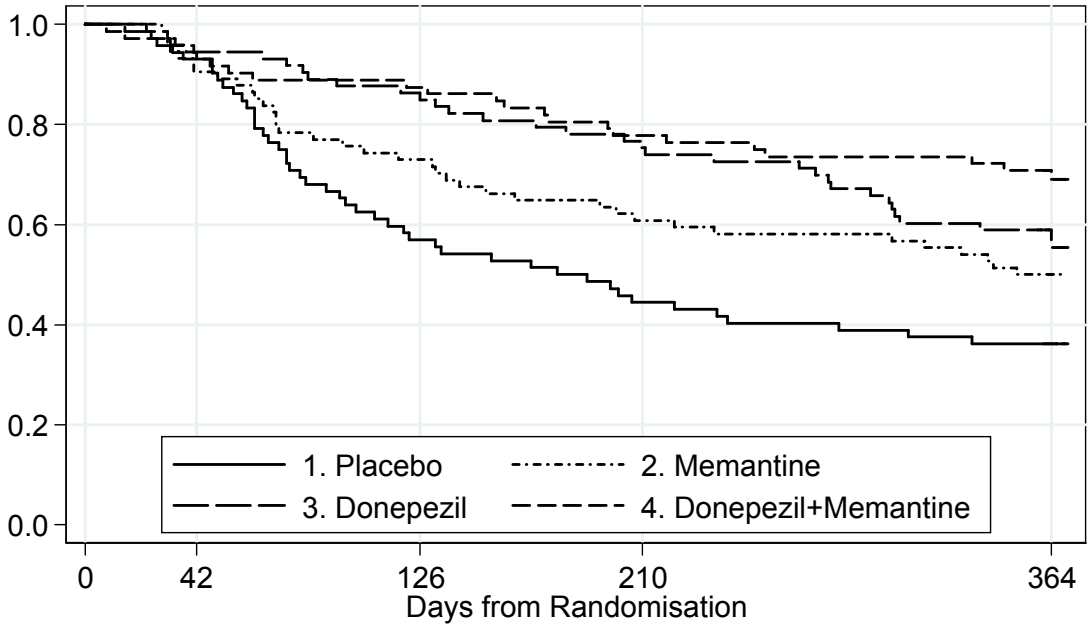
Table 3.6: Unblinding of patients

	Treatment Arm	Date of Unblinding	Date of Request	Date of Randomisation	Centre	Patient / Carer	Reason for Unblinding	Requested by	Authorised by	Performed by
1.	Memantine	17/06/2008	29/05/2008	11/04/2008	Imperial	P09006 / P09006A	Alzheimer's disease had deteriorated significantly and family requested unblinding to inform continuing treatment. Allocation sent to patient's carer as per principal investigator's request.	Dr. Craig Ritchie, Local Principal Investigator	Prof. Rob Howard, Chief Investigator	Patrick Phillips, trial statistician
2.	Placebo	27/03/2009	27/03/2009	27/01/2009	Cambridge	P04005 / C04005A	Rapid deterioration in functioning over preceding two weeks. Patient refusing to accept medication	Dr. Warrender, General Practitioner	Dr. Andrew Graham, consultant neurologist	Guy's Toxicology Unit (Emergency hotline)
3.	Donepezil	11/06/2009	02/06/2009	11/04/2008	Birmingham	P03003 / C03003A	End of trial.	Jane Dyer, research nurse	Prof. Rob Howard, Chief Investigator	Patrick Phillips, trial statistician
4.	Placebo	01/07/2009	01/07/2009	25/06/2009	Cambridge	P04009 / C04009A	The unblinding information was **only** given to the treating physician in A&E. The GP was not informed of the treatment allocation in correspondence. None of the site staff or trial team were made aware of the treatment allocation and this patient has therefore continued in the trial.	Dr. Quyyum, General Practitioner	Prof. Rob Howard, Chief Investigator	Guy's Toxicology Unit (Emergency hotline)

	Treatment Arm	Date of Unblinding	Date of Request	Date of Randomisation	Centre	Patient / Carer	Reason for Unblinding	Requested by	Authorised by	Performed by
5.	Donepezil	25/09/09	25/09/09	26/08/2008	Leicester	P07014 / C07014A	Patient's condition deteriorated since stopping trial 3 weeks ago. Consultant wants to prescribe medication.	Dr Richard Prettyman. Lead Consultant in Old Age Psychiatry, Leicestershire Partnership NHS Trust	Prof. Rob Howard, Chief Investigator	Guy's Toxicology Unit (Emergency hotline)
6.	Memantine	05/11/2009	05/11/2009	10/11/2009	Leicester	P07022 / C07022A	End of trial	Dr. Chakrabarti, consultant psychiatrist	Prof. Rob Howard, Chief Investigator	Guy's Toxicology Unit (Emergency hotline)
7.	Memantine	07/05/2010	21/01/2010	01/10/2009	Glasgow	P06009 / C06009A	The patient's wife requested the unblinding following SAE – upper GI bleeding	Dr. Alan Hughes, Local Principle Investigator	Prof. Rob Howard, Chief Investigator	Patrick Phillips, Trial Statistician

Figure 3.7: Kaplan-Meier actuarial plot of time to permanent discontinuation of trial medications

The table below the graph gives the total number of patients still in the trial and still on treatment at each visit time by treatment group.



1.	72	67	41	32	20
2.	74	67	54	45	27
3.	73	69	63	55	34
4.	72	68	63	56	38

Log rank test for equality of survivor functions: p=0.0001. There is therefore strong evidence that the time to permanent discontinuation of treatment does differ by treatment arm.

4. Protocol Violations and Deviations

Definitions:

A. **Protocol Violation**. Serious non-compliance with the protocol resulting in exclusion of a patient from the trial.
B. **Protocol Deviation**. Non-serious unforeseen circumstances, the resolution of which can be agreed between the Trial Manager and Principal Investigator either in advance or after the event

Decision-making

A. Protocol Violation. The patient is normally discontinued from trial medication (except in cases given below). The patient can also be discontinued from follow-up if requested.

Exceptions:

1. Randomisation errors that were not picked up on by the database (these were only flagged by the database after 05/02/2009) are not discontinued from trial medication.
2. A patient is normally withdrawn from trial medication if compliance is less than 70% on 2 consecutive occasions or if the patient is off medication for a significant period, unless the case has been discussed with the Chief Investigator and approval is given for the patient to continue on trial medication.

B. Protocol Deviation. Agreement is reached – the patient continues in trial, or withdraws by their own decision.

Table 4.1: Protocol violations

	Patient	Centre	Treatment Arm	Date of Randomisation	Date of Event	Result of Event	Description of Event	Reason for Event
1	P03001	Birmingham	Memantine	22/02/2008	06/04/2008	Patient to continue	Prohibited medicine used	Admitted to A&E and given open label donepezil
2	P12003	Nottingham	Donepezil	23/04/2008	23/04/2008	Patient to continue	Randomisation Error	Randomised more than 7 days after screening
3	P15006	Warwick	Donepezil	27/06/2008	27/06/2008	Patient to continue	Randomisation Error	Inclusion criteria not met: Patient not maintained on donepezil for 6 weeks prior to randomisation

	Patient	Centre	Treatment Arm	Date of Randomisation	Date of Event	Result of Event	Description of Event	Reason for Event
4	P12001	Nottingham	Donepezil + Memantine	05/03/2008	14/07/2008	Patient to continue	Patient failing to comply with study requirements	Patient refused to take trial medication
5	P06003	Glasgow	Donepezil + Memantine	13/06/2008	25/07/2008	Discontinued from follow-up	Patient failing to comply with study requirements	Patient admitted to IP care and missed visit
6	P03002	Birmingham	Placebo	04/04/2008	27/07/2008	Patient to continue	Patient failing to comply with study requirements	Wife felt patient had deteriorated and took patient off medications
7	P12001	Nottingham	Donepezil + Memantine	05/03/2008	30/09/2008	Trial meds withdrawn only	Patient failing to comply with study requirements	Patient refused to take trial medication
8	P15005	Warwick	Memantine	27/05/2008	01/10/2008	Patient to continue	Poor compliance with trial medications	Carer believed that patient was not taking medications correctly.
9	P15014	Warwick	Donepezil	22/01/2009	14/04/2009	Patient to continue	Trial meds temporarily missed/stopped	Patient admitted to hospital and not aware that patient was in DOMINO trial.
10	P04014	Cambridge	Donepezil + Memantine	23/09/2009	23/09/2009	Patient to continue	Randomisation error	Inclusion criteria not met: Patient not maintained on donepezil for 6 weeks before randomisation.
11	P03026	Birmingham	Donepezil	02/10/2009	20/11/2009	Patient to continue	Trial meds temporarily missed/stopped	Stopped trial medications for 14 days.
12	P08009	Maudsley	Donepezil	27/04/2009	04/12/2009	Patient to continue	Prohibited medicine used	Patient admitted to hospital and given open label 10mg Aricept
13	P12016	Nottingham	Placebo	27/10/2009	18/01/2010	Patient to continue	Trial meds temporarily missed/stopped	Care home discontinued trial meds without consent of carer. Carer restarted patient on trial meds.
14	P07036	Leicester	Donepezil + Memantine	06/07/2009	03/02/2010	Patient to continue	Prohibited medicine used	Patient given donepezil 10mg for 7 weeks
15	P13034	Oxford	Donepezil	16/09/2009	19/04/2010	Patient to continue	Assessment completed with different carer	First carer not available at visit
16	P09019	Imperial	Memantine	21/07/2009	10/06/2010	Patient to continue	Prohibited medicine used	Patient went to hospital for hernia operation and given open label Aricept
17	P04015	Cambridge	Memantine	24/09/2009	02/07/2010	Patient to continue	Patient failing to comply with study requirements	Not given trial medications while in respite
18	P11025	Newcastle	Donepezil + Memantine	14/12/2009	14/12/2010	None - end of trial	Patient failing to comply with study requirements	Patient refused trial medications over at least 5 week period
19	P03035	Birmingham	Donepezil	25/02/2010	01/03/2011	None - end of trial	Trial medications left with carer after end of trial	Trial medications left with carer for 9 days after end of trial before collecting

Table 4.2: Protocol deviations

	Placebo Donepezil		Donepezil		Total
	Placebo Memantine	Memantine	Placebo Memantine	Memantine	
Total Randomised	**73**	**76**	**73**	**73**	**295**
Incorrectly performed or missing assessment	1 (2%)	4 (6%)	2 (4%)	7 (11%)	14 (6%)
Study visits outside set times	39 (78%)	38 (58%)	32 (65%)	43 (69%)	152 (67%)
Patient failing to comply with study requirements	5 (10%)	13 (20%)	8 (16%)	6 (10%)	32 (14%)
Delay in starting trial medications	1 (2%)	7 (11%)	1 (2%)	2 (3%)	11 (5%)
Trial medications temporarily missed or stopped	4 (8%)	3 (5%)	6 (12%)	4 (6%)	17 (8%)
Total protocol deviations	50	65	49	62	226

5. Safety

The degree to which the clinician considers the serious adverse event related to the trial medication (Causality, ranging from *not related* to *definitely related*) is recorded for each symptom rather than each event.
Where several symptoms (and therefore several causality ratings) are recorded for a single event, the event is classified by the expectedness and causality of the main symptom reported.

Table 5.1: Serious Adverse Events (SAEs) by expectedness and causality

This table reflects the total number of SAEs reported. Some patients experienced more than one event.

			Placebo Donepezil		Donepezil		Total
			Placebo Memantine	Memantine	Placebo Memantine	Memantine	
Total Randomised			**73**	**76**	**73**	**73**	**295**
Expectedness and Causality of Event N (%)	**Expected**	**Definite**	0	0	0	0	**0**
		Probable	0	0	0	0	**0**
		Possible	2 (4%)	2 (4%)	0	2 (5%)	**6* (3%)**
		Unlikely	5 (10%)	2 (4%)	5 (11%)	3 (7%)	**15 (8%)**
		Not related	6 (12%)	2 (4%)	2 (4%)	3 (7%)	**13 (7%)**
	Unexpected	**Definite**	0	0	0	0	**0**
		Probable	0	0	0	0	**0**
		Possible	0	0	0	0	**0**
		Unlikely	13 (25%)	14 (31%)	6 (13%)	4 (9%)	**37 (20%)**
		Not related	26 (50%)	25 (56%)	34 (72%)	31 (72%)	**116 (62%)**
	Total		**52**	**45**	**47**	**43**	**187**

*A total of 6 events were classified as Serious Adverse Reactions (SARs) since they were *possibly* related to the trial medications. There were no Suspected Unexpected Serious Adverse Reactions (SUSARs) reported.

Table 5.2: Incidence of SAEs reported

Number of SAEs reported per patient	Placebo Donepezil		Donepezil		Total
	Placebo Memantine	Memantine	Placebo Memantine	Memantine	
0	42 (58%)	46 (61%)	40 (55%)	44 (60%)	**172 (58%)**
1	17 (23%)	19 (25%)	21 (29%)	19 (26%)	**76 (26%)**
2	9 (12%)	8 (11%)	10 (14%)	7 (10%)	**34 (12%)**
3	3 (4%)	2 (3%)	2 (3%)	2 (3%)	**9 (3%)**
4	2 (3%)	1 (1%)	0	1 (1%)	**4 (1%)**
Total	**73**	**76**	**73**	**73**	**295**

Test for association between treatment and incidence of SAEs p=0.767 (Poisson regression). There is no evidence that incidence of SAEs differs by treatment allocation.

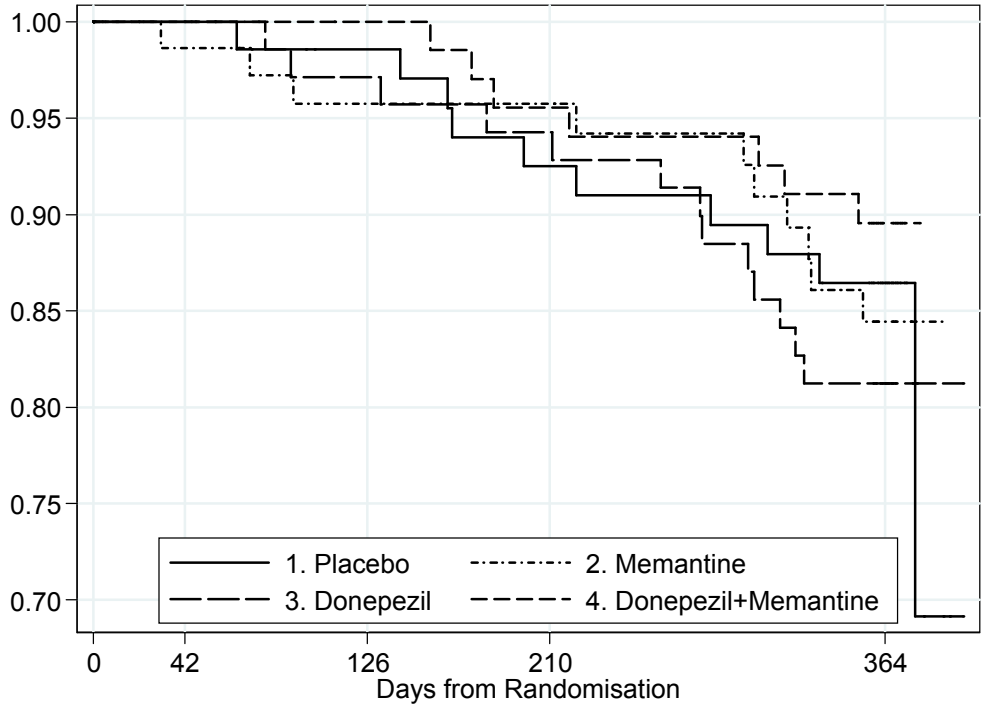
Table 5.3: Deaths by causality

		Placebo Donepezil		Donepezil		Total
		Placebo Memantine	Memantine	Placebo Memantine	Memantine	
Total Randomised		**73**	**76**	**73**	**73**	**295**
Event Causality N (%)	**Definite**	0	0	0	0	0
	Probable	0	0	0	0	0
	Possible	1 (10%)	0	0	0	1* (3%)
	Unlikely	3 (30%)	2 (20%)	3 (23%)	1 (14%)	9 (23%)
	Not related	6* (60%)	8 (80%)	10 (77%)	6 (86%)	30 (75%)
	Total	10	10	13	7	40

* P11022 on the double placebo completed the 52 week visit, and died soon afterwards. This patient is included in this table, but not in the CONSORT flowchart, table 1.6.

The only death classified as possibly related to treatment was on the double placebo arm. There were no deaths that we considered related to either donepezil or memantine.

Figure 5.4: Kaplan-Meier survival plot of time to death



Log rank test for equality of survivor functions: p=0.589. There is therefore no evidence that the survival time differs by treatment arm.

Table 5.5: Listing of all reported Suspected Unexpected Serious Adverse Reactions (SUSARs)

No SUSARs were reported.

Table 5.6: Listing of all reported Serious Adverse Reactions (SARs)

	Expectedness and Causality	Patient	Treatment Arm	Centre	Date of Randomisation	Date of Event	Seriousness	Action taken	Main and associated symptoms (as listed on form)
1.	Expected and Possibly related	P14003	Memantine	Southampton	26/02/2008	23/05/2008	Persistent/ significant disability/ incapacity	Trial meds stopped permanently	Vomiting; Change In Colour Of Stool And Urine
2.		P06003	Donepezil + Memantine	Glasgow	13/06/2008	23/07/2008	Requires inpatient hospitalisation	Trial meds stopped permanently	Vomiting; Irritable Behaviour; Increased Incontinence
3.		P09002	Placebo	Imperial	04/03/2008	03/11/2008	Requires inpatient hospitalisation	None	Agitation; Aggression
4.		P09015	Placebo	Imperial	21/04/2009	29/07/2009	Requires inpatient hospitalisation	Trial meds stopped permanently	Confusion/Agression; Alzheimer's Disease; UTI
5.		P06009	Memantine	Glasgow	01/10/2009	02/12/2009	Life - threatening	Trial meds stopped permanently	Gastrointestinal Bleed
6.		P15023	Donepezil + Memantine	Warwick	06/11/2009	26/05/2010	Requires inpatient hospitalisation	Trial meds stopped temporarily	Asthma; Breathing Difficulties

Table 5.7: Listing of all reported Serious Adverse Events (SAEs)

	Expectedness and Causality	Patient	Treatment Arm	Centre	Date of Randomisation	Date of Event	Seriousness	Action taken	Main and associated symptoms (as listed on form)
1.		P11004	Donepezil + Memantine	Newcastle	29/04/2008	12/06/2008	emergency respite	None	Increased Distress; Urinary Incontinence
2.		P12007	Donepezil	Nottingham	11/06/2008	18/06/2008	Requires inpatient hospitalisation	Trial meds stopped temporarily	Deterioration Of Mobility; UTI
3.		P15003	Placebo	Warwick	21/04/2008	26/06/2008	Requires inpatient hospitalisation	None	Increased Disorientation; Collapse; Increased Incontinence
4.		P11003	Donepezil	Newcastle	17/04/2008	18/07/2008	emergency respite followed by permanent care home	Trial meds stopped permanently	Increased Agitation And Behavioural Changes; Neck Spasm; UTI
5.		P14004	Placebo	Southampton	08/04/2008	16/09/2008	Requires inpatient hospitalisation	None	Paranoid Ideas, Visual Hallucinations Increased Confusion
6.		P09003	Donepezil + Memantine	Imperial	11/03/2008	03/10/2008	Requires inpatient hospitalisation	None	UTI
7.		P11006	Placebo	Newcastle	25/06/2008	25/11/2008	Emergency Respite from 25/11/2008	None	Agitated Behaviour
8.		P12003	Donepezil	Nottingham	23/04/2008	17/02/2009	Death	None	Unable To Swallow
9.		P05006	Placebo	Dundee	18/02/2009	25/04/2009	Death	Trial meds stopped permanently	Death
10.		P09017	Donepezil + Memantine	Imperial	01/05/2009	01/10/2009	Death	None	UTI; Lacerated Foot; Pneumonia
11.		P11012	Donepezil	Newcastle	16/12/2008	29/10/2009	Requires inpatient hospitalisation	None	Fainted At Home On 29Th Oct 2009; Dizziness

	Expectedness and Causality	Patient	Treatment Arm	Centre	Date of Randomisation	Date of Event	Seriousness	Action taken	Main and associated symptoms (as listed on form)
12.		P09014	Donepezil	Imperial	02/04/2009	16/01/2010	Requires inpatient hospitalisation	Trial meds stopped permanently	Fracture Of The Neck Of Femur
13.		P09016	Memantine	Imperial	24/04/2009	15/02/2010	Requires inpatient hospitalisation	Trial meds stopped permanently	UTI And Infected Bed Sore
14.		P11024	Placebo	Newcastle	07/12/2009	26/02/2010	Requires inpatient hospitalisation	Trial meds stopped permanently	Increased Agitation
15.		P09019	Memantine	Imperial	21/07/2009	28/05/2010	Prolongs current inpatient hospitalisation	None	Falling/Couldn't Stand
16.	Expected and Not related	P01007	Placebo	Bath	10/12/2008	12/01/2009	Requires inpatient hospitalisation	Trial meds stopped permanently	Exacerbation Of Dementia; Increased Paranoia; Psychotic Behaviour; Abnormal Gait
17.		P15008	Donepezil + Memantine	Warwick	21/10/2008	01/05/2009	Requires inpatient hospitalisation	None	Oesophageal Stricture; Nausea; Retching
18.		P08004	Placebo	Maudsley	14/10/2008	24/05/2009	Death	Trial meds stopped permanently	Deceased
19.		P04012	Donepezil	Cambridge	27/08/2009	14/10/2009	Requires inpatient hospitalisation	Trial meds stopped permanently	?Stroke; Ischemic Heart Disease
20.		P03023	Memantine	Birmingham	10/07/2009	02/02/2010	Requires inpatient hospitalisation	Trial meds stopped temporarily	Generalised Seizure
21.		P09020	Donepezil	Imperial	21/07/2009	12/02/2010	Requires inpatient hospitalisation	None	Disorientated After Fall
22.		P09019	Memantine	Imperial	21/07/2009	27/05/2010	Requires inpatient hospitalisation	Trial meds stopped temporarily	Hernia Operation

	Expectedness and Causality	Patient	Treatment Arm	Centre	Date of Randomisation	Date of Event	Seriousness	Action taken	Main and associated symptoms (as listed on form)
23.		P09022	Placebo	Imperial	22/09/2009	11/06/2010	Requires inpatient hospitalisation	Trial meds stopped permanently	Fracture Of Neck Of Femur
24.		P09022	Placebo	Imperial	22/09/2009	15/06/2010	Prolongs current inpatient hospitalisation	Trial meds stopped permanently	Chest Infection; Pneumonia
25.		P13039	Placebo	Oxford	04/02/2010	19/07/2010	Death	None	Pt Died Of Alzheimer's Disease
26.		P11025	Donepezil + Memantine	Newcastle	14/12/2009	14/09/2010	Requires inpatient hospitalisation	Trial meds stopped temporarily	Agitation
27.		P11022	Placebo	Newcastle	14/10/2009	15/09/2010	Requires inpatient hospitalisation	None	UTI; Fall-Fractured R Clavicle
28.		P14019	Donepezil + Memantine	Southampton	01/12/2009	08/10/2010	Requires inpatient hospitalisation	None	Aggressive Behaviour
29.	Unexpected a nd Unlikely to be related	P03001	Memantine	Birmingham	22/02/2008	04/04/2008	Requires inpatient hospitalisation	None	Fracture Of 3 Bones In Neck
30.		P12003	Donepezil	Nottingham	23/04/2008	19/05/2008	Requires inpatient hospitalisation	Trial meds stopped temporarily	Sepsis; Rectal Bleed; Collapsed
31.		P03001	Memantine	Birmingham	22/02/2008	10/06/2008	Requires inpatient hospitalisation	Trial meds stopped temporarily	Agitation
32.		P09010	Donepezil + Memantine	Imperial	21/05/2008	11/08/2008	Requires inpatient hospitalisation	None	Chest Infection
33.		P07003	Donepezil	Leicester	26/03/2008	19/09/2008	Prolongs current inpatient hospitalisation	Trial meds stopped permanently	Chest Infection; Dysphagia
34.		P12001	Donepezil + Memantine	Nottingham	05/03/2008	20/09/2008	Requires inpatient hospitalisation	Trial meds stopped permanently	Stroke; Right Sided Weakness

	Expectedness and Causality	Patient	Treatment Arm	Centre	Date of Randomisation	Date of Event	Seriousness	Action taken	Main and associated symptoms (as listed on form)
35.		P03009	Memantine	Birmingham	12/08/2008	30/09/2008	Requires inpatient hospitalisation	None	Tremor
36.		P09012	Placebo	Imperial	27/08/2008	30/10/2008	Requires inpatient hospitalisation	None	Fall & Fractured Nose; Bruising To Face; Lacerations To Nose And Forehead
37.		P11006	Placebo	Newcastle	25/06/2008	26/12/2008	Requires inpatient hospitalisation	None	Fractured Neck Of Femur; Reduced Mobility; Pressure Sore On Right Heel
38.		P13002	Placebo	Oxford	26/02/2008	22/01/2009	Death	Trial meds stopped permanently	Suspected Stroke; Left Sided Weakness; Loss Of Speech
39.		P09012	Placebo	Imperial	27/08/2008	29/01/2009	Requires inpatient hospitalisation	None	Seizure
40.		P09012	Placebo	Imperial	27/08/2008	27/02/2009	Requires inpatient hospitalisation	None	Broken Hip; Swollen Leg; Pain In Leg
41.		P05006	Placebo	Dundee	18/02/2009	01/03/2009	Requires inpatient hospitalisation	None	Fall; Fractured Hip
42.		P05005	Memantine	Dundee	10/02/2009	15/03/2009	Requires inpatient hospitalisation	None	Abscess To Groin
43.		P15008	Donepezil + Memantine	Warwick	21/10/2008	17/03/2009	Requires inpatient hospitalisation	Trial meds stopped temporarily	Retching And Vomiting
44.		P13005	Placebo	Oxford	09/05/2008	23/03/2009	Requires inpatient hospitalisation	None	Broken Leg
45.		P08004	Placebo	Maudsley	14/10/2008	06/04/2009	Requires inpatient hospitalisation	Trial meds stopped temporarily	Agitation; Poor Sleep; Poor Dietary Intake; Pain In Hip; UTI Sepsis (Klebsiella)
46.		P05005	Memantine	Dundee	10/02/2009	17/04/2009	Requires inpatient hospitalisation	Trial meds stopped permanently	?Urinary Tract Infection; Reduced Mobility

	Expectedness and Causality	Patient	Treatment Arm	Centre	Date of Randomisation	Date of Event	Seriousness	Action taken	Main and associated symptoms (as listed on form)
47.		P13010	Donepezil	Oxford	16/07/2008	17/04/2009	Death	Trial meds stopped permanently	Stroke; Left Sided Weakness
48.		P07011	Donepezil	Leicester	18/07/2008	02/06/2009	Requires inpatient hospitalisation	None	Challenging Behaviour
49.		P07029	Donepezil + Memantine	Leicester	18/03/2009	13/06/2009	Requires inpatient hospitalisation	Trial meds stopped temporarily	Diarrhoea
50.		P09016	Memantine	Imperial	24/04/2009	17/06/2009	Requires inpatient hospitalisation	None	Infcetive Exac Of Asthma
51.		P03015	Placebo	Birmingham	06/02/2009	29/08/2009	Requires inpatient hospitalisation	None	Fall
52.		P13023	Placebo	Oxford	03/03/2009	17/09/2009	Death	None	Heart Attack - Acute MI
53.		P13027	Placebo	Oxford	17/04/2009	30/09/2009	Requires inpatient hospitalisation	Trial meds stopped permanently	Neck Pain; Restricted Mobility
54.		P03015	Placebo	Birmingham	06/02/2009	05/10/2009	Requires inpatient hospitalisation	Trial meds stopped permanently	Seizure
55.		P15019	Placebo	Warwick	02/06/2009	10/10/2009	Requires inpatient hospitalisation	Trial meds stopped permanently	Unable To Walk; Unresponsive
56.		P01015	Memantine	Bath	13/10/2009	19/10/2009	Requires inpatient hospitalisation	None	Head Trauma From A Fall; Pyrexia
57.		P03018	Donepezil	Birmingham	14/04/2009	02/11/2009	Requires inpatient hospitalisation	None	Fall
58.		P05007	Memantine	Dundee	01/07/2009	03/11/2009	Requires inpatient hospitalisation	None	?Urinary Tract Infection; Immobility; Tachycardia
59.		P07037	Donepezil	Leicester	19/08/2009	27/11/2009	Prolongs current inpatient hospitalisation	None	Raised Potassium Levels

	Expectedness and Causality	Patient	Treatment Arm	Centre	Date of Randomisation	Date of Event	Seriousness	Action taken	Main and associated symptoms (as listed on form)
60.		P06009	Memantine	Glasgow	01/10/2009	29/11/2009	Requires inpatient hospitalisation	None	Knee Pain (Gout)
61.		P03017	Memantine	Birmingham	24/03/2009	11/12/2009	Requires inpatient hospitalisation	None	Patient Felt Unwell; Leaning Towards Left Side
62.		P01016	Memantine	Bath	02/11/2009	12/12/2009	Requires inpatient hospitalisation	None	Suspected UTI
63.		P10011	Memantine	Manchester	23/07/2009	25/01/2010	Requires inpatient hospitalisation	None	Diarrhoea For Several Weeks
64.		P15020	Memantine	Warwick	18/06/2009	20/05/2010	Requires inpatient hospitalisation	Trial meds stopped temporarily	Fall; High Temperature; Dehydrated
65.		P05007	Memantine	Dundee	01/07/2009	08/06/2010	Requires inpatient hospitalisation	Trial meds stopped permanently	UTI/Chest Infection; Reduced Mobility; Pyrexia
66.	Unexpected and Not related	P13008	Memantine	Oxford	23/05/2008	24/05/2008	Requires inpatient hospitalisation	None	Fracture Following Fall
67.		P07005	Donepezil	Leicester	14/04/2008	02/06/2008	Requires inpatient hospitalisation	None	Patient Agitated And Aggressive
68.		P12008	Placebo	Nottingham	07/07/2008	12/08/2008	overdose on trial medication	Dose changed	Overdose On Trial Medication
69.		P15003	Placebo	Warwick	21/04/2008	13/08/2008	Requires inpatient hospitalisation	None	Fall
70.		P11002	Memantine	Newcastle	13/03/2008	15/08/2008	Requires inpatient hospitalisation	None	?UTI, ?Stroke
71.		P11002	Memantine	Newcastle	13/03/2008	25/09/2008	Requires inpatient hospitalisation	None	?DVT
72.		P03006	Placebo	Birmingham	09/06/2008	13/10/2008	Requires inpatient hospitalisation	None	Fractured Femur
73.		P11003	Donepezil	Newcastle	17/04/2008	25/10/2008	Requires inpatient hospitalisation	Trial meds stopped permanently	Generally Unwell; Reduced Nutritional Intake; Reduced Mobility

	Expectedness and Causality	Patient	Treatment Arm	Centre	Date of Randomisation	Date of Event	Seriousness	Action taken	Main and associated symptoms (as listed on form)
74.		P07004	Memantine	Leicester	28/03/2008	28/10/2008	Requires inpatient hospitalisation	Trial meds stopped temporarily	Urinary Tract Infection
75.		P09003	Donepezil + Memantine	Imperial	11/03/2008	18/11/2008	Requires inpatient hospitalisation	None	Dehydration
76.		P15004	Donepezil	Warwick	22/04/2008	29/11/2008	Requires inpatient hospitalisation	None	Chest Infection; Incontinence; Decreased Mobility
77.		P07009	Placebo	Leicester	14/07/2008	04/12/2008	Requires inpatient hospitalisation	None	General Deterioration
78.		P11002	Memantine	Newcastle	13/03/2008	24/12/2008	Death	Trial meds stopped permanently	Frailty; Pressure Sores (Heel); ?DVT; Reduced Mobility
79.		P13013	Memantine	Oxford	23/10/2008	29/12/2008	Persistent/ significant disability/ incapacity	Trial meds stopped permanently	Infection Of Unknown Cause Or Site; Unable To Weight Bear Or Mobilise; Difficulty Swallowing; Increased Confusion
80.		P12005	Donepezil	Nottingham	09/05/2008	03/01/2009	Requires inpatient hospitalisation	Trial meds stopped permanently	Bladder Retention; Agitation
81.		P08004	Placebo	Maudsley	14/10/2008	11/01/2009	Requires inpatient hospitalisation	Trial meds stopped temporarily	No Injury Sustained. Admitted To Hospital Due To 'Precarious Home Situation.'
82.		P11013	Memantine	Newcastle	18/12/2008	13/01/2009	Death	Trial meds stopped permanently	Reduced Mobility
83.		P13013	Memantine	Oxford	23/10/2008	13/01/2009	Requires inpatient hospitalisation	None	Infection Broncho Pneumonia
84.		P07009	Placebo	Leicester	14/07/2008	15/01/2009	Prolongs current inpatient hospitalisation	None	Collapse

	Expectedness and Causality	Patient	Treatment Arm	Centre	Date of Randomisation	Date of Event	Seriousness	Action taken	Main and associated symptoms (as listed on form)
85.		P13006	Donepezil	Oxford	09/05/2008	19/01/2009	Requires inpatient hospitalisation	None	Cardiovascular Syncope Collapse And UTI; Collapse; Hypotension; Diarrhoea
86.		P07023	Placebo	Leicester	01/12/2008	21/01/2009	Requires inpatient hospitalisation	None	Chest Infection; Difficulty Breathing; Unable To Walk
87.		P15004	Donepezil	Warwick	22/04/2008	22/01/2009	Death	None	Dysphagia
88.		P07023	Placebo	Leicester	01/12/2008	27/01/2009	Patient was given 3 tablets of Donepezil/placebo & 1 tablet of Memantine a day for 7 days.	Dose changed	Overdose Of Donepezil/Placebo
89.		P03001	Memantine	Birmingham	22/02/2008	10/02/2009	Requires inpatient hospitalisation	Trial meds stopped permanently	Increased Confusion
90.		P13005	Placebo	Oxford	09/05/2008	15/02/2009	Requires inpatient hospitalisation	None	Fall # Collarbone
91.		P12007	Donepezil	Nottingham	11/06/2008	25/02/2009	Requires inpatient hospitalisation	Trial meds stopped temporarily	Fracture To Wrist
92.		P13022	Donepezil + Memantine	Oxford	23/02/2009	02/03/2009	Requires inpatient hospitalisation	None	Urine Infection; Broken Arm From Fall
93.		P12004	Donepezil	Nottingham	21/04/2008	04/03/2009	Requires inpatient hospitalisation	None	Injury To Face
94.		P12004	Donepezil	Nottingham	21/04/2008	04/03/2009	Prolongs current inpatient hospitalisation	None	Increase Aggression
95.		P07011	Donepezil	Leicester	18/07/2008	09/03/2009	Requires inpatient hospitalisation	None	Cancer Of The Womb
96.		P07023	Placebo	Leicester	01/12/2008	13/03/2009	Requires inpatient hospitalisation	Trial meds stopped temporarily	Wouldn't Eat Or Drink; Urinary Tract Infection

	Expectedness and Causality	Patient	Treatment Arm	Centre	Date of Randomisation	Date of Event	Seriousness	Action taken	Main and associated symptoms (as listed on form)
97.		P07021	Memantine	Leicester	20/10/2008	02/04/2009	Requires inpatient hospitalisation	Trial meds stopped permanently	Chest Infection; Urine Infection
98.		P12007	Donepezil	Nottingham	11/06/2008	03/04/2009	Prolongs current inpatient hospitalisation	Trial meds stopped permanently	Dehydration
99.		P10006	Donepezil + Memantine	Manchester	04/02/2009	06/04/2009	Requires inpatient hospitalisation	None	Left Sided Chest Pain Documented As Non Cardiac Chest Pain; Clammy; Low Oxygenation
100.		P03014	Donepezil	Birmingham	23/01/2009	08/04/2009	Requires inpatient hospitalisation	None	Breast Cancer
101.		P13007	Donepezil	Oxford	20/05/2008	12/04/2009	Requires inpatient hospitalisation	None	Diarrhoea & Vomiting
102.		P15008	Donepezil + Memantine	Warwick	21/10/2008	14/04/2009	Requires inpatient hospitalisation	Trial meds stopped temporarily	Vomiting
103.		P15014	Donepezil	Warwick	22/01/2009	15/04/2009	Requires inpatient hospitalisation	Trial meds stopped permanently	Chest Infection
104.		P07023	Placebo	Leicester	01/12/2008	21/04/2009	Requires inpatient hospitalisation	None	Patient Choking; Unable To Swallow
105.		P03013	Donepezil + Memantine	Birmingham	09/01/2009	30/04/2009	Requires inpatient hospitalisation	None	Fall
106.		P12006	Donepezil + Memantine	Nottingham	04/06/2008	06/05/2009	Requires inpatient hospitalisation	None	Deterioration Of Mental Condition
107.		P15014	Donepezil	Warwick	22/01/2009	31/05/2009	Requires inpatient hospitalisation	None	Diarrhoea
108.		P15018	Donepezil + Memantine	Warwick	15/05/2009	15/06/2009	Requires inpatient hospitalisation	None	UTI

	Expectedness and Causality	Patient	Treatment Arm	Centre	Date of Randomisation	Date of Event	Seriousness	Action taken	Main and associated symptoms (as listed on form)
109.		P03013	Donepezil + Memantine	Birmingham	09/01/2009	18/06/2009	Requires inpatient hospitalisation	Trial meds stopped permanently	Chest Infection
110.		P15018	Donepezil + Memantine	Warwick	15/05/2009	19/06/2009	Requires inpatient hospitalisation	Trial meds stopped temporarily	Aggression; Agitation
111.		P07009	Placebo	Leicester	14/07/2008	21/06/2009	Requires inpatient hospitalisation	None	Fall - Fractured Hip
112.		P04009	Placebo	Cambridge	25/06/2009	30/06/2009	Requires inpatient hospitalisation	None	Severe Pain Below R Rib Cage
113.		P03008	Donepezil + Memantine	Birmingham	21/07/2008	09/07/2009	Requires inpatient hospitalisation	None	Query- Epileptic Fit
114.		P01005	Placebo	Bath	19/11/2008	13/07/2009	Requires inpatient hospitalisation	None	T.I.A
115.		P03017	Memantine	Birmingham	24/03/2009	15/07/2009	Requires inpatient hospitalisation	None	Unknown: Confused
116.		P10011	Memantine	Manchester	23/07/2009	30/07/2009	patient has taken two doses of trial medication given by two family members	None	No Symptoms Reported
117.		P09012	Placebo	Imperial	27/08/2008	01/08/2009	Requires inpatient hospitalisation	Trial meds stopped permanently	Gastroenteritis; Fluid On Lungs; Diarrhoea
118.		P03012	Donepezil	Birmingham	19/12/2008	05/08/2009	Requires inpatient hospitalisation	None	Water Infection; Confusion
119.		P13022	Donepezil + Memantine	Oxford	23/02/2009	08/09/2009	Requires inpatient hospitalisation	None	UTI; Deterioration Mobility; Increased Confusion
120.		P03026	Donepezil	Birmingham	02/10/2009	10/10/2009	Requires inpatient hospitalisation	None	Fall; Bruising
121.		P15015	Placebo	Warwick	10/03/2009	20/10/2009	Requires inpatient hospitalisation	None	Loss Of Mobility

	Expectedness and Causality	Patient	Treatment Arm	Centre	Date of Randomisation	Date of Event	Seriousness	Action taken	Main and associated symptoms (as listed on form)
122.		P11017	Donepezil + Memantine	Newcastle	30/03/2009	04/11/2009	Death	Trial meds stopped permanently	Myocardial Infarction
123.		P12009	Memantine	Nottingham	25/11/2008	06/11/2009	Requires inpatient hospitalisation	None	Fracture; Unable To Mobilize Independently
124.		P03027	Donepezil + Memantine	Birmingham	26/10/2009	16/11/2009	Life - threatening	None	Pain In The Knee, Hip
125.		P07037	Donepezil	Leicester	19/08/2009	25/11/2009	Requires inpatient hospitalisation	None	Patient Unwell/Off His Legs
126.		P11020	Donepezil	Newcastle	29/06/2009	27/11/2009	Persistent/ significant disability/ incapacity	Trial meds stopped permanently	Septicaemia Secondary To Gall Bladder Infection & UTI; Vomiting And Diarrhoea (Secondary To Hospital Acquired Infection); DVT Right Ll; Bed Bound
127.		P15019	Placebo	Warwick	02/06/2009	29/11/2009	Requires inpatient hospitalisation	Trial meds stopped permanently	Fall
128.		P12012	Donepezil	Nottingham	28/04/2009	30/11/2009	Requires inpatient hospitalisation	None	Aggression
129.		P08009	Donepezil	Maudsley	27/04/2009	04/12/2009	Requires inpatient hospitalisation	Trial meds stopped temporarily	Severe Back Pain; Reduced Mobility; Wedge Fractures Of Spine; Mini Stroke Additionally Diagnosed Following Scan Diagnosed 10/12/09
130.		P07036	Donepezil + Memantine	Leicester	06/07/2009	11/12/2009	patient given donepezil 10mg od for 7 weeks	None	Patient Taken Donepezil 10Mg
131.		P12010	Donepezil + Memantine	Nottingham	16/01/2009	15/12/2009	Requires inpatient hospitalisation	Trial meds stopped permanently	Shortness Of Breath; Difficulty In Mobilizing

	Expectedness and Causality	Patient	Treatment Arm	Centre	Date of Randomisation	Date of Event	Seriousness	Action taken	Main and associated symptoms (as listed on form)
132.		P12012	Donepezil	Nottingham	28/04/2009	15/12/2009	Requires inpatient hospitalisation	None	Pneumonia; Shortness Of Breath
133.		P10013	Donepezil + Memantine	Manchester	11/08/2009	18/12/2009	Requires inpatient hospitalisation	Trial meds stopped permanently	2 Falls At Home. Incontinent And Another Fall At 5Am; Hemiporesis; Slurred Speech
134.		P11023	Donepezil	Newcastle	24/11/2009	30/12/2009	Requires inpatient hospitalisation	None	Urinary Tract Infection
135.		P03021	Memantine	Birmingham	15/05/2009	31/12/2009	Requires inpatient hospitalisation	Trial meds stopped permanently	Carer Became Ill No one To Look After Husband
136.		P12012	Donepezil	Nottingham	28/04/2009	14/01/2010	Death	None	Death
137.		P01009	Donepezil	Bath	23/02/2009	17/01/2010	Requires inpatient hospitalisation	None	Chest Pain/ Panic Attack
138.		P08010	Placebo	Maudsley	18/08/2009	18/01/2010	Death	None	Aspiration Pneumonia; Kidney Failure
139.		P03017	Memantine	Birmingham	24/03/2009	23/01/2010	Requires inpatient hospitalisation	None	UTI, Lower Respiratory Tract Infection; Poor Mobility; Not Eating, Drinking
140.		P14020	Placebo	Southampton	01/12/2009	24/01/2010	Requires inpatient hospitalisation	Trial meds stopped temporarily	Urinary Tract Infection; Constipation
141.		P10013	Donepezil + Memantine	Manchester	11/08/2009	06/02/2010	Prolongs current inpatient hospitalisation	None	Aspiration Pneumonia; Hemiparesis; Slurred Speech
142.		P11018	Donepezil	Newcastle	07/04/2009	13/02/2010	Requires inpatient hospitalisation	None	Dehydration (From Persistent Diarrhoea); Chest Infection
143.		P03017	Memantine	Birmingham	24/03/2009	17/02/2010	Death	None	Cardiac Arrest
144.		P08006	Memantine	Maudsley	03/03/2009	17/02/2010	Life - threatening	Trial meds stopped permanently	Pneumonia; ? Mild M.I.; Blood Infection; Bladder Infection; Unable To Swallow
145.		P03020	Donepezil + Memantine	Birmingham	20/04/2009	20/02/2010	Death	None	Pneumonia

	Expectedness and Causality	Patient	Treatment Arm	Centre	Date of Randomisation	Date of Event	Seriousness	Action taken	Main and associated symptoms (as listed on form)
146.		P11018	Donepezil	Newcastle	07/04/2009	21/02/2010	Prolongs current inpatient hospitalisation	None	Broken Forearm; Hospital Acquired Infection - Norovirus
147.		P15018	Donepezil + Memantine	Warwick	15/05/2009	12/03/2010	Requires inpatient hospitalisation	Trial meds stopped temporarily	Constipation; Leg Pain
148.		P07041	Donepezil + Memantine	Leicester	22/01/2010	22/03/2010	Requires inpatient hospitalisation	Trial meds stopped temporarily	Shortness Of Breath
149.		P07041	Donepezil + Memantine	Leicester	22/01/2010	27/03/2010	Requires inpatient hospitalisation	None	Shortness Of Breath
150.		P08013	Donepezil	Maudsley	20/10/2009	29/03/2010	Requires inpatient hospitalisation	None	? Left Lacunar Infarct; Right Sided Weakness
151.		P11020	Donepezil	Newcastle	29/06/2009	29/03/2010	Requires inpatient hospitalisation	Trial meds stopped permanently	Sudden Physical Deterioration
152.		P15015	Placebo	Warwick	10/03/2009	01/04/2010	Requires inpatient hospitalisation	None	Unconscious
153.		P07041	Donepezil + Memantine	Leicester	22/01/2010	12/04/2010	Requires inpatient hospitalisation	None	Gastritis; Nausea & Vomiting
154.		P04011	Donepezil + Memantine	Cambridge	03/08/2009	16/04/2010	Requires inpatient hospitalisation	Trial meds stopped permanently	General Deterioration; Reduced Mobility; Swallowing Difficulties; ?UTI; Swallowing Difficulties
155.		P04006	Donepezil + Memantine	Cambridge	10/06/2009	20/04/2010	Requires inpatient hospitalisation	Trial meds stopped temporarily	Collapse With Right-Sided Weakness; Left Parietal Infarct; Right Facial Droop; Dysarthria

	Expectedness and Causality	Patient	Treatment Arm	Centre	Date of Randomisation	Date of Event	Seriousness	Action taken	Main and associated symptoms (as listed on form)
156.		P07045	Memantine	Leicester	04/03/2010	20/04/2010	patient took husbands medication in error on 2 occasions	None	Patient Took Husbands Medication In Error
157.		P08014	Donepezil + Memantine	Maudsley	20/10/2009	20/04/2010	Requires inpatient hospitalisation	Trial meds stopped permanently	Aggression
158.		P10018	Placebo	Manchester	25/02/2010	22/04/2010	Requires inpatient hospitalisation	None	Chest Infection
159.		P03025	Placebo	Birmingham	26/08/2009	26/04/2010	Requires inpatient hospitalisation	Trial meds stopped temporarily	Immobile
160.		P13039	Placebo	Oxford	04/02/2010	30/04/2010	Requires inpatient hospitalisation	None	UTI And Dehydration
161.		P15018	Donepezil + Memantine	Warwick	15/05/2009	09/05/2010	Requires inpatient hospitalisation	Trial meds stopped temporarily	Distressed; Psychotic/Delusional; Shouting
162.		P03024	Donepezil + Memantine	Birmingham	24/08/2009	10/05/2010	Requires inpatient hospitalisation	Trial meds stopped temporarily	Urinary Tract Infection
163.		P13039	Placebo	Oxford	04/02/2010	21/05/2010	Prolongs current inpatient hospitalisation	Trial meds stopped permanently	Urinary Sepsis
164.		P01013	Memantine	Bath	20/08/2009	25/05/2010	Requires inpatient hospitalisation	Trial meds stopped permanently	Fractured Tibia; Fall
165.		P04010	Placebo	Cambridge	14/07/2009	06/06/2010	Requires inpatient hospitalisation	None	Right Lateral Ankle Cellulitis; Delirium; Pain; Pyrexia
166.		P13034	Donepezil	Oxford	16/09/2009	08/06/2010	No adverse event noted	None	Drug Error

	Expectedness and Causality	Patient	Treatment Arm	Centre	Date of Randomisation	Date of Event	Seriousness	Action taken	Main and associated symptoms (as listed on form)
167.		P04011	Donepezil + Memantine	Cambridge	03/08/2009	14/06/2010	Life - threatening	None	Obstructed Or Twisted Intestine; Pain; Distended Abdomen
168.		P08012	Memantine	Maudsley	21/09/2009	15/06/2010	Requires inpatient hospitalisation	Trial meds stopped temporarily	? Chest Or Urinary Infection; Postural Hypotension; Increased Confusion; Shortness Of Breath; Falls; Pneumonia
169.		P15024	Memantine	Warwick	09/11/2009	01/07/2010	Requires inpatient hospitalisation	Trial meds stopped temporarily	UTI
170.		P08013	Donepezil	Maudsley	20/10/2009	09/07/2010	Requires inpatient hospitalisation	Trial meds stopped permanently	Sepsis - Unknown Cause - Initial Diagnosis; Dehydration; Pulmonary Embolism; Fatigue; Weight Loss; Bilateral Periventicular Low Attenuations; Mini Strokes; Swallowing Difficulties; Oral Thrush; Pneumonia
171.		P03024	Donepezil + Memantine	Birmingham	24/08/2009	28/07/2010	Requires inpatient hospitalisation	Trial meds stopped temporarily	Blood Clot Lungs
172.		P04015	Memantine	Cambridge	24/09/2009	01/08/2010	Requires inpatient hospitalisation	None	Chest Infection; Chest Pain
173.		P01017	Donepezil	Bath	25/11/2009	15/08/2010	Death	None	Collapse At Home
174.		P15024	Memantine	Warwick	09/11/2009	01/09/2010	Requires inpatient hospitalisation	None	UTI
175.		P08014	Donepezil + Memantine	Maudsley	20/10/2009	06/09/2010	Requires inpatient hospitalisation	None	Urosepsis; Agitation/Aggression; Disinhibited Behaviours

	Expectedness and Causality	Patient	Treatment Arm	Centre	Date of Randomisation	Date of Event	Seriousness	Action taken	Main and associated symptoms (as listed on form)
176.		P12020	Memantine	Nottingham	10/02/2010	13/09/2010	Requires inpatient hospitalisation	None	Aggression
177.		P04019	Memantine	Cambridge	01/12/2009	29/09/2010	Requires inpatient hospitalisation	None	Falls And Decreased Mobility; Painful Leg; MRSA
178.		P11022	Placebo	Newcastle	14/10/2009	27/10/2010	Death	None	Pulmonary Embolism; DVT
179.		P10016	Donepezil + Memantine	Manchester	17/02/2010	21/11/2010	Requires inpatient hospitalisation	Trial meds stopped temporarily	Chest Infection
180.		P07043	Donepezil	Leicester	12/02/2010	16/12/2010	Requires inpatient hospitalisation	Trial meds stopped permanently	Fall
181.		P04020	Donepezil	Cambridge	05/01/2010	03/01/2011	Requires inpatient hospitalisation	Trial meds stopped permanently	UTI; ? Mild TIA; Reduced Mobility; Reduced Appetite; Cognitive Decline

6. Adherence to trial medications

Adherence is calculated primarily from the trial medications dispensing and returns logs except for pack 4 which was often returned some time after the end of the trial. Data from pill counts are used when packs were not returned or for pack 4.

All patients on all arms should be taking 4 tablets daily for the duration of the trial.

Table 6.1: Overall adherence by centre

	Percentage adherence over whole trial						
	0%-	**25%-**	**50%-**	**70%**	**95%-**	**Total**	**Adherent (70%-100%)**
Bath	5 (31%)	3 (19%)	0	2 (13%)	6 (38%)	**16**	8 (50%)
Birmingham	8 (22%)	4 (11%)	2 (6%)	6 (17%)	16 (44%)	**36**	22 (61%)
Cambridge	4 (21%)	1 (5%)	3 (16%)	5 (26%)	6 (32%)	**19**	11 (58%)
Dundee	2 (18%)	2 (18%)	2 (18%)	1 (9%)	4 (36%)	**11**	5 (45%)
Glasgow	2 (25%)	2 (25%)	0	1 (13%)	3 (38%)	**8**	4 (50%)
Leicester	8 (24%)	4 (12%)	1 (3%)	8 (24%)	13 (38%)	**34**	21 (62%)
Maudsley	3 (23%)	2 (15%)	2 (15%)	2 (15%)	4 (31%)	**13**	6 (46%)
Imperial	8 (29%)	3 (11%)	2 (7%)	8 (29%)	7 (25%)	**28**	15 (54%)
Manchester	3 (21%)	2 (14%)	1 (7%)	2 (14%)	6 (43%)	**14**	8 (57%)
Newcastle	5 (21%)	2 (8%)	4 (17%)	3 (13%)	10 (42%)	**24**	13 (54%)
Nottingham	2 (12%)	2 (12%)	2 (12%)	6 (35%)	5 (29%)	**17**	11 (65%)
Oxford	4 (11%)	2 (6%)	2 (6%)	8 (23%)	19 (54%)	**35**	27 (77%)
Southampton	5 (28%)	1 (6%)	0	2 (11%)	10 (56%)	**18**	12 (67%)
Warwick	4 (18%)	4 (18%)	0	6 (27%)	8 (36%)	**22**	14 (64%)
Total	**63 (21%)**	**34 (12%)**	**21 (7%)**	**60 (20%)**	**117 (40%)**	**295**	**177 (60%)**

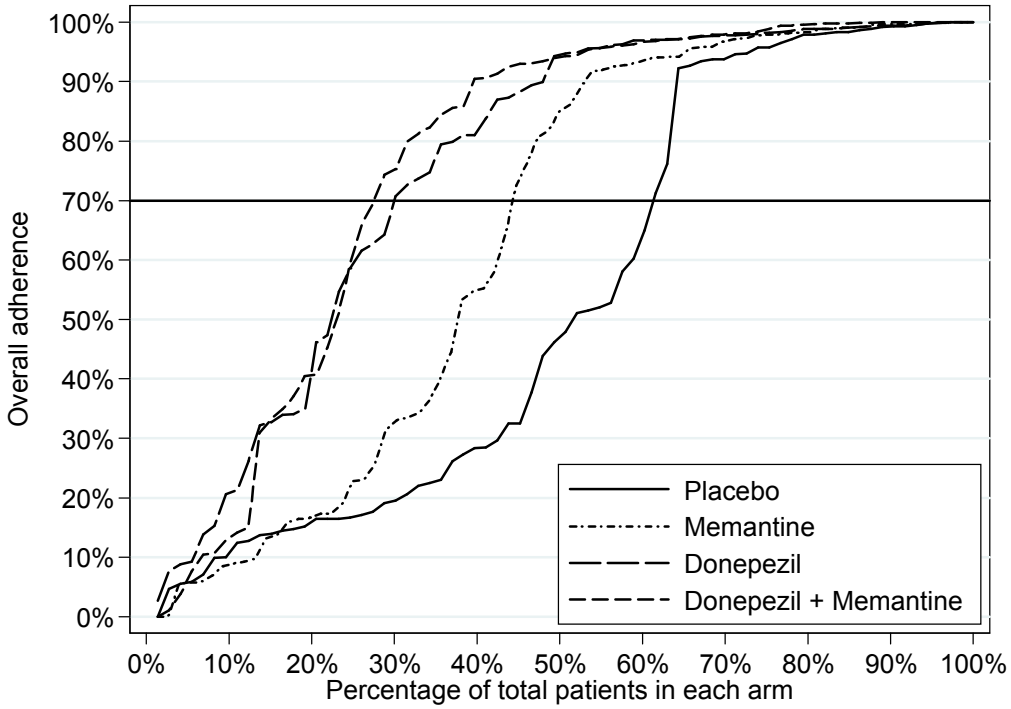
Table 6.2: Overall adherence by treatment arm

	Percentage adherence over whole trial						
	0%-	**25%-**	**50%-**	**70%-**	**95%-**	**Total**	**Adherent (70%-100%)**
Placebo	26 (36%)	11 (15%)	7 (10%)	9 (12%)	20 (27%)	**73**	29 (40%)
Memantine	20 (26%)	8 (11%)	5 (7%)	16 (21%)	27 (36%)	**76**	43 (57%)
Donepezil	8 (11%)	8 (11%)	5 (7%)	17 (23%)	35 (48%)	**73**	52 (71%)
Donepezil + Memantine	9 (12%)	7 (10%)	4 (5%)	18 (25%)	35 (48%)	**73**	53 (73%)
Total	**63 (21%)**	**34 (12%)**	**21 (7%)**	**60 (20%)**	**117 (40%)**	**295**	177 (60%)

Figure 6.3: Overall adherence by treatment arm

This graph shows the distribution of adherence across patients in each treatment arm. On the vertical axis is the overall adherence to trial medications. On the horizontal axis is the cumulative percentage of patients having the specified adherence or less.

A horizontal line is plotted at 70% showing what proportion of patients on each arm have overall adherence of 70% or less, i.e. are non-adherent.



7. Descriptive summary of outcomes

Figure 7.1: Standardised Mini-Mental State Examination (sMMSE) by visit and treatment arm

Each assessment score and the mean are plotted in this figure for each visit and treatment arm with an interval showing 1 standard deviation either side of the mean. sMMSE scores at baseline must be greater or equal to 5 and less than or equal to 13 to be eligible for the trial. The sMMSE is a measure of cognitive function in elderly people. Scores range from 30 (unimpaired) to 0 (impaired).

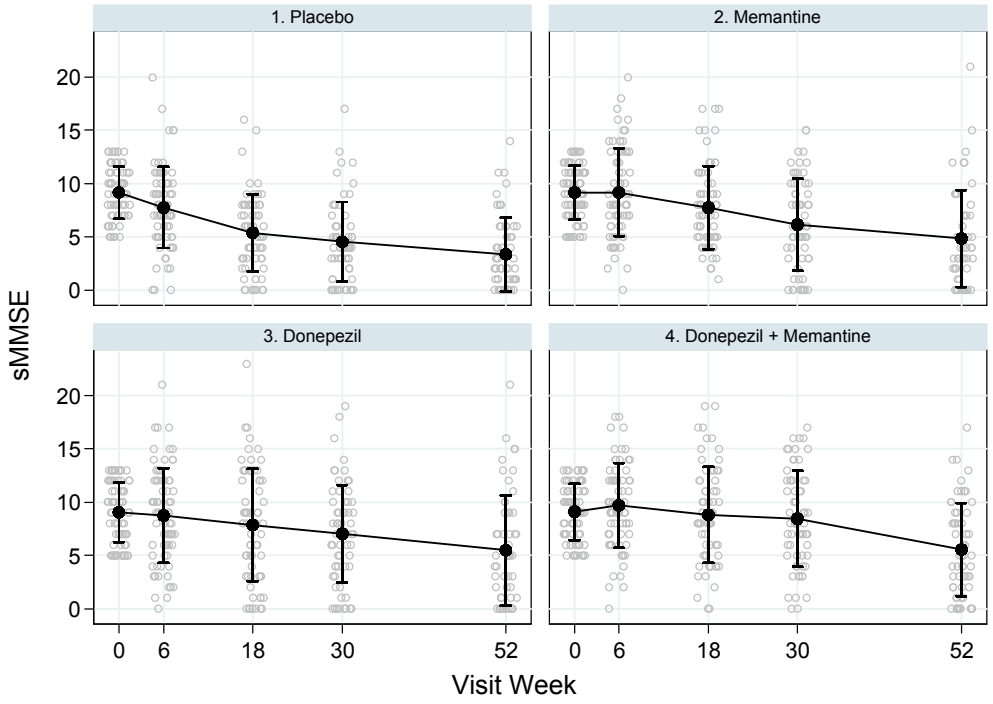


Table 7.2: Standardised Mini-Mental State Examination (sMMSE) by visit and treatment arm

Median (IQR)	Placebo Donepezil		Donepezil		Overall
	Placebo Memantine	Memantine	Placebo Memantine	Memantine	
Total Randomised	**73**	**76**	**73**	**73**	**295**
Baseline Visit	9.1 (2.4)	9.2 (2.5)	9.0 (2.8)	9.1 (2.6)	**9.1 (2.6)**
6 Week Visit	7.7 (3.8)	9.2 (4.1)	8.7 (4.5)	9.7 (4.0)	**8.8 (4.1)**
18 Week Visit	5.4 (3.6)	7.8 (3.9)	7.8 (5.3)	8.8 (4.5)	**7.5 (4.5)**
30 Week Visit	4.6 (3.7)	6.1 (4.3)	7.0 (4.6)	8.4 (4.5)	**6.6 (4.5)**
52 Week Visit	3.3 (3.5)	4.8 (4.6)	5.5 (5.2)	5.6 (4.4)	**4.8 (4.5)**

Figure 7.3: Bristol Activities of Daily Living Scale (BADLS) by visit and treatment arm

Each assessment score and the mean are plotted in this figure for each visit and treatment arm with an interval showing 1 standard deviation either side of the mean. The BADLS is an assessment of activities of daily living in dementia. Scores range from 0 (unimpaired) to 60 (impaired).

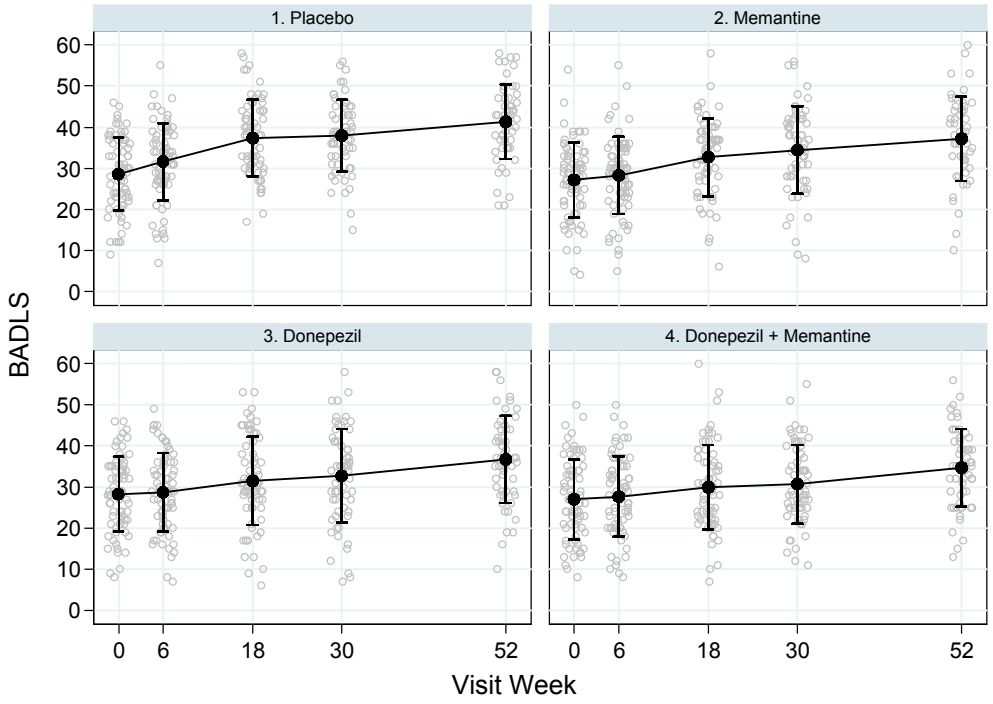


Table 7.4: Bristol Activities of Daily Living Scale (BADLS) by visit and treatment arm

Median (IQR)	Placebo Donepezil		Donepezil		Overall
	Placebo Memantine	Memantine	Placebo Memantine	Memantine	
Total Randomised	**73**	**76**	**73**	**73**	**295**
Baseline Visit	28.6 (8.9)	27.1 (9.0)	28.2 (9.0)	26.9 (9.8)	27.7 (9.2)
6 Week Visit	31.6 (9.5)	28.2 (9.4)	28.8 (9.5)	27.7 (9.7)	29.1 (9.6)
18 Week Visit	37.4 (9.3)	32.6 (9.5)	31.5 (10.8)	29.9 (10.3)	32.8 (10.3)
30 Week Visit	37.9 (8.7)	34.5 (10.7)	32.7 (11.4)	30.7 (9.6)	33.9 (10.4)
52 Week Visit	41.4 (9.1)	37.2 (10.3)	36.7 (10.6)	34.7 (9.4)	37.4 (10.1)

Figure 7.5: Neuropsychiatric Inventory (NPI) by visit and treatment arm

The NPI is a secondary endpoint. The NPI is used to measure the caregiver's assessment of frequency and severity of behavioural and psychiatric symptoms of dementia (BPSD). Scores range from 0 (no disturbance) to 144 (maximum disturbance).

Each assessment score and the mean are plotted in this figure for each visit and treatment arm with an interval showing 1 standard deviation either side of the mean.

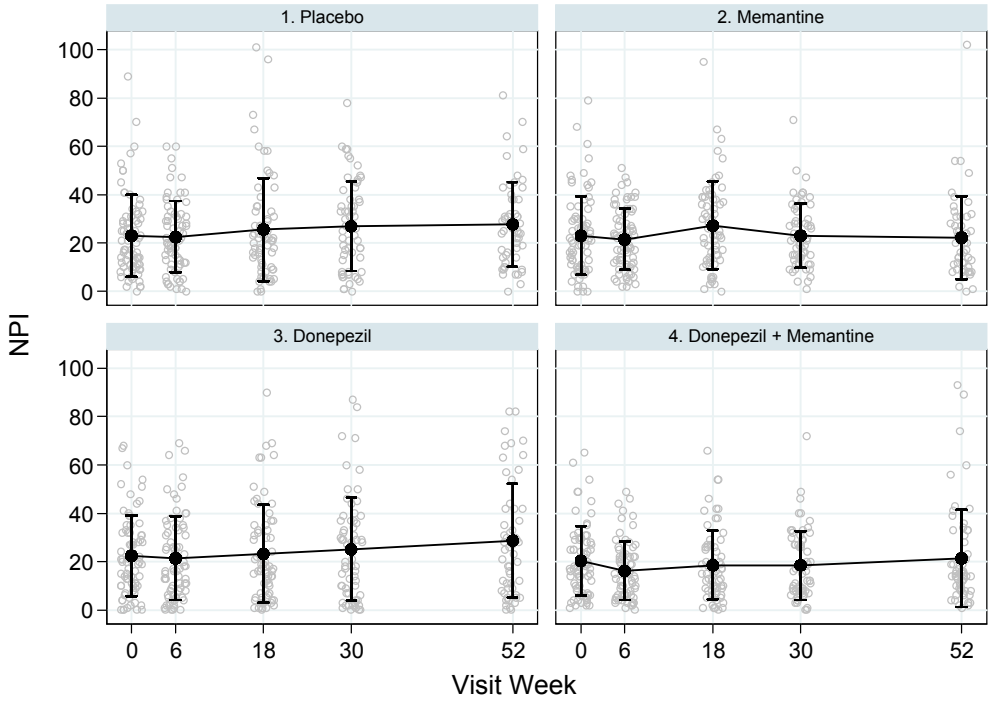


Table 7.6: Neuropsychiatric Inventory (NPI) by visit and treatment arm

Median (IQR)	Placebo Donepezil		Donepezil		Overall
	Placebo Memantine	Memantine	Placebo Memantine	Memantine	
Total Randomised	**73**	**76**	**73**	**73**	**295**
Baseline Visit	22.9 (17.0)	23.1 (16.2)	22.3 (16.7)	20.3 (14.4)	22.2 (16.1)
6 Week Visit	22.5 (14.8)	21.5 (12.5)	21.5 (17.3)	16.2 (12.1)	20.5 (14.5)
18 Week Visit	25.5 (21.4)	27.3 (18.1)	23.3 (20.2)	18.6 (14.2)	23.6 (18.8)
30 Week Visit	27.0 (18.5)	23.0 (13.3)	25.1 (21.3)	18.4 (14.2)	23.4 (17.4)
52 Week Visit	27.7 (17.5)	22.3 (17.2)	28.6 (23.4)	21.4 (20.2)	25.0 (19.9)

Figure 7.7: General Health Questionnaire 12 (GHQ-12) by visit and treatment arm

The GHQ-12 is a secondary endpoint. The GHQ-12 is used to measure levels of psychological distress in the carers of study patients. Scores range from 0 (not distressed) to 12 (distressed).

Each assessment score and the mean are plotted in this figure for each visit and treatment arm with an interval showing 1 standard deviation either side of the mean.

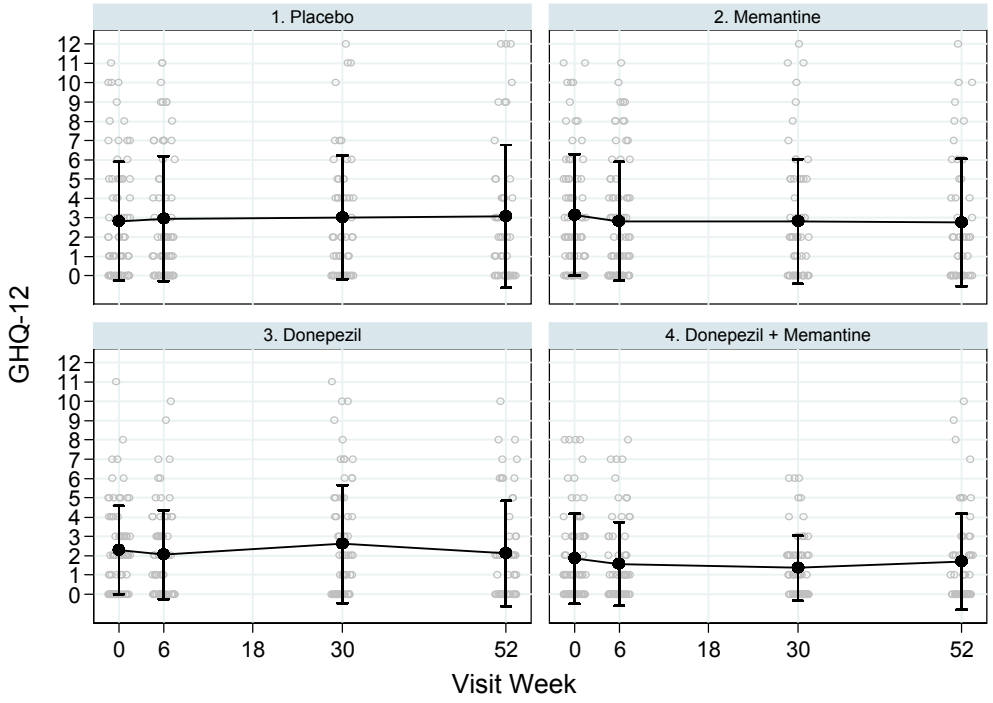


Table 7.8: General Health Questionnaire 12 (GHQ-12) by visit and treatment arm

Median (IQR)	Placebo Donepezil		Donepezil		Overall
	Placebo Memantine	Memantine	Placebo Memantine	Memantine	
Total Randomised	**73**	**76**	**73**	**73**	**295**
Baseline Visit	2.8 (3.1)	3.1 (3.1)	2.3 (2.3)	1.8 (2.3)	2.5 (2.8)
6 Week Visit	2.9 (3.2)	2.8 (3.1)	2.1 (2.3)	1.6 (2.2)	2.4 (2.8)
30 Week Visit	3.0 (3.2)	2.8 (3.2)	2.6 (3.1)	1.4 (1.7)	2.4 (2.9)
52 Week Visit	3.1 (3.7)	2.8 (3.3)	2.1 (2.7)	1.7 (2.5)	2.4 (3.1)

Figure 7.9: DEMQOL-Proxy by visit and treatment arm

The DEMQOL-Proxy is a secondary endpoint. DEMQOL–Proxy is a disease specific instrument for evaluating health-related quality of life (HRQoL) in dementia completed by the carer. Scores range from 31 (minimum HRQoL) to 124 (maximum HRQoL).

Each assessment score and the mean are plotted in this figure for each visit and treatment arm with an interval showing 1 standard deviation either side of the mean.

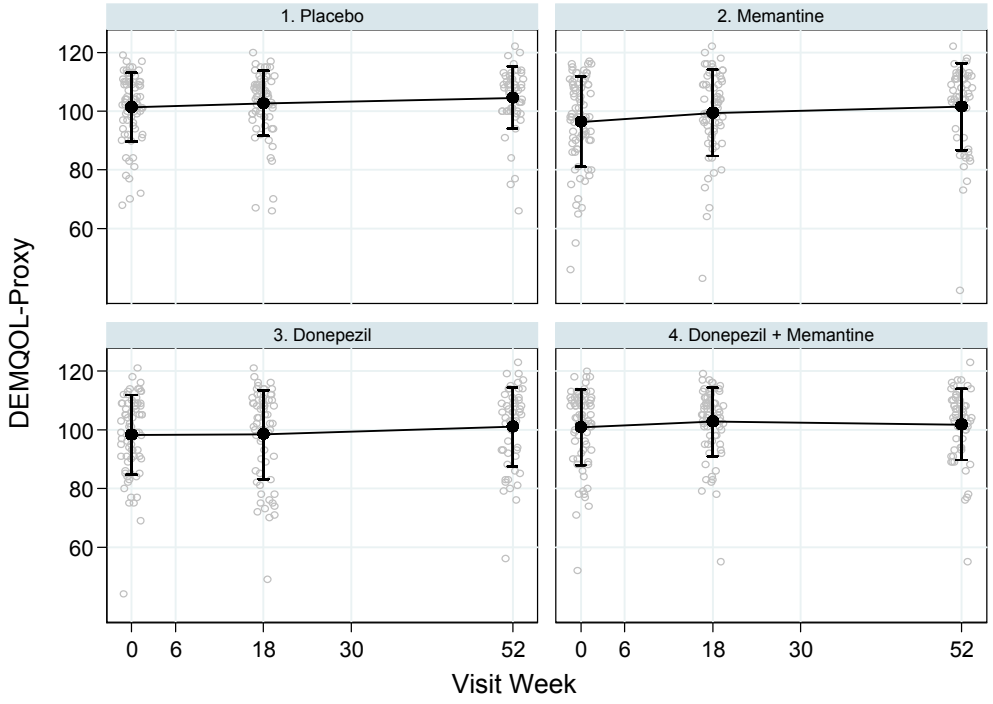


Table 7.10: DEMQOL-Proxy by visit and treatment arm

Median (IQR)	Placebo Donepezil		Donepezil		Overall
	Placebo Memantine	Memantine	Placebo Memantine	Memantine	
Total Randomised	**73**	**76**	**73**	**73**	**295**
Baseline Visit	101.4 (11.7)	96.5 (15.3)	98.3 (13.5)	100.9 (12.9)	99.3 (13.5)
18 Week Visit	102.7 (11.1)	99.5 (14.8)	98.5 (15.1)	102.8 (11.7)	100.9 (13.3)
52 Week Visit	104.7 (10.6)	101.6 (14.9)	101.0 (13.4)	101.9 (12.1)	102.3 (12.8)

8. Primary analysis of Primary Outcomes

The primary analyses of the effect of Donepezil and Memantine on BADLS and SMMSE will be analysed using multilevel modelling repeated measures (MMRM) regression methods, adjusted for baseline scores and minimisation factors (centre, duration of donepezil prior to randomisation, baseline sMMSE and age).
To allow for non-linear trends over time, the scheduled visit week is used in the regression model rather than the real visit date. The treatment by time interaction term is included as a fixed effect to allow for the differences between treatments to vary over time.
Considering the factorial nature of the trial, the same MMRM model is also fitted combining arms; first comparing donepezil with placebo, and secondly comparing memantine with placebo.

Different random effect structures were fitted and the models compared using the Akaike Information Criterion (AIC). The following random effects structures were fitted:

- patient-specific intercept only,
- random intercept and random effects for each visit with the
  - identity covariance structure,
  - independent covariance structure,
  - exchangeable covariance structure,
  - unstructured covariance structure.

In each of the following models, the fifth random effects structure (random intercept and random effects for each visit with the unstructured covariance structure) resulted in the lowest AIC and was therefore selected as the model that best fits the data.

All the analyses in section 8 are on an intention-to-treat population. All patients randomised and having taken at least one dose of treatment are included in these analyses.

Table 8.1: Estimated difference in sMMSE from placebo by visit

	Difference in sMMSE with 95% confidence interval*			
	Visit 2 (Week 6, 42 days)	**Visit 3 (Week 18, 126 days)**	**Visit 4 (Week 30, 210 days)**	**Visit 5 (Week 52, 364 days)**
Placebo	–	–	–	–
Memantine	1.3 (0.3, 2.3)	2.3 (1.2, 3.4)	1.6 (0.5, 2.8)	1.3 (-0.1, 2.6)
Donepezil	1.3 (0.4, 2.3)	2.8 (1.7, 3.9)	2.8 (1.6, 3.9)	2.4 (1.1, 3.8)
Donepezil + Memantine	2.1 (1.1, 3.1)	3.5 (2.4, 4.6)	4.2 (3.0, 5.3)	2.7 (1.4, 4.0)
Test for Interaction between Donepezil and Memantine	0.4175	0.0456	0.756	0.272
Total patients with non-missing sMMSE score	**284**	**263**	**246**	**217**

Global test for interaction between donepezil and memantine across all weeks: p = 0.177

*This is an estimate of the average difference in sMMSE at the specified visit compared to the score in the placebo arm from the MMRM analysis.

Figure 8.2: Estimated difference in sMMSE from placebo by visit

The figure below is a graphical representation of the results of the MMRM analysis showing model-based estimates with 95% confidence intervals.

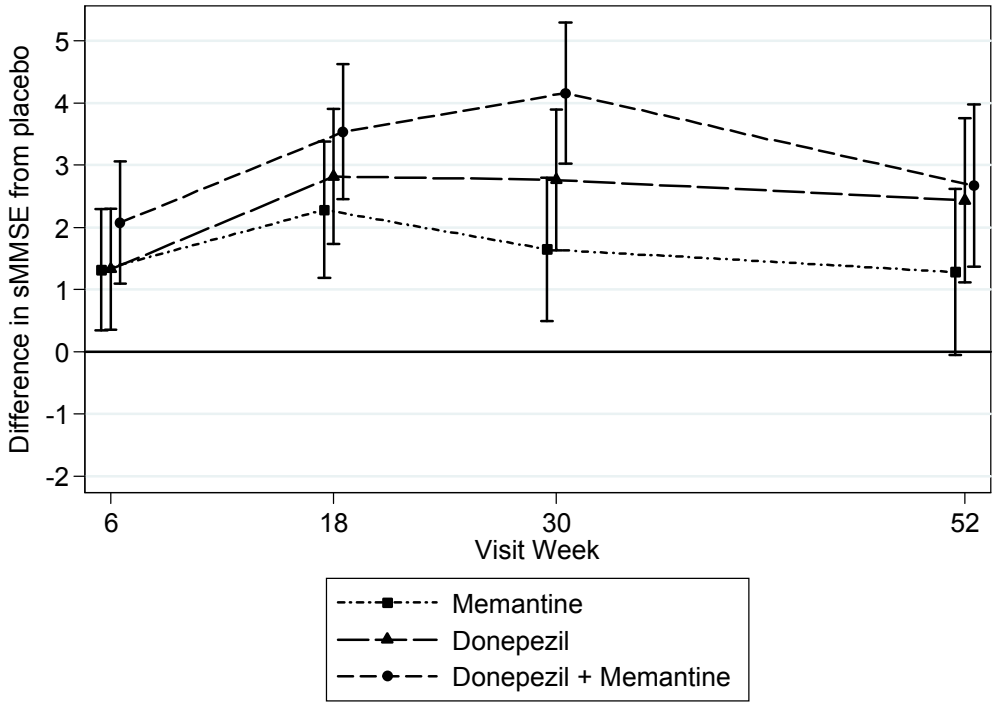


Table 8.3: Estimated pooled difference in sMMSE at the margins comparing active with placebo by visit

	Difference in sMMSE with 95% confidence interval			
	Visit 2 (Week 6, 42 days)	**Visit 3 (Week 18, 126 days)**	**Visit 4 (Week 30, 210 days)**	**Visit 5 (Week 52, 364 days)**
Donepezil vs. Placebo	1.0 (0.4, 1.7)	2.0 (1.3, 2.8)	2.6 (1.8, 3.4)	1.9 (1.0, 2.8)
Memantine vs. Placebo	1.0 (0.3, 1.7)	1.5 (0.7, 2.3)	1.5 (0.7, 2.3)	0.7 (-0.2, 1.7)

Figure 8.4: Estimated pooled difference in sMMSE at the margins comparing active with placebo by visit

The figure below is a graphical representation of the results of the MMRM analysis showing model-based estimates with 95% confidence intervals. The graphs correspond to the comparison of donepezil versus placebo (on the left) and memantine versus placebo (on the right).

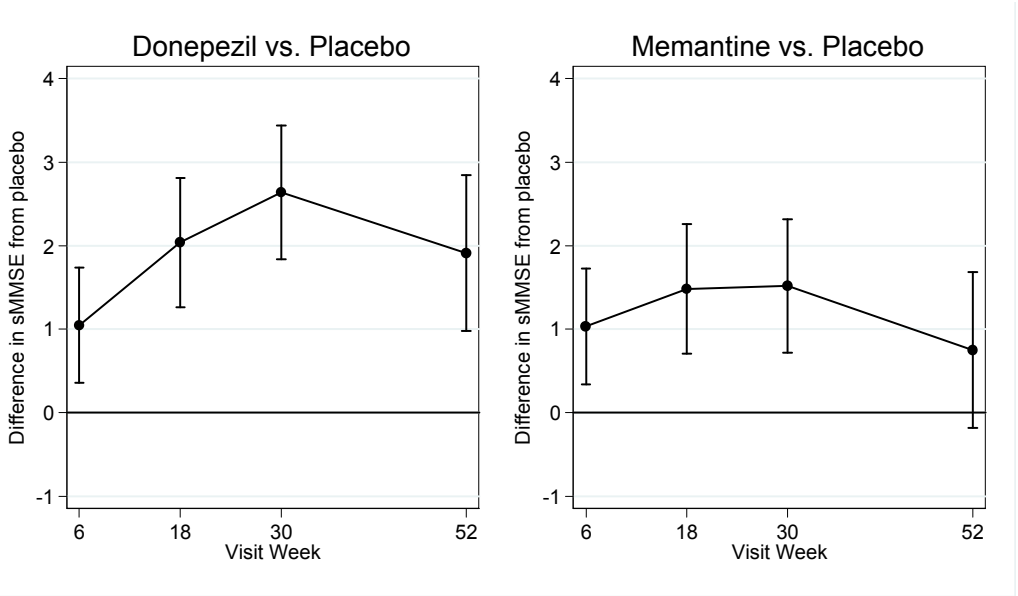


Table 8.5: Estimated mean sMMSE by visit and treatment arm

	Mean sMMSE with 95% confidence interval			
	Visit 2 (Week 6, 42 days)	Visit 3 (Week 18, 126 days)	Visit 4 (Week 30, 210 days)	Visit 5 (Week 52, 364 days)
Placebo	7.7 (7.0, 8.4)	5.2 (4.5, 6.0)	4.3 (3.5, 5.1)	2.8 (1.9, 3.8)
Memantine	9.0 (8.3, 9.7)	7.5 (6.7, 8.3)	5.9 (5.1, 6.7)	4.1 (3.2, 5.1)
Donepezil	9.0 (8.4, 9.7)	8.1 (7.3, 8.8)	7.0 (6.2, 7.8)	5.3 (4.3, 6.2)
Donepezil + Memantine	9.8 (9.1, 10.5)	8.8 (8.0, 9.5)	8.4 (7.6, 9.2)	5.5 (4.6, 6.4)

Figure 8.6: Estimated mean sMMSE by visit and treatment arm

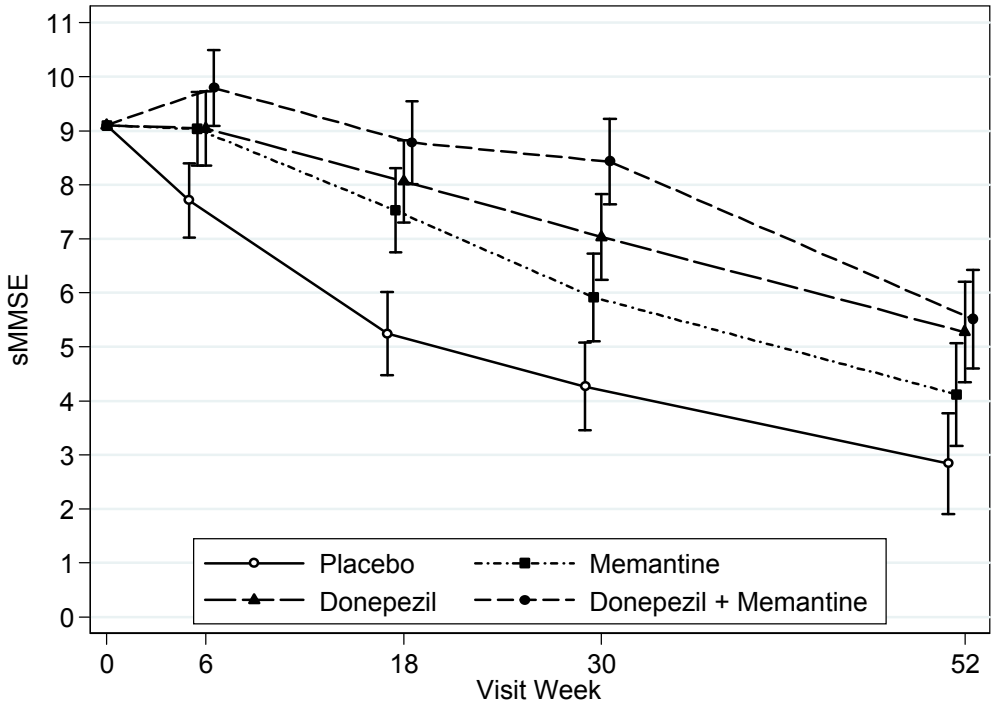


Table 8.7: Estimated pooled mean sMMSE at the margins by visit

	Difference in sMMSE with 95% confidence interval			
	Visit 2 (Week 6, 42 days)	**Visit 3 (Week 18, 126 days)**	**Visit 4 (Week 30, 210 days)**	**Visit 5 (Week 52, 364 days)**
Placebo Donepezil	8.4 (7.9, 8.9)	6.4 (5.8, 6.9)	5.1 (4.5, 5.7)	3.5 (2.8, 4.1)
Active Donepezil	9.4 (8.9, 9.9)	8.4 (7.9, 9.0)	7.7 (7.2, 8.3)	5.4 (4.7, 6.0)
Placebo Memantine	8.4 (7.9, 8.9)	6.7 (6.1, 7.2)	5.7 (5.1, 6.2)	4.1 (3.4, 4.7)
Active Memantine	9.4 (8.9, 9.9)	8.2 (7.6, 8.7)	7.2 (6.6, 7.8)	4.8 (4.2, 5.5)

Figure 8.8: Estimated pooled mean sMMSE at the margins by visit

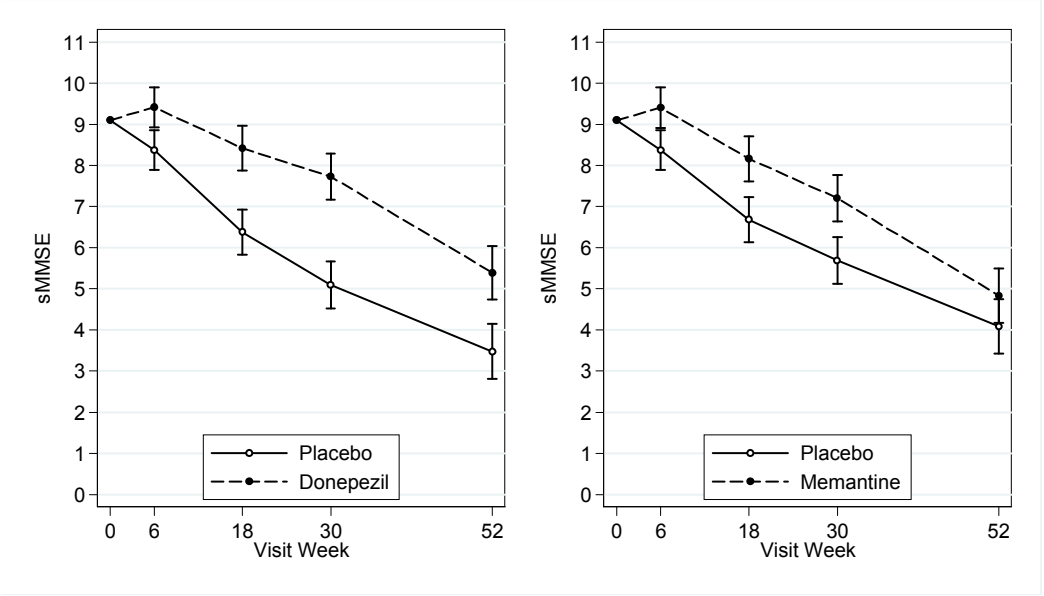


Table 8.9: Estimated difference in BADLS from placebo by visit

	Difference in BADLS with 95% confidence interval*			
	Visit 2 (Week 6, 42 days)	**Visit 3 (Week 18, 126 days)**	**Visit 4 (Week 30, 210 days)**	**Visit 5 (Week 52, 364 days)**
Placebo	–	–	–	–
Memantine	-1.8 (-3.5, -0.0)	-3.3 (-5.6, -1.0)	-3.0 (-5.6, -0.3)	-2.8 (-5.8, 0.1)
Donepezil	-2.5 (-4.2, -0.8)	-5.3 (-7.6, -3.0)	-5.0 (-7.6, -2.4)	-3.7 (-6.7, -0.8)
Donepezil + Memantine	-2.1 (-3.8, -0.3)	-6.1 (-8.4, -3.8)	-5.8 (-8.4, -3.2)	-4.8 (-7.7, -1.9)
Test for Interaction between Donepezil and Memantine	0.0765	0.1234	0.2514	0.4089
Total patients with non-missing BADLS score	**284**	**263**	**246**	**218**

Global test for interaction between donepezil and memantine across all weeks: p = 0.425

*This is an estimate of the average difference in BADLS at the specified visit compared to the score in the placebo arm from the MMRM analysis.

Figure 8.10: Estimated difference in BADLS from placebo by visit

The figure below is a graphical representation of the results of the MMRM analysis showing model-based estimates with 95% confidence intervals.

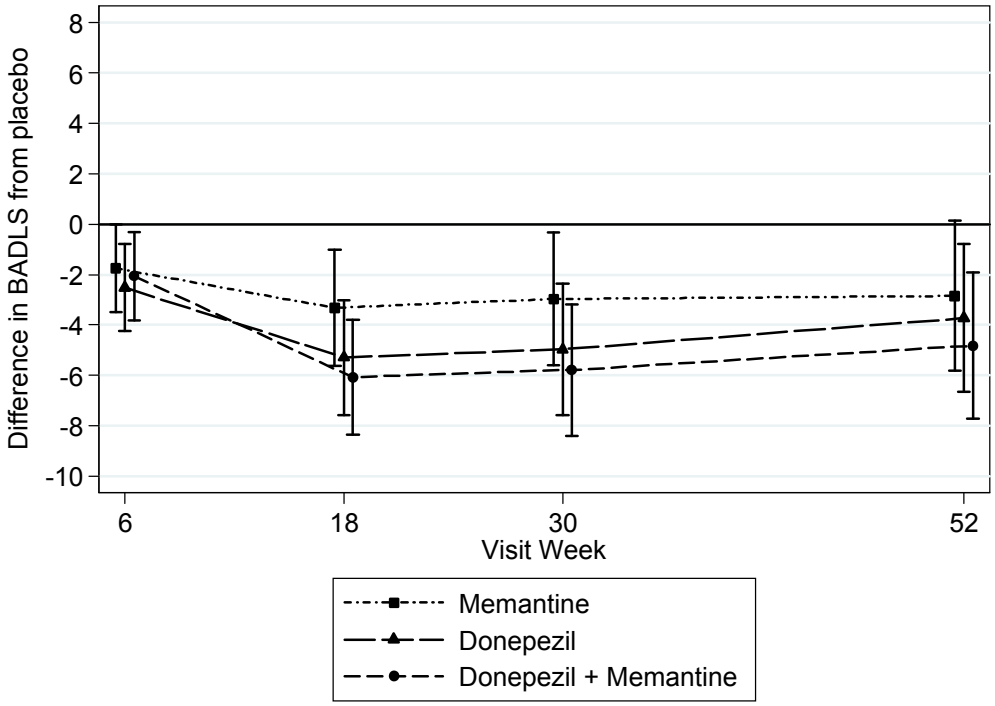


Table 8.11: Estimated pooled difference in BADLS at the margins comparing active with placebo by visit

	Difference in BADLS with 95% confidence interval			
	Visit 2 (Week 6, 42 days)	**Visit 3 (Week 18, 126 days)**	**Visit 4 (Week 30, 210 days)**	**Visit 5 (Week 52, 364 days)**
Donepezil vs. Placebo	-1.4 (-2.7, -0.2)	-4.0 (-5.6, -2.4)	-3.9 (-5.7, -2.1)	-2.9 (-4.9, -0.8)
Memantine vs. Placebo	-0.6 (-1.9, 0.6)	-2.0 (-3.7, -0.4)	-1.9 (-3.7, -0.0)	-2.0 (-4.0, 0.1)

Figure 8.12: Estimated pooled difference in BADLS at the margins comparing active with placebo by visit

The figure below is a graphical representation of the results of the MMRM analysis showing model-based estimates with 95% confidence intervals. The graphs correspond to the comparison of donepezil versus placebo (on the left) and memantine versus placebo (on the right).

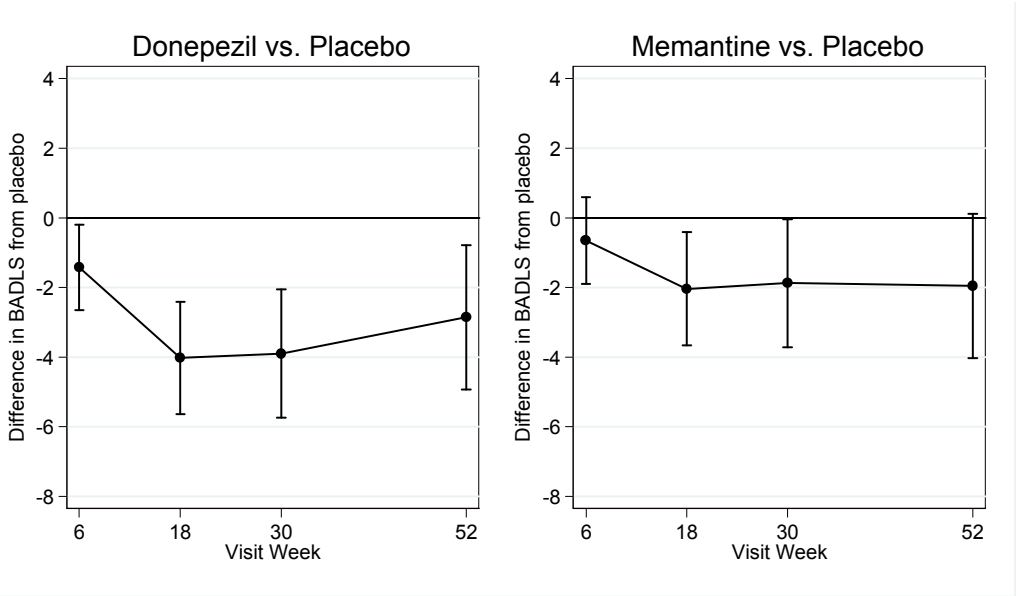


Table 8.13: Estimated mean BADLS by visit and treatment arm

	Mean BADLS with 95% confidence interval			
	Visit 2 (Week 6, 42 days)	Visit 3 (Week 18, 126 days)	Visit 4 (Week 30, 210 days)	Visit 5 (Week 52, 364 days)
Placebo	30.5 (29.2, 31.7)	36.6 (34.9, 38.2)	37.8 (35.9, 39.6)	41.3 (39.2, 43.4)
Memantine	28.7 (27.5, 29.9)	33.3 (31.6, 34.9)	34.8 (32.9, 36.7)	38.5 (36.3, 40.6)
Donepezil	27.9 (26.7, 29.2)	31.3 (29.7, 32.9)	32.8 (31.0, 34.6)	37.6 (35.5, 39.6)
Donepezil + Memantine	28.4 (27.2, 29.7)	30.5 (28.9, 32.1)	32.0 (30.2, 33.8)	36.5 (34.4, 38.5)

Figure 8.14: Estimated mean BADLS by visit and treatment arm

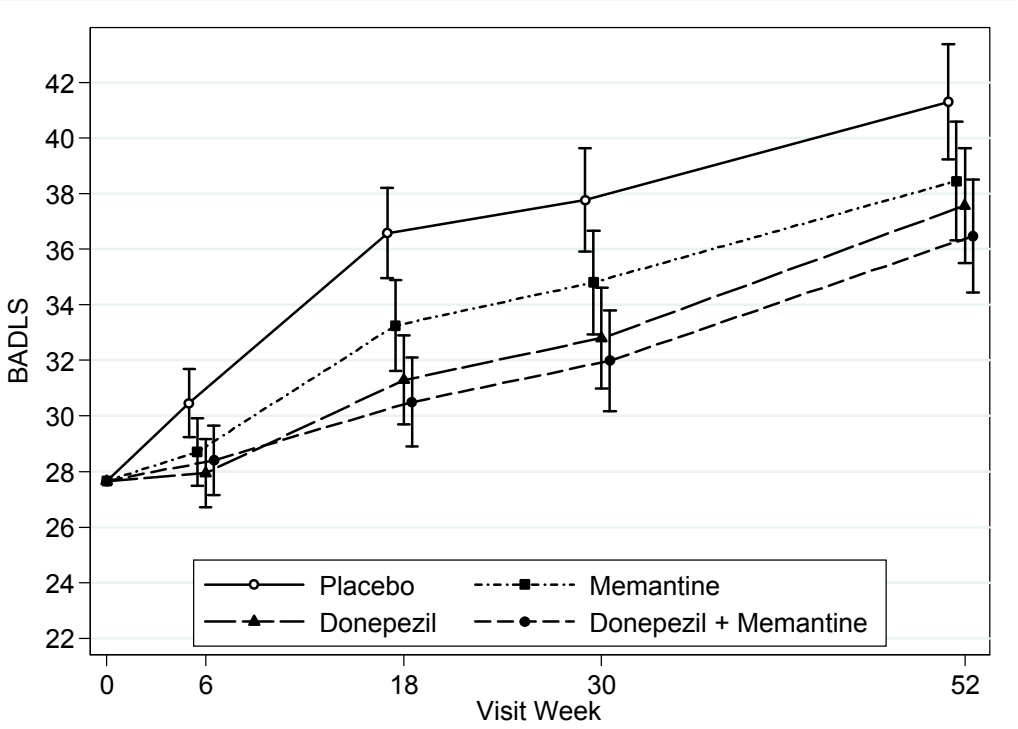
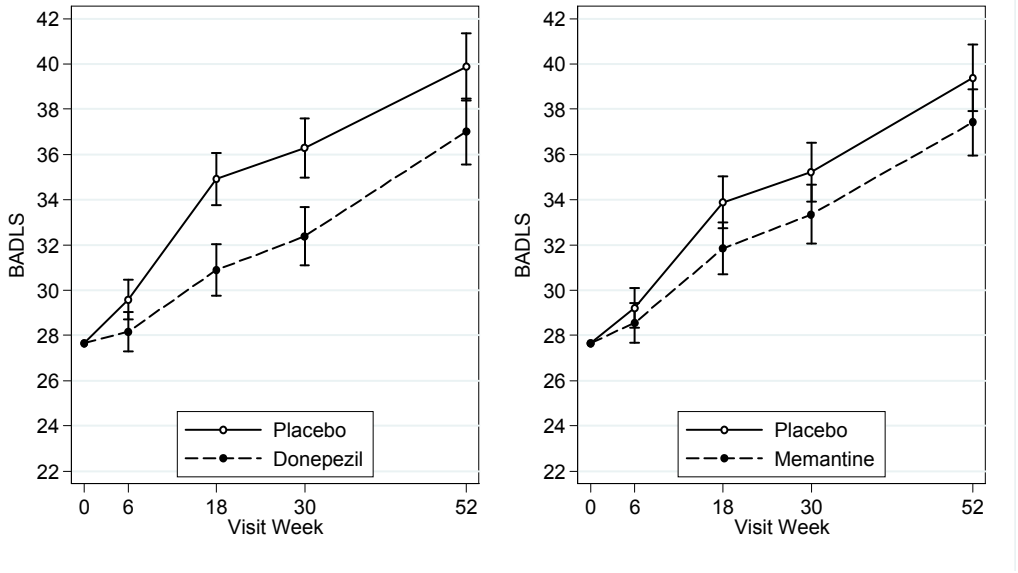


Table 8.15: Estimated pooled mean BADLS at the margins by visit

	Difference in BADLS with 95% confidence interval			
	Visit 2 (Week 6, 42 days)	**Visit 3 (Week 18, 126 days)**	**Visit 4 (Week 30, 210 days)**	**Visit 5 (Week 52, 364 days)**
Placebo Donepezil	29.6 (28.7, 30.5)	34.9 (33.8, 36.1)	36.3 (35.0, 37.6)	39.9 (38.4, 41.4)
Active Donepezil	28.2 (27.3, 29.0)	30.9 (29.8, 32.0)	32.4 (31.1, 33.7)	37.0 (35.6, 38.5)
Placebo Memantine	29.2 (28.3, 30.1)	33.9 (32.7, 35.0)	35.2 (33.9, 36.5)	39.4 (37.9, 40.8)
Active Memantine	28.6 (27.7, 29.4)	31.8 (30.7, 33.0)	33.3 (32.0, 34.7)	37.4 (36.0, 38.9)

Figure 8.16: Estimated pooled mean BADLS at the margins by visit



9. Secondary sensitivity analyses of the primary outcomes

Table 9.1: Definition of the per protocol population

	Placebo Donepezil		Donepezil		Total
	Placebo Memantine	Memantine	Placebo Memantine	Memantine	
Randomised	**73**	**76**	**73**	**73**	**295**
Didn't start treatment	1	2	0	1	**4**
Total in ITT Analysis	**72**	**74**	**73**	**72**	**291**
Less than 70% adherence	43	31	21	19	**114**
Taken open label donepezil or memantine during trial	0	1	0	1	**2**
Randomised in error	0	0	2	1	**3**
Total in Per Protocol Analysis	**29**	**42**	**50**	**51**	**172**

Table 9.2: Distribution of actual days of visit from randomisation

Median days (IQR)	Placebo Donepezil		Donepezil		Total
	Placebo Memantine	Memantine	Placebo Memantine	Memantine	
Total Randomised	**73**	**76**	**73**	**73**	**295**
Screening Visit	-1 (-2-0)	-1 (-2-0)	0 (-1-0)	-1 (-4-0)	**-1 (-2-0)**
Baseline Visit	-1 (-2-0)	-1 (-1-0)	0 (-1-0)	-1 (-3-0)	**-1 (-2-0)**
6 Week Visit (42 days)	43 (42-48)	43 (42-48)	44 (42-47)	43 (42-46)	**43 (42-47)**
18 Week Visit (126 days)	127 (126-130)	127 (126-130)	127 (126-131)	126 (125-130)	**127 (126-130)**
30 Week Visit (210 days)	212 (210-215)	212 (209-216)	212 (210-216)	211 (209-215)	**211 (209-216)**
52 Week Visit (364 days)	365 (364-368)	365 (363-370)	366 (364-368)	364 (363-368)	**365 (364-368)**

Table 9.3: Summary of follow-up visits eligible for per protocol analysis

The protocol states that assessments should be carried out within 7 days either side of the designated follow up date (calculated from randomisation) where possible. The exception to this is the week 6 assessment. As this is to ascertain any drug withdrawal effects, the assessment cannot take place prior to week 6 but may take place up to 7 days afterwards.

Assessment data from visits outside these visit windows are excluded from the per protocol analysis, as are visits after discontinuation of treatment.

Tables 9.4 to 9.11 show the results of the MMRM analysis of the primary outcomes on the per protocol sub-population.

		Placebo Donepezil		Donepezil		Total
		Placebo Memantine	Memantine	Placebo Memantine	Memantine	
Total Randomised		**73**	**76**	**73**	**73**	**295**
6 Week Visit	**Total visits**	**71**	**73**	**72**	**68**	**284**
	Outside window	16	18	12	16	**62**
	Post-discontinuation	3	4	2	1	**10**
	Per Protocol	**52**	**51**	**58**	**51**	**212**
18 Week Visit	**Total visits**	**65**	**64**	**67**	**67**	**263**
	Outside window	7	6	7	8	**28**
	Post-discontinuation	21	9	4	4	**38**
	Per Protocol	**37**	**49**	**56**	**55**	**197**
30 Week Visit	**Total visits**	**60**	**60**	**63**	**63**	**246**
	Outside window	7	7	11	14	**39**
	Post-discontinuation	25	13	8	5	**51**
	Per Protocol	**28**	**40**	**44**	**44**	**156**
52 Week Visit	**Total visits**	**55**	**51**	**54**	**58**	**218**
	Outside window	6	6	5	6	**23**
	Post-discontinuation	26	11	13	7	**57**
	Per Protocol	**23**	**34**	**36**	**45**	**138**

Table 9.4: Per protocol analysis: Estimated difference in sMMSE from placebo by visit

	Difference in sMMSE with 95% confidence interval*			
	Visit 2 (Week 6, 42 days)	**Visit 3 (Week 18, 126 days)**	**Visit 4 (Week 30, 210 days)**	**Visit 5 (Week 52, 364 days)**
Placebo	–	–	–	–
Memantine	0.8 (-0.8, 2.4)	2.6 (1.0, 4.1)	2.3 (0.8, 3.9)	2.0 (0.2, 3.9)
Donepezil	0.8 (-0.7, 2.3)	3.3 (1.8, 4.7)	3.2 (1.7, 4.7)	3.1 (1.3, 5.0)
Donepezil + Memantine	1.6 (0.1, 3.2)	3.6 (2.1, 5.1)	3.8 (2.2, 5.3)	3.2 (1.4, 5.0)
Test for Interaction between Donepezil and Memantine	0.966	0.0261	0.0777	0.1186
Total patients with non-missing sMMSE score	**134**	**153**	**143**	**135**

Global test for interaction between donepezil and memantine across all weeks: p = 0.206

*This is an estimate of the average difference in sMMSE at the specified visit compared to the score in the placebo arm from the MMRM analysis.

Figure 9.5: Per protocol analysis: Estimated difference in sMMSE from placebo by visit

The figure below is a graphical representation of the results of the MMRM analysis showing model-based estimates with 95% confidence intervals.

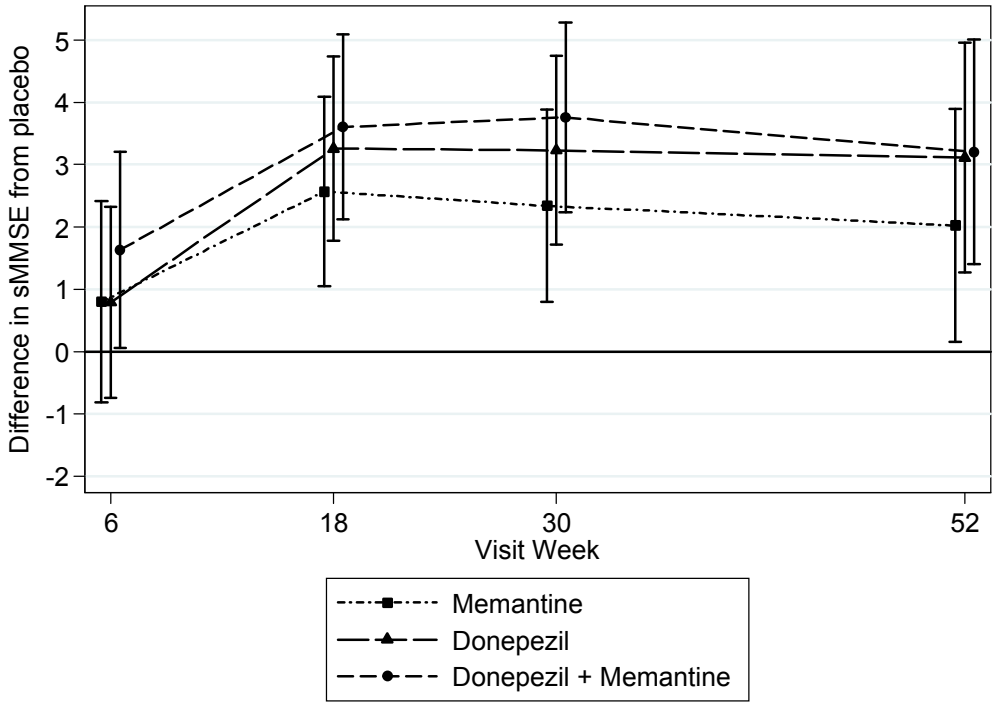


Table 9.6: Per protocol analysis: Estimated pooled difference in sMMSE at the margins comparing active with placebo by visit

	Difference in sMMSE with 95% confidence interval			
	Visit 2 (Week 6, 42 days)	**Visit 3 (Week 18, 126 days)**	**Visit 4 (Week 30, 210 days)**	**Visit 5 (Week 52, 364 days)**
Donepezil vs. Placebo	0.8 (-0.2, 1.8)	2.0 (1.0, 3.0)	2.2 (1.2, 3.2)	2.0 (0.8, 3.2)
Memantine vs. Placebo	0.8 (-0.2, 1.9)	1.3 (0.3, 2.2)	1.3 (0.3, 2.3)	0.9 (-0.3, 2.1)

Figure 9.7: Per protocol analysis: Estimated pooled difference in sMMSE at the margins comparing active with placebo by visit

The figure below is a graphical representation of the results of the MMRM analysis showing model-based estimates with 95% confidence intervals. The graphs correspond to the comparison of donepezil versus placebo (on the left) and memantine versus placebo (on the right).

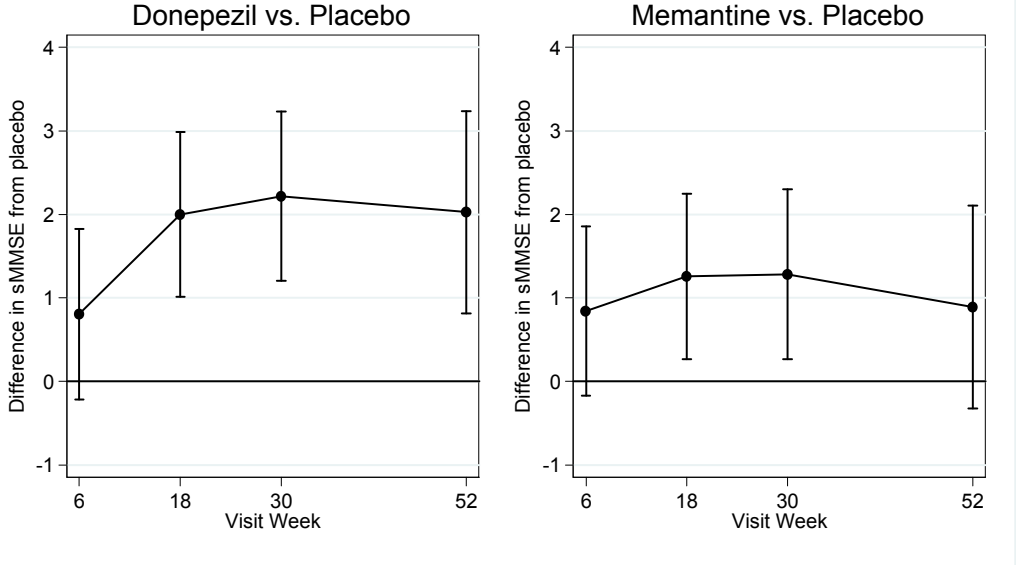


Table 9.8: Per protocol analysis: Estimated difference in BADLS from placebo by visit

	Difference in BADLS with 95% confidence interval*			
	Visit 2 (Week 6, 42 days)	**Visit 3 (Week 18, 126 days)**	**Visit 4 (Week 30, 210 days)**	**Visit 5 (Week 52, 364 days)**
Placebo	–	–	–	–
Memantine	-1.0 (-3.6, 1.7)	-2.7 (-5.7, 0.4)	-3.4 (-6.7, -0.1)	-4.1 (-7.6, -0.6)
Donepezil	-0.6 (-3.2, 1.9)	-4.4 (-7.3, -1.4)	-4.7 (-7.9, -1.5)	-4.7 (-8.2, -1.3)
Donepezil + Memantine	-0.2 (-2.9, 2.4)	-4.6 (-7.6, -1.6)	-4.5 (-7.7, -1.3)	-4.0 (-7.4, -0.7)
Test for Interaction between Donepezil and Memantine	0.4341	0.22	0.0993	0.0371
Total patients with non-missing BADLS score	**134**	**153**	**143**	**135**

Global test for interaction between donepezil and memantine across all weeks: p = 0.309

*This is an estimate of the average difference in BADLS at the specified visit compared to the score in the placebo arm from the MMRM analysis.

Figure 9.9: Per protocol analysis: Estimated difference in BADLS from placebo by visit

The figure below is a graphical representation of the results of the MMRM analysis showing model-based estimates with 95% confidence intervals.

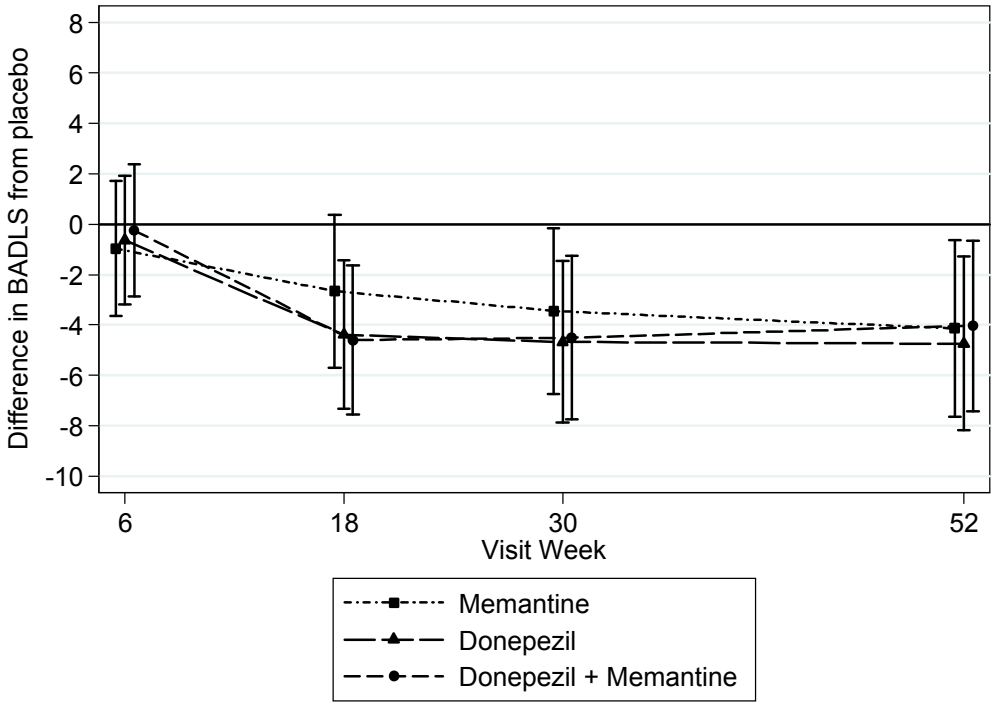


Table 9.10: Per protocol analysis: Estimated pooled difference in BADLS at the margins comparing active with placebo by visit

	Difference in BADLS with 95% confidence interval			
	Visit 2 (Week 6, 42 days)	**Visit 3 (Week 18, 126 days)**	**Visit 4 (Week 30, 210 days)**	**Visit 5 (Week 52, 364 days)**
Donepezil vs. Placebo	0.1 (-1.6, 1.8)	-3.0 (-5.0, -1.1)	-2.7 (-4.8, -0.5)	-2.0 (-4.3, 0.3)
Memantine vs. Placebo	-0.1 (-1.8, 1.5)	-1.2 (-3.2, 0.7)	-1.3 (-3.5, 0.8)	-1.3 (-3.6, 1.0)

Figure 9.11: Per protocol analysis: Estimated pooled difference in BADLS at the margins comparing active with placebo by visit

The figure below is a graphical representation of the results of the MMRM analysis showing model-based estimates with 95% confidence intervals. The graphs correspond to the comparison of donepezil versus placebo (on the left) and memantine versus placebo (on the right).

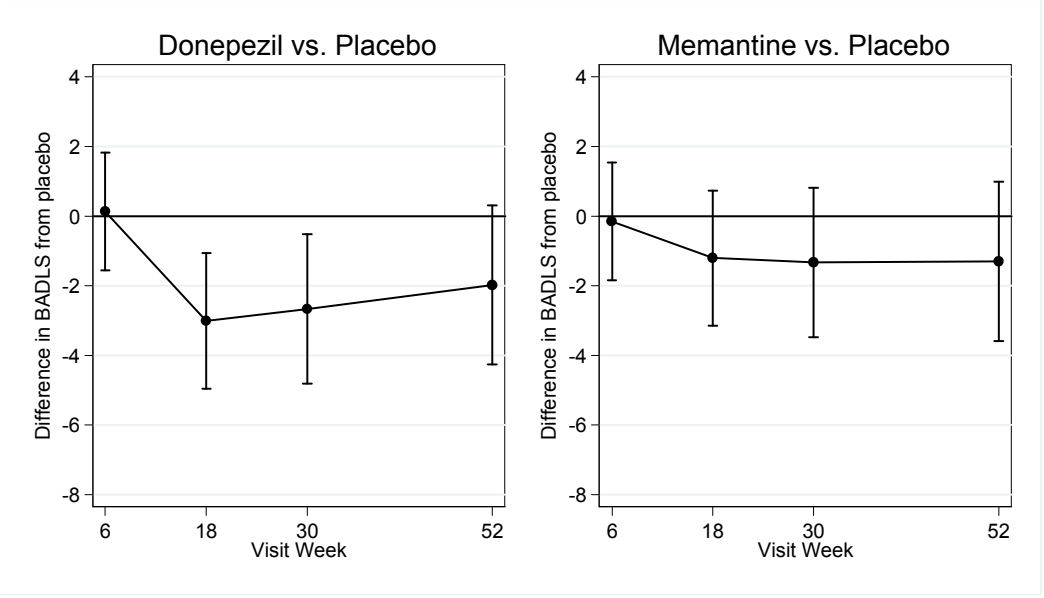


Table 9.12: Two-group t-test of change from baseline of all available sMMSE results comparing each treatment with placebo

Mean difference (δ) in sMMSE change from baseline and p-value	Visit 2 (Week 6, 42 days)		Visit 3 (Week 18, 126 days)		Visit 4 (Week 30, 210 days)		Visit 5 (Week 52, 364 days)	
	δ	p-value	δ	p-value	δ	p-value	δ	p-value
Memantine	1.44	0.0075	2.36	<0.0001	1.58	0.0098	1.36	0.0499
Donepezil	1.14	0.0308	2.64	<0.0001	2.7	<0.0001	2.09	0.0028
Donepezil + Memantine	2.00	0.0002	3.40	<0.0001	3.87	<0.0001	2.35	0.0004

Table 9.13: Two-group t-test of change from baseline of all available BADLS results comparing each treatment with placebo

Mean difference (δ) in sMMSE change from baseline and p-value	Visit 2 (Week 6, 42 days)		Visit 3 (Week 18, 126 days)		Visit 4 (Week 30, 210 days)		Visit 5 (Week 52, 364 days)	
	δ	p-value	δ	p-value	δ	p-value	δ	p-value
Memantine	-1.61	0.1367	-3.52	0.0072	-2.73	0.0831	-3.12	0.0637
Donepezil	-2.23	0.016	-5.15	<0.0001	-4.67	0.0016	-3.38	0.046
Donepezil + Memantine	-1.82	0.0696	-5.82	<0.0001	-5.48	0.0001	-4.46	0.0073

Table 9.14: Estimated difference in sMMSE from placebo by visit using multiple imputation to impute missing outcomes

	Difference in sMMSE with 95% confidence interval			
	Visit 2 (Week 6, 42 days)	Visit 3 (Week 18, 126 days)	Visit 4 (Week 30, 210 days)	Visit 5 (Week 52, 364 days)
Placebo	–	–	–	–
Memantine	1.4 (0.4, 2.3)	2.0 (0.9, 3.1)	1.4 (0.2, 2.6)	1.4 (0.1, 2.6)
Donepezil	1.3 (0.3, 2.3)	2.7 (1.6, 3.9)	2.7 (1.5, 3.8)	2.2 (1.1, 3.3)
Donepezil + Memantine	2.0 (1.0, 3.0)	3.3 (2.2, 4.4)	3.7 (2.5, 4.9)	2.5 (1.4, 3.7)

Table 9.15: Estimated pooled difference in sMMSE at the margins comparing active with placebo by visit using multiple imputation to impute missing outcomes

	Difference in sMMSE with 95% confidence interval			
	Visit 2 (Week 6, 42 days)	Visit 3 (Week 18, 126 days)	Visit 4 (Week 30, 210 days)	Visit 5 (Week 52, 364 days)
Donepezil vs. Placebo	1.0 (0.3,1.7)	2.0 (1.2,2.8)	2.5 (1.7,3.3)	1.7 (0.9,2.5)
Memantine vs. Placebo	1.0 (0.3,1.7)	1.3 (0.5,2.1)	1.2 (0.4,2.1)	0.8 (0.0,1.7)

Table 9.16: Estimated difference in BADLS from placebo by visit using multiple imputation to impute missing outcomes

	Difference in BADLS with 95% confidence interval			
	Visit 2 (Week 6, 42 days)	Visit 3 (Week 18, 126 days)	Visit 4 (Week 30, 210 days)	Visit 5 (Week 52, 364 days)
Placebo	–	–	–	–
Memantine	-1.8 (-3.6, -0.1)	-3.3 (-5.5, -1.2)	-2.3 (-4.9, 0.4)	-2.8 (-6.0, 0.5)
Donepezil	-2.5 (-4.3, -0.8)	-5.1 (-7.3, -3.0)	-4.5 (-6.9, -2.1)	-3.2 (-5.9, -0.6)
Donepezil + Memantine	-2.2 (-4.1, -0.4)	-5.6 (-7.8, -3.4)	-5.6 (-8.2, -3.0)	-4.2 (-7.2, -1.1)

Table 9.17: Estimated pooled difference in BADLS at the margins comparing active with placebo by visit using multiple imputation to impute missing outcomes

	Difference in BADLS with 95% confidence interval			
	Visit 2 (Week 6, 42 days)	Visit 3 (Week 18, 126 days)	Visit 4 (Week 30, 210 days)	Visit 5 (Week 52, 364 days)
Donepezil vs. Placebo	-1.5 (-2.7, -0.2)	-3.7 (-5.3, -2.2)	-3.9 (-5.8, -2.1)	-2.3 (-4.1, -0.5)
Memantine vs. Placebo	-0.8 (-2.1, 0.5)	-1.9 (-3.4, -0.3)	-1.7 (-3.5, 0.2)	-1.8 (-4.1, 0.4)

10. Analyses of Secondary Endpoints

Table 10.1: Estimated difference in NPI from placebo by visit

	Difference in NPI with 95% confidence interval*			
	Visit 2 (Week 6, 42 days)	**Visit 3 (Week 18, 126 days)**	**Visit 4 (Week 30, 210 days)**	**Visit 5 (Week 52, 364 days)**
Placebo	–	–	–	–
Memantine	-1.6 (-5.3, 2.2)	0.5 (-4.9, 5.9)	-5.0 (-10.2, 0.1)	-6.2 (-12.8, 0.4)
Donepezil	-0.9 (-4.6, 2.7)	-2.5 (-7.8, 2.8)	-2.2 (-7.2, 2.9)	-0.2 (-6.8, 6.3)
Donepezil + Memantine	-5.3 (-9.0, -1.5)	-6.8 (-12.1, -1.4)	-8.3 (-13.4, -3.2)	-5.5 (-11.9, 1.0)
Test for Interaction between Donepezil and Memantine	0.303	0.2158	0.757	0.8339
Total patients with non-missing NPI score	**283**	**262**	**246**	**217**

Global test for interaction between donepezil and memantine across all weeks: p = 0.576

*This is an estimate of the average difference in NPI at the specified visit compared to the score in the placebo arm from the MMRM analysis.

Figure 10.2: Estimated difference in NPI from placebo by visit

The figure below is a graphical representation of the results of the MMRM analysis showing model-based estimates with 95% confidence intervals.

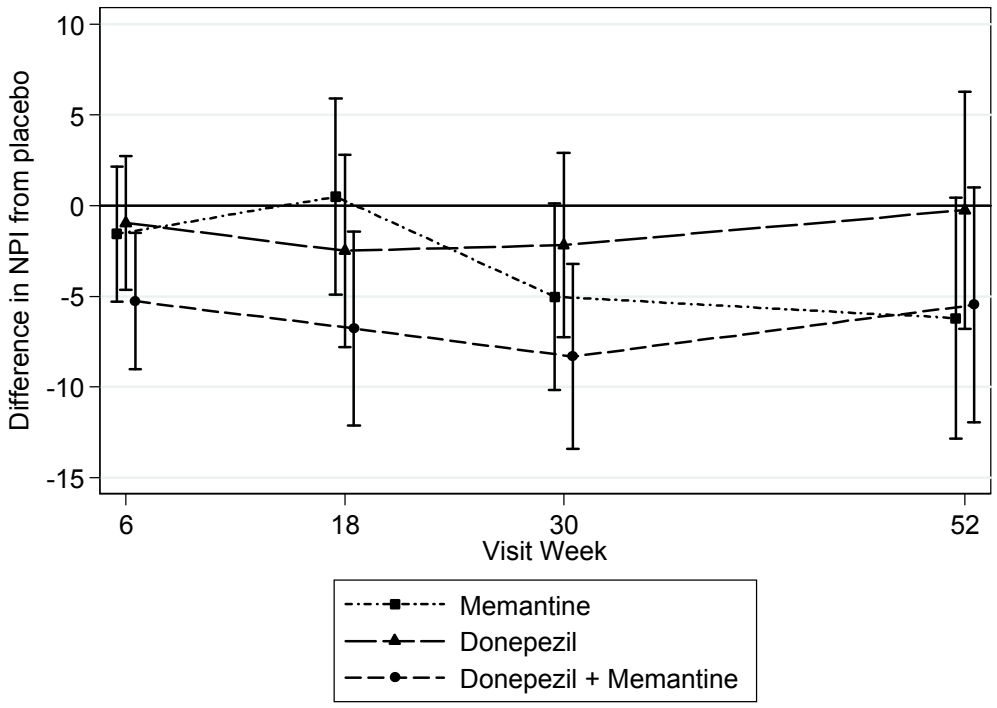


Table 10.3: Estimated pooled difference in NPI at the margins comparing active with placebo by visit

	Difference in NPI with 95% confidence interval			
	Visit 2 (Week 6, 42 days)	**Visit 3 (Week 18, 126 days)**	**Visit 4 (Week 30, 210 days)**	**Visit 5 (Week 52, 364 days)**
Donepezil vs. Placebo	-2.3 (-4.9, 0.3)	-4.9 (-8.6, -1.1)	-2.7 (-6.3, 0.9)	0.3 (-4.4, 4.9)
Memantine vs. Placebo	-2.9 (-5.6, -0.3)	-1.9 (-5.7, 1.9)	-5.6 (-9.2, -2.0)	-5.7 (-10.3, -1.0)

Figure 10.4: Estimated pooled difference in NPI at the margins comparing active with placebo by visit

The figure below is a graphical representation of the results of the MMRM analysis showing model-based estimates with 95% confidence intervals. The graphs correspond to the comparison of donepezil versus placebo (on the left) and memantine versus placebo (on the right).

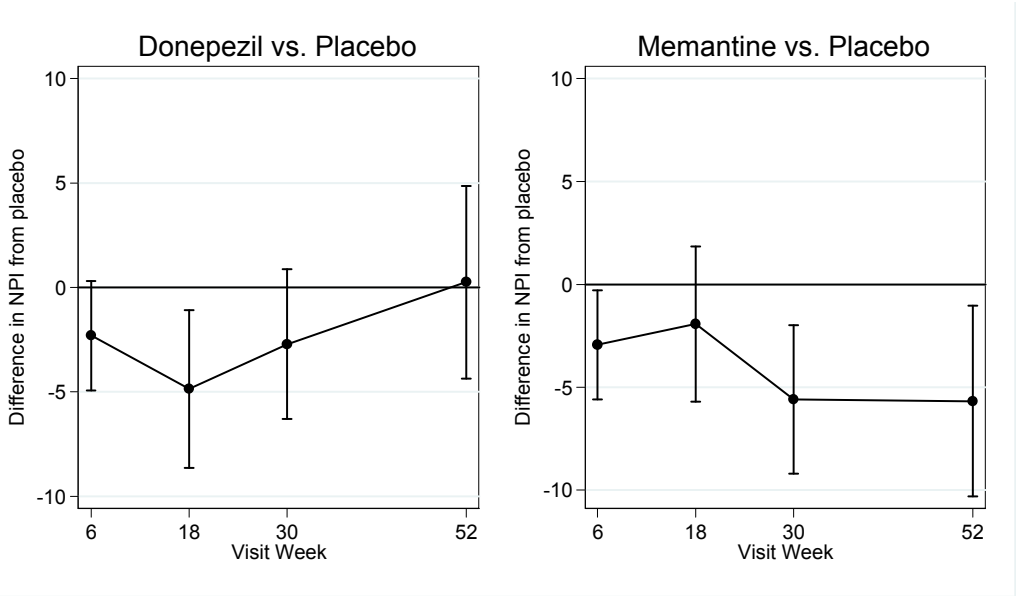


Table 10.5: Estimated mean NPI by visit and treatment arm

	Mean NPI with 95% confidence interval			
	Visit 2 (Week 6, 42 days)	**Visit 3 (Week 18, 126 days)**	**Visit 4 (Week 30, 210 days)**	**Visit 5 (Week 52, 364 days)**
Placebo	22.5 (19.9, 25.2)	26.1 (22.3, 29.9)	27.4 (23.8, 31.1)	28.1 (23.5, 32.7)
Memantine	21.0 (18.3, 23.6)	26.6 (22.8, 30.4)	22.4 (18.8, 26.1)	21.9 (17.2, 26.6)
Donepezil	21.6 (19.0, 24.2)	23.6 (19.9, 27.3)	25.3 (21.7, 28.8)	27.9 (23.2, 32.5)
Donepezil + Memantine	17.3 (14.6, 19.9)	19.3 (15.6, 23.1)	19.1 (15.6, 22.7)	22.6 (18.1, 27.2)

Figure 10.6: Estimated mean NPI by visit and treatment arm

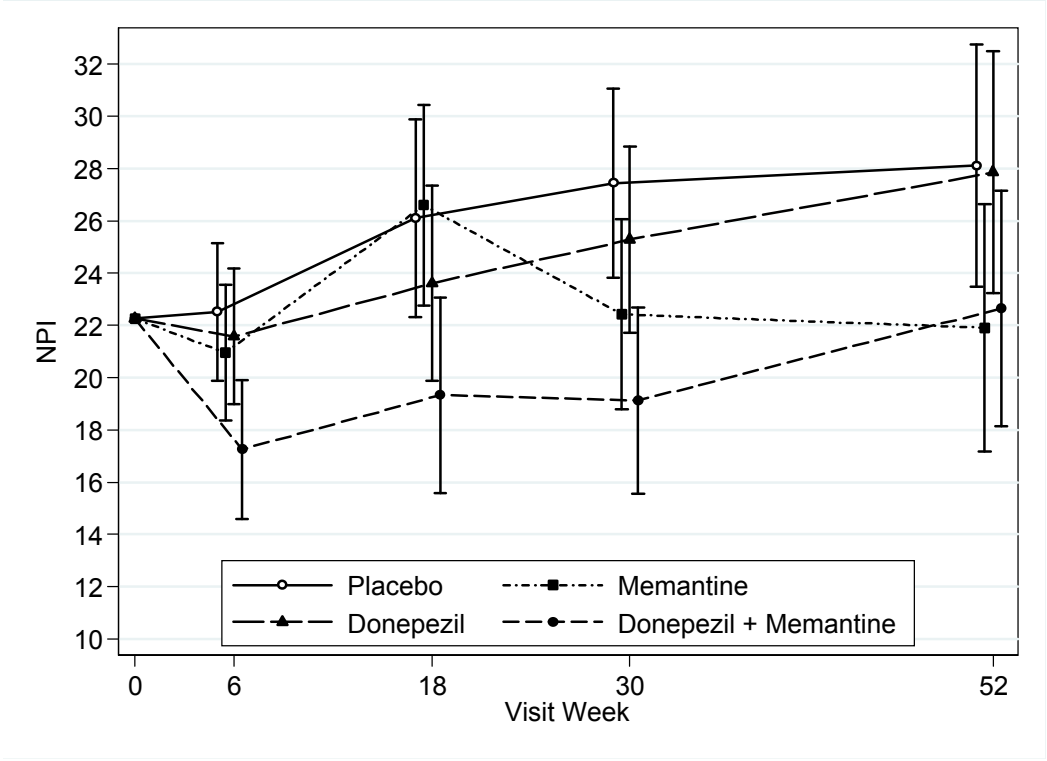


Table 10.7: Estimated pooled mean NPI at the margins by visit

	Difference in NPI with 95% confidence interval			
	Visit 2 (Week 6, 42 days)	**Visit 3 (Week 18, 126 days)**	**Visit 4 (Week 30, 210 days)**	**Visit 5 (Week 52, 364 days)**
Placebo Donepezil	21.7 (19.9, 23.6)	26.3 (23.7, 29.0)	24.9 (22.4, 27.5)	25.0 (21.7, 28.3)
Active Donepezil	19.4 (17.6, 21.3)	21.5 (18.8, 24.1)	22.2 (19.7, 24.7)	25.3 (22.1, 28.5)
Placebo Memantine	22.1 (20.2, 23.9)	24.8 (22.2, 27.5)	26.3 (23.8, 28.9)	28.0 (24.7, 31.3)
Active Memantine	19.1 (17.3, 21.0)	22.9 (20.2, 25.6)	20.7 (18.2, 23.3)	22.3 (19.1, 25.6)

Figure 10.8: Estimated pooled mean NPI at the margins by visit

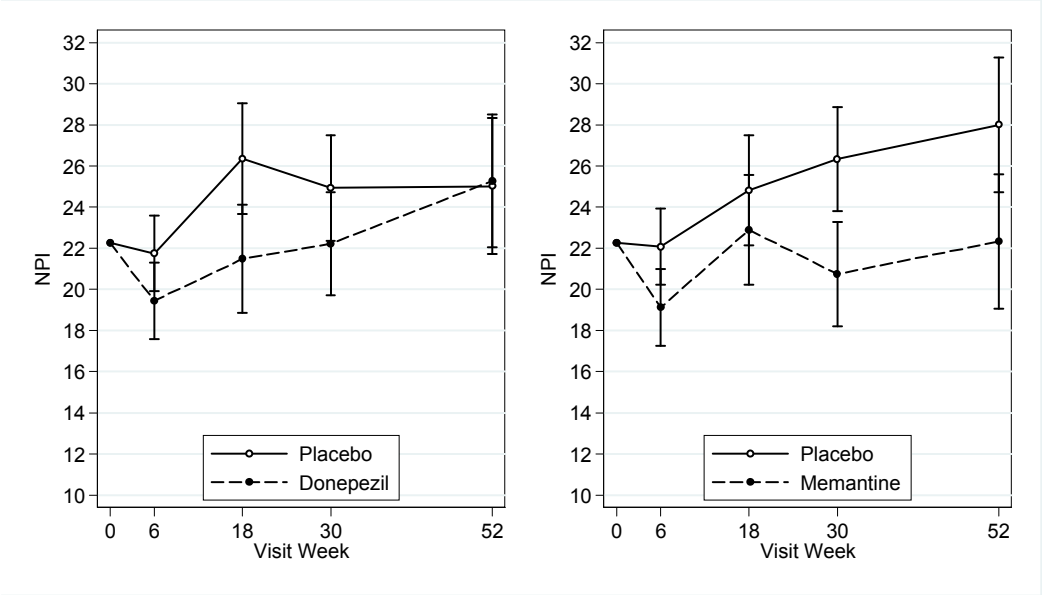


Table 10.9: Estimated difference in DEMQOL-proxy from placebo by visit

	Difference in DEMQOL-proxy with 95% confidence interval*	
	Visit 3 (Week 18, 126 days)	**Visit 5 (Week 52, 364 days)**
Placebo	–	–
Memantine	0.2 (-3.6, 4.1)	1.0 (-3.5, 5.4)
Donepezil	-2.7 (-6.4, 1.1)	-1.9 (-6.3, 2.4)
Donepezil + Memantine	0.8 (-2.9, 4.5)	-1.9 (-6.2, 2.3)
Test for Interaction between Donepezil and Memantine	0.2363	0.7653
Total patients with non-missing DEMQOL-proxy score	**263**	**218**

Global test for interaction between donepezil and memantine across all weeks: p = 0.3197

*This is an estimate of the average difference in DEMQOL-proxy at the specified visit compared to the score in the placebo arm from the MMRM analysis.

Figure 10.10: Estimated difference in DEMQOL-proxy from placebo by visit

The figure below is a graphical representation of the results of the MMRM analysis showing model-based estimates with 95% confidence intervals.

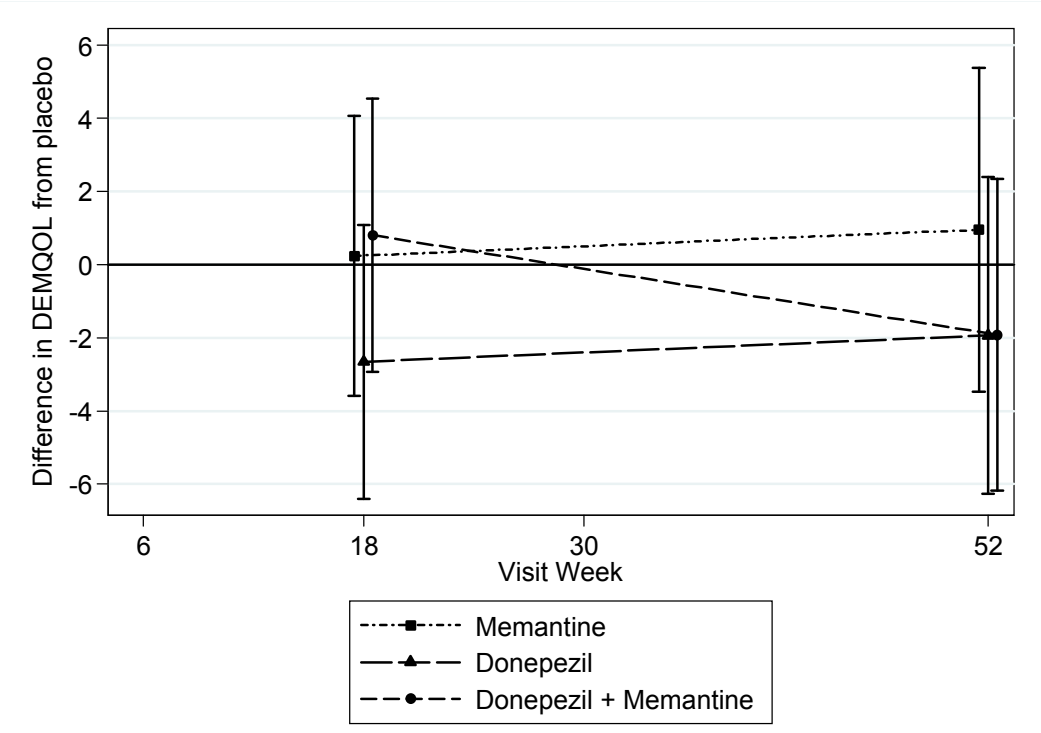


Table 10.11: Estimated pooled difference in DEMQOL-proxy at the margins comparing active with placebo by visit

	Difference in DEMQOL-proxy with 95% confidence interval	
	Visit 3 (Week 18, 126 days)	**Visit 5 (Week 52, 364 days)**
Donepezil vs. Placebo	-1.1 (-3.7, 1.6)	-2.4 (-5.5, 0.7)
Memantine vs. Placebo	1.9 (-0.8, 4.6)	0.5 (-2.6, 3.6)

Figure 10.12: Estimated pooled difference in DEMQOL-proxy at the margins comparing active with placebo by visit

The figure below is a graphical representation of the results of the MMRM analysis showing model-based estimates with 95% confidence intervals. The graphs correspond to the comparison of donepezil versus placebo (on the left) and memantine versus placebo (on the right).

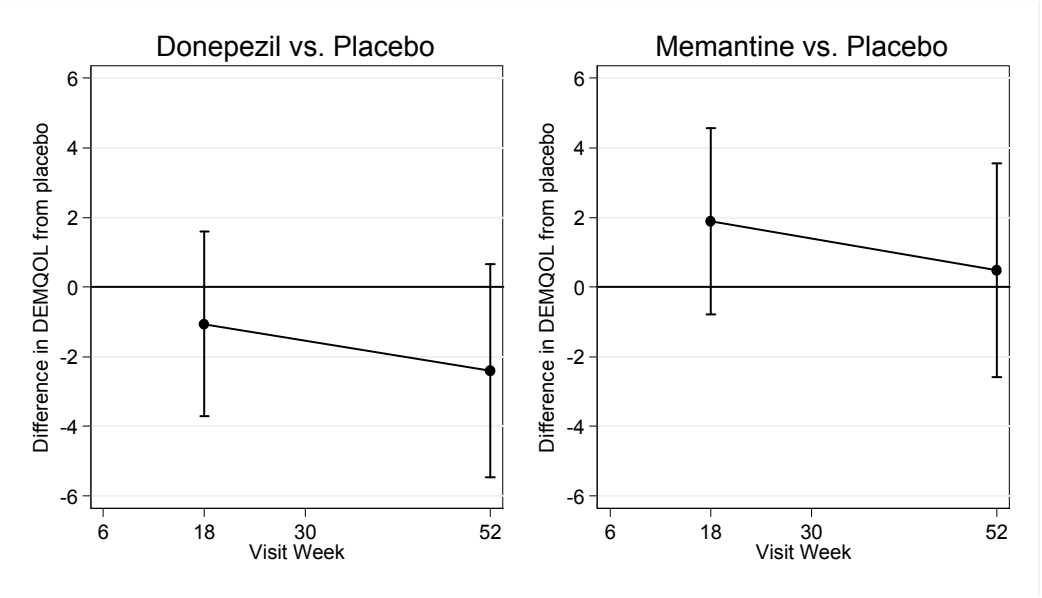


Table 10.13: Estimated mean DEMQOL-proxy by visit and treatment arm

	Difference in DEMQOL-proxy with 95% confidence interval	
	Visit 3 (Week 18, 126 days)	**Visit 5 (Week 52, 364 days)**
Placebo	101.1 (98.4, 103.8)	102.9 (99.8, 105.9)
Memantine	101.3 (98.6, 104.0)	103.8 (100.7, 107.0)
Donepezil	98.4 (95.8, 101.1)	101.0 (97.9, 104.0)
Donepezil + Memantine	101.9 (99.3, 104.5)	101.0 (98.0, 103.9)

Figure 10.14: Estimated mean DEMQOL-proxy by visit and treatment arm

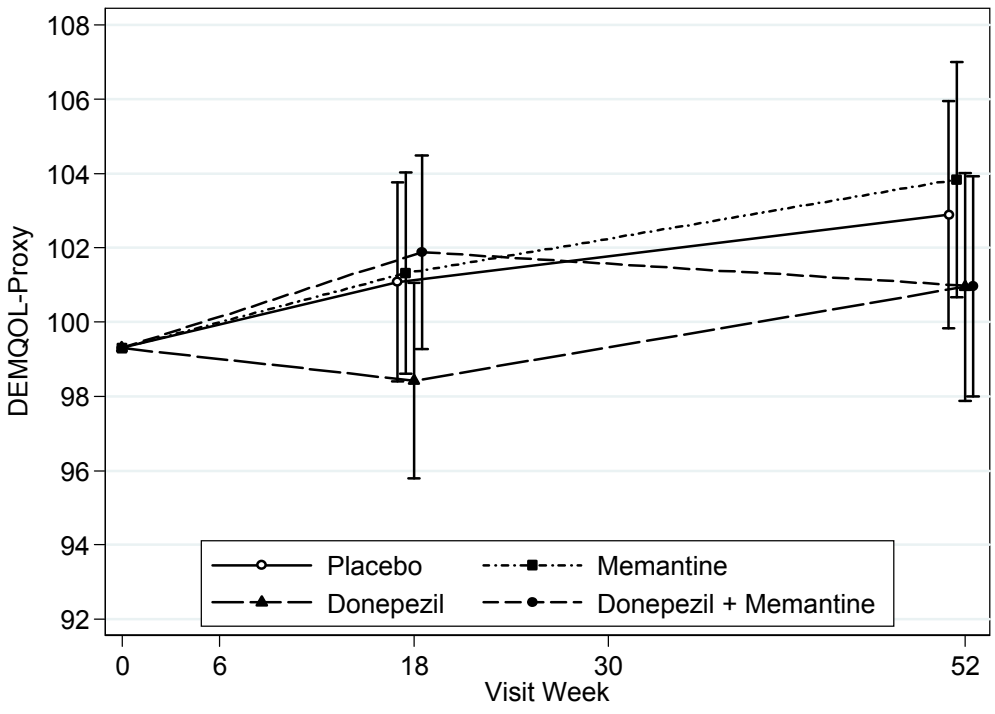


Table 10.15: Estimated pooled mean DEMQOL-proxy at the margins by visit

	Difference in DEMQOL-proxy with 95% confidence interval	
	Visit 3 (Week 18, 126 days)	**Visit 5 (Week 52, 364 days)**
Placebo Donepezil	101.2 (99.3, 103.1)	103.3 (101.2, 105.5)
Active Donepezil	100.1 (98.3, 102.0)	100.9 (98.8, 103.1)
Placebo Memantine	99.7 (97.8, 101.6)	101.9 (99.7, 104.0)
Active Memantine	101.6 (99.7, 103.5)	102.4 (100.2, 104.5)

Figure 10.16: Estimated pooled mean DEMQOL-proxy at the margins by visit

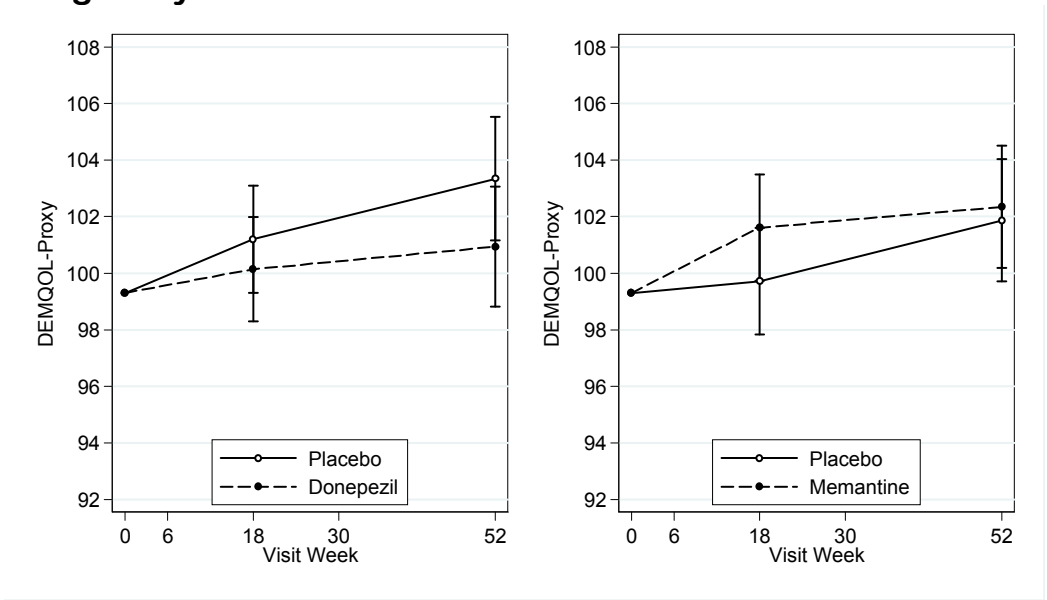


Table 10.17: Estimated difference in GHQ-12 from placebo by visit

	Difference in GHQ-12 with 95% confidence interval*		
	Visit 2 (Week 6, 42 days)	**Visit 4 (Week 30, 210 days)**	**Visit 5 (Week 52, 364 days)**
Placebo	–	–	–
Memantine	-0.3 (-1.1, 0.4)	-0.5 (-1.4, 0.4)	-0.6 (-1.7, 0.5)
Donepezil	-0.6 (-1.3, 0.1)	-0.2 (-1.1, 0.7)	-1.0 (-2.1, 0.1)
Donepezil + Memantine	-0.8 (-1.6, -0.1)	-1.2 (-2.1, -0.3)	-1.0 (-2.1, 0.1)
Test for Interaction between Donepezil and Memantine	0.9012	0.4425	0.4487
Total patients with non-missing GHQ-12 score	**282**	**236**	**197**

Global test for interaction between donepezil and memantine across all weeks: p = 0.5618

*This is an estimate of the average difference in GHQ-12 at the specified visit compared to the score in the placebo arm from the MMRM analysis.

Figure 10.18: Estimated difference in GHQ-12 from placebo by visit

The figure below is a graphical representation of the results of the MMRM analysis showing model-based estimates with 95% confidence intervals.

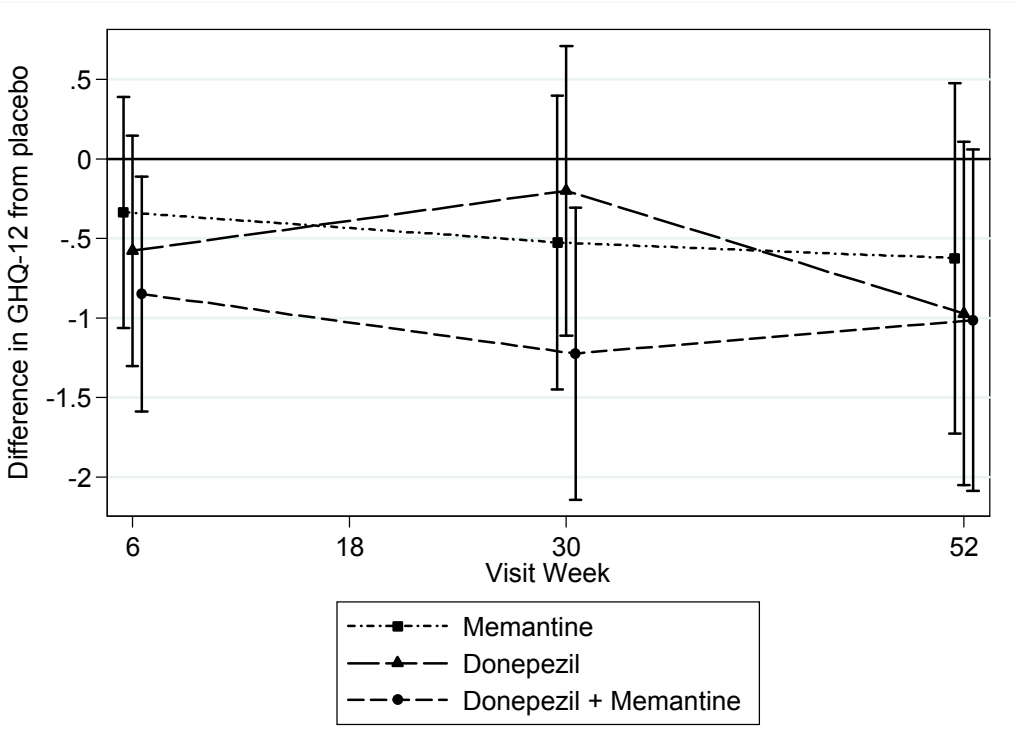


Table 10.19: Estimated pooled difference in GHQ-12 at the margins comparing active with placebo by visit

	Difference in GHQ-12 with 95% confidence interval		
	Visit 2 (Week 6, 42 days)	**Visit 4 (Week 30, 210 days)**	**Visit 5 (Week 52, 364 days)**
Donepezil vs. Placebo	-0.5 (-1.1, -0.0)	-0.5 (-1.1, 0.2)	-0.7 (-1.4, 0.1)
Memantine vs. Placebo	-0.3 (-0.8, 0.2)	-0.8 (-1.4, -0.2)	-0.3 (-1.1, 0.4)

Figure 10.20: Estimated pooled difference in GHQ-12 at the margins comparing active with placebo by visit

The figure below is a graphical representation of the results of the MMRM analysis showing model-based estimates with 95% confidence intervals. The graphs correspond to the comparison of donepezil versus placebo (on the left) and memantine versus placebo (on the right).

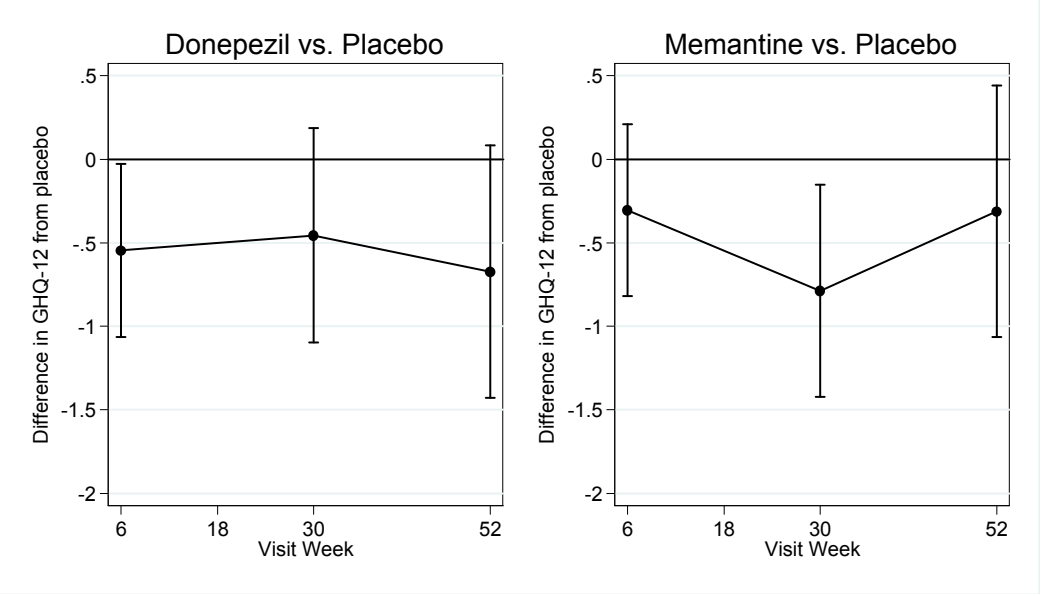


Table 10.21: Estimated mean GHQ-12 by visit and treatment arm

	Mean GHQ-12 with 95% confidence interval		
	Visit 2 (Week 6, 42 days)	**Visit 4 (Week 30, 210 days)**	**Visit 5 (Week 52, 364 days)**
Placebo	2.8 (2.3, 3.3)	3.0 (2.3, 3.6)	3.0 (2.3, 3.8)
Memantine	2.5 (1.9, 3.0)	2.4 (1.8, 3.1)	2.4 (1.7, 3.2)
Donepezil	2.2 (1.7, 2.7)	2.8 (2.1, 3.4)	2.1 (1.3, 2.8)
Donepezil + Memantine	1.9 (1.4, 2.5)	1.7 (1.1, 2.4)	2.0 (1.3, 2.8)

Figure 10.22: Estimated mean GHQ-12 by visit and treatment arm

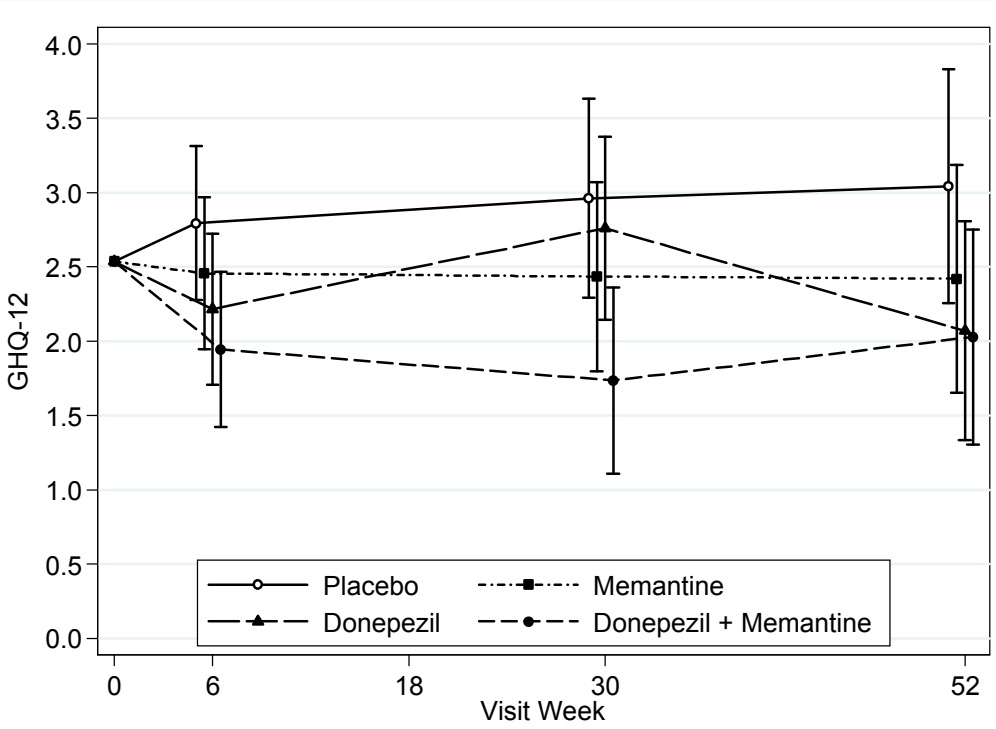


Table 10.23: Estimated pooled mean GHQ-12 at the margins by visit

	Mean GHQ-12 with 95% confidence interval		
	Visit 2 (Week 6, 42 days)	Visit 4 (Week 30, 210 days)	Visit 5 (Week 52, 364 days)
Placebo Donepezil	2.6 (2.3, 3.0)	2.7 (2.2, 3.2)	2.7 (2.2, 3.3)
Active Donepezil	2.1 (1.7, 2.4)	2.2 (1.8, 2.7)	2.1 (1.5, 2.6)
Placebo Memantine	2.5 (2.1, 2.9)	2.9 (2.4, 3.3)	2.5 (2.0, 3.1)
Active Memantine	2.2 (1.8, 2.6)	2.1 (1.6, 2.5)	2.2 (1.7, 2.7)

Figure 10.24: Estimated pooled mean GHQ-12 at the margins by visit

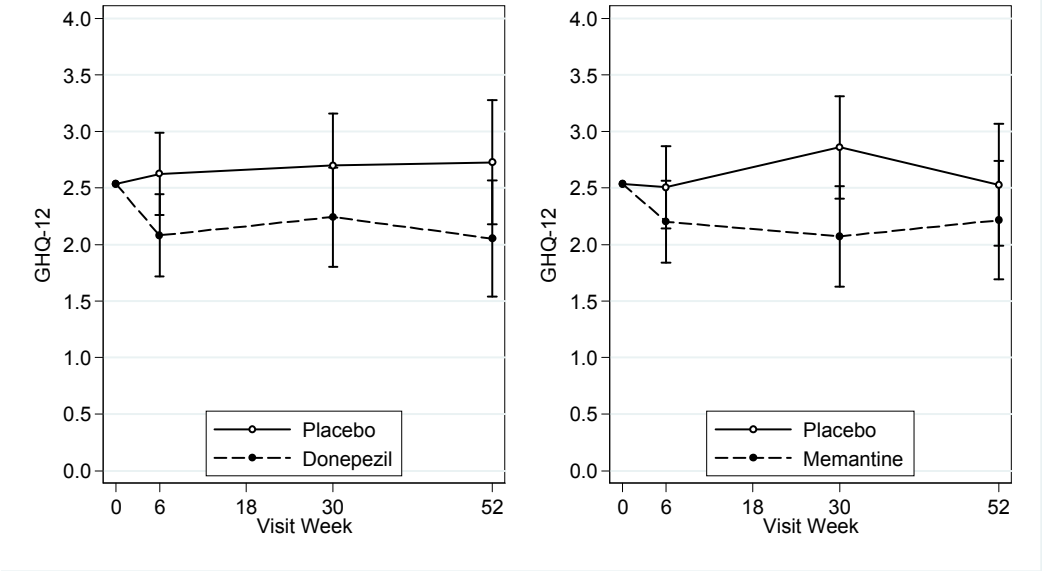


Table 10.25: Estimated odds ratio of being a case on GHQ-12 compared to placebo by visit

The GHQ-12 score can be dichotomised by considering those with a score of 3 or more as cases and those with a score of 2 or less as non-cases.

	Odds ratio with 95% confidence interval*		
	Visit 2 (Week 6, 42 days)	**Visit 4 (Week 30, 210 days)**	**Visit 5 (Week 52, 364 days)**
Placebo	–	–	–
Memantine	1.3 (0.5, 3.5)	0.5 (0.2, 1.5)	0.5 (0.1, 1.7)
Donepezil	0.9 (0.3, 2.5)	0.7 (0.2, 2.2)	0.3 (0.1, 1.2)
Donepezil + Memantine	0.5 (0.2, 1.4)	0.2 (0.0, 0.5)	0.3 (0.1, 1.1)
Test for Interaction between Donepezil and Memantine	0.236	0.289	0.494
Total patients with non-missing GHQ-12 score	**282**	**236**	**197**

Global test for interaction between donepezil and memantine across all weeks: p = 0.3499

*This is the estimated ratios of odds with 95% confidence interval of having a score of 3 or more (a case) comparing each arm with placebo.

Figure 10.26: Estimated odds ratio of being a case on GHQ-12 compared to placebo by visit

The figure below is a graphical representation of the results of the analysis above showing model-based estimates of odds ratios with 95% confidence intervals.

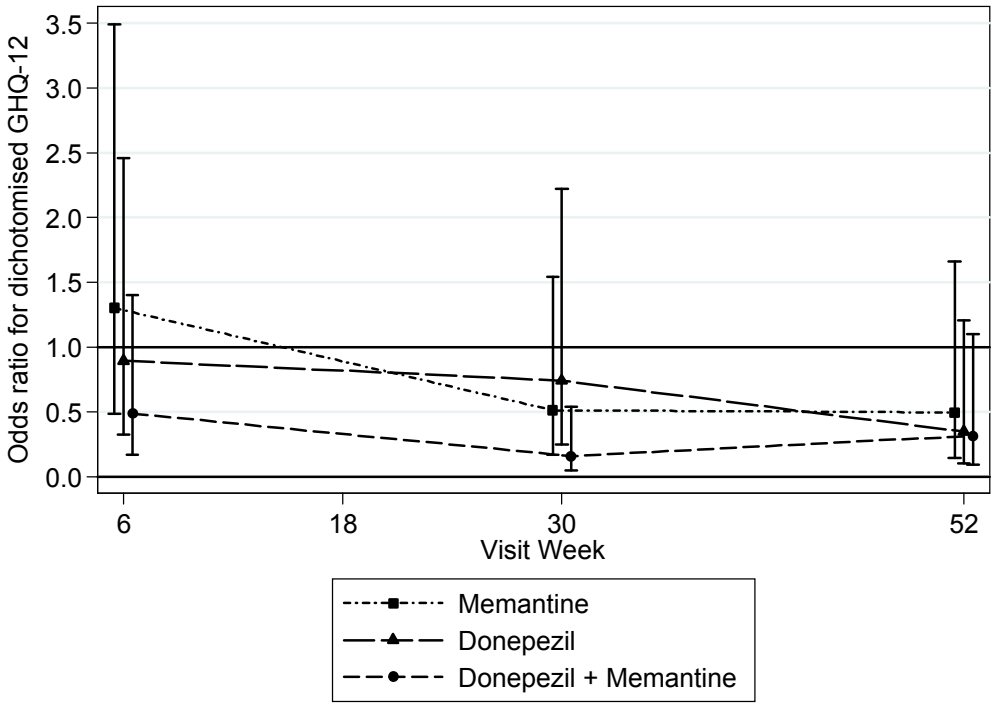


Table 10.27: Estimated odds ratio at the margins of being a case on GHQ-12 comparing active with placebo by visit

	Odds ratio with 95% confidence interval		
	Visit 2 (Week 6, 42 days)	**Visit 4 (Week 30, 210 days)**	**Visit 5 (Week 52, 364 days)**
Donepezil vs. Placebo	0.6 (0.3, 1.2)	0.5 (0.2, 1.1)	0.5 (0.2, 1.1)
Memantine vs. Placebo	0.9 (0.4, 1.8)	0.3 (0.2, 0.8)	0.7 (0.3, 1.6)

Figure 10.28: Estimated odds ratio at the margins of being a case on GHQ-12 comparing active with placebo by visit

The figure below is a graphical representation of the results of the analysis above showing model-based estimates of odds ratios with 95% confidence intervals. The graphs correspond to the comparison of donepezil versus placebo (on the left) and memantine versus placebo (on the right).

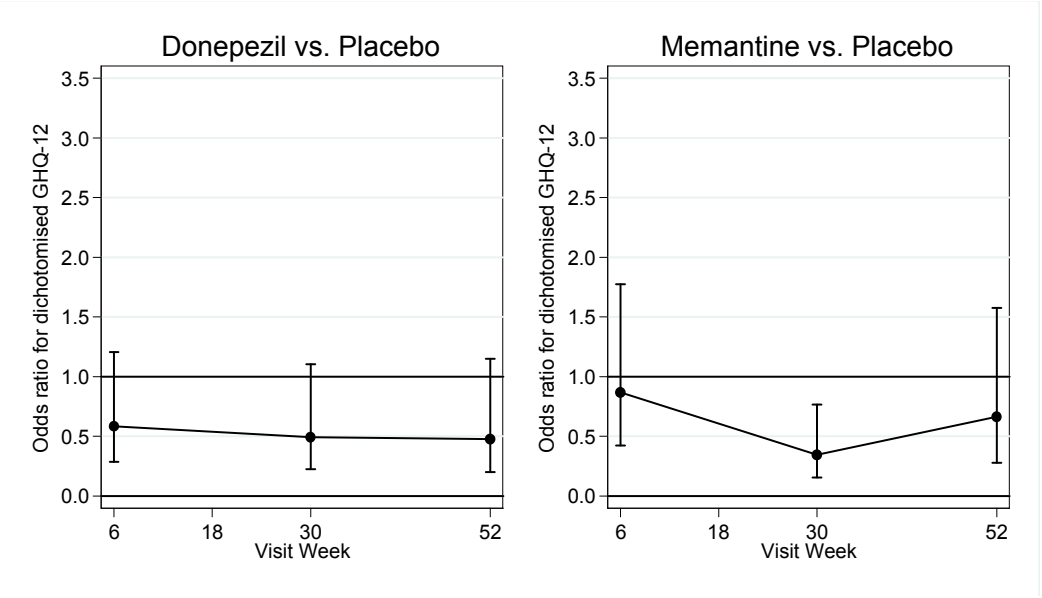


Table 10.29: Estimated probability of being a case on GHQ-12 by visit and treatment arm

	Probability of being a case (GHQ-12 ≥ 3) with 95% confidence interval		
	Visit 2 (Week 6, 42 days)	**Visit 4 (Week 30, 210 days)**	**Visit 5 (Week 52, 364 days)**
Placebo	0.3 (0.2, 0.5)	0.4 (0.3, 0.6)	0.4 (0.2, 0.6)
Memantine	0.4 (0.2, 0.6)	0.3 (0.2, 0.5)	0.2 (0.1, 0.4)
Donepezil	0.3 (0.2, 0.5)	0.4 (0.2, 0.6)	0.2 (0.1, 0.4)
Donepezil + Memantine	0.2 (0.1, 0.3)	0.1 (0.0, 0.2)	0.2 (0.1, 0.3)

Figure 10.30: Estimated probability of being a case on GHQ-12 by visit and treatment arm

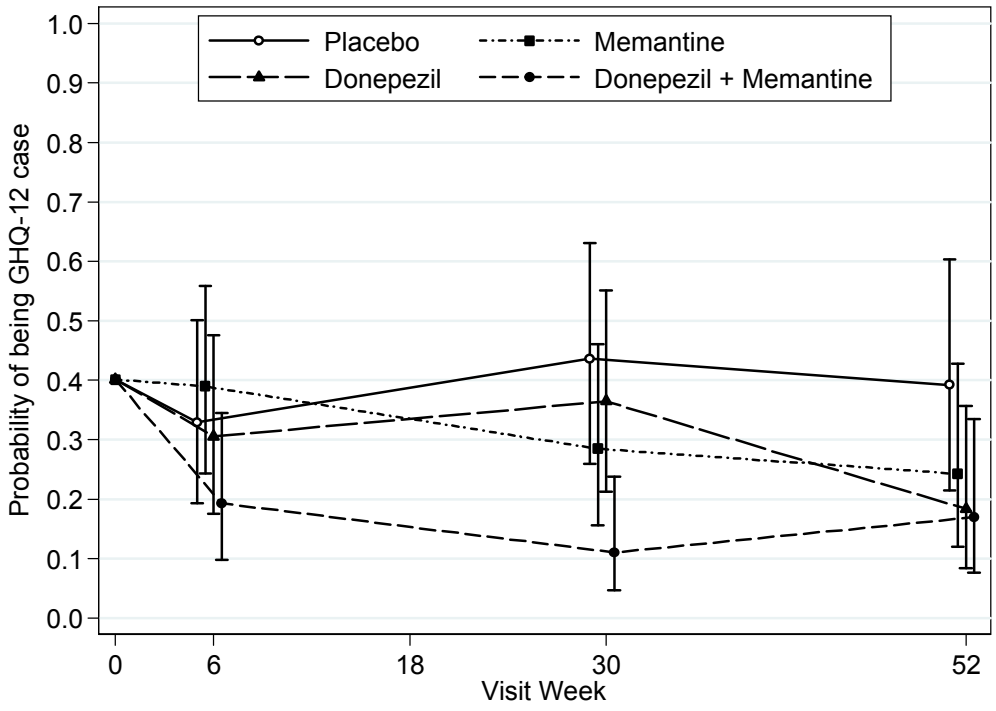


Table 10.31: Estimated probability of being a case on GHQ-12 at the margins by visit

	Probability of being a case (GHQ-12 ≥ 3) with 95% confidence interval		
	Visit 2 (Week 6, 42 days)	**Visit 4 (Week 30, 210 days)**	**Visit 5 (Week 52, 364 days)**
Placebo Donepezil	0.4 (0.3, 0.5)	0.4 (0.2, 0.5)	0.3 (0.2, 0.5)
Active Donepezil	0.2 (0.2, 0.4)	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)
Placebo Memantine	0.3 (0.2, 0.4)	0.4 (0.3, 0.5)	0.3 (0.2, 0.4)
Active Memantine	0.3 (0.2, 0.4)	0.2 (0.1, 0.3)	0.2 (0.1, 0.3)

Figure 10.32: Estimated probability of being a case on GHQ-12 at the margins by visit

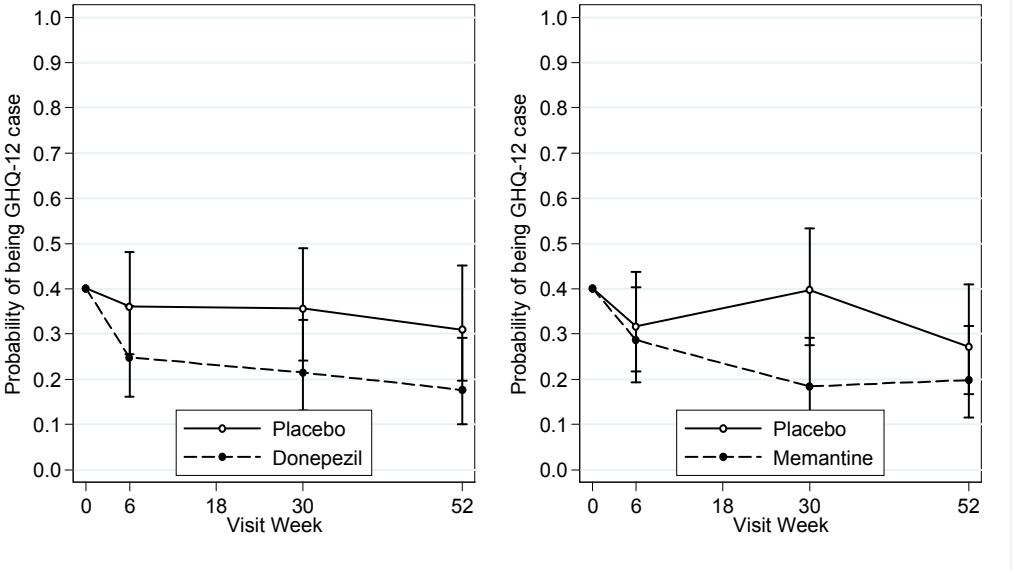


Table 10.33: Overall quality of life from DEMQOL-proxy by visit and by treatment arm

The final question (question 32) on the DEMQOL-proxy stands alone and is not included in the overall score. The question is as follows: 'How would you say that the patient would rate his / her quality of life overall?'

Included in the table below in the p-value from the Cuzick non-parametric test for trend across ordered groups comparing each active treatment arm with double placebo at week 18 and at week 52.

	N (%)	Placebo Donepezil		Donepezil		Total
		Placebo Memantine	Memantine	Placebo Memantine	Memantine	
	Total Randomised	**73**	**76**	**73**	**73**	**295**
Baseline	**Very Good**	9 (13%)	9 (12%)	9 (12%)	13 (18%)	**40 (14%)**
	Good	31 (44%)	34 (46%)	33 (45%)	35 (49%)	**133 (46%)**
	Fair	25 (35%)	22 (30%)	23 (32%)	17 (24%)	**87 (30%)**
	Poor	6 (8%)	9 (12%)	8 (11%)	7 (10%)	**30 (10%)**
	Total non-missing	**71**	**74**	**73**	**72**	**290**
Week 18	**Very Good**	4 (6%)	3 (5%)	6 (9%)	5 (7%)	**18 (7%)**
	Good	30 (47%)	26 (41%)	29 (43%)	31 (46%)	**116 (44%)**
	Fair	18 (28%)	20 (31%)	21 (31%)	26 (39%)	**85 (32%)**
	Poor	12 (19%)	15 (23%)	11 (16%)	5 (7%)	**43 (16%)**
	Total non-missing	**64**	**64**	**67**	**67**	**262**
	Comparison with double placebo		p = 0.355	p = 0.844	p = 0.496	
Week 52	**Very Good**	4 (7%)	5 (10%)	4 (8%)	5 (9%)	**18 (8%)**
	Good	19 (35%)	15 (29%)	27 (51%)	25 (44%)	**86 (40%)**
	Fair	16 (29%)	16 (31%)	13 (25%)	16 (28%)	**61 (28%)**
	Poor	16 (29%)	15 (29%)	9 (17%)	11 (19%)	**51 (24%)**
	Total non-missing	**55**	**51**	**53**	**57**	**216**
	Comparison with double placebo		p = 0.942	p = 0.092	p = 0.205	

PRINCIPAL OR COORDIANTING INVESTIGATOR(S) SIGNATURE(S) OR SPONSOR'S RESPONSIBLE MEDICAL OFFICER

STUDY TITLE: Donepezil & Memantine in Moderate to Severe Alzheimer's Disease

REPORT AUTHOR(S): Professor Rob Howard (Chief Investigator)

I have read this report and confirm to the best of my knowledge it accurately describes the conduct and results of the study

INVESTIGATOR: Prof Rob Howard **SIGNATURE(S):** _____

AFFILIATION: Institute of Psychiatry, King's College London

DATE: _____

APPENDIX I – Information Sheets & Consent Forms

CARER INFORMATION SHEET
DOMINO – AD Trial (Final v 4.0, dated 04/08/08)

Title: Donepezil and Memantine in Moderate to Severe Alzheimer's disease (DOMINO-AD).

Introduction
The person for whom you care is being invited to take part in a 1-year clinical trial to see whether the Alzheimer's disease medications donepezil (also known as Aricept) or memantine (also known as Ebixa) can continue to help people with moderate to severe Alzheimer's disease. If they take part, we will also need you to provide information to the researcher. Before you both decide to participate it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

Please ask us if there is anything that is not clear, or if you would like more information. Neither you nor the person for whom you care has to take part in the study, and their normal care will not be affected if you decide not to participate.

What is the purpose of this study?
The aim of this study is to see whether the Alzheimer's disease medications donepezil or memantine can continue to help people with moderate to severe Alzheimer's disease who are already receiving treatment with donepezil. Some people would not continue to receive this medication as part of their NHS treatment according to current NHS rules because it is unclear whether there is any ongoing benefit. The study will help us to understand the best medications for people with moderate to severe Alzheimer's disease and to look at whether the medications provide value for money.

We know that donepezil is safe and helps memory and every day function in people with mild and moderate Alzheimer's disease, but we do not know whether these benefits continue later in the disease or whether there are any differences in the benefits of receiving treatment with donepezil or the other type of Alzheimer's disease medication called memantine. There is evidence that people who are more severely affected by Alzheimer's disease may show improvements in memory if they are started on drugs like donepezil but we do not know if people who are already receiving treatment with these drugs will benefit if they continue past the stage of being moderately affected. In addition, we do not know whether either treatment gives good value for money in this group of individuals.

Why have we been chosen?

You have both been invited to take part in the study because, in the opinion of their doctor, the person for whom you care has moderate or severe Alzheimer's disease, has been receiving treatment with donepezil, and has reached a point in their illness where their doctor is unsure that their medication is continuing to benefit them. Approximately 800 people in total will help us with the study across the UK.

Do we have to take part?
No. It is entirely up to you both as to whether or not you take part. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show you have agreed to take part and that you agree the person for whom you care can take part. We will also ask the person for whom you care to sign a consent form, if they are able, to show they agreed to take part.

If you decide to take part either of you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care that the person for whom you care receives.

Even if you decide to take part in the study the doctor may withdraw the person for whom you care from the study at any time if he/she feels it is best for them to stop taking the treatment. This will not affect the ongoing medical care of the person for whom you care, and their doctor will continue to look after them as always.

What will happen if we take part?
Your main participation will last for 1 year. During this year the person for whom you care will take the trial medicines and will have 5 assessments at home or in a clinic. At each assessment the person for whom you care will be asked questions to test their memory and other aspects of brain function. You will be asked questions about their behaviour, everyday function and general health as well as questions about the type of services and support you are both receiving. You will also be asked questions about your own general health. This will take approximately 1.5 hours of your time and 1 hours of their time. If you did need to come to a clinic transport will be arranged and any money you have to pay will be paid back to you. We will then telephone you for a short conversation every 6 months for 3 years after the person for whom you care stops taking the trial medication to find out how they are progressing. Your total length of participation in the trial will therefore be about 4 years.

Before taking part in the study and receiving study medication the person for whom you care would need to be assessed to make sure that they were suitable to take part. This would take place as part of the first visit.

Because we don't yet know whether there are ongoing benefits from taking donepezil or memantine, we need to compare the effects of treatment to those of placebo or dummy medication (A placebo is a

dummy treatment such as a pill which looks like the real treatment but is not. It contains no active ingredient). Once you have agreed to enter the trial, a computer will put the person for whom you care in one of four treatment groups with equal chances of each treatment being the one they will receive. There is therefore a 1 in 4 chance they will receive dummy tablets. There is a 1 in 2 chance that they will not continue to be treated with donepezil, even if you or the person for whom you care believes this would remain of benefit to them. Allocating treatment this way means that the groups of people getting each treatment should be similar. If there are any differences between how the groups do, it must be due to the treatment.

Each treatment group will mean the person for whom you care has to take 4 tablets a day. They could be allocated to one of the following four groups:

1. donepezil and memantine – they will take both donepezil and memantine tablets
2. memantine only – they will take a memantine tablet and a dummy donepezil tablet
3. donepezil only – they will take a donepezil tablet and a dummy memantine tablet
4. placebo tablets only – both the tablets they take will be dummy tablets

If the person for whom you care is in the group only taking placebo tablets (group 4), it is important to note that they would have all their study related condition medication withdrawn.

Importantly, neither you, the person for whom you care, nor your study doctor will know what medications you are taking (although, if your study doctor needs to find out he/she can do so).

We will write to the GP of the person for whom you care to tell them they are taking part in this study and advise them of any other medications which should not be taken.

What do we have to do?

If you do decide to take part, it will be important for you and the person for whom you care to come to your assessment visits and for them to take the study medicine as your study doctor tells you. It will also be important to bring all the medication wallets to each assessment so that the doctor will know they are taking their medications correctly.

Unfortunately, if the person for whom you care is already taking part in a clinical trial, they will not be able to take part in this study.

What are the medications that are being tested?

Donepezil and memantine are both licensed and safe treatments for people with Alzheimer's disease that are widely prescribed in many countries.

What are the side effects of taking part?
Both donepezil and memantine are very safe medications that are well tolerated by people with Alzheimer's disease, but as with any medicines some side-effects may occur.

In studies comparing donepezil to dummy treatments, a slight increase in side effects has been seen in people taking donepezil. The most common side effects are sickness, diarrhoea, reduced appetite and occasionally vomiting. When they have happened, these side effects are mostly mild and short-lived, but sometimes are more severe. In studies comparing memantine to dummy treatments, the chance of having side effects is the same when taking memantine as with dummy medication. No individual side effects occurred in more than 5 out of 100 people. No studies have been carried out which look at the side effects when both drugs are taken together so we do not know if this causes different side effects or makes no difference.

Although these are very safe treatments it is still important to take care and you should tell the study doctor about any side effects that the person for whom you care has.

What are the possible disadvantages and risks of taking part?
In total, the person for whom you care will have a detailed assessment on 5 occasions over a year, with short telephone interviews every six months for a further 4 years. The assessments may cause a mild degree of anxiety and can lead to people becoming tired.

What are the possible benefits of taking part?
There is some evidence that donepezil and memantine give clinical benefits for people with moderate to severe Alzheimer's disease including improvements in memory and function. We therefore would hope that participants will gain at least some benefit from these therapies. However, the main benefit of this trial will be proving how best to treat patients with moderate – severe Alzheimer's disease in the future.

What if new information becomes available?
Sometimes during the course of a research study new information becomes available about the medication that is being studied. If this happens, the study doctor will tell you both about it and discuss with you whether you both want to continue in the study. If you both decide to continue you may both be asked to sign an updated informed consent form. If either of you decides to withdraw, your study doctor will make arrangements for the care of the person for whom you care to continue. Also, on receiving new information, your study doctor may consider it to be in the best interests of the person for whom you care to withdraw from the study. He/she will explain the reasons and arrange for their continued care.

If the study is stopped for any reason we will tell you and make arrangements for the continuing care of the person for whom you care.

What happens when the research study stops?
After completing the 1-year of study medication, the study doctor will discuss the most appropriate treatment options for the person for whom you care, based upon their condition and the treatments which are available.

Although in the UK donepezil is licensed for the treatment of moderate Alzheimer's disease and memantine licensed for the treatment of severe Alzheimer's disease, it is unlikely that these medications will be available to the person for whom you care on the NHS at the end of the study, as is the case now.

What will happen if we don't want to carry on with the study?
You can stop taking part in the study at anytime. If the person for whom you care wants to stop taking the medications but carry on coming for their assessment visits, that is ok. Unfortunately they cannot take the medications but stop coming to their assessment visits. If you decide to stop taking part in the study entirely, we will keep the data collected already and will need to use this data.

Stopping the trial medication could be associated with a temporary increase in agitation or similar symptoms in the person for whom you care and we would therefore advise you and your doctor to watch for these symptoms.

What if I have a complaint?
If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions. You can contact them on (LOCAL CONTACT NUMBER). If you remain unhappy and wish to complain formally, you can do this through the NHS complaints procedure. You can get the details of how to do this at your hospital

What if something goes wrong?
If the person for whom you care is harmed as a result of taking part in this study, you may claim compensation. The Sponsor of the study will pay compensation where injury is sustained by virtue of participation in the trial, irrespective of the need to prove negligence. Further details of the basis of compensation will be available on request.

Will my taking part in this study be kept confidential?
Yes, all the information which is collected about you and the person for whom you care during the course of the research will be kept strictly confidential, and any information which leaves the hospital will have your names and addresses removed so that you cannot be recognised.

The researcher will ask you and the person for whom you care questions and record this on a paper form. The information on these forms (but not your names or addresses) will then be stored on a computer accessible only to certain authorised people. The paper forms will be stored securely in a locked cabinet, accessible only to the trial team and authorised people. The medical records of the person for whom you care will also be inspected as part of the monitoring of the study by your medical and study team and other authorised people. The data will be stored for at least 10 years.

The authorised people who may see the information and medical records are people from the organisation running the study and from regulatory and audit authorities (who make sure the study is high quality and running correctly.)

The trial manager (at King's College London) will have access to the personal details of both of you, such as your names and addresses in case we need to contact you.

We will tell the GP of the person for whom you care that they are taking part in this study.

What will happen to the results of the research study?
The results of the research will be published in medical journals. However, both of your names and any details which could identify you will not be published and will be kept secret. Your study doctor will be told the results of the study and you will be kept up to date with a study newsletter.

Who is organising and funding the research?
The study is being funded by the Medical Research Council in the UK and the Alzheimer's Society and organized by King's College London.

Who has reviewed the study?
All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by Scotland A Research Ethics Committee.

Contact Details for Further Information
Should anything happen, or if you experience any discomfort, you will always be able to contact someone involved in the study. The person you should contact is:
Name:
Position
Telephone number:
24 hour contact number:

Please ask your study doctor to explain anything that you, or the person for whom you cares, does not understand. If you decide to join the study, please sign the following forms (Informed Consent),

which state that you and the person for whom you care (if applicable) have read the information sheets, and that you understand all the above written information about the study. You will be given a copy of this form, and the Informed Consent Forms to keep.

Thank you for considering participating in this study.

PATIENT INFORMATION SHEET
DOMINO – AD Trial (Final v 4.0, dated 04/08/08)

Title: Donepezil and Memantine in Moderate to Severe Alzheimer's disease (DOMINO-AD).

Introduction

We are inviting you and your carer to take part in a 1-year clinical trial to see whether the Alzheimer's disease medications donepezil (also known as Aricept) or memantine (also known as Ebixa) can continue to help people with moderate to severe Alzheimer's disease. Before you both decide to participate it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

Please ask us if there is anything that is not clear, or if you would like more information. You do not have to take part in the study, and your normal care will not be affected if you decide not to participate.

What is the purpose of this study?

The aim of this study is to see whether the Alzheimer's disease medications donepezil or memantine can continue to help people with moderate to severe Alzheimer's disease who are already receiving treatment with donepezil. Some people would not continue to receive this medication as part of their NHS treatment according to current NHS rules because it is unclear whether there is any ongoing benefit. The study will help us to understand the best medications for people with moderate to severe Alzheimer's disease and to look at whether the medications provide value for money.

We know that donepezil is safe and helps memory and every day function in people with mild and moderate Alzheimer's disease, but we do not know whether these benefits continue later in the disease or whether there are any differences in the benefits of receiving treatment with donepezil or the other type of Alzheimer's disease medication called memantine. There is evidence that people who are more severely affected by Alzheimer's disease may show improvements in memory if they are started on drugs like donepezil but we do not know if people who are already receiving treatment with these drugs will benefit if they continue past the stage of being moderately affected. In addition, we do not know whether either treatment gives good value for money in this group of individuals.

Why have I been chosen?

You and your carer have been invited to take part in the study because, in the opinion of your doctor, you have moderate or severe Alzheimer's disease, have been receiving treatment with donepezil, and have reached a point in your illness where your doctor is unsure that your medication is continuing to benefit you. Approximately 800 people in total will help us with the study across the UK.

Do I have to take part?
No. It is entirely your decision whether or not you take part. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show you have agreed to take part. We will also ask your carer to sign a consent form to show they and you have agreed to take part.

If you decide to take part you and your carer are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.

Even if you decide to take part in the study your doctor may withdraw you from the study at any time if he/she feels it is best for you to stop taking the treatment. This will not affect your ongoing medical care, and your doctor will continue to look after you as always.

What will happen to me if I take part?
Your main participation will last for 1 year. During this year you will take the trial medicines and will have 5 assessments at home or in a clinic. At each assessment you and your carer will be asked questions to test your memory and other aspects of brain function. Your carer will also be asked questions about your behaviour, everyday function and general health as well as questions about the type of services and support you are receiving. This will take approximately 1 hour of your time and 1.5 hours of your carer's time. If you did need to come to a clinic transport will be arranged and any money you have to pay will be paid back to you. We will then telephone you and your carer for a short conversation every 6 months for 3 years after you stop taking the trial medication to find out how you are progressing. Your total length of participation in the trial will therefore be about 4 years.

Before taking part in the study and receiving study medication you would need to be assessed to make sure that you were suitable to take part. This would take place as part of the first visit.

Because we don't yet know whether there are ongoing benefits from taking donepezil or memantine, we need to compare the effects of treatment to those of placebo or dummy medication (A placebo is a dummy treatment such as a pill which looks like the real treatment but is not. It contains no active ingredient). Once you have agreed to enter the trial, a computer will put you in one of four treatment groups with equal chances of each treatment being the one you will receive. There is therefore a 1 in 4 chance you will receive dummy tablets. There is a 1 in 2 chance you will not continue to be treated with donepezil, even if you or your carer believe this would remain of benefit to you. Allocating treatment this way means that the groups of people getting each treatment should be similar. If there are any differences between how the groups do, it must be due to the treatment.

Each treatment group will mean you have to take 4 tablets a day. You could be allocated to one of the following four groups:

1. donepezil and memantine – you will take both donepezil and memantine tablets
2. memantine only – you will take a memantine tablet and a dummy donepezil tablet
3. donepezil only – you will take a donepezil tablet and a dummy memantine tablet
4. placebo tablets only – both the tablets you take will be dummy tablets

If you are in the group only taking placebo tablets (group 4), it is important to note that you will have all your study related condition medication withdrawn.

Importantly, neither you nor your study doctor will know what medications you are taking (although, if your study doctor needs to find out he/she can do so).

We will write to your GP to tell them you are taking part in this study and advise them of any other medications which you should not take

What do I have to do?
If you do decide to take part, it will be important for you and your carer to come to your assessment visits and for you to take the study medicine as your study doctor tells you. It will also be important to bring all your medication wallets to each assessment so that the doctor will know you are taking your medications correctly.

Unfortunately, if you are already taking part in a clinical trial, you will not be able to take part in this study.

What are the medications that are being tested?
Donepezil and memantine are both licensed and safe treatments for people with Alzheimer's disease that are widely prescribed in many countries.

What are the side effects of taking part?
Both donepezil and memantine are very safe medications that are well tolerated by people with Alzheimer's disease, but as with any medicines some side-effects may occur.

In studies comparing donepezil to dummy treatments, a slight increase in side effects has been seen in people taking donepezil. The most common side effects are sickness, diarrhoea, reduced appetite and occasionally vomiting. When they have happened, these side effects are mostly mild and short-lived, but sometimes are more severe. In studies comparing memantine to dummy treatments, the chance of having side effects is the same when taking memantine as with dummy medication. No individual side effects occurred in more than 5 out of 100 people. No studies have been carried out which look

at the side effects when both drugs are taken together so we do not know if this causes different side effects or makes no difference.

Although these are very safe treatments it is still important to take care and you and your carer should tell your study doctor about any side effects you have.

What are the possible disadvantages and risks of taking part?
In total, you and your carer will have a detailed assessment on 5 occasions over a year, with short telephone interviews every six months for a further 4 years. The assessments may cause a mild degree of anxiety and can lead to people becoming tired.

What are the possible benefits of taking part?
There is some evidence that donepezil and memantine give clinical benefits for people with moderate to severe Alzheimer's disease including improvements in memory and function. We therefore would hope that participants will gain at least some benefit from these therapies. However, the main benefit of this trial will be proving how best to treat patients with moderate – severe Alzheimer's disease in the future.

What if new information becomes available?
Sometimes during the course of a research study new information becomes available about the medication that is being studied. If this happens, your study doctor will tell you about it and discuss with you and your carer whether you want to continue in the study. If you decide to continue you may be asked to sign an updated informed consent form. If you decide to withdraw, your study doctor will make arrangements for your care to continue. Also, on receiving new information, your study doctor may consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your continued care.

If the study is stopped for any reason we will tell you and make arrangements for your continuing care.

What happens when the research study stops?
After completing the 1-year of study medication, your study doctor will discuss the most appropriate treatment options for you, based upon your condition and the treatments which are available.

Although in the UK donepezil is licensed for the treatment of moderate Alzheimer's disease and memantine licensed for the treatment of severe Alzheimer's disease, it is unlikely that these medications will be available to you on the NHS at the end of the study, as is the case for you now.

What will happen if I don't want to carry on with the study?

You can stop taking part in the study at anytime. If you want to stop taking the medications but carry on coming for your assessment visits, that is ok. Unfortunately you cannot take the medications but stop coming to your assessment visits. If you decide to stop taking part in the study entirely, we will keep the data collected already and will need to use this data.

Stopping your trial medication could be associated with a temporary increase in agitation or similar symptoms and we would therefore advise your doctor and your carer to watch you for these symptoms.

What if I have a complaint?
If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions. You can contact them on (LOCAL CONTACT NUMBER). If you remain unhappy and wish to complain formally, you can do this through the NHS complaints procedure. You can get the details of how to do this at your hospital

What if something goes wrong?
If you are harmed as a result of taking part in this study, you may claim compensation. The Sponsor of the study will pay compensation where injury is sustained by virtue of participation in the trial, irrespective of the need to prove negligence. Further details of the basis of compensation will be available on request.

Will my taking part in this study be kept confidential?
Yes, all the information which is collected about you during the course of the research will be kept strictly confidential, and any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised

The researcher will ask you and your carer questions and record this on a paper form. The information on these forms (but not your name or address) will then be stored on a computer accessible only to certain authorised people. The paper forms will be stored securely in a locked cabinet, accessible only to the trial team and authorised people. Your medical records will also be inspected as part of the monitoring of the study by your medical and study team and other authorised people. Your data will be stored for at least 10 years.

The authorised people who may see your information and medical records are people from the organisation running the study and from regulatory and audit authorities (who make sure the study is high quality and running correctly.)

The trial manager (at King's College London) will have access to your personal details such as your name and address in case we need to contact you. We will tell your GP you are taking part in this study.

What will happen to the results of the research study?

The results of the research will be published in medical journals. However, your name and any details which could identify you will not be published and will be kept secret. Your study doctor will be told the results of the study and you will be kept up to date with a study newsletter.

Who is organising and funding the research?
The study is being funded by the Medical Research Council in the UK and the Alzheimer's Society and organized by King's College London.

Who has reviewed the study?
All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by Scotland A Research Ethics Committee.

Contact Details for Further Information
Should anything happen, or if you experience any discomfort, you will always be able to contact someone involved in the study. The person you should contact is:
Name:
Position
Telephone number:
24 hour contact number:

Please ask your study doctor to explain anything that you, or your carer, do not understand. If you decide to join the study, please sign the following forms (Informed Consent), which state that you and your carer have read this form, and that you understand all the above written information about the study. You will be given a copy of this form, and the Informed Consent Forms to keep.

Thank you for considering participating in this study.

Addendum to Carer and Patient Information Sheets (V1.0 04/12/08)

Dear

RE: Donepezil and Memantine in Moderate to Severe Alzheimer's disease (DOMINO-AD).

When you agreed to join the DOMINO-AD Study there was an error in the Carer or Patient Information Sheet given to you. We have checked this with our Research Ethics Committee (Scotland A) and they suggested writing to you to draw your attention to it. The statement below, found on page 5 of the Carer & Patient Information Sheets contains the following error:

"What are the possible disadvantages and risks of taking part?
In total, you and your carer will have a detailed assessment on 5 occasions over a year, with short telephone interviews every six months for a further 4 years. The assessments may cause a mild degree of anxiety and can lead to people becoming tired.**"**

The statement should read "…short telephone interviews every six months for a further 3 years…", not 4 years as stated in the Carer & Patient Information Sheets Final Version 4.0 dated 04/08/08.

If you need further information please contact the DOMINO-AD Trial Manager on: 020 7848 0024.

Note to Research Worker:

This addendum updates Carer & Patient Information Sheets Final Version 4 .0 dated 04/08/08. A copy should be sent to all carers and participants drawing their attention to the error in the statement above. A copy should be attached to the patient and carer information sheets filed in the medical notes and with the Source Data Worksheets.

CARER CONSENT FORM (Final v3.1, 11/09/08)

Title: Donepezil and memantine in moderate to severe Alzheimer's disease (DOMINO-AD).

Please initial

1. I confirm that I have read the carer information sheet dated 04/08/08, version 4.0 and have had the opportunity to ask questions. _____

2. I understand my participation is voluntary and that the patient and myself are free to withdraw at any time, without giving any reason, and without our medical care or legal rights being affected _____

3. I agree to cooperate in the conduct of this study, to immediately report any unusual symptoms which the patient suffers, to ensure the patient takes their study medication as instructed and attends all clinic visits. _____

4. I understand I will be asked questions about the patient's condition and about my views. _____

5. I understand that the Trial Manager will have access to my personal details and give permission for them to be held by the trial manager. _____

6. I understand I will receive a signed copy of this form _____

7. I agree to take part in the study _____

Name of Patient's Carer _____

Signature_____

Date _____/_____/_____

Name of Investigator_____

Investigators signature _____

Date _____/_____/_____

Please put the original in the site file with 1 copy to the carer, 1 copy to the GP, 1 copy in the patient's medical notes and 1 copy in the patient's trial notes

PATIENT INFORMED CONSENT FORM (Final v3.1, 11/09/08)
Donepezil and memantine in moderate to severe Alzheimer's disease (DOMINO-AD).

Please initial

1. I confirm that I have read and understood the information sheet dated 04/08/08, version 4.0 for the above study and have had the opportunity to ask questions. _____

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected. _____

3. I understand that my carer will be asked questions about me and I agree to this

4. I understand that sections of any of my medical notes may be looked at by responsible individuals as part of study monitoring or from the ethics committee or regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. _____

5. I understand that the Trial Manager will have access to my personal details and give permission for them to hold them _____

6. I agree to my General Practitioner being informed of my participation in this trial. _____

7. I understand I will receive a signed copy of this form _____

8. I agree to take part in this study _____

Name of Patient _____

Signature_____

Date _____/_____/_____

Name of Investigator_____

Signature_____

Date _____/_____/_____

Name of witness (if necessary) _____

Signature_____

Date _____/_____/_____

Please put the original in the site file with 1 copy to the carer/patient, 1 copy to the GP, 1 copy in the patient's medical notes and 1 copy in the patient's trial notes

CONSENT FORM - to consent on behalf of a non-competent patient (Final v 1.1, dated 11/09/08)

Title: Donepezil and memantine in moderate to severe Alzheimer's disease (DOMINO-AD).

Please initial

1. I confirm that I have read the carer information sheet dated 04/08/08, version 4.0 for the above study (if able) and have had the opportunity to ask questions. _____

2. I confirm that the patient has received information, according to thier capacity of understanding, regarding the trial, its risks and its benefits. _____

3. I understand the participation of the patient is voluntary and that they are free to withdraw at any time, without giving any reason, and without their medical care or legal rights being affected _____

4. I understand that sections of the patient's medical notes may be looked at by responsible individuals as representatives of the sponsor or part of study monitoring or from the ethics committee or regulatory authorities, where it is relevant to the patient taking part in research. _____

5. I understand that the Trial Manager will have access to the personal details of the patient and give permission for these to be held by the trial manager _____

6. I agree to the patient's GP being involved in their involvement in this study

7. I confirm the patient has not refused to be part of the study, nor shown undue distress at being involved and I also consent to their participation. _____

Name of Patient (Printed)_____

Relationship to Patient (please specify)_____

Name of Patient's Legal Representative _____

Signature_____

Date _____/_____/_____

Name of Investigator_____

Investigators signature _____

Date _____/_____/_____

Please put the original in the site file with 1 copy to the carer, 1 copy to the GP, 1 copy in the patient's medical notes and 1 copy in the patient's trial notes

APPENDIX II – Investigators & Administrative Structure

Centre details with Principal Investigators		
Name	**Centre details**	**Affiliation**
Prof Roy Jones	01 – Bath	The Research Institute for Care of Older People, Bath
Dr Peter Passmore	02 - Belfast	Belfast Health & Social Care Trust
Dr Peter Bentham	03 – Birmingham	Birmingham and Solihull Mental Health Trust
Dr Tom Dening	04 - Cambridge	Cambridgeshire & Peterborough Mental Health Partnership NHS Trust
Dr David Findlay	05 – Dundee	Tayside Health Board
Dr Alan Hughes	06 – Glasgow	NHS Greater Glasgow & Clyde
Prof James Lindesay	07 - Leicester	University of Leicester
Prof Robert Howard	08 – London Maudsley	Institute of Psychiatry
Dr Craig Ritchie	09 – London Imperial	Imperial College
Prof Alistair Burns Dr. Ashley Baldwin	10 – Manchester	Manchester University 5-Boroughs Partnership NHS Trust
Prof Ian McKeith	11 - Newcastle	Newcastle University
Dr Rob Jones	12 - Nottingham	Nottingham University
Dr Rupert McShane	13 – Oxford	Oxford Radcliffe Hospital Oxford & Buckinghamshire NHS Partnership Trust
Prof Clive Holmes	14 – Southampton	University of Southampton
Dr Bartley Sheehan	15 - Warwick	University of Warwick

Trial Steering Committee Members	
Name	**Role**
Prof Cornelius Katona	Chair
Ken Wilson	Independent Old Age Psychiatrist
Robert Hills	Independent Statistician
Prof Robert Howard	Chief Investigator
Tony Johnson	Statistician

Independent Data Monitoring Committee Members	
Name	**Role**
Brian Lawlor	Chair
Tony Bayer	Independent Physician
Deborah Ashby	Independent Statistician

Trial Management Group Members	
Name	**Role**
Prof Robert Howard	Chair
All investigators	n/a
Health Economists	n/a
Trial Manager	Secretary to the TMG
Data manager	n/a

APPENDIX III – References

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