PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.
For publications based on this study, see associated bibliography.

PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Lipitor®/atorvastatin calcium

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NCT NO.: NCT00151502

PROTOCOL NO.: A2581078

PROTOCOL TITLE: An 80-week, randomized, multi-center, parallel-group, double-blind study of the efficacy and safety of atorvastatin 80 mg plus an acetylcholinesterase inhibitor versus an acetylcholinesterase inhibitor alone in the treatment of mild to moderate Alzheimer's disease

Study Center(s): Multicenter study with 87 centers recruiting subjects; 7 centers in Australia, 3 centers in Austria, 8 centers in Canada, 4 centers in Denmark, 9 centers in Germany, 5 centers in South Africa, 6 centers in Spain, 4 centers in Sweden, 7 centers in the United Kingdom, and 34 centers in the United States

Study Initiation and Completion Dates: 11 November 2002 to 11 July 2007

Phase of Development: Phase 3

Study Objective(s): The purpose of this study was to evaluate the efficacy, safety, and tolerability of atorvastatin 80 mg in combination with a cholinesterase inhibitor (donepezil 10 mg) in the treatment of subjects with mild to moderate Alzheimer's disease.

The primary objective of this study was to demonstrate the superiority of the effects of combined treatment with atorvastatin plus an acetylcholinesterase inhibitor (donepezil 10 mg) to treatment with an acetylcholinesterase inhibitor (donepezil 10 mg) alone on cognition and global function as assessed by the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) and the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC), respectively.

Based on input from the FDA, an additional confirmatory-primary objective is to demonstrate the superiority of the effects of combined treatment with atorvastatin plus an acetylcholinerase inhibitor (donepezil) to treatment with an acetylcholinerase inhibitor (donepezil) alone on rate of change in whole brain and whole hippocampus volumes.

The secondary objectives were:

- To demonstrate the superiority of combined atorvastatin plus an acetylcholinesterase inhibitor (donepezil) treatment to donepezil alone on other clinical measures of AD, including: behavior, as measured by the Neuropsychiatric Inventory (NPI); general cognitive status, as measured by the Mini-Mental Status Examination (MMSE); overall dementia severity as measured by the Clinical Dementia Rating-Sum of Boxes (CDR-SB), and daily function as assessed by the Alzheimer's Disease Functional Assessment and Change Scale (ADFACS).

- To seek additional evidence for disease modifying effects of combined atorvastatin plus an acetylcholinesterase inhibitor (donepezil) treatment: by instituting an 8-week atorvastatin withdrawal maneuver after the primary measures had been collected at Visit 9/Month 18. Superior performance on clinical measures by the withdrawal arm at Visit 10/Month 20, relative to the placebo plus donepezil 10 mg arm, would provide evidence in support of disease modification.

- To understand the effects of combining atorvastatin plus donepezil versus donepezil alone on individual cholesterol/lipid components [apolipoprotein B (ApoB), apolipoprotein E (ApoE), serum total cholesterol, serum LDL-C, serum VLDL-C, triglycerides and HDL-C].

- To assess the effects of combined atorvastatin 80 mg plus donepezil 10 mg versus donepezil alone on caregiver burden and Patient Healthcare Resource Utilization Questionnaire.

METHODS

Study Design This was a multi-center, double-blind, randomized, parallel group study with 3 phases. All subjects were required to be taking a stable dose of 10 mg donepezil for ≥3 months prior to Screening. Approximately 600 subjects with mild to moderate Alzheimer's disease were to be randomized in this study at approximately 100 centers worldwide, with approximately 300 subjects receiving atorvastatin 80 mg plus an acetylcholinesterase inhibitor (donepezil 10 mg) and approximately 300 subjects receiving placebo plus an acetylcholinesterase inhibitor (donepezil 10 mg). The study consisted of 3 phases:

1. A Screening visit (-14 to –1 Days) to determine eligibility prior to randomization.

2. A 72-week randomized, double-blind treatment period in which all subjects were randomized to receive either atorvastatin 80 mg plus donepezil 10 mg, or matching placebo plus donepezil 10 mg (this is the group for primary endpoint assessment).

3. An 8-week randomized, double-blind atorvastatin 80 mg withdrawal maneuver, resulting in a third group; subjects were randomized at Baseline so that at Month 18 they either:

    - Continued with matching placebo plus donepezil 10 mg
      or

- Continued with atorvastatin 80 mg plus donepezil 10 mg
  or

- Withdrawal from treatment with atorvastatin 80 mg so that the subjects received 8 weeks of matching placebo plus donepezil 10 mg

This resulted in the following 3 groups of subjects in this study:

1. Subjects randomized to receive atorvastatin 80 mg plus donepezil 10 mg for 18 months and then to receive matching placebo and donepezil 10 mg for the last 8 weeks (2 months) (primary analysis)

2. Subjects randomized to receive matching placebo plus donepezil 10 mg for 20 months

3. Subjects randomized to receive atorvastatin 80 mg plus donepezil 10 mg for 20 months

The ratio of these three groups was 3:4:1.

A subset of the 100 sites (approximately 50 sites) were to participate in a MRI substudy.

There were clinic visits at Screening, Baseline, Week 6, and Months 3, 6, 9, 12, 15, 18 and 20. The maximum duration of exposure to the study drug for an individual subject, including the withdrawal phase, was 80 weeks (20 months).

Number of Subjects (Planned and Analyzed): Approximately 600 subjects were to be randomized in this study worldwide; 300 in each treatment group. A total of 639 subjects were treated; 314 in the atorvastatin + donepezil group and 325 in the placebo + donepezil group.

Diagnosis and Main Criteria for Inclusion: Male and female subjects, age 50 to 90 years, inclusive, with diagnosis of mild to moderate Alzheimer's disease and a cranial computerized tomography (CT) or magnetic resonance imaging (MRI) within the last 12 months consistent with a diagnosis of probable Alzheimer's disease and without any other clinically significant comorbid pathologies

Study Treatment: The subjects included in this study received either atorvastatin 80 mg plus 10 mg donepezil or placebo plus 10 mg donepezil for 72 weeks. A subset of subjects were withdrawn from the treatment of atorvastatin 80 mg plus 10 mg donepezil at Week 72, and started to receive placebo plus 10 mg donepezil for 8 weeks. Subjects received study drug and/or background drug for a total of 80 weeks.

Efficacy Evaluations: The primary efficacy measures, Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) and Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change Scale (ADCS-CGIC) were performed at Screening, Baseline and Months 3, 6, 9, 12, 15, 18 and 20.

For the confirmatory primary analyses, the MRI was done at baseline and Month 18. The measures of interest from the MRI were brain boundary shift integral and regional brain atrophy (hippocampal atrophy) adjusted for baseline whole volume brain volume.

Secondary efficacy measures and timing included the following:

- Mini-Mental State Examination (MMSE) and Modified Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) were performed at Screening, Baseline and Months 3, 6, 9, 12, 15, 18 and 20;

- Clinical Dementia Rating-Sum of Boxes (CDR-SB) was performed at Baseline and Months 12, 18 and 20;

- Neuropsychiatric Inventory (NPI) and Alzheimer's Disease Functional Assessment and Change Scale (ADFACS) were performed at Baseline and Months 6, 12, and 18.

Safety Evaluations: Safety evaluations included adverse events (AEs), serious adverse events (SAEs), clinical laboratory measurements, electrocardiogram (ECG), vital signs, neurological examination, and physical examinations.

Statistical Methods There were 3 analysis populations in this study.

The **safety population** was defined as all randomized subjects who had taken at least one dose of active study medication or placebo and provided any follow-up information.

The **modified intent-to-treat (MITT) population** was used for all efficacy analyses (except the analysis of MRI assessments). The MITT population was defined as those subjects who had received at least one dose of study medication and who had both baseline and at least one follow-up evaluation.

The **MRI substudy population** was all subjects with valid baseline and post-baseline MRI assessments. The MRI substudy population was the analysis population for the confirmatory primary analyses.

The primary efficacy assessments were scales that consisted of several cognitive domains. For any scales with more than 15% of domains missing, missing data was imputed using the worst case scenario. However, a scale with less than 15% of domains missing was considered as partially missing and the average scale of the existing domains was used to impute the missing domain. The primary efficacy measures were performed at Screening, Baseline and Months 3, 6, 9, 12, 15, 18 and 20 and were as follows:

- Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog).

- Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change Scale (ADCS-CGIC).

For the confirmatory primary analyses, the measures of interest from the MRI were brain boundary shift integral and regional brain atrophy (hippocampal atrophy) adjusted for

baseline whole volume brain volume. This applied both to the brain and hippocampus measurements.

The secondary efficacy measures were as follows:

- Mini-Mental State Examination (MMSE)
- Clinical Dementia Rating-Sum of Boxes (CDR-SB)
- Neuropsychiatric Inventory (NPI)
- Alzheimer's Disease Functional Assessment and Change Scale (ADFACS)
- Modified Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)

Other efficacy assessments included Caregiver Burden and Subject Assessment.

The "15%" rule was also be utilized for the secondary efficacy measures.

All statistical tests of significance were performed at the 5% level of significance, and were 2-sided tests (unless otherwise specified).

The primary analysis was considered positive if both co-primary variables (ADAS-Cog and ADCS-CGIC) showed significant ($p<0.05$) effect in favor of the treatment arm containing atorvastatin. The confirmatory primary hypothesis was considered positive if, in addition to a positive primary analysis, both MRI endpoints (whole brain and whole hippocampus volume) showed significant ($p<0.05$) effect in favor of the treatment arm containing atorvastatin.

For the primary and secondary efficacy parameters, a repeated measures, mixed effects analysis was performed. The mixed model approach was used because of the relatively long length of the study and the ability of this model to better handle missing data than last observation carried forward (LOCF). For each primary efficacy variable additional analyses were done using LOCF.

For the confirmatory primary analyses, treatment difference was tested using an ANCOVA model with rate of change from baseline to Month 18 in whole (brain or hippocampus) volume as the dependent variable, and treatment arm and baseline volume as independent variables. The LOCF approach was used for this analysis.

When ADCS-CGIC was used as score, the baseline value was not available. For ADAS-Cog and all other scores, the dependent variable was change from baseline.

The primary comparison was the difference between the two treatments in mean score across the 72 weeks period. Secondary comparisons included differences between the two treatments at different visits estimated from the mixed effects model. Secondary efficacy variables were assessed according to the same model.

To analyze the data obtained during the withdrawal maneuver of Month 18 to Month 20, Month 18 data was used as Baseline. The change from Month 18 for all quantitative data (except ADCS-CGIC where the raw score was used) was analyzed using ANCOVA. In the model of ANCOVA, the Baseline value (Month 18) was included as a covariate and center was not included as a factor in the model. The major focus of the analysis was the comparison between the withdrawal arm and the donepezil 10 mg group on change from Months 18 to 20.

Total cholesterol, LDL-C, HDL-C, VLDL-C, triglycerides, ApoE, and ApoB were summarized by treatment arm and visit number.

RESULTS

Subject Disposition and Demography: Subject disposition is summarized in Table S`.

Table S1. Disposition of Subjects

Disposition of Subjects	Atorvastatin + Donepezil n	(%)	Placebo + Donepezil n	(%)
Screened N=1008				
Assigned to study treatment	314		326	
Treated	314		325	
Completed	207	(65.9)	245	(75.2)
Discontinued	107	(34.1)	80	(24.5)
Analyzed for efficacy				
Modified intent-to-treat (MITT) population	297	(94.6)	317	(97.2)
Analyzed for safety				
Adverse events	311	(99.0)	323	(99.1)
Laboratory data	306	(97.5)	321	(98.5)

Discontinuations occurring outside the lag period have been attributed to the last study treatment received.
Three atorvastatin subjects and 2 placebo subjects received treatment, but had no AE records, so they are removed from the number summarized due to AEs in this table.
According to this table, the number of subjects analyzed for AEs is 311+323; these are the subjects who took study drug and had a post-baseline AE assessment. In the AE analysis, the number of treated subjects was used (314 and 325).

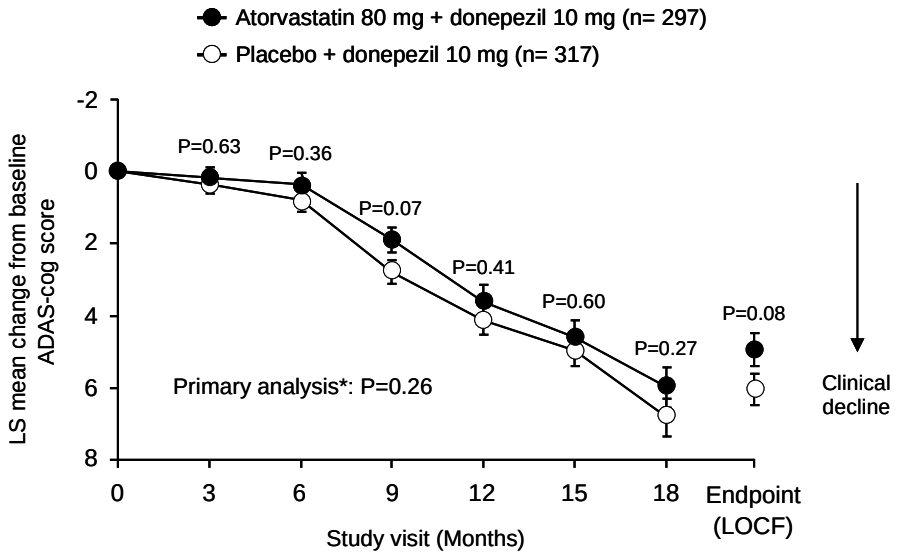
A larger proportion of subjects in the atorvastatin + donepezil group than in the placebo + donepezil group discontinued the study (34.1% and 24.6%, respectively).

In the atorvastatin + donepezil group and placebo + donepezil group the mean age was 74.4 and 73.1 years, respectively, and the mean BMI was 25.0 and 25.1 kg/m^2, respectively. In both the atorvastatin + donepezil group and placebo + donepezil group the majority of subjects were white and slightly over half of the subjects were female (52.9% and 51.1%, respectively). Dementia history was similar between the treatment groups.

Efficacy Results: Atorvastatin + donepezil compared to placebo + donepezil was not associated with significant benefit on cognition and global function measures over 72 weeks in subjects with mild to moderate AD.

For the primary comparison, there was a numerically smaller decline in ADAS-COG from baseline to Month 18 in the atorvastatin + donepezil group than in the placebo + donepezil group, however, this difference was not statistically significant (p=0.26) (Figure S1).

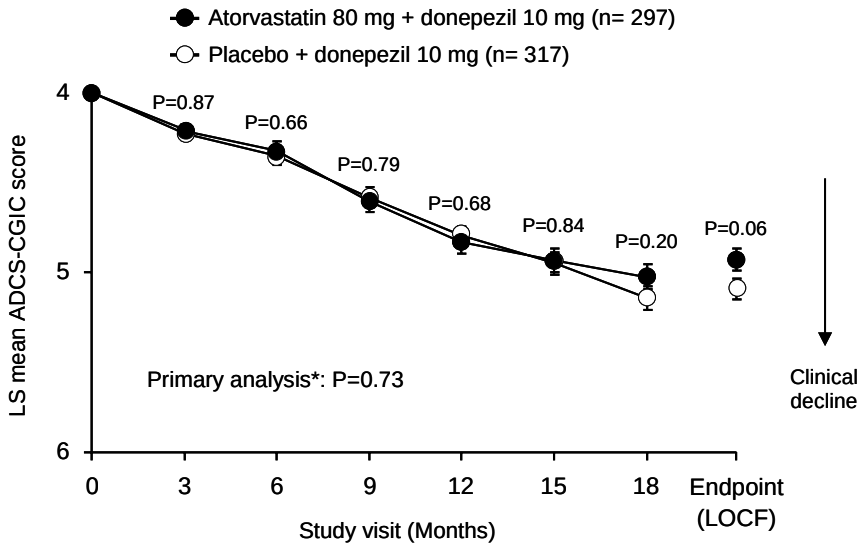
Figure S1. Alzheimers Disease Assessment Scale-Cognitive Subscale Over Time, MITT Population



*Repeated measures of ADAS cog change from baseline with baseline score as covariate

For the primary comparison for ADCS-CGIC, the clinical decline in the overall raw score from baseline to Month 18 in the atorvastatin + donepezil group and the placebo + donepezil group was similar (p=0.73) (Figure S2).

Figure S2. Alzheimers Disease Cooperative Study-Clinical Global Impression Change Scale Over Time, MITT Population



*Repeated measures of ADCS CGIC score

In the MRI substudy, there was a significantly smaller mean decrease in hippocampus volume from baseline to Month 18 in the atorvastatin + donepezil group (N=32) compared to the placebo + donepezil group (N=32) (110.71 and 173.89 mm^3/year, respectively, p=0.0241). The mean annualized boundary shift integral (BSI) was similar between the atorvastatin + donepezil group (N=28) compared to the placebo + donepezil group (N=30) (p=0.9419).

For the MMSE, CDR-SB, NPI, ADFACS, and the Mod ADAS-COG the overall clinical decline from baseline to Month 18 in the atorvastatin + donepezil group and the placebo + donepezil group was similar. There was no difference between the atorvastatin + donepezil group and the placebo + donepezil in caregiver burden or the patient healthcare resource utilization.

By Month 3, mean LDL-C decreased -72.4 mg/dL (% change -50.2) in the atorvastatin + donepezil group and -1.0 mg/dL (% change -0.2) in the placebo + donepezil group. These changes remained constant through Month 18. Larger decreases were also observed in the atorvastatin + donepezil group than the placebo + donepezil group for total cholesterol, triglycerides, and ApoE. There was little change in HDL-C in either treatment group.

Safety Results: An overview of adverse events is presented in Table S2.

Table S2. Overview of Adverse Events, ITT Population

	All Causality				Treatment Related			
	Atorvastatin + Donepezil N=314		Placebo + Donepezil N=325		Atorvastatin + Donepezil N=314		Placebo + Donepezil N=325	
Number of AEs	1134		1247		192		102	
Subjects with AEs	272	(86.6)	277	(85.2)	103	(32.8)	61	(18.8)
Subjects with severe AEs	50	(15.9)	51	(15.7)	6	(1.9)	3	(0.9)
Subjects DC due to AEs	56	(17.8)	31	(9.5)	36	(11.5)	5	(1.5)
Subjects with dose reduced or temporary DC due to AEs	21	(6.7)	23	(7.1)	4	(1.3)	2	(0.6)

DC=discontinued; AE=adverse event
Includes data up to 30 days after last dose of study drug.
Except for the number of AEs subjects are counted only once per treatment in each row.
Five atorvastatin subjects and one placebo subject are listed as discontinued due to AEs on the AE CRF, but have other reasons for discontinuation on the subject summary page.

All causality AEs that occurred with an incidence of 5% in either treatment group are presented in Table S3.

Table S3. Treatment-Emergent All Causality AEs That Occurred With an Incidence of ≥5% in Either Treatment Group, Safety Population

AE Preferred Term, n (%)	Atorvastatin + Donepezil N=314		Placebo + Donepezil N=325	
Upper respiratory tract infection	44	(14.0)	40	(12.3)
Urinary tract infection	30	(9.6)	33	(10.2)
Diarrhea	29	(9.2)	18	(5.5)
Accidental injury	27	(8.6)	32	(9.8)
Agitation	23	(7.3)	24	(7.4)
Back pain	21	(6.7)	21	(6.5)
Bone fracture – accidental	19	(6.1)	22	(6.8)
Hepatic enzymes increased	17	(5.4)	3	(0.9)
Anorexia	16	(5.1)	6	(1.8)
Nausea	16	(5.1)	16	(4.9)
Weight decrease	16	(5.1)	13	(4.0)
Phosphatase alkaline increased	16	(5.1)	4	(1.2)
Arthralgia	15	(4.8)	17	(5.2)
Dementia	13	(4.1)	20	(6.2)
Insomnia	13	(4.1)	23	(7.1)
Rhinitis	11	(3.5)	17	(5.2)
Accidental fall	10	(3.2)	18	(5.5)

Includes data up to 30 days after last dose of study treatment.

The most common all causality AEs in both the atorvastatin + donepezil and placebo + donepezil groups were upper respiratory tract infections (14.0% and 12.3%, respectively) and urinary tract infection (9.6% and 10.2%, respectively).

The most common treatment-emergent treatment related AEs in the atorvastatin + donepezil group were hepatic enzymes increased (4.5%), SGOT increased (4.5%), SGPT increased (4.1%) and alkaline phosphatase increased (4.1%). No treatment-emergent treatment related AEs occurred in at least 2% of subjects in the placebo + donepezil group.

A larger proportion of subjects in the atorvastatin + donepezil than the placebo + donepezil groups discontinued due to all causality (17.8% and 9.5%, respectively) or treatment related (11.5% and 1.5%, respectively) AEs (Table S2). The most common AEs leading to discontinuation in the atorvastatin + donepezil group were hepatic enzymes increased and hepatic function abnormal (Table S4).

Table S4. Treatment-Emergent All Causality and Treatment Related AEs Most Frequently Associated With Discontinuation of Treatment (≥1.0% All Causality Incidence in Either Treatment Group)

	All Causality				Treatment Related			
	Atorvastatin + Donepezil N=314		Placebo + Donepezil N=325		Atorvastatin + Donepezil N=314		Placebo + Donepezil N=325	
	n	(%)	n	(%)	n	(%)	n	(%)
Any AE	56	(17.8)	31	(9.5)	36	(11.5)	5	(1.5)
Hepatic enzymes increased	9	(2.9)	1	(0.3)	9	(2.9)	1	(0.3)
Hepatic function abnormal	7	(2.2)	0	(0.0)	7	(2.2)	0	(0.0)
Diarrhea	6	(1.9)	0	(0.0)	6	(1.9)	0	(0.0)
Nausea	6	(1.9)	0	(0.0)	6	(1.9)	0	(0.0)
Dementia	5	(1.6)	7	(2.2)	0	(0.0)	0	(0.0)
SGOT (AST) increased	4	(1.3)	0	(0.0)	4	(1.3)	0	(0.0)
SGPT (ALT) increased	4	(1.3)	0	(0.0)	4	(1.3)	0	(0.0)
Creatine phosphokinase increased	3	(1.0)	0	(0.0)	2	(0.6)	0	(0.0)
Vomiting	3	(1.0)	0	(0.0)	3	(1.0)	0	(0.0)

Includes data up to 30 days after last dose of study treatment.

Nine subjects (2.9%) in the atorvastatin + donepezil group and 6 subjects (1.8%) in the placebo + donepezil group died during the study. The reasons for death in the atorvastatin + donepezil group were congestive cardiac failure, pneumonia, death, aspiration pneumonia, acute renal failure, gastric perforation, myocardial infarction, sudden cardiac death/atrioventricular block complete, and dementia Alzheimer's type. The reasons for death in the placebo + donepezil group were death not otherwise specified, rectal cancer, rectal cancer/metastasis, myocardial infarction, pneumonia, and myocardial infarction.

A total of 60 (19.1%) atorvastatin-treated and 69 (21.2%) placebo-treated subjects experienced serious adverse events (SAEs). The most common SAE in the atorvastatin and placebo groups was fall (9 and 13 subjects, respectively). SAEs of particular interest during the study were hepatitis, liver disorder, and rhabdomyolysis in 3 subjects in the atorvastatin + donepezil group, and back pain in 1 subject in the placebo + donepezil group. All causality serious adverse events reported by the investigator that occurred on or after Day 1 of the study in at least 2 subjects in either treatment group are summarized in Table S5.

Table S5. SAEs That Occurred in ≥2 Subjects in Either Treatment Group

AE Preferred Term, n (%)	Atorvastatin + Donepezil N=314	Placebo + Donepezil N=325
Any SAE[a]	60 (19.1)	69 (21.2)
Fall	9	13
Myocardial infarction	4	5
Wrist fracture	3	3
Diarrhea	2	1
Inguinal hernia	2	2
Small intestinal obstruction	2	0
Pneumonia	2	3
Dehydration	2	0
Parathyroid tumor benign	2	0
Dementia Alzheimer's type	2	0
Benign prostatic hyperplasia	2	0
Pulmonary edema	2	0
Vomiting	2	0
Gastrointestinal haemorrhage[b]	2	0
Hip fracture	1	4
Syncope	1	6
Aggression	1	3
Vertigo	0	2
Appendicitis perforated	0	2
Rib fracture	0	2
Metastasis	0	2
Prostate cancer	0	2
Rectal cancer	0	2
Cerebrovascular accident	0	3
Agitation	0	2
Confusional state	0	2
Delirium	0	2
Sick sinus syndrome	0	2

CONCLUSION(S):

- In this first large scale trial evaluating statins as a treatment for mild to moderate AD, atorvastatin add on therapy to donepezil was not associated with significant benefit compared to placebo (donepezil alone) on cognition and global function measures over 72 weeks.

- In the MRI sub-study, there was a significantly smaller mean decrease in hippocampus volume from baseline to Month 18 in the atorvastatin + donepezil group compared to the placebo + donepezil group (110.71 and 173.89 mm^3/year, respectively, p=0.0241), but without differences in the overall brain volume changes.

- By Month 3, mean LDL-C decreased -72.4 mg/dL (% change -50.2) in the atorvastatin + donepezil group and -1.0 mg/dL (% change -0.2) in the placebo + donepezil group.

These changes remained constant through Month 18. Larger decreases were also observed in the atorvastatin + donepezil group than the placebo + donepezil group for total cholesterol, triglycerides, and ApoE. There was little change in HDL-C in either treatment group.

- Atorvastatin 80 mg/day was generally well tolerated and the incidence of liver and muscle adverse events were consistent with the atorvastatin product label.