The Atorvastatin/Donepezil in Alzheimer's Disease (LEADe) Study: Effect of Atorvastatin on Alzheimer's Disease Progression by ApoE4 Genotype

D Larry Sparks[1], Miia Kivipelto[2], Rachelle Doody[3], Howard Feldman[4], Roy W Jones[5], David Waters[6], Eve Pickering[7], Xiaolan Hu[7], Stephanie Hall[7], Andrei Breazna[7], David A DeMicco[7], Judith Hey-Hadavi[7], Rachel J Schindler[7]

[1]*Ralph & Muriel Roberts Laboratory For Neurodegenerative Research, SunHealth Research Institute, Sun City, AZ, USA;* [2]*Aging Research Center, Karolinska Institutet, Stockholm, Sweden;* [3]*Baylor College of Medicine, Houston, TX, USA;* [4]*University of British Columbia and Vancouver Hospital, Vancouver, BC, Canada;* [5]*The Research Institute for the Care of Older People, Royal United Hospital, Bath, United Kingdom;* [6]*San Francisco General Hospital, San Francisco, CA, USA;* [7]*Pfizer Inc, New York, NY, USA*

INTRODUCTION

- Increasing evidence suggests that elevated cholesterol levels in mid-life are associated with increased risk of developing Alzheimer's disease (AD),[1-3] and that statins might have a protective effect against AD and dementia.[4-7]
- Furthermore, numerous studies have demonstrated that the *ApoE e4* allele of the cholesterol transporter apolipoprotein E (apoE) is the most important and consistent genetic risk factor for late-onset AD.[8-10]
- The Atorvastatin/Donepezil in Alzheimer's Disease (LEADe) study tested the hypothesis that a statin (atorvastatin 80 mg/day) provides a benefit on the course of mild-to-moderate AD in patients receiving background therapy of a cholinesterase inhibitor (donepezil 10 mg/day).
- The main LEADe study showed no significant differences between the treatment groups for the co-primary end points of change in AD Assessment Scale-cognitive subscale (ADAS-cog) and AD Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC).[11]

OBJECTIVES

- In this pre-planned analysis we reassessed the co-primary end points of change in ADAS-cog and ADCS-CGIC scale scores for differences between subgroups of patients according to their *ApoE e4* (+/-) allele status.

METHODS

Study Design

- The design of the LEADe study has been described previously.[12]
- Eligible patients were men and women aged 50–90 years with mild-to-moderate AD (Mini-mental state examination [MMSE] score 13–25).
- A computed tomography or MRI brain scan consistent with the diagnosis of probable AD and without significant comorbid abnormalities was required within the previous 12 months.
- All patients had to have been receiving donepezil 10 mg for at least 3 months prior to screening.
- At study entry, subjects had to have low-density lipoprotein cholesterol (LDL-C) levels of 95–195 mg/dL.
- Subjects with diabetes mellitus who had stable blood sugars with diet or treatment with antidiabetic agents were permitted to enter the study if they had HbA_{1c} levels of <10% and fasting serum glucose levels of <170 mg/dL and LDL-C levels of 95–135 mg/dL.
- At the start of the double-blind 72-week treatment period, subjects receiving existing treatment with donepezil 10 mg were randomized to atorvastatin 80 mg or placebo. At Week 72, subjects entered a double-blind 8-week atorvastatin withdrawal period: subjects receiving atorvastatin 80 mg plus donepezil 10 mg were re-randomized to receive either atorvastatin 80 mg plus donepezil 10 mg or placebo plus donepezil 10 mg; subjects receiving placebo plus donepezil 10 mg continued to receive the same treatment.

Efficacy Outcomes

- The co-primary efficacy outcomes were change from baseline in ADAS-cog and ADCS-CGIC scale scores.
- Subjects were assessed for *ApoE e4* status and treatment interaction.

Statistical Analysis

- In the primary analysis, a repeated measures, mixed effects analysis was performed for the primary efficacy parameters.
- 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 primary analysis was performed on the modified intention-to-treat (MITT) population, defined as randomized patients who received at least 1 dose of study medication and had both baseline and at least 1 follow-up study evaluation.
- In this analysis, the pre-specified model for ADAS-cog for the genotyped subjects included treatment, gender, age, *ApoE e4* carrier status (+/-), study visit, and baseline ADAS-cog as main effects, along with the interaction of treatment with gender, *ApoE e4* carrier status, and study visit. The treatment by *ApoE e4* carrier status interaction term assesses whether or not the treatment effect is affected by *ApoE e4* carrier status. A similar model was fit for ADCS-CGIC, but with no correction for baseline status.
- Because only a subset of patients were genotyped, we examined the baseline characteristics of the genotyped and non-genotyped patients.
- Post hoc exploratory analyses were carried out to examine possible causes of the results observed in the pre-specified analysis. Additional terms of baseline cholesterol (≥200 mg/dL, yes/no), baseline MMSE, and baseline CDR, along with their interaction with treatment were also assessed in the model.

RESULTS

Baseline Characteristics

- Of 641 patients randomized in the 72-week double-blind treatment phase of LEADe, 514 subjects consented to genotyping. A total of 489 patients (231 on atorvastatin 80 mg, 258 on placebo) within the MITT population had complete genotype data and were included within this analysis.
- Demographic characteristics for patients with complete genotype data were similar to patients without complete genotype data and to the overall MITT population, and were well balanced between treatment groups. Baseline MMSE was slightly higher in the non-genotyped group, compared with the genotyped group (Table 1).

Table 1: Baseline demographics of MITT population by genotyping status

	Overall MITT Population		Genotyped Patients		Non-genotyped Patients	
	PBO + DPZ 10 mg (n=317)	ATV 80 mg + DPZ 10 mg (n=297)	PBO + DPZ 10 mg (n=258)	ATV 80 mg + DPZ 10 mg (n=231)	PBO + DPZ 10 mg (n=59)	ATV 80 mg + DPZ 10 mg (n=59)
Age, years	73.2	74.0	73.3	73.7	73.1	74.6
Male, %	49.0	47.0	48.8	47.6	50.8	49.2
White, %	96.8	95.6	98.1	95.7	91.5	94.9
Total-C, mg/dL	223.1	225.1	222.5	224.4	224.0	227.8
LDL-C, mg/dL	141.9	143.9	140.9	144.4	145.0	142.1
Triglycerides, mg/dL	131.9	131.0	134.8	134.0	118.6	121.3
HDL-C, mg/dL	63.0	63.8	63.1	61.9	63.1	69.3
MMSE	21.9	21.8	21.9	21.7	21.8	22.0
ADAS-cog	22.5	22.3	22.3	22.4	23.6	21.6
CDR	5.9	5.7	5.8	5.7	6.4	5.6
ADFACS	13.1	13.2	12.9	13.4	14.3	12.0
NPI	9.6	9.7	9.7	9.4	9.0	10.6

ATV, atorvastatin; DPZ, donepezil; PBO, placebo; ADFACS, AD Functional Assessment and Change Scale; CDR, Clinical Dementia Rating; NPI, Neuropsychiatric Inventory; HDL-C, high-density lipoprotein cholesterol; Total-C, total cholesterol

- A total of 140 patients (60.6%) receiving atorvastatin 80 mg and 154 patients (59.7%) receiving placebo were carriers of the *ApoE e4* allele (Table 2). The distribution of *ApoE* genotypes was not significantly different between the 2 treatment arms ($P=0.98$), and was similar to that observed in populations of Caucasian AD patients.[13]

Cognitive Outcomes

- In the primary analysis, atorvastatin therapy was not associated with a significant effect on ADAS-cog score, compared with placebo (Figure 1A).
- In this analysis, in the genotyped group, atorvastatin therapy was associated with a significantly reduced decline in ADAS-cog score from baseline, compared with placebo ($P=0.04$) (Figure 1B); however, *ApoE e4* status had no significant effect on change in ADAS-cog score ($P=0.22$) and there was no significant *ApoE e4* status–treatment interaction ($P=0.88$) or gender–treatment interaction ($P=0.12$).
- None of the explanatory terms added post hoc had a statistically significant contribution on the change in ADAS-cog score except baseline MMSE ($P=0.04$), where higher baseline MMSE scores predicted a smaller decline in cognition, regardless of treatment; and baseline CDR ($P<0.001$), where higher baseline scores predicted a greater decline in cognition, regardless of treatment. Cholesterol ≥200 mg/dL had no significant contribution on the change in ADAS-cog score.

Table 2: Distribution of ApoE genotypes by treatment group

Treatment arm/ AD populations, n (%)	E4/E4	E3/E4	E2/E4	E3/E3	E2/E3	E2/E2
Placebo + donepezil 10 mg (n=258)	34 (13.2)	117 (45.3)	3 (1.1)	88 (34.1)	16 (6.2)	0 (0.0)
Atorvastatin 80 mg + donepezil 10 mg (n=231)	33 (14.3)	105 (45.5)	2 (0.9)	75 (32.5)	16 (6.9)	0 (0.0)
Observed frequency in AD populations[12]	340 (14.6)	986 (42.4)	65 (2.8)	804 (34.6)	123 (5.3)	7 (0.3)

- In the primary analysis, atorvastatin therapy was not associated with a significant effect on ADCS-CGIC score, compared with placebo (Figure 2A).
- In this analysis, in the genotyped group, for the co-primary end point of ADCS-CGIC score, there was no significant effect of atorvastatin treatment, compared with placebo ($P=0.89$) (Figure 2B). Furthermore, *ApoE e4* status had no significant effect on ADCS-CGIC score ($P=0.20$) and there was no significant *ApoE e4* status–treatment interaction ($P=0.14$) or gender–treatment interaction ($P=0.31$).

Figure 1: Mean change in ADAS-cog score by treatment assignment in (A) the overall MITT population and (B) the genotyped MITT population

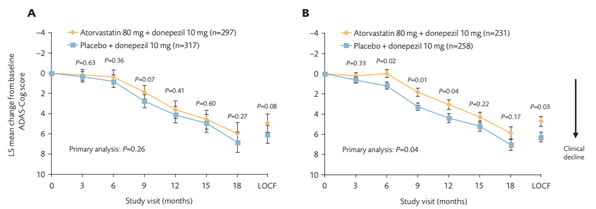
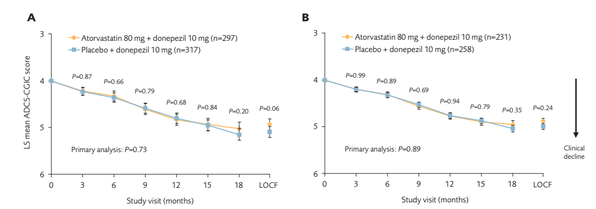


Figure 2: Mean ADCS-CGIC score by treatment assignment in (A) the overall MITT population and (B) the genotyped MITT population



- Similar to the post hoc analysis of ADAS-cog, adding the exploratory terms to the ADCS-CGIC model resulted in statistical significance for the main effects of baseline MMSE ($P<0.001$), where higher baseline MMSE scores predicted a lesser clinical decline, regardless of treatment; and baseline CDR ($P<0.001$), where higher baseline CDR scores predicted a greater clinical decline, regardless of treatment. Cholesterol ≥200 mg/dL had no significant contribution on the ADCS-CGIC score.
- Overall, 8 out of the 97 centers did not collect samples for genotyping. Approximately half of the non-genotyped patients within the MITT population were recruited by these centers.
- Because some centers did not perform genotyping, the significant treatment effect observed in the genotyped group but not the overall population may have been due to significant differences between the two populations. In order to examine this, a model was developed to show change in ADAS-cog by genotyping status. This analysis suggests that for change in ADAS-cog score, there were significant differences in the treatment effect between the genotyped and non-genotyped groups (Table 3). A similar analysis of the ADCS-CGIC shows an effect of genotyping status, but no treatment effect (Table 4).

Table 3: Mean change in ADAS-cog score by treatment assignment and genotyping status

	Genotyped	Non-genotyped
Placebo + donepezil 10 mg	3.59 (0.34)	2.01 (0.59)
Atorvastatin 80 mg + donepezil 10 mg	2.70 (0.36)	3.13 (0.60)

LS mean change (SE)

Table 4: Mean ADCS-CGIC score by treatment assignment and genotyping status

	Genotyped	Non-genotyped
Placebo + donepezil 10 mg	4.65 (0.04)	4.78 (0.09)
Atorvastatin 80 mg + donepezil 10 mg	4.63 (0.05)	4.78 (0.09)

LS mean (SE)

Safety

- No safety analysis was performed for the genotyped and non-genotyped patient groups.
- In the overall MITT population, 60 patients (19.1%) in the atorvastatin 80 mg plus donepezil 10 mg group experienced serious adverse events, compared with 67 patients (20.6%) in the placebo plus donepezil 10 mg group.
- Incidence of persistent elevations in liver enzymes (2 measurements of alanine aminotransferase and/or aspartate aminotransferase >3 x upper limit of normal, obtained 4–10 days apart) was 2.6% in the atorvastatin 80 mg plus donepezil 10 mg group and 0.0% in the placebo plus donepezil 10 mg group.
- No patients had persistent elevations in creatine phosphokinase values.

SUMMARY

- The primary analysis of the LEADe study showed that in AD patients receiving background donepezil therapy, atorvastatin treatment was not associated with significant cognitive benefits—as measured by change in ADAS-cog and ADCS-CGIC scores—compared with placebo.[11]
- In this pre-planned, post hoc analysis of the population of genotyped patients, compared with placebo, atorvastatin therapy was associated with a significant benefit on the primary end point of change in ADAS-cog score; however, *ApoE e4* status had no significant effect on change in ADAS-cog score and there was no significant *ApoE e4* status–treatment interaction or gender–treatment interaction.
- Exploratory analyses suggest that for change in ADAS-cog score, there were significant differences in the treatment effect between the genotyped and non-genotyped groups, which may have been related to differences between centers, but was not related to *ApoE* genotype, gender, or baseline cholesterol levels.
- Co-therapy with donepezil plus high-dose atorvastatin was well tolerated in patients with mild-to-moderate AD.

REFERENCES **1.** Yaffe K, et al. Serum lipoprotein levels, statin use, and cognitive function in older women. *Arch Neurol.* 2002;59(3):378-384. **2.** Whitmer RA, et al. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology.* 2005;64(2):277-281. **3.** Kivipelto M, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ.* 2001;322(7300):1447-1451. **4.** Jick H, et al. Statins and the risk of dementia. *Lancet.* 2000;356(9242):1627-1631. **5.** Rockwood K, et al. Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people. *Arch Neurol.* 2002;59(2):223-227. **6.** Wolozin B, et al. Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors. *Arch Neurol.* 2000;57(10):1439-1443. **7.** Wolozin B, et al. Simvastatin is associated with a reduced incidence of dementia and Parkinson's disease. *BMC Med.* 2007;5:20. **8.** Corder EH, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science.* 1993;261(5123):921-923. **9.** Wolozin B, et al. Re-assessing the relationship between cholesterol, statins and Alzheimer's disease. *Acta Neurol Scand Suppl.* 2006;185:63-70. **10.** Poirier J, et al. Apolipoprotein E polymorphism and Alzheimer's disease. *Lancet.* 1993;342(8873):697-699. **11.** Feldman H, on behalf of the LEADe Steering Committee. The LEADe Study: A randomized controlled trial investigating the effect of atorvastatin on cognitive and global function in patients with mild to moderate AD receiving background therapy of donepezil. The 60th Annual Meeting of the American Academy of Neurology, Chicago, IL; April 12–19, 2008. **12.** Bertram L, et al. The AlzGene database. Alzheimer Research Forum. Available at: http://www.alzgene.org. Accessed: June 1, 2008.

ACKNOWLEDGEMENTS **The LEADe Steering Committee:** Howard Feldman, Rachelle Doody, Roy Jones, Miia Kivipelto, David Lawrence Sparks, David Waters.
This study was sponsored by Pfizer Inc, New York. Editorial support was provided by Chris Cadman, PhD, of Envision Pharma and was funded by Pfizer Inc.

Presented at the International Congress on Alzheimer's Disease, July 26–31, 2008; Chicago, Illinois