THERAPEUTIC COMBINATION FOR TREATMENT OF ALZHEIMER'S DISEASE

The present application claims priority under 35 U.S.C. section 119(e) to United States Provisional Application Serial Numbers 60,562,141 filed April 16, 2004.

FIELD OF THE INVENTION

The present invention relates to compositions useful for the treatment of Alzheimer's Disease. The invention further relates to methods of using such compositions to treat subjects, including humans, suffering from Alzheimer's Disease.

BACKGROUND OF THE INVENTION

Alois Alzheimer in 1906 was the first to describe the unique neuropathologic features of what we now call Alzheimer's disease (AD), in the brain of a patient with progressive dementia (Alzheimer A. Ueber eine eigenartige erkrankung der hirnrinde. *Z Gesamte Neurol Psychiat.* 18:177; 1907). Over 5% of individuals over the age of 65 are estimated to be affected by dementia (Hofman A, Rocca WA, Brayne C, Breteler MM, Clarke M, Cooper B, et al. The prevalence of dementia in Europe: A collaborative study of 1980-1990 findings. EURODEM Prevalence Research Group. *Int J Epidemiol,* 20(3): 736-748; 1991). Between 60 and 70% of dementias are attributed to Alzheimer's disease ("AD"). According to the Alzheimer's Association, one in ten people over 65 years of age, and nearly half of those over 85 years of age suffer from AD. Currently, over 4 million Americans suffer from this disease. It is estimated that this number will increase to 14 million in the year 2050 (Brookmeyer R and Gray S. Methods for projecting the incidence and prevalence of chronic diseases in aging populations: Application to Alzheimer's disease. *Stat Med,* 19(11-12): 1481-1493; 2000).

Alzheimer's disease is a chronic neurodegenerative disorder that is manifested by cognitive declines in learning and memory. It is accompanied by

diffuse structural abnormalities in the brain. A growing body of evidence suggests that beta amyloid (Aβ) plays an important role in this multifactorial degenerative process (De Strooper B and Annaert W. Proteolytic processing and cell biological functions of the amyloid precursor protein. *J Cell Sci,* 113:1857-1870; 2000). However, in a review by Emmerling and co-workers (Emmerling MR, Spiegel K, Hall ED, LeVine H, Walker LC, Schwarz RD and Gracon S. Emerging strategies for the treatment of Alzheimer's disease at the Millennium. *Emerging Drugs,* 4:35-86; 1999), they described AD as "...no longer viewed solely as a disease of neurotransmitter deficits or amyloid deposition. Rather, it is a combination of events (amyloidosis, neurofibrillary pathology, inflammation, oxidative stress and cerebral vascular insufficiency) that conspire to produce this dementia."

Acetylcholine esterase inhibitors are known to be useful in the treatment of AD. Examples of known acetylcholine esterase inhibitors include donepezil (Aricept®), tacrine (Cognex®), rivastigmine (Exelon®) and galantamine (Reminyl). Aricept® is disclosed in the following U.S. patents, all of which are fully incorporated herein by reference: 4,895,841, 5,985,864, 6,140,321, 6,245,911 and 6,372,760. Exelon® is disclosed in U.S. Patent Nos. 4,948,807 and 5,602,176 which are fully incorporated herein by reference.

Cognex® is disclosed in U.S. Patent Nos. 4,631,286 and 4,816,456 (fully incorporated herein by reference). Remynil® is disclosed in U.S. Patent Nos. 4,663,318 and 6,099,863 which are fully incorporated herein by reference.

Cholesterol may play an important role in the development and progression of AD. The synthesis and secretion of various lipid particles occurs differentially in the periphery and the brain. Importantly, further research is needed to understand the potentially critical role of transport and metabolism of lipid particles both in the periphery and the brain in AD (Beisiegel U and Spector AA. Lipids and lipoproteins in the brain. *Current Opinion in Lipidology,* 12:243-244; 2001).

Cholesterol modulates the processing of amyloid precursor protein (APP) and associated Aβ production as demonstrated through *in vitro* and animal model studies (Emmerling MR, Spiegel K, Hall ED, LeVine H, Walker LC, Schwarz RD and Gracon S. Emerging strategies for the treatment of Alzheimer's disease at the

Millennium. *Emerging Drugs,* 4:35-86; 1999). Excess cholesterol in culture or animal diet results in an increase in processing of amyloid precursor protein (APP) and production of Aβ. Removing cholesterol from culture or animal diets results in a reduction in the processing of APP and production of Aβ (Bergmann C, Runz H, Jakala P and Hartmann T. Diversification of gamma secretase versus beta-secretase inhibition by cholesterol depletion. *Neurobiol Aging,* 21:S278; 2000). Statins inhibit *de novo* synthesis by blocking a critical step in the pathway, conversion of HMG-CoA to mevalonate. Lowering cholesterol through HMG-CoA-reductase inhibitors, known as statins, has a similar effect on the processing of APP and the production of Aβ (Austen BM, Frears ER and Davies H. Cholesterol upregulatr es production of Abeta 1-40 and 1-42 in transfected cells. *Neurobiol Aging,* 21:S254; 2000).

In normal human subjects treated with, for example, lovastatin, serum Aβ concentrations are reduced in a dose-dependent manner (Friedhoff LT, Cullen EI, Geoghagen NS, Buxbaum JD. Treatment with controlled-release lovastatin decreases serum concentrations of human beta-amyloid (Aβ) peptide. *Int J Neuropsychopharmacol.,* 4(2):127-30; June 2001). These data suggest that a lowering of serum cholesterol is correlated with a reduction in APP and β amyloid. Such reduction could result in a modification of disease progression and an improvement in cognitive and behavioral function.

It has been suggested that the role of serum ApoE in the development of AD may not be through cholesterol, but more directly on Aβ aggregation (Golde TE and Eckman CB. Cholesterol modulation as an emerging strategy for the treatment of Alzheimer's disease. *Drug Discovery Today,* 6(2): 1049-1055; 2001). Advancing age, female gender and family history are clear risk factors for AD. Additional risk factors include smoking, body mass, blood pressure, and lipid values. However, as the disease progresses, the relative importance of these risk factors may change (Corti MC, Guralnik JM, Salive ME, Harris T, Ferrucci L, Glynn RJ, Havlik RJ. Clarifying the direct relation between total cholesterol levels and death from coronary heart disease in older persons. *Ann Intern Med,* 126:753-760; 1997). In general, the diagnosis of AD is associated with raised serum cholesterol several decades earlier (Kivipelto M, Helkala EL, Heanninen T and

others. Midlife vascular risk factors and late-life mild cognitive impairment – A population-based study. *Neurology,* 322:1447-1451; 2001).

Early work by Sparks and co-workers (Sparks, DL, Hunsaker JC and others. Cortical senile plaques in coronary artery disease, aging and Alzheimer's disease. *Neurobiology of Aging,* 11(6): 601-607; 1990) demonstrated AD-like neuropathologic lesions in non-demented CAD patients. Epidemiological work has demonstrated an association between high fat diets and the risk of AD (Desmond DW, Tatemichi TK, Paik M, Stern Y. Risk factors for cerebrovascular disease as correlates of cognitive function in a stroke-free cohort. *Arch Neurol,* 50:162-166; 1993). Diets that are so-called cardioprotective have been shown to reduce the risk of developing AD (Forette F, Seux ML, Staessen JA and others. Prevention of dementia in randomized double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet,* 352:1347-1351; 1998).

Recent retrospective studies point to a positive relationship between the use of cholesterol-lowering agents, namely statins, and a reduction in cholesterol and risk of developing AD (Jick H, Zornberg GL, Jick SS, Seshadri S and Drachman DA. Statins and the risk of dementia. *The Lancet, 356:1627*-1631; 2000).

Atorvastatin is a member of the statin class of lipid regulators for use in the treatment of hypercholesterolemia. United States Patent No. 4,681,893 (fully incorporated herein by reference) and United States Patent No. 5,273,995 (fully incorporated herein by reference) disclose atorvastatin (Lipitor®). Other statins include lovastatin, fluvastatin, cerivastatin, pravastatin, simvastatin and rosuvastatin.

SUMMARY OF THE INVENTION

The present invention provides a pharmaceutical composition comprising an amount of an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof; an amount of atorvastatin or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier or diluent.

The present invention further provides a method for treating a mammal suffering from Alzheimer's Disease comprising administering to said mammal a therapeutically effective amount of a first compound, said first compound being an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a second compound, said second compound being atorvastatin or a pharmaceutically acceptable salt thereof.

Further provided is a method for preventing Alzheimer's Disease in a mammal comprising administering to said mammal a therapeutically effective amount of a first compound, said first compound being an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a second compound, said second compound being atorvastatin or a pharmaceutically acceptable salt thereof.

Further provided is a method for treating a mammal which has been diagnosed as suffering from Alzheimer's Disease or the risk of Alzheimer's Disease, which would benefit from therapy by the combined administration of both (a) and (b) below, and therefore administration of both (a) and (b) has been prescribed, which comprises administering to said mammal so diagnosed and prescribed an amount of a first active ingredient (a), said first active ingredient (a) being an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof; and an amount of a second active ingredient (b), said second active ingredient (b) being atorvastatin or a pharmaceutically acceptable salt thereof wherein said first active ingredient (a) and said second active ingredient (b) are administered together in a single pharmaceutical composition with a pharmaceutically acceptable carrier or diluent.

Further provided is a method for treating or preventing Alzheimer's Disease in a mammalwhich has been examined for Alzheimer's Disease by a medical practitioner and diagnosed as in need of therapy for said Alzheimer's

Disease by the joint administration of the active ingredients designated as (a) and (b) below, which comprises a therapeutically effective amount of a first active ingredient (a), said first active ingredient (a) being an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a second active ingredient (b), said second active ingredient (b) being atorvastatin, or a pharmaceutically acceptable salt thereof; wherein said first active ingredient (a) and said second active ingredient (b) are administered together in a single pharmaceutical composition with a pharmaceutically acceptable carrier or diluent.

Further provided is a kit for acheiving a therapeutic effect in a mammal comprising a therapeutically effective amount of an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a first unit dosage form; a therapeutically effective amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a second unit dosage form; and container means for containing said first and second dosage forms.

Further provided is a first pharmaceutical composition for use with a second pharmaceutical compostion for achieving an Alzheimer's Disease-modifying effect in a mammal suffering from Alzheimer's Disease, which Alzheimer's Disease-modifying effect is greater than the sum of the effects achieved by administering said first and second pharmaceutical compositions separately wherein said first pharmaceutical composition comprises an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, and wherein said second pharmaceutical composition comprises and an amount of an acetylcholine esterase inhibitor or a pharmaceutically acceptable carrier or diluent.

Further provided is a pharmaceutical composition comprising an amount of an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof; an amount of a statin or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier or diluent.

Further provided is a method for treating a mammal suffering from Alzheimer's Disease comprising administering to said mammal a therapeutically effective amount of a first compound, said first compound being an acetylcholine

esterase inhibitor or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a second compound, said second compound being a statin or a pharmaceutically acceptable salt thereof.

Further provided is a method for preventing Alzheimer's Disease in a mammal comprising administering to said mammal a therapeutically effective amount of a first compound, said first compound being an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a second compound, said second compound being a statin or a pharmaceutically acceptable salt thereof.

Further provided is a method for treating a mammal which has been diagnosed as suffering from Alzheimer's Disease or the risk of Alzheimer's Disease, which would benefit from therapy by the combined administration of both (a) and (b) below, and therefore administration of both (a) and (b) has been prescribed, which comprises administering to said mammal so diagnosed and prescribed an amount of a first active ingredient (a), said first active ingredient (a) being an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof; and an amount of a second active ingredient (b), said second active ingredient (b) being a statin or a pharmaceutically acceptable salt thereof wherein said first active ingredient (a) and said second active ingredient (b) are administered together in a single pharmaceutical composition with a pharmaceutically acceptable carrier or diluent.

Further provided is a method for treating or preventing Alzheimer's Disease in a mammal which has been examined for Alzheimer's Disease by a medical practitioner and diagnosed as in need of therapy for said Alzheimer's Disease by the joint administration of the active ingredients designated as (a) and (b) below, which comprises a therapeutically effective amount of a first active ingredient (a), said first active ingredient (a) being an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a second active ingredient (b), said second active ingredient (b) being a statin, or a pharmaceutically acceptable salt thereof;
wherein said first active ingredient (a) and said second active ingredient (b) are administered together in a single pharmaceutical composition with a pharmaceutically acceptable carrier or diluent.

Further provided is a kit for acheiving a therapeutic effect in a mammal comprising a therapeutically effective amount of an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a first unit dosage form; a therapeutically effective amount of a statin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a second unit dosage form; and container means for containing said first and second dosage forms.

Further provided is a first pharmaceutical composition for use with a second pharmaceutical composition for achieving an Alzheimer's Disease-modifying effect in a mammal suffering from Alzheimer's Disease, which Alzheimer's Disease-modifying effect is greater than the sum of the effects achieved by administering said first and second pharmaceutical compositions separately wherein said first pharmaceutical composition comprises an amount of a statin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, and wherein said second pharmaceutical composition comprises and an amount of an acetylcholine esterase inhibitor or a pharmaceutically acceptable carrier or diluent.

The present invention further provides a pharmaceutical composition comprising an amount of donepezil or a pharmaceutically acceptable salt thereof; an amount of atorvastatin or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier or diluent.

Further provided is a method for treating a mammal suffering from Alzheimer's Disease comprising administering to said mammal a therapeutically effective amount of a first compound, said first compound being donepezil or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a second compound, said second compound being atorvastatin or a pharmaceutically acceptable salt thereof.

Further provided is a method for preventing Alzheimer's Disease in a mammal comprising administering to said mammal a therapeutically effective amount of a first compound, said first compound being donepezil or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a second compound, said second compound being atorvastatin or a pharmaceutically acceptable salt thereof.

Further provided is a method for treating a mammal which has been diagnosed as suffering from Alzheimer's Disease or the risk of Alzheimer's Disease, which would benefit from therapy by the combined administration of both (a) and (b) below, and therefore administration of both (a) and (b) has been prescribed, which comprises administering to said mammal so diagnosed and prescribed, an amount of a first active ingredient (a), said first active ingredient (a) being donepezil or a pharmaceutically acceptable salt thereof; and an amount of a second active ingredient (b), said second active ingredient (b) being atorvastatin or a pharmaceutically acceptable salt thereof wherein said first active ingredient (a) and said second active ingredient (b) are administered together in a single pharmaceutical composition with a pharmaceutically acceptable carrier or diluent.

Further provided is a method for treating Alzheimer's Disease in a mammal which has been examined for Alzheimer's Disease by a medical practitioner and diagnosed as in need of therapy for said Alzheimer's Disease by the joint administration of the active ingredients designated as (a) and (b) below, which comprises a therapeutically effective amount of a first active ingredient (a), said first active ingredient (a) being donepezil or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a second active ingredient (b), said second active ingredient (b) being atorvastatin, or a pharmaceutically acceptable salt thereof; wherein said first active ingredient (a) and said second active ingredient (b) are administered together in a single pharmaceutical composition with a pharmaceutically acceptable carrier or diluent.

Further provided is a kit for acheiving a therapeutic effect in a mammal comprising a therapeutically effective amount of donepezil or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a first unit dosage form; a therapeutically effective amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a second unit dosage form; and container means for containing said first and second dosage forms.

Further provided is a first pharmaceutical composition for use with a second pharmaceutical compostion for achieving an Alzheimer's Disease-modifying effect in a mammal suffering from Alzheimer's Disease, which Alzheimer's Disease-modifying effect is greater than the sum of the effects

achieved by administering said first and second pharmaceutical compositions separately wherein said first pharmaceutical composition comprises an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, and wherein said second pharmaceutical composition comprises and an amount of donepezil or a pharmaceutically acceptable carrier or diluent.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a pharmaceutical composition comprising an amount of an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof; an amount of atorvastatin or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier or diluent.

Further provided is the above composition comprising the hemicalcium salt of atorvastatin.

Further provided is the above composition comprising from about 0.2 mg. to about 20 mg. of an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof and about 5 mg. to about 80 mg. of atorvastatin or a pharmaceutically acceptable salt thereof.

Further provided is the pharmaceutical composition comprising a fixed combination selected from the group consisting of: atorvastatin calcium, 5 mg active and an acetylcholine esterase inhibitor, 10 mg active; atorvastatin calcium, 10 mg active and an acetylcholine esterase inhibitor, 10 mg active; atorvastatin calcium, 20 mg active and an acetylcholine esterase inhibitor, 10 mg active; atorvastatin calcium, 40 mg active and an acetylcholine esterase inhibitor, 10 mg active; atorvastatin calcium, 80 mg active and an acetylcholine esterase inhibitor, 10 mg active; atorvastatin calcium, 5 mg active and an acetylcholine esterase inhibitor, 5 mg active; atorvastatin calcium, 10 mg active and an acetylcholine esterase inhibitor, 5 mg active; atorvastatin calcium, 20 mg active and an acetylcholine esterase inhibitor, 5 mg active; atorvastatin calcium, 40 mg active and an acetylcholine esterase inhibitor, 5 mg active; and atorvastatin calcium, 80 mg active and an acetylcholine esterase inhibitor, 5 mg active.

Further provided is a method for treating a mammal suffering from Alzheimer's Disease comprising administering to said mammal a therapeutically effective amount of a first compound, said first compound being an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a second compound, said second compound being atorvastatin or a pharmaceutically acceptable salt thereof.

Further provided is a method for preventing Alzheimer's Disease in a mammal comprising administering to said mammal a therapeutically effective

amount of a first compound, said first compound being an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a second compound, said second compound being atorvastatin or a pharmaceutically acceptable salt thereof.

Further provided is a method for treating a mammal which has been diagnosed as suffering from Alzheimer's Disease or the risk of Alzheimer's Disease, which would benefit from therapy by the combined administration of both (a) and (b) below, and therefore administration of both (a) and (b) has been prescribed, which comprises administering to said mammal so diagnosed and prescribed an amount of a first active ingredient (a), said first active ingredient (a) being an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof; and an amount of a second active ingredient (b), said second active ingredient (b) being atorvastatin or a pharmaceutically acceptable salt thereof wherein said first active ingredient (a) and said second active ingredient (b) are administered together in a single pharmaceutical composition with a pharmaceutically acceptable carrier or diluent.

Further provided is a method for treating or preventing Alzheimer's Disease in a mammal which has been examined for Alzheimer's Disease by a medical practitioner and diagnosed as in need of therapy for said Alzheimer's Disease by the joint administration of the active ingredients designated as (a) and (b) below, which comprises a therapeutically effective amount of a first active ingredient (a), said first active ingredient (a) being an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a second active ingredient (b), said second active ingredient (b) being atorvastatin, or a pharmaceutically acceptable salt thereof; wherein said first active ingredient (a) and said second active ingredient (b) are administered together in a single pharmaceutical composition with a pharmaceutically acceptable carrier or diluent.

Further provided is a kit for acheiving a therapeutic effect in a mammal comprising a therapeutically effective amount of an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a first unit dosage form; a therapeutically effective amount of atorvastatin or a pharmaceutically acceptable salt thereof and a

pharmaceutically acceptable carrier or diluent in a second unit dosage form; and container means for containing said first and second dosage forms.

Further provided is a first pharmaceutical composition for use with a second pharmaceutical compostion for achieving an Alzheimer's Disease-modifying effect in a mammal suffering from Alzheimer's Disease, which Alzheimer's Disease-modifying effect is greater than the sum of the effects achieved by administering said first and second pharmaceutical compositions separately wherein said first pharmaceutical composition comprises an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, and wherein said second pharmaceutical composition comprises and an amount of an acetylcholine esterase inhibitor or a pharmaceutically acceptable carrier or diluent.

Further provided is a method for stabilizing symptoms of Alzheimer's Disease in a mammal requiring stabilization comprising administering to said mammal a stabilizing amount of the above-described pharmaceutical composition.

Further provided is the method wherein said stabilization is assessed by the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog). Further provided is the method wherein said stabilization is assessed by the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change scale (ADCS-CGIC).

Still further, the present invention provides a pharmaceutical composition comprising an amount of an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof; an amount of a statin or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier or diluent.

Further provided is the above pharmaceutical composition comprising from about 0.2 mg. to about 20 mg. of an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof and about 5 mg. to about 80 mg. of a statin or a pharmaceutically acceptable salt thereof.

Further provided is the above pharmaceutical composition comprising a fixed combination selected from the group consisting of: a statin, 5 mg active and an acetylcholine esterase inhibitor, 10 mg active; a statin, 10 mg active and an acetylcholine esterase inhibitor, 10 mg active; a statin, 20 mg active and an acetylcholine esterase inhibitor, 10 mg active; atorvastatin calcium, 40 mg active

and an acetylcholine esterase inhibitor, 10 mg active; a statin, 80 mg active and an acetylcholine esterase inhibitor, 10 mg active; a statin, 5 mg active and an acetylcholine esterase inhibitor, 5 mg active; a statin, 10 mg active and an acetylcholine esterase inhibitor, 5 mg active; a statin, 20 mg active and an acetylcholine esterase inhibitor, 5 mg active; a statin, 40 mg active and an acetylcholine esterase inhibitor, 5 mg active; and a statin, 80 mg active and an acetylcholine esterase inhibitor, 5 mg active.

Further provided is a method for treating a mammal suffering from Alzheimer's Disease comprising administering to said mammal:a therapeutically effective amount of a first compound, said first compound being an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a second compound, said second compound being a statin or a pharmaceutically acceptable salt thereof.

Further provided is a method for preventing Alzheimer's Disease in a mammal comprising administering to said mammal a therapeutically effective amount of a first compound, said first compound being an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a second compound, said second compound being a statin or a pharmaceutically acceptable salt thereof.

Further provided is a method for treating a mammal which has been diagnosed as suffering from Alzheimer's Disease or the risk of Alzheimer's Disease, which would benefit from therapy by the combined administration of both (a) and (b) below, and therefore administration of both (a) and (b) has been prescribed, which comprises administering to said mammal so diagnosed and prescribed an amount of a first active ingredient (a), said first active ingredient (a) being an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof; and an amount of a second active ingredient (b), said second active ingredient (b) being a statin or a pharmaceutically acceptable salt thereof wherein said first active ingredient (a) and said second active ingredient (b) are administered together in a single pharmaceutical composition with a pharmaceutically acceptable carrier or diluent.

Further provided is a method for treating or preventing Alzheimer's Disease in a mammal which has been examined for Alzheimer's Disease by a

medical practitioner and diagnosed as in need of therapy for said Alzheimer's Disease by the joint administration of the active ingredients designated as (a) and (b) below, which comprises a therapeutically effective amount of a first active ingredient (a), said first active ingredient (a) being an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a second active ingredient (b), said second active ingredient (b) being a statin, or a pharmaceutically acceptable salt thereof; wherein said first active ingredient (a) and said second active ingredient (b) are administered together in a single pharmaceutical composition with a pharmaceutically acceptable carrier or diluent.

Further provided is a kit for acheiving a therapeutic effect in a mammal comprising a therapeutically effective amount of an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a first unit dosage form; a therapeutically effective amount of a statin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a second unit dosage form; and container means for containing said first and second dosage forms.

Further provided is a first pharmaceutical composition for use with a second pharmaceutical composition for achieving an Alzheimer's Disease-modifying effect in a mammal suffering from Alzheimer's Disease, which Alzheimer's Disease-modifying effect is greater than the sum of the effects achieved by administering said first and second pharmaceutical compositions separately wherein said first pharmaceutical composition comprises an amount of a statin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, and wherein said second pharmaceutical composition comprises and an amount of an acetylcholine esterase inhibitor or a pharmaceutically acceptable carrier or diluent.

Further provided is a method for stabilizing symptoms of Alzheimer's Disease in a mammal requiring stabilization comprising administering to said mammal a stabilizing amount of the above-described pharmaceutical composition.

Further provided is the above method wherein said stabilization is assessed by the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog).

Further provided is the method wherein said stabilization is assessed by the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change scale (ADCS-CGIC).

Still further, the present invention provides a pharmaceutical composition comprising an amount of donepezil or a pharmaceutically acceptable salt thereof; an amount of atorvastatin or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier or diluent.

Further provided is the above pharmaceutical composition comprising the hemicalcium salt of atorvastatin. Further provided is the composition comprising donepezil HCl.

Further provided is the above pharmaceutical composition comprising from about 0.2 mg. to about 20 mg. of donepezil or a pharmaceutically acceptable salt thereof and about 5 mg. to about 80 mg. of atorvastatin or a pharmaceutically acceptable salt thereof.

Further provided is the above pharmaceutical composition comprising a fixed combination selected from the group consisting of atorvastatin calcium, 5 mg active and donepezil, 10 mg active; atorvastatin calcium, 10 mg active and donepezil, 10 mg active; atorvastatin calcium, 20 mg active and donepezil, 10 mg active; atorvastatin calcium, 40 mg active and donepezil, 10 mg active; atorvastatin calcium, 80 mg active and donepezil, 10 mg active; atorvastatin calcium, 5 mg active and donepezil, 5 mg active; atorvastatin calcium, 10 mg active and donepezil, 5 mg active; atorvastatin calcium, 20 mg active and donepezil, 5 mg active; atorvastatin calcium, 40 mg active and donepezil, 5 mg active; and atorvastatin calcium, 80 mg active and donepezil, 5 mg active.

Further provided is a method for treating a mammal suffering from Alzheimer's Disease comprising administering to said mammal a therapeutically effective amount of a first compound, said first compound being donepezil or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a second compound, said second compound being atorvastatin or a pharmaceutically acceptable salt thereof.

Further provided is a method for preventing Alzheimer's Disease in a mammal comprising administering to said mammal a therapeutically effective amount of a first compound, said first compound being donepezil or a

pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a second compound, said second compound being atorvastatin or a pharmaceutically acceptable salt thereof.

Further provided is the above method comprising the hemicalcium salt of atorvastatin. Further provided is the method comprising donepezil HCl.

Further provided is a method for treating a mammal which has been diagnosed as suffering from Alzheimer's Disease or the risk of Alzheimer's Disease, which would benefit from therapy by the combined administration of both (a) and (b) below, and therefore administration of both (a) and (b) has been prescribed, which comprises administering to said mammal so diagnosed and prescribed an amount of a first active ingredient (a), said first active ingredient (a) being donepezil or a pharmaceutically acceptable salt thereof; and an amount of a second active ingredient (b), said second active ingredient (b) being atorvastatin or a pharmaceutically acceptable salt thereof wherein said first active ingredient (a) and said second active ingredient (b) are administered together in a single pharmaceutical composition with a pharmaceutically acceptable carrier or diluent.

Further provided is the above method wherein the active ingredient (b) is the hemicalcium salt of atorvastatin. Further provided is the method wherein the active ingredient (a) is donepezil HCl.

Further provided is a method for treating Alzheimer's Disease in a mammal which has been examined for Alzheimer's Disease by a medical practitioner and diagnosed as in need of therapy for said Alzheimer's Disease by the joint administration of the active ingredients designated as (a) and (b) below, which comprises a therapeutically effective amount of a first active ingredient (a), said first active ingredient (a) being donepezil or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a second active ingredient (b), said second active ingredient (b) being atorvastatin, or a pharmaceutically acceptable salt thereof; wherein said first active ingredient (a) and said second active ingredient (b) are administered together in a single pharmaceutical composition with a pharmaceutically acceptable carrier or diluent.

Further provided is the above method wherein the active ingredient (b) is the hemicalcium salt of atorvastatin. Further provided is the method wherein the active ingredient (a) is donepezil HCl.

Further provided is a kit for acheiving a therapeutic effect in a mammal comprising a therapeutically effective amount of donepezil or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a first unit dosage form; a therapeutically effective amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a second unit dosage form; and container means for containing said first and second dosage forms.

Further provided is a first pharmaceutical composition for use with a second pharmaceutical compostion for achieving an Alzheimer's Disease-modifying effect in a mammal suffering from Alzheimer's Disease, which Alzheimer's Disease-modifying effect is greater than the sum of the effects achieved by administering said first and second pharmaceutical compositions separately wherein said first pharmaceutical composition comprises an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, and wherein said second pharmaceutical composition comprises and an amount of donepezil or a pharmaceutically acceptable carrier or diluent.

Further provided is a method for stabilizing symptoms of Alzheimer's Disease in a mammal requiring stabilization comprising administering to said mammal a stabilizing amount of the above-described pharmaceutical composition.

Further provided is the above method wherein said stabilization is assessed by the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog). Further provided is the above method wherein said stabilization is assessed by the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change scale (ADCS-CGIC).

One embodiment of the present invention is an improved method for stabilizing symptoms of Alzheimer's disease in a mammal in need of stabilization comprising administering atorvastatin plus the acetylcholinesterase inhibitor donepezil, which is improved over treatment with a donepezil alone, as measured by cognition and global function, in particular 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 scale (ADCS-

CGIC), respectively. As used herein, "stabilizing" means no further decline in the above referenced measures (ADAS-Cog and ADCS-CGIC) over time.

A further embodiment of the invention is a pharmaceutical formulation of combined statin, for example, atorvastatin plus an acetylcholinesterase inhibitor (for example, donepezil) having an AD-disease-modifying effect.

A further embodiment of this invention is a pharmaceutical formulation of a combination of a statin, for example, atorvastatin, plus an acetylcholine esterase inhibitor, for example, donepezil, that siginificantly slows the progression and reduces the deterioration of Alzheimer's Disease.

"Combined treatment" as used herein means administering a statin, for example, atorvastatin and an acetylcholine esterase inhibitor, for example, donepezil together in a single pharmaceutical compositon with a pharmaceutically acceptable carrier or diluent.

"Alzheimer's Disease modifying effect" or "stabilization" as used herein means no further decline in AD symptoms in a mammal suffering from AD. An "Alzheimer's Disease stabilizing amount" as used herein means the dosage required to achieve such stabilization of AD symptioms in such mammal.

Other clinical measures of AD as well as the disease-modifying effects of an AD treatment regime include the following: 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).

Further, measuring brain volume and metabolism through MRI and MRS provides indication of disease modifying effects of an AD treatment regime. MRI measures include whole brain, ventricular, and hippocampal volumes. MRS measures include N-acetylaspartate (NAA) and myoinositol (MI). Evidence of disease modification is demonstrated by differences between treatment groups in these measures.

Further, measuring peripheral biomarkers of AD, specifically plasma levels of β-amyloid peptide (Aβ1-40, Aβ1-42), cerebrosterol (24S-hydroxycholesterol), and S 100b provide indication of disease-modifying effects of an AD treatment regime. Evidence of disease modification is demonstrated by differences between treatment groups in these measures.

As used herein, the term "patient" means all mammals including humans. Examples of patients include humans, cows, dogs, cats, goats, sheep, pigs, and rabbits.

A "therapeutically effective amount" is an amount of a compound of the present invention that when administered to a patient ameliorates a symptom of AD.

The term "a pharmaceutically acceptable salt" refers to the relatively non-toxic, inorganic and organic acid or base addition salts of compounds of the present invention. These salts can be prepared in situ during the final isolation and purification of the compounds or by separately reacting the purified compound in its free form with a suitable organic or inorganic acid or base and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. (See, for example, Berge S.M., et al., "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977;66:1-19, which is incorporated herein by reference.) The free base form may be regenerated by contacting the salt form with a base. While the free base may differ from the salt form in terms of physical properties, such as solubility, the salts are equivalent to their respective free bases for the purposes of the present invention.

The compositions of the present invention are suitable to be administered to a patient for the treatment, control, or prevention of Alzheimer's Disease. The terms "treatment", "treating", "controlling", "preventing" and the like, refers to reversing, alleviating, or inhibiting the progress of the disease or condition to which such term applies, or one or more symptoms of such disease or condition. As used herein, these terms also encompass, depending on the condition of the patient, preventing the onset of a disease or condition or of symptoms associated with a disease or condition, including reducing the severity of a disease or condition or symptoms associated therewith prior to affliction with said disease or condition. Such prevention or reduction prior to affliction refers to administration of the compound of the invention to a subject that is not at the time of administration afflicted with the disease or condition. "Preventing" also encompasses preventing the recurrence of a disease or condition or of symptoms associated therewith. Accordingly, the compositions of the present invention can be administered to a patient alone or as part of a composition that contains other components such as excipients, diluents, and carriers, all of which are well-known in the art. The compositions can be administered to humans and animals either orally, rectally, parenterally (intravenously, intramuscularly, or subcutaneously), intracisternally, intravaginally, intraperitoneally, intravesically, locally (powders, ointments, or drops), or as a buccal or nasal spray.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for

example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid; (b) binders, as for example, carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (c) humectants, as for example, glycerol; (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (e) solution retarders, as for example paraffin; (f) absorption accelerators, as for example, quaternary ammonium compounds; (g) wetting agents, as for example, cetyl alcohol and glycerol monostearate; (h) adsorbents, as for example, kaolin and bentonite; and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethyleneglycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well-known in the art. They may contain opacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used are polymeric substances and waxes. The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the

active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administrations are preferably suppositories which can be prepared by mixing the compounds of the present invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol, or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt in the rectum or vaginal cavity and release the active component.

Dosage forms for topical administration of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

In general, statins are administered in the following dosage amounts: simvastatin, generally about 2.5 mg to about 160 mg and preferably about 10 mg to about 40 mg; pravastatin, generally about 2.5 mg to about 160 mg and preferably about 10 mg to about 40 mg; cerivastatin, generally about 25 micrograms to about 5 mg and preferably about 1 mg to about 3.2 mg; fluvastatin, generally about 2.5 mg to about 160 mg and preferably about 20 mg to about 80

mg; lovastain, generally about 2.5 mg to about 160 mg and preferably about 10 mg to about 80 mg; and atorvastatin, generally about 2.5 mg to about 160 mg and preferably about 10 mg to about 80 mg.

The specific dosage used, however, can vary. For example, the dosage can depend on a numbers of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well-known to those skilled in the art.

Methods of preparing various pharmaceutical compositions with a certain amount of active ingredient are known, or will be apparent in light of this disclosure, to those skilled in this art. For examples of methods of preparing pharmaceutical compositions, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 15th Edition (1975).

Since the present invention has an aspect that related to the treatment of the disease/conditions described herein with a combination of active ingredients which may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. The kit comprises two separate pharmaceutical compositins: a compound of the present inventino, a prodrug thereof or a salt of such compound or prodrug and a second compound as described above. The kit comprises means for containing the separate compositions such as a container, a divided bottle or a divided foil packet. Typically, the kit comprises directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparetn plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shpae of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and

the stheet of relatively stiff material is sealed against the plastic foil at the fact of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such taht the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

It mat be desirable to provide a memory aid on the kit, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, e.g., as follows "First Week, Monday, Tuesday, ...etc... Second Week, Monday, Tuesday,..." etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several pills or capsules to be taken on a given day. Also, a daily dose of compounds of the present invention can consist of one tablet or capsule whil a daily dose of the second compound can consist of several tablets or capusles and vice versa. The memory aid should reflect this.

In another specific embodiment of the invention, a dispenser designed to dispense the daily doses one at a time in the order of their inteded use is provided. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter which indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

FORMULATIONS

The compositions of the present invention can be administered alone or in combination with one or more therapeutic agents. These include, for example, other agents for treating, preventing or controlling Alzheimer's Disease.

The compositions are thus well suited for convenient administration to mammals for the prevention and treatment of AD.

The following examples further illustrate typical formulations of the compositions provided by the invention. As used herein, "compound" means an acetylcholine esterase inhibitor or a statin, including donepezil and atorvastatin, respectively.

Formulation 1

Ingredient	Amount
compound 1	5 to 80 mg
compound 2	5 to 80 mg
sodium benzoate	5 mg
isotonic saline	1000 mL

The above ingredients are mixed and dissolved in the saline for IV administration to a patient.

Formulation 2

Ingredient	Amount
compound 1	5 to 80 mg
compound 2	5 to 80 mg
cellulose, microcrystalline	400 mg
stearic acid	5 mg
silicon dioxide	10 mg
sugar, confectionery	50 mg

The above ingredients are blended to uniformity and pressed into a tablet that is well suited for oral administration to a patient.

Formulation 3

Ingredient	Amount
compound 1	5 to 80 mg
compound 2	5 to 80 mg

Starch, dried	250 mg
magnesium stearate	10 mg

The above ingredients are combined and milled to afford material suitable for filling hard gelatin capsules administered to a patient.

Formulation 4

Ingredient	Amount % wt./(total wt.)
Compound 1 Compound 2	5 to 80 mg 5 to 80 mg
Polyethylene glycol 1000	32 to 75
Polyethylene glycol 4000	16 to 25

The above ingredients are combined via melting and then poured into molds.

While embodiments of the invention have been illustrated and described, it is not intended that these embodiments illustrate and describe all possible forms of the invention. Rather, the words used in the specification are words of description rather than limitation, and it is understood that various changes may be made without departing from the spirit and scope of the invention.

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

The ADAS-Cog is an 11-item scale designed to assess the severity of cognitive impairments in AD patients. Items include word recall, naming objects and fingers, following commands, constructional praxis, ideational praxis, orientation, word recognition, spoken language ability, comprehension of spoken language, word finding difficulty in spontaneous speech, and remembering test instructions. Total scores range from 0-70, with 70 indicating worse cognition. For this study, two additional items have been added to the ADAS-Cog. These are delayed word recall and concentration/distractibility. When these two additional items are combined with the original 11-item ADAS-Cog, the instrument will be referred to as the Modified ADAS-Cog.

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

The ADCS-CGIC is the ADCS version of a clinician's interview based impression of change plus caregiver input (CIBIC-Plus). It is a global rating of change in patient function derived through comprehensive interviews of the subject and caregiver by an independent clinician.

Clinical Dementia Rating-Sum of Boxes (CDR-SB)

The CDR-SB is a measure of dementia severity in six domains that assess cognition and function: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.

Neuropsychiatric Inventory (NPI)

The Neuropsychiatric Inventory (NPI) is a 12-item scale of behavioral disturbances commonly occurring in dementia subjects: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor activity, sleep, and appetite and eating disorders. Through a structured interview with the caregiver, each of the 12 behaviors is assessed. The frequency (0-4) and severity (0-3) of each behavior are determined and multiplied for a total score of 0-144. Higher scores indicate more psychopathology. In addition, the degree of caregiver distress (0-5) is also determined for each behavior.

Alzheimer's Disease Functional Assessment and Change Scale (ADFACS)

The ADFACS is a 16-item functional assessment instrument based on instrumental and basic activities of daily living (ADL) scales commonly used in clinical research. It includes 6 basic ADLs (toileting, feeding, dressing, personal hygiene and grooming, bathing and walking) and 10 instrumental ADLs (ability to use the telephone, household tasks, using household appliances, handling money, shopping, food preparation, ability to get around inside and outside home, hobbies and leisure activities, handling personal mail, and grasp of situations or explanations). The assessment of each item is based on an interview of the subject's caregiver. Each of the basic ADL items is scored on a scale of 0 (no impairment) to 4 (very severe impairment), giving a basic ADL total score of 0-

24. Each of the instrumental ADL items is scored on a scale of 0 (no impairment) to 3 (severe impairment) giving an instrumental ADL total score of 0-30. The overall 16 item ADFACS therefore has a total score range of 0 -54.

Mini-Mental State Examination (MMSE):

The MMSE is a brief, widely used test for assessing overall cognitive state. The MMSE measures selected aspects of cognition such as memory, orientation, attention, language, and praxis on a scale of 0-30. Lower scores indicate greater cognitive impairment.

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

The Modified ADAS-Cog is the same instrument as the 11-item ADAS-Cog described above with the addition of two items - Delayed Word Recall and Concentration/Distractibility.

Clinical Dementia Rating-Sum of Boxes (CDR-SB):

The CDR-SB is a measure of dementia severity in six domains that assess cognition and function: memory, orientation, judgment and problem solving, community affairs, and home and hobbies. The rating for each domain will be agreed upon by the subject's assessment team (excluding the clinician conducting the ADCS-CGIC) after consideration of the results from all tests conducted during a clinic visit. The CDR-SB consensus discussion should include the interview notes and rating of the ADCS-CGIC interviewer, but the ADCS-CGIC interviewer does not participate in the CDR-SB discussion. The ratings in each of the domains are summed to provide a global clinical measure, the Sum of the Boxes.

Neuropsychiatric Inventory (NPI):

The Neuropsychiatric Inventory (NPI) is a 12-item scale of behavioral disturbances commonly occurring in dementia subjects: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor activity, sleep, and appetite and eating. Through a structured interview with the caregiver, each of the 12 behaviors is assessed. The frequency (0-4) and severity (0-3) of

each behavior are determined and multiplied for a total score of 0-144. Higher scores indicate more psychopathology. In addition, the degree of caregiver distress (0-5) is also determined for each behavior.

Alzheimer's Disease Functional Assessment and Change Scale (ADFACS):

The ADFACS is a 16-item functional assessment instrument based on instrumental and basic activities of daily living (ADL) scales commonly used in clinical research. It includes 6 basic ADLs (toileting, feeding, dressing, personal hygiene and grooming, bathing and walking) and 10 instrumental ADLs (use of telephone, household tasks, using household appliances, managing money, shopping, food preparation, ability to get around inside and outside home, hobbies and leisure activities, handling personal mail, and grasp of situations or explanations). The assessment of each item is based on an interview of the subject's caregiver. Each of the basic ADL items is scored on a scale of 0 (no impairment) to 4 (very severe impairment), giving a basic ADL total score of 0-24. Each of the instrumental ADL items is scored on a scale of 0 (no impairment) to 3 (severe impairment) giving an instrumental ADL total score of 0-30. The overall 16 item ADFACS therefore has a total score range of 0 -54.

Disease Modification

Withdrawal Phase:

The randomized withdrawal design has been proposed (Leber 1996, 1997) as a study design to assess drug-induced changes in the progression of AD (Leber P. Observations and suggestions on antidementia drug development. *Alzheimer Disease and Associated Disorders,* 10(1):S31-S35; 1996). The International Working Group on the Harmonization of Guidelines (in AD) endorsed this concept (Bodick N, Forette F, Hadler D, et al. Protocols to demonstrate the slowing of Alzheimer's disease progression. Position paper from the International Working Group on Harmonization of Dementia Drug Guidelines. The Disease Progression Sub-Group. *Alzheimer Dis Assoc Disord,* 11 (suppl 3): 50-3; 1997.) In the randomized withdrawal design, following treatment with a potential

disease-modifying agent for sufficient duration, active treatment is withdrawn (subgroup of subjects remain on active treatment, and a subgroup is withdrawn). If the treatment, (for example, in this case atorvastatin), has only a symptomatic effect, then the performance of subjects switched to placebo would be expected to decrease to the level of performance of the subject group that was on placebo from the very beginning. There has been at least one published clinical trial in AD utilizing this design (Rother M, Erkinjuntti T, Roessner M et al.. Propentofylline in the treatment of Alzheimer's disease and vascular dementia: A review of Phase III trials. *Dement Geriatr Cogn Disord,* 9(1):36-43; 1998).

MRI / MRS Substudy: Neuroimaging: Magnetic Resonance Imaging (MRI) / Magnetic Resonance Spectroscopy (MRS)

As cognitive decline in AD advances, commensurate changes in brain volume occur, leading to progressive atrophy. Histopathological and radiological studies have shown that there are significant differences between the size of certain brain structures as well as the rate of atrophy between patients with AD and normal controls. As the severity of disease progresses, these changes can be monitored through the use of MRI to measure structural volume as an in vivo measure of gross atrophy (Kesslak, JP, Nalcioglu O, Cotman CW. Quantification of magnetic resonance scans for hippocampal and parahippocampal atrophy in Alzheimer's disease. *Neurology,* 41: 57; 1991).

These differences are most marked in areas associated with memory and other cognitive functions. Studies have highlighted the utility of medial temporal lobe structures, and particularly hippocampus, as well as ventricular and whole brain volume to monitor disease progression (Friedhoff LT, Cullen EI, Geoghagen NS, Buxbaum JD. Treatment with controlled-release lovastatin decreases serum concentrations of human beta-amyloid (Aβ) peptide. *Int J Neuropsychopharmacol.,* 4(2):127-30; June 2001). Specifically, hippocampal atrophy has been demonstrated to be a sensitive and early indicator of AD, and studies have shown the ability to differentiate between mild to moderate AD and normal controls with sensitivity and specificity of about 90% each. Moreover, degree of hippocampal atrophy has been shown to correlate with severity of memory loss (Laasko MP, Soininen H, Partanen K et al. MRI of the hippocampus

in Alzheimer's disease: sensitivity, specificity and analysis of the incorrectly classified subjects. *Neurolobiol Aging,* 19: 23-31; 1998).

As treatments for AD are developed, the question remains as to whether such therapies are only symptomatic, or also disease modifying.

With the use of an MRI scanner and specific software, Magnetic Resonance Spectroscopy (MRS) can measure biochemical metabolites in a brain region of interest. In AD, studies have demonstrated particular changes in two metabolites: N-acetyl aspartate (NAA) and myoinositol (MI). NAA, produced primarily by neurons, is a marker of neuronal mitochondrial metabolism and thus neuronal integrity, has been shown to be decreased in various brain regions in AD patients (Klunk, W, Panchalingam K, Moosy J, McClure R, Pettigrew J. N-acetyl-L aspartate and other amino acid metabolites in Alzheimer's disease brain: a preliminary proton nuclear magnetic resonance study. *Neurology,* 42: 1578-1585; 1992). Conversely, MI, generated in astrocytes and a marker of gliosis, has been shown to be increased in this population. Taken together, studies have shown high sensitivity and specificity for identifying patients with mild to moderate AD (Shonk TK, Moats R, Gifford P, Michaelis T, Mandingo JC, Izumi J, Ross BD. Probable Alzheimer's disease: diagnosis with proton MR spectroscopy. *Radiology,* 195:65-72; 1995). Thus, such measures could serve as a monitor of disease progression and response to therapy.

The measures of interest from the MRI are global brain atrophy and regional brain atrophy (hippocampal atrophy) as defined by the rate of change in the global or regional volumes, Δvolume/time. The measures of interest for the MRS are the change in N-acetylaspartate to creatine (NAA/Cr) and normalized NAA levels in the frontal cortex and occipital cortex, as well as MI/Cr and MI/NAA and normalized MI levels.

"Peripheral Biomarkers", as used herein, refers to proteins, peptides and lipids, which are found in blood and are implicated in the pathophysiology of Alzheimer's disease.

Peripheral Biomarkers, specifically plasma levels of β-amyloid peptide (Aβ1-40, Aβ1-42), cerebrosterol (24S-hydroxycholesterol), and S 100b are evidence for disease modifying effects of combined statin, e.g., for example,

atorvastatin plus an acetylcholinesterase inhibitor (for example, donepezil). Apolipoprotein B (ApoB), Apolipoprotein E (ApoE) (Davignon J, Gregg RE, Sing CE. Apolipoprotein E polymorphism and atherosclerosis. *Arteriosclerosis,* 8:1-21; 1988), serum total cholesterol, serum LDL-C, serum VLDL-C, cerebrosterol, triglycerides and HDL-C] and RBC acetylcholinesterase inhibition (RBC AChE-I) are further biomarkers of disease modification or progress.

Plasma biomarkers of interest include plasma β-amyloid peptide (Aβ1-40, Aβ1-42), S 100b and 24-hydroxycholesterol (cerebrosterol).

Plasma Aβ levels are elevated in several familial forms of AD and in first-degree relatives of AD patients prior to the onset of disease (Golde TE, Eckman CB, Younkin SG. Biochemical detection of Abeta isoforms: implications for pathogenesis, diagnosis, and treatment of Alzheimer's disease. *Biochim Biophys Acta.*, 26; 1502(1):172-87; 26-July-2000). These findings imply an association of elevated plasma Aβ levels and with risk of AD. A retrospective study in an aged population (average age > 80 years) revealed that subjects with higher plasma Aβ levels had an increased risk for an AD diagnosis over the next 3 years (Mayeux R, Tang MX, Jacobs DM, Manly J, Bell K, Merchant C, Small SA, Stern Y, Wisniewski HM, Mehta PD. Plasma amyloid beta-peptide 1–42 and incipient Alzheimer's disease. *Ann Neurol.*, 46(3): 412-6; Sep 1999). A recent study indicates that the level of plasma Aβ can be reduced in human subjects by treatment with an HMG-CoA reductase inhibitor (Friedhoff LT, Cullen EI, Geoghagen NS, Buxbaum JD. Treatment with controlled-release lovastatin decreases serum concentrations of human beta-amyloid (Aβ) peptide. *Int J Neuropsychopharmacol.*, 4(2):127-30; June 2001).

Cerebrosterol (24 S-hydroxycholesterol) is mostly produced in the brain (Bjorkhem I, Lutjohann D, Diczfalusy U, Stahle L, Ahlborg G, and Wahren J. Cholesterol homeostasis in human brain: turnover of 24S-hydroxycholesteroal and evidence for a cerebral origin of most of this oxysterol in the circulation. *J Lipid Res,* 39:1594-1600; 1998), (Bretillon L, Lutjohann D, Stahle L, Widhe T, Bindl L, Eggertsen G, Diczfalusy U, Bjorkhem I), moves across the blood-brain barrier ([61]Lutjohann D, Breuer O, Ahlborg G and others. Cholesterol homeostasis in human brain: eveidence for an age-dependent flux of 24S-hydroxycholesterol

from the brain into the circulation. *Proc Natl Acad Sci USA,* 93:9799-9804; 1996) and is found in higher concentrations in the plasma of patients with early-onset AD (Lutjohann D, Papassotiropoulos A, Bjorkhem I and others. Plasma 24S-hydroxycholesterol (cerebrosterol) is increased in Alzheimer and vascular demented patients. *J Lipid Res,* 41:195-198; 2000). Locatelli and co-workers (Locatelli S, Lutjohann D, Schmidt HH, Otto C, Beisiegel U, von Bergmann K. Reduction of plasma 24S-hydroxycholesterol (cerebrosterol) levels using high-dosage simvastatin in patients with hypercholesterolemia: evidence that simvastatin affects cholesterol metabolism in the human brain. *Arch Neurol.*, 59(2): 213-6; Feb 2002.) demonstrated that simvastatin reduced total cholesterol and cerebrosterol in the plasma of hypercholesterolemic patients.

S 100b is an intercellular signaling molecule, involved in the regulation of calcium levels (Mrak RE, Griffin WS. The role of activated astrocytes and of the neurotrophic cytokine S100B in the pathogenesis of Alzheimer's disease. *Neurobiol Aging*, 22(6): 915-22. Review; Nov-Dec 2001). Activated astrocytes have elevated levels of S 100b resulting from brain injury and inflammation. The level of S 100b in CSF of mild to moderate AD patients is elevated relative to age-matched control subjects (Peskind ER, Griffin WS, Akama KT, Raskind MA, Van Eldik LJ. Cerebrospinal fluid S100B is elevated in the earlier stages of Alzheimer's disease. *Neurochem Int.*, 39(5-6): 409-413; Nov-Dec 2001). An increase in S 100b in brain can also result in elevated levels of S 100b in blood.

As used herein, the following terms have the meanings shown.

AChE	Acetylcholinesterase
AD	Alzheimer's Disease
ADAS-Cog Subscale	Alzheimer's Disease Assessment Scale – Cognitive
ADCS-CGIC	Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change
ADFACS Scale	Alzheimer's Disease Functional Assessment and Change
ADL	Activities of daily living
ADRDA-NINCDS	Alzheimer's Disease Diagnostic Criteria for Dementia of the Alzheimer's Type Muliple Cognitive Deficits
AE	Adverse Event
APP	Amyloid precursor protein
FDA	Food and Drug Administration
ALT	Alanine aminotransferase (ALAT) = Glutamate pyruvate transaminase (GPT)
ANCOVA	Analysis of covariance
ANOVA	Analysis of Variance
ApoE	Apolipoprotein E
AST	Aspartate aminotransferase (ASAT) = Glutamate oxalacetate transaminase (GOT)
BP	Blood pressure
BPM	Beats per minute
BUN	Blood urea nitrogen
CAD	Coronary artery disease
CDR-SB	Clinical Dementia Rating-Sum of Boxes
CFR	Code of Federal Regulations
CI	Confidence interval
CIBIC-Plus	Clinician's Interviewed-Based Impression of Change plus caregiver input

CGIC	Clinical Global Impression of Change
CPK	Creatinine phosphokinase
CRF	Case Report Form
CRO	Clinical Research Organisation
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Cranial computerized tomography
CVA	Cerebrovascular accident
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association, Fourth Edition – Revised 1987
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECT	Electro-convulsive therapy
EDTA	Ethylene diamine tetraacetate
EEG	Electroencephalogram
ELISA	Enzyme-linked immunosorbent assay
GCP	Good Clinical Practice
HAM-D	Hamilton Depression Scale
HDL	High density lipoprotein
HIS	Hachinski Ischemia Scale
HIV	Human immonodeficiency virus
HMG-CoA	Hydroxymethylglutaryl Co-enzyme A
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IPI	International Product Information
IRB	Institutional Review Board
LDL	Low density lipoprotein
LOCF	Last observation carried forward
MANOVA	Multivariate Analysis of Variance
MDD	Major Depressive Disorder
MI	Myoinositol
MITT	Modified intent to treat population

MMSE	Mini Mental Status Examination
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NAA	N-acetylaspartate
NAA/Cr	N-acetylaspartate to creatine
NPH	Normal pressure hydrocephalus
NPI	Neuropsychiatric Inventory
NSAID	Nonsteroidal anti-inflammatory drug
PI	Package Insert
PRN	pro re nata = on an as needed basis
QD	Daily
RBC	Red blood cell count
RBC AChE-I	Red blood cell count acetylcholinesterase inhibition
ROI	Region of Interest
RPR	Rapid plasma regain
RR	Risk Ratio
SAE	Serious Adverse Event
SOP	Standard Operation Procedure
TSH	Thyroid stimulating hormone
TFT	Thyroid function test
ULN	Upper limit of normal

DSM-IV DIAGNOSTIC CRITERIA FOR DEMENTIA OF THE ALZHEIMER'S TYPE (ALZHEIMER'S DISEASE)

Dementia

Dementia is characterized by the development of multiple cognitive deficits (including memory impairment) that are due to the direct physiological effects of a general medical condition, to the persisting effects of a substance, or to multiple etiologies, (e.g., the combined effects of cerebrovascular disease and Alzheimer's disease).

Diagnostic Features

The essential feature of a dementia is the development of multiple cognitive deficits that include memory impairment and at least one of the following cognitive disturbances: aphasia, apraxia, agnosia, or a disturbance in executive functioning. The cognitive deficits must be sufficiently severe to cause impairment in occupational or social functioning and must represent a decline from a previously higher level of functioning. A diagnosis of a dementia should not be made if the cognitive deficits occur exclusively during the course of a delirium. However, a dementia and a delirium may both be diagnosed if the dementia is present at times when the delirium is not present. Dementia may be etiologically related to a general medical condition, to the persisting effects of substance use (including toxin exposure), or to a combination of these factors. Memory impairment is required to make the diagnosis of a dementia and is a prominent early symptom (Criterion A1). Individuals with dementia become impaired in their ability to learn new material, or they forget previously learned material. Most individuals with dementia have both forms of memory impairment, although it is sometimes difficult to demonstrate the loss of previously learned material early in the course of the disorder. They may lose valuables like wallets and keys, forget food cooking on the stove, and become lost in unfamiliar neighborhoods. In advanced stages of dementia, memory impairment is so severe that the person forgets his or her occupation, schooling, birthday, family members and sometimes-even name.

Memory may be formally tested by asking the person to register, retain, recall, and recognize information. The ability to learn new information may be assessed by asking the individual to learn a list of words. The individual is requested to repeat the words (registration), to recall the information after a delay of several minutes (retention, recall), and to recognize the words from a multiple list (recognition). Individuals with difficulty learning new information are not helped by clues or prompts (e.g., multiple-choice questions) because they did not learn the material initially.

In contrast, individuals with primarily retrieval deficits can be helped by clues and prompts because their impairment is in the ability to access their memories. Remote memory may be tested by asking the individual to recall personal information or past material that the individual found of interest (e.g., politics, sports, entertainment). It is also useful to determine (from the individual and informants) the impact of the memory disturbances on an individual's functioning (e.g., ability to work, shop, cook, pay bills, return home without getting lost).

Deterioration of language function (aphasia) may be manifested by difficulty producing the names of individuals and objects (Criterion A2a). The speech of individuals with aphasia may become vague or empty, with long circumlocutory phrases and excessive use of terms of indefinite reference such as "thing" and "it". Comprehension of spoken and written language and repetition of language may also be compromised. In the advanced stages of dementia, individuals may be mute or have a deteriorated speech pattern characterized by echolalia (i.e., echoing what is heard) or palilalia (i.e., repeating sounds or words over and over). Language is tested by asking the individual to name objects in the room (e.g., tie, dress, desk, lamp) or body parts (e.g., nose, chin, shoulder), follow commands ("Point at the door and then at the table"), or repeat phrases ("no ifs, ands, or buts").

Individuals with dementia may exhibit apraxia (i.e., impaired ability to execute motor activities despite intact motor abilities, sensory function, and comprehension of the required task) (Criterion A2b). They will be impaired in their ability to pantomime the use of objects (e.g., combing hair) or to execute known motor acts (e.g. waving goodbye). Apraxia may contribute to deficits in

cooking, dressing, and drawing. Motor skill disturbances may be tested by asking the individual to execute motor functions (e.g., to show how to brush teeth, to copy intersecting pentagons, to assemble blocks, or to arrange sticks in specific designs).

Individuals with dementia may exhibit agnosia (i.e., failure to recognize or identify objects despite intact sensory function) (Criterion A2c). For example, the individual may have normal visual acuity but lose the ability to recognize objects such as chairs or pencils. Eventually they may be unable to recognize family members or even their own reflection in the mirror. Similarly, they may have normal tactile sensation, but be unable to identify objects placed in their hands by touch alone (e.g., a coin or keys).

Disturbances in executive functioning are a common manifestation of dementia (Criterion A2d) and may be related especially to disorders of the frontal lobe or associated subcortical pathways. Executive functioning involves the ability to think abstractly and to plan, initiate, sequence, monitor, and stop complex behavior. Impairment in abstract thinking may be manifested by the individual having difficulty coping with novel tasks and avoiding situations that require the processing of new and complex information.

The ability to abstract can be formally assessed by asking the person to find similarities or differences between related words. Executive dysfunction is also evident in a reduced ability to shift mental sets, to generate novel verbal or nonverbal information, and to execute serial motor activities. Tests for executive function include asking the individual to count to 10, recite the alphabet, subtract serial 7s, state as many animals as possible in 1 minute, or draw a continuous line consisting of alternating m's and n's. It is also useful to determine (from the individual and informants) the impact of the disturbances in executive functioning on the individual's daily life (e.g., ability to work, plan activities, budget).

The items in both Criterion A1 (memory impairment) and Criterion A2 (aphasia, apraxia, agnosia, or disturbance in executive functioning) must be severe enough to cause significant impairment in social or occupational functioning (e.g., going to school, working, shopping, dressing, bathing, handling finances, and other activities of daily living) and must represent a decline from a previous level of functioning (Criterion B). The nature and degree of impairment are variable

and often depend on the particular social setting of the individual. The same level of cognitive impairment may significantly impair an individual's ability to perform a complex job, but not a job that is less demanding. Standardized published rating scales that measure physical maintenance (e.g., personal hygiene), intellectual functioning, and the ability to use implements or tools (e.g., telephone, washing machine) can be used to measure the severity of impairment.

Dementia is not diagnosed if these symptoms occur exclusively during the course of a delirium. However, a delirium may be superimposed on a preexisting dementia, in which case both diagnoses should be given.

DEMENTIA OF THE ALZHEIMER TYPE

Diagnostic Features

The cognitive deficits (Criterion A) and the required impairment (Criterion B) are discussed above. The onset of Dementia of the Alzheimer's Type is gradual and involves continuing cognitive decline (Criterion C). Because of the difficulty of obtaining direct pathological evidence of the presence of Alzheimer's disease, the diagnosis can be made only when other etiologies for the dementia have been ruled out. Specifically, the cognitive deficits are not due to other central nervous system conditions that cause progressive deficits in memory or cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease), systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B_{12} deficiency, HIV infection), or the persisting effects of a substance (e.g., alcohol) (Criterion D). If there is an additional etiology (e.g. head trauma worsening a Dementia of the Alzheimer's Type) both types of dementia should be coded (see Dementia Due to Multiple Etiologies, page 154). Dementia of the Alzheimer's Type should not be diagnosed if the symptoms occur exclusively during delirium (Criterion E).

However, delirium may be superimposed on a preexisting Dementia of the Alzheimer's Type, in which case the With Delirium subtype should be indicated. Finally, the cognitive deficits are not better accounted for by another Axis I disorder (e.g., Major Depressive Disorder or Schizophrenia) (Criterion F).

DIAGNOSTIC CRITERIA FOR DEMENTIA OF THE ALZHEIMER'S TYPE:

A. The development of multiple cognitive deficits manifested by both

(1) memory impairment (impaired ability to learn new information or to recall previously learned information)

(2) one (or more) of the following cognitive disturbances:

(a) aphasia (language disturbance)

(b) apraxia (impaired ability to carry out motor activities despite intact motor function)

(c) agnosia (failure to recognize or identify objects despite intact sensory function)

(d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. The course is characterized by gradual onset and continuing cognitive decline.

D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:

(1) other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal pressure hydrocephalus, brain tumor)

(2) systemic conditions that are known to cause dementia, (e.g., hypothyroidism, vitamin B_{12} or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)

(3) substance-induced conditions.

E. The deficits do not occur exclusively during the course of a delirium.

F. The disturbance is not better accounted for by another Axis I disorder (e.g., Major Depressive Disorder, Schizophrenia).

Types (including DSM-IV code)

Dementia of the Alzheimer Type, Late Onset (onset after age 65)

290.30 with delirium

290.20 with delusions

290.21 with depressed mood

290.00 uncomplicated

Dementia of the Alzheimer Type, Early Onset (onset at age 65 or below)

290.11 with delirium

290.12 with delusions

290.13 with depressed mood

290.10 uncomplicated

CLINICAL DIAGNOSIS OFALZHEIMER'S DISEASE– NINCDS-ADRDA CRITERIA

A. Criteria for Dementia Syndrome

Dementia is the decline of memory and other cognitive functions in comparison with the patient's previous level of function as determined by a history of decline in performance and by abnormalities noted from clinical examination and neuropsychological tests. A diagnosis of dementia cannot be made when consciousness is impaired by delirium, drowsiness, stupor, or coma or when other clinical abnormalities prevent adequate evaluation of mental status. Dementia is a diagnosis based on behavior and cannot be determined by computerized tomography, electroencephalography, or other laboratory instructions, although specific causes of dementia may be identified by these means.

B. Criteria for Alzheimer's Disease

Alzheimer's disease is a progressive, dementing disorder, usually of middle or late life. The clinical criteria for the diagnosis of PROBABLE, POSSIBLE and DEFINITE Alzheimer's disease are outlined in Table 1. A clinical diagnosis of probable Alzheimer's disease can be made with confidence if there is a typical insidious onset of dementia with progression and if there are no other systemic or brain diseases that could account for the progressive memory and other cognitive deficits. Among the disorders that must be excluded are manic depressive disorder, Parkinson's disease, multiinfarct dementia, and drug intoxication; less commonly encountered disorders that may cause dementia include thyroid disease, pernicious anemia, luetic brain disease and other chronic infections of the nervous system, subdural hematoma, occult hydrocephalus, Huntington's disease, Creutzfeldt-Jakob disease, and brain tumors.

A diagnosis of definite Alzheimer's disease requires histopathologic confirmation. A clinical diagnosis of possible Alzheimer's disease may be made in the presence of other significant diseases, particularly if, on clinical judgment, Alzheimer's disease is considered the more likely cause of the progressive dementia. The clinical diagnosis of possible rather than probable Alzheimer's disease may be used if the presentation or course is somewhat aberrant. The

information needed to apply these criteria is obtained by standard methods of examination: the medical history; neurologic; psychiatric, and clinical examinations; neuropsychological tests; and laboratory studies.

Table 1. Criteria for Clinical Diagnosis of Alzheimer's Disease

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's Disease include:

dementia established status by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale or some similar examination, and confirmed by neuropsychological tests;

deficits in two or more areas of cognition;

progressive worsening of memory and other cognitive functions;

no disturbances of consciousness;

onset between ages 40 and 90, most often after age 65; and

absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE Alzheimer's Disease is supported by:

progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);

impaired activities of daily living and altered patterns of behavior;

family history of similar disorders, particularly if confirmed neuropathologically; and

laboratory results;

normal lumbar puncture as evaluated by standard techniques,

normal pattern or nonspecific changes in EEG, such as increased slowwave activity, and

evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include: plateaus in the course of progression of the illness;

associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts,

sexual disorders and weight loss; other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;

seizures in advanced disease; and

CT normal for age.

IV. Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:

sudden, apoplectic onset;

focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and

seizures or gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of POSSIBLE Alzheimer's Disease:

may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the resence of variations in the onset, in the presentation, or in the clinical course;

may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia; and

should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

VI. Criteria for diagnosis of DEFINITE Alzheimer's Disease are:

the clinical criteria for probable Alzheimer's disease and

histopathologic evidence obtained from a biopsy or autopsy.

VII. Classification of Alzheimer's Disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:

familial occurrence;

onset before age of 65;

presence of trisomy-21; and

coexistence of other relevant conditions such as Parkinson's disease.

EXPERIMENTAL

The utility of the compositions of the present invention as medical agents in the treatment of Alzheimer's Disease in mammals (e.g. humans) or at risk for developing AD is demonstrated by the activity of the compositions of this invention in the clinical protocol described below.

This is a multi-center, double-blind, randomized, parallel group study with phases. Approximately 600 mild to moderate Alzheimer's disease male and female human subjects are studied. Treatment groups are divided into approximately 300 subjects in the atorvastatin 80 mg plus donepezil 10 mg treatment arm, and approximately 300 subjects in the placebo plus donepezil 10 mg treatment arm.

During a 72-week (18-month) double-blind treatment period, all subjects receive donepezil 10 mg (300 subjects per arm, 600 subjects total). These subjects are randomly assigned by a 1:1 ratio to receive the addition of atorvastatin 80 mg or matching placebo. At the end of 18 months, the treatment arms are separated. The subjects receiving placebo plus an acetylcholinesterase inhibitor (donepezil 10 mg) continue with this drug regimen. One-fourth of the subjects receiving atorvastatin 80 mg plus an acetylcholinesterase inhibitor (donepezil 10 mg) continue with this drug regimen. The other three-fourths of the subjects switch from atorvastatin 80 mg to receive placebo plus an acetylcholinesterase inhibitor (donepezil 10 mg). The groups continue on this course for 8 weeks.

Approximately 200 subjects are additionally evaluated by MRI/MRS.

This is a multi-center, double-blind, randomized, parallel group study with 3 phases. All subjects are required to be taking a stable dose of 10 mg donepezil or the subject acetylcholine esteroase inhibitor for $\geq$ 3 months prior to Screening.



Screening	Double-Blind Treatment	Double-Blind
Day – 14 to Day -1	Phase	Withdrawal Phase
	72 Weeks	8 Weeks

*A similar procedure may be followed using any statin and any acetylcholine esterase inhibitor.

Study Visits

Screening Visit 1 (Days – 14 to –1)

Screening must be performed within -14 to -1 days to drug administration. Prior to study entry the following screening procedures are performed:

- obtain written informed consent(s)
- record medical history
- verify conformance with entry criteria
  - complete physical examination
  - record height and weight
  - complete neurological examination
  - vital signs
  - laboratory assessments, urinalysis, chemistry, hematology, serology, archived serum sample and full lipid profile
  - 12-lead electrocardiogram (ECG)
  - MRI / CT scan (only if a previous MRI / CT scan is unavailable to confirm diagnosis of mild to moderate Alzheimer's disease within 12 months of Screening).
  - review all concomitant medications
  - Mini-Mental State Examination (MMSE)
  - Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)
  - Rosen Modified Hachinski (subjects must have less than or equal to 4 at Screening for inclusion)
  - assign the unique 8-digit subject number, that must not be assigned to another subject.
  - schedule next visit (Visit 2 / Baseline)

Procedures During the Study Drug Treatment Period

Visit 2 Baseline / Randomization Visit 2 (Day 0)

- verify conformance with entry criteria
- complete physical examination
- record weight
- complete neurological examination
    - vital signs
    - laboratory assessments, urinalysis, chemistry, hematology, plasma biomarker sampling, anonymized genotyping sample, donepezil levels and RBC AchE
    - Mini-Mental State Examination (MMSE)
    - Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)
    - Alzheimer's Disease Cooperative Study-Clinical's Global Impression of Change scale (ADCS-CGIC)
- Neuropsychiatric Inventory (NPI)
- Clinical Dementia Rating-Sum of Boxes (CDR-SB)
- Alzheimer's Disease Functional Assessment and Change Scale (ADFACS)
- Caregiver Burden Questionnaire
- Patient Healthcare Resource Utilization Questionnaire
    - assign the lowest available randomization number. This number must not be reassigned to another subject.
- dispense study medication for Visit 2
- schedule next visit (Visit 3 / Week 6)
- record concomitant medications
- record adverse events

Visit 3 / Week 6 (Day 42)

- laboratory assessments, chemistry and hematology
- schedule next visit (Visit 4 / Month 3)
- record concomitant medications
- record adverse events

Visit 4 / Month 3 (Day 84)

- modified physical examination assessment
- record weight

- vital signs
- laboratory assessments, chemistry, hematology, full lipid profile, and plasma biomarker sampling
- Mini-Mental State Examination (MMSE)
- Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)
- Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change scale (ADCS-CGIC)
- record study medication taken since Visit 2

- assess compliance with study medication regimen
- collect all medication containers
- dispense study medication for Visit 4
- schedule next visit (Visit 5 / Month 6)
- record all concomitant medications
- record adverse events

Visit 5 / Month 6 (Day 168)

- vital signs
- record weight
- laboratory assessments, urinalysis, chemistry, hematology, full lipid profile and plasma biomarker sampling
- 12-Lead electrocardiogram (ECG)
- Mini-Mental State Examination (MMSE)
- Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)
- Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change scale (ADCS-CGIC)
- Neuropsychiatric Inventory (NPI)
- Alzheimer's Disease Functional Assessment and Change Scale (ADFACS)
- Caregiver Burden Questionnaire
- Patient Healthcare Resource Utilization Questionnaire

- record study medication taken since Visit 4
- assess compliance with study medication regimen
- collect all medication containers
- dispense study medication for Visit 5

- schedule next visit (Visit 6 / Month 9)
- record all concomitant medications
- record adverse events

Visit 6 / Month 9 (Day 252)

- modified physical examination assessment
- record weight
- vital signs
- Mini-Mental State Examination (MMSE)
- Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)
- Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change scale (ADCS-CGIC)
- record study medication taken since Visit 5
- assess compliance with study medication regimen
- collect all medication containers
- dispense study medication for Visit 6
- schedule next visit (Visit 7 / Month 12)
- record all concomitant medications
- record adverse events

Visit 7 / Month 12 (Day 336)

- complete physical examination
- complete neurological examination
- record weight
- vital signs
- laboratory assessments, urinalysis, chemistry, hematology, full lipid profile and plasma biomarker sampling
- Mini-Mental State Examination (MMSE)
- Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)
- Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change scale (ADCS-CGIC)
- Neuropsychiatric Inventory (NPI)
- Clinical Dementia Rating-Sum of Boxes (CDR-SB)

- Alzheimer's Disease Functional Assessment and Change Scale (ADFACS)
- Caregiver Burden Questionnaire

Patient Healthcare Resource Utilization Questionnaire

- record all study medication taken since Visit 6
- assess compliance with study medication regimen
- collect all medication containers
- dispense study medication for Visit 7
- schedule next visit (Visit 8 / Month 15)
- record all concomitant medications
- record adverse events

Visit 8 / Month 15 (Day 420)

- vital signs
- record weight
- Mini-Mental State Examination (MMSE)
- Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)
- Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change scale (ADCS-CGIC)
- record all study medication taken since Visit 7
- assess compliance with study medication regimen
- collect all medication containers
- dispense study medication for Visit 8
- schedule next visit (Visit 9 / Month 18)
- record all concomitant medications
- record adverse events

Visit 9 / Month 18 (Day 504) –Withdrawal Maneuver First Visit/MRI sub-study participation ends/Early Termination Visit for Double-Blind Portion

- complete physical examination
- complete neurological examination
- vital signs
- record weight

- laboratory assessments, urinalysis, chemistry, hematology, full lipid profile, archived serum sample and plasma biomarker sampling, donepezil levels and RBC AChE-I
- 12-Lead electrocardiogram (ECG)
- Mini-Mental State Examination (MMSE)
- Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)
- Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change scale (ADCS-CGIC)
- Neuropsychiatric Inventory (NPI)
- Clinical Dementia Rating-Sum of Boxes (CDR-SB)
- Alzheimer's Disease Functional Assessment and Change Scale (ADFACS)
- Caregiver Burden Questionnaire
- Patient Healthcare Resource Utilization Questionnaire
- record study medication taken since Visit 8
- assess compliance with study medication regimen
- collect all medication containers
- dispense study medication for Visit 9 (Withdrawal Maneuver Medication)
- schedule next visit (Visit 10 / Month 20)
- record all concomitant medications
- record adverse events

Visit 10 / Month 20 (Day 560) Final Visit/Early Termination Visit for Withdrawal Maneuver Treatment Arm

- complete physical examination
- record weight
- vital signs
- laboratory assessments, urinalysis, chemistry, hematology, full lipid profile and plasma biomarker sampling
- 12-Lead electrocardiogram (ECG)
- Mini-Mental State Examination (MMSE)
- Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)
- Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change scale (ADCS-CGIC)

- Clinical Dementia Rating-Sum of Boxes (CDR-SB)
- record study medication taken since Visit 9
- assess compliance with study medication regimen
- collect all medication containers
- record all concomitant medications
- record adverse events

Laboratory Determinations:

Subjects are to fast for 12 hours prior to the test, and should have no vigorous exercise and no change in diet the day before the test. If the subject is not fasting, the clinic visit must be rescheduled as soon as possible. Subject's posture should be standardized for lipid blood draws. The subjects should be in the sitting position (no longer than 5 minutes). A tourniquet may be used (no longer than 2 minutes), but must be released prior to the blood draw.

The following laboratory tests are to be performed .

- Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell, and platelet count, differential (if WBC is abnormal) including neutrophils, lymphocytes, monocytes, eosinophils and basophils.
- Clinical Chemistry: albumin, glucose, alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), creatinine, uric acid, chloride, potassium, total protein, sodium, phosphorus, calcium, globulin, lactate dehydrogenase, C Reactive Protein, alanine transaminase (ALT), aspartate transaminase (AST), and CPK. If ALT or AST are > 3x upper limit of normal (ULN), the subject must return within 1 week for a repeat test. If the value remains > 3x ULN, the subject should be withdrawn from the study, and follow-up measurements of ALT/AST should continue until the abnormality has resolved. If CPK > 5x ULN, then CPK-MB should be performed. If CPK is > 10x ULN then the subject must be excluded, and follow-up measurements of CPK should continue until the abnormality has resolved.
- Lipid Profile: total cholesterol, LDL-C, HDL-C, VLDL-C, triglycerides, and apolipoproteins (ApoE and ApoB); Direct LDL-C measurements will be performed regardless of triglyceride level. Safety measures, blinded. Samples will be collected at Screening, Months 3, 6, 12, 18 and 20 for analysis.

- Thyroid Profile: thyroid stimulating hormone (TSH) and serum thyroxine (T_4) (at Screening only)
- Serology: Hepatitis C and RPR (positive tests to be confirmed with a specific test Screening only).
- Vitamins: Vitamin B_{12} and RBC folate levels (Screening only)
- Glycemic Control: HbA_1C level (Screening only)
- Urinalysis: dipstick of freshly voided specimen to evaluate pH, leukocytes, nitrite, urobilinogen, specific gravity, protein, glucose, ketones, and blood. The urinalysis will be performed at Screening, Baseline, Months 6, 12, 18 and 20.

Laboratory assessments are performed at Screening, Baseline, Week 6, Months 3, 6, 12, 18 and 20 (unless otherwise noted above). In clinically noteworthy abnormal laboratory test value noted after Screening (other than ALT/AST/CPK, for which guidelines are given above), the test should be approved by the study Medical Monitor and repeated immediately and followed up until it has returned to the normal range and/or an adequate explanation of the abnormality is found.

12-Lead Electrocardiogram

The electrocardiogram (ECG) is a complete, standard 12-lead recording. The ECG is be performed at Screening, Months 6, 18 and 20.

Vital Signs, Body Weight and Height

Vital signs are obtained at Screening, Baseline, Months 3, 6, 9, 12, 15, 18, and 20. These will include body temperature (oral), respiration rate, pulse rate and systolic and diastolic blood pressuresdetermined in the sitting position. Recordings will be made after the subject has been seated for 5 minutes. Body weight (kg) without shoes is measured. Height will be recorded in cm at Screening. Weight is recorded at Screening, Baseline, and Months 3, 6, 9, 12, 15, 18 and 20.

Complete Physical Examination

A complete physical examination is performed at Screening, Baseline, Months 12, 18 and 20. General physical well being will be assessed by evaluation

of the head, eyes, ears, nose, throat, neck, heart, chest, lungs, abdomen, extremities, peripheral pulses, skin and other physical conditions of note (breasts, genitourinary and rectal are optional). Any other assessments necessary to establish Baseline status or evaluate symptoms or AEs should also be performed. An AE form must be completed for all changes identified after Screening as clinically noteworthy. Height without shoes will be recorded at Screening only. Weight is recorded at each visit.

Physical Status Assessment

Brief routine physical examination: general physical status is assessed by a brief physical examination at Months 3 and 9. The subject and caregiver must be queried regarding changes in physical status since the previous examination done at Screening. Weight is recorded at each visit.

Neurological Examination

A complete neurological examination is performed at clinic visits Screening, Baseline, Months 12 and 18. This examination includes evaluation of the cranial nerves (including visual fields), motor, sensory, brainstem, cerebellar and autonomic functions.

Screening CT or MRI

If not conducted within the past 12 months, a CT scan or MRI must be completed. For subjects not participating in the MRI / MRS Substudy, a MRI is required only if the CT results are equivocal for meeting diagnostic criteria.

Psychometric Examinations

A certified rater is required for the administration of the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog); the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change scale (ADCS-CGIC); and the Neuropsychiatric Inventory (NPI) scales.

The same certified rater should perform all psychometric examinations at approximately the same time of day. All changes in raters for a given assessment must be noted in the subject's source documents. Psychometric testing should

occur after laboratory testing, and only after subjects have had the opportunity to eat.

Mini-Mental State Examination (MMSE)

The MMSE is a brief, widely used test for assessing overall cognitive state. The MMSE measures selected aspects of cognition such as memory, orientation, attention, language, and praxis on a scale of 0-30. Lower scores indicate greater cognitive impairment. The MMSE is performed at Screening, Baseline and Months 3, 6, 9, 12, 15, 18 and 20.

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

The ADAS-Cog is an 11-item scale designed to assess the severity of cognitive impairments in AD patients. Items include word recall, naming objects and fingers, following commands, constructional praxis, ideational praxis, orientation, word recognition, spoken language ability, comprehension of spoken language, word finding difficulty in spontaneous speech, and remembering test instructions. Total scores range from 0-70, with 70 indicating worse cognition. For this study, two additional items have been added to the ADAS-Cog. These are delayed word recall and concentration/distractibility. When these two additional items are combined with the original 11-item ADAS-Cog, the instrument will be referred to as the Modified ADAS-Cog. It will be necessary to ensure that the subject is able to complete the Modified ADAS-Cog for inclusion into the study. The Modified ADAS -Cog is performed at Screening, Baseline and Months 3, 6, 9, 12, 15, 18 and 20.

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

The ADCS-CGIC is the ADCS version of a clinician's interview based impression of change plus caregiver input (CIBIC-Plus). It is a global rating of change in patient function derived through comprehensive interviews of the subject and caregiver by an independent clinician. At Baseline only, clinical information about the subject from any other sources should be used to generate Baseline notes such as other assessment team members, medical history, physical exam, and rating scale and test results from the Screening and Baseline visits. The subject and

caregiver will always be interviewed separately; the subject will be interviewed first. Videotapes of the subject and caregiver interviews are also required at Baseline. After the Baseline visit, the clinician should refer to his/her Baseline notes and videotaped interviews but is prevented from reviewing other study procedures/results or discussing the subject with other members of the assessment team. The clinician rates the subject on a 7-point scale to assess the degree of change from baseline: 1-marked improvement, 2-moderate improvement, 3-minimal improvement, 4-no change, 5-minimal worsening, 6-moderate worsening, and 7-marked worsening. Only these Baseline notes and videotaped interviews will be available to the clinician during the conduct of each post-Baseline interview and rating (Schneider LS, Olin JT, Doody RS, Clark CM, Morris JC, Reisberg G, Schmitt FA, Grundman M, Thomas RG, Ferris SH and the Alzheimer's Disease Cooperative Study. Validity and reliability of the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. *Alzheimer's Dis. Assoc. Disorder*, 2: S22-S32; 1997).

The clinician alone must make decisions about change without consulting other staff. At the beginning of each interview, the clinician should caution the interviewee to refrain from mentioning any side effects he/she may be experiencing. The assessment of change from Baseline is made at Months 3, 6, 9, 12, 15 and 18. The assessment of change at Month 20 (at the end of the withdrawal phase of the study) is made relative to Baseline, but relative to Month 18.

Clinical Dementia Rating-Sum of Boxes (CDR-SB)

The CDR-SB is a measure of dementia severity in six domains that assess cognition and function: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The rating for each domain will be agreed upon by the subject's assessment team (excluding the clinician conducting the ADCS-CGIC) after consideration of the results from all tests conducted during a clinic visit. The CDR consensus discussion should include the interview notes and rating of the ADCS-CGIC interviewer, but the ADCS-CGIC interviewer does not participate in the CDR discussion. The ratings

in each of the domains are summed to provide a global clinical measure, the Sum of the Boxes. The CDR-SB is performed at Baseline, Months 12, 18 and 20.

Neuropsychiatric Inventory (NPI)

The Neuropsychiatric Inventory (NPI) is a 12-item scale of behavioral disturbances commonly occurring in dementia subjects: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor activity, sleep, and appetite and eating disorders. Through a structured interview with the caregiver, each of the 12 behaviors is assessed. The frequency (0-4) and severity (0-3) of each behavior are determined and multiplied for a total score of 0-144. Higher scores indicate more psychopathology. In addition, the degree of caregiver distress (0-5) is also determined for each behavior. The NPI is performed at Baseline, Months 6, 12 and 18.

Alzheimer's Disease Functional Assessment and Change Scale (ADFACS)

The ADFACS is a 16-item functional assessment instrument based on instrumental and basic activities of daily living (ADL) scales commonly used in clinical research. It includes 6 basic ADLs (toileting, feeding, dressing, personal hygiene and grooming, bathing and walking) and 10 instrumental ADLs (ability to use the telephone, household tasks, using household appliances, handling money, shopping, food preparation, ability to get around inside and outside home, hobbies and leisure activities, handling personal mail, and grasp of situations or explanations). The assessment of each item is based on an interview of the subject's caregiver. Each of the basic ADL items is scored on a scale of 0 (no impairment) to 4 (very severe impairment), giving a basic ADL total score of 0-24. Each of the instrumental ADL items is scored on a scale of 0 (no impairment) to 3 (severe impairment) giving an instrumental ADL total score of 0-30. The overall 16 item ADFACS therefore has a total score range of 0 -54. The ADFACS is performed at Baseline, Months 6, 12 and 18.

Neuroimaging: Brain Morphology and Metabolism

In this MRI / MRS Substudy, Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS) will be used as secondary efficacy

variables to assess effects of treatment on measures of disease progression in the brain. MRI is performed at Baseline and at Visit 9 / Month 18 to assess brain volumetric changes (global and regional atrophy). MRS will be performed at the same visits to assess endogenous brain metabolites, including N-acetylaspartate (NAA) and Myoinositol (MI).

The analyses of interest for the MRI are global brain atrophy and regional brain atrophy (hippocampal atrophy) as defined by the rate of change in the global or regional volumes, Δvolume/time. The analysis of interest for the MRS is the change in N-acetylaspartate to creatine (NAA/Cr) and normalized NAA levels in the frontal cortex and occipital cortex, as well as MI/Cr and MI/NAA and normalized MI levels. Given the logistical complexity of obtaining neuroimaging scans, these are performed in a subgroup of approximately 200 subjects.

Peripheral Biomarkers

Proteins, peptides and lipids, which are found in blood and are implicated in the pathophysiology of Alzheimer's disease, are measured in the study population.

Plasma Biomarkers

Plasma biomarkers of interest include plasma β-amyloid peptide (Aβ1-40, Aβ1–42), S 100b and 24-hydroxycholesterol (cerebrosterol). Plasma biomarkers are collected at Baseline, Months 3, 6, 12, 18 and 20 for analysis.

The plasma fraction from 10 mL of whole blood will be collected in EDTA for each subject. The samples are quickly frozen at - 70°C and stored at the site.

Serum Biomarkers:

The lipid profile of subjects is assessed by measuring: total cholesterol, LDL–C, HDL-C, VLDL-C, triglycerides, and apolipoproteins (ApoE and ApoB). Assay of the serum samples for lipids and lipoproteins are conducted. Serum biomarkers are collected at Screening, Months 3, 6, 12, 18 and 20 for analysis. Screening sample is considered baseline since Screening is within two weeks of the Baseline visit.

Donepezil Plasma Level and RBC Acetylcholinesterase Inhibition (RBC AChE-I):

Seven milliliters (7 mL) of whole blood is collected at Baseline and Month 18 (see Appendix I) for the measurement of RBC AChE-I in subjects. Plasma concentrations of donepezil is correlated with measured acetylcholinesterase activity in red blood cells.

Analysis of donepezil plasma concentrations:

Using a high performance liquid chromatographic method, donepezil concentration is quantified. Prior to the analysis of study samples, the assay sensitivity, specificity & reproducibility is documented.

Analysis of RBC Cholinesterase Inhibition:

Using a radioenzymatic method, the activity of acetylcholinesterase in red blood cells is measured. Prior to use in this study, the assay sensitivity, specificity and reproducibility is documented.

Caregiver Burden and Health Economics

Caregiver Assessments – Caregiver Burden Questionnaire - Baseline

Caregiver assessments include measurement of the subject's caregiver burden by the Caregiver Burden Questionnaire. At Baseline the questionnaire consists of two main sections, caregiver time (3 questions) and subject accommodation (i.e., living situation; 1 question). The caregiver time section consists of questions applicable to the 4 weeks preceding the Baseline Visit. The subject accommodation section assesses the current living situation.

Definition of Efficacy Endpoints

Primary Efficacy

The primary efficacy measures and measurement time points are as follows:

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

The ADAS-Cog is an 11-item scale designed to assess the severity of cognitive impairments in AD subjects. Items include word recall, naming objects and fingers, following commands, constructional praxis, ideational praxis,

orientation, word recognition, spoken language ability, comprehension of spoken language, word finding difficulty in spontaneous speech, and remembering test instructions. Total scores range from 0-70, with 70 indicating worse cognition. The ADAS -Cog is performed at Screening, Baseline and Months 3, 6, 9, 12, 15, 18 and 20.

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

The ADCS-CGIC is the ADCS version of a clinician's interview based impression of change plus caregiver input (CIBIC-Plus). It is a global rating of change in subject function derived through comprehensive interviews of the subject and caregiver by an independent clinician. At Baseline only, clinical information about the subject from any other sources should be used to generate baseline notes such as other assessment team members, medical history, physical exam, and rating scale and test results from the Screening and Baseline visits. Videotapes of the subject and caregiver interviews are also required at Baseline. After the Baseline visit, the clinician should refer to his/her Baseline notes and videotaped interviews but is prevented from reviewing other study procedures/results or discussing the subject with other members of the assessment team The clinician rates the subject on a 7-point scale to assess the degree of change from Baseline: 1-marked improvement, 2-moderate improvement, 3-minimal improvement, 4-no change, 5-minimal worsening, 6-moderate worsening, 7-marked worsening. Only these Baseline note and videotaped interviews will be available to the clinician during the conduct of each post-Baseline interview and rating (Schneider LS, Olin JT, Doody RS, Clark CM, Morris JC, Reisberg G, Schmitt FA, Grundman M, Thomas RG, Ferris SH and the Alzheimer's Disease Cooperative Study. Validity and reliability of the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. *Alzheimer's Dis. Assoc. Disorder*, 2: S22-S32; 1997).

The clinician alone must make decisions about change without consulting other staff. At the beginning of each interview, the clinician should caution the interviewee to refrain from mentioning any side effects he/she may be experiencing. The assessment of change from Baseline is made at Months 3, 6, 9, 12, 15 and 18. The assessment of change at Month 20 (at the end of the

withdrawal phase of the study) is not made relative to Baseline, but relative to Month 18.

Secondary Efficacy Variable(s) – Psychometric Examinations

The secondary clinical efficacy measures and time points are as follows:

Mini-Mental State Examination (MMSE):

The MMSE is a brief, widely used test for assessing overall cognitive state. The MMSE measures selected aspects of cognition such as memory, orientation, attention, language, and praxis on a scale of 0-30. Lower scores indicate greater cognitive impairment. The MMSE is performed at Screening, Baseline and Months 3, 6, 9, 12, 15, 18 and 20.

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

The Modified ADAS-Cog is the same instrument as the 11-item ADAS-Cog described above with the addition of two items - Delayed Word Recall and Concentration/Distractibility. The Modified ADAS-Cog is performed at Screening, Baseline and Months 3, 6, 9, 12, 15, 18 and 20.

Clinical Dementia Rating-Sum of Boxes (CDR-SB):

The CDR-SB is a measure of dementia severity in six domains that assess cognition and function: memory, orientation, judgment and problem solving, community affairs, and home and hobbies. The rating for each domain is agreed upon by the subject's assessment team (excluding the clinician conducting the ADCS-CGIC) after consideration of the results from all tests conducted during a clinic visit. The CDR-SB consensus discussion should include the interview notes and rating of the ADCS-CGIC interviewer, but the ADCS-CGIC interviewer does not participate in the CDR-SB discussion. The ratings in each of the domains are summed to provide a global clinical measure, the Sum of the Boxes. The CDR-SB is performed at Baseline, Months 12, 18 and 20.

Neuropsychiatric Inventory (NPI):

The Neuropsychiatric Inventory (NPI) is a 12-item scale of behavioral disturbances commonly occurring in dementia subjects: delusions, hallucinations,

agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor activity, sleep, and appetite and eating. Through a structured interview with the caregiver, each of the 12 behaviors is assessed. The frequency (0-4) and severity (0-3) of each behavior are determined and multiplied for a total score of 0-144. Higher scores indicate more psychopathology. In addition, the degree of caregiver distress (0-5) is also determined for each behavior. The NPI is performed at Baseline, Months 6, 12 and 18.

Alzheimer's Disease Functional Assessment and Change Scale (ADFACS):

The ADFACS is a 16-item functional assessment instrument based on instrumental and basic activities of daily living (ADL) scales commonly used in clinical research. It includes 6 basic ADLs (toileting, feeding, dressing, personal hygiene and grooming, bathing and walking) and 10 instrumental ADLs (use of telephone, household tasks, using household appliances, managing money, shopping, food preparation, ability to get around inside and outside home, hobbies and leisure activities, handling personal mail, and grasp of situations or explanations). The assessment of each item is based on an interview of the subject's caregiver. Each of the basic ADL items is scored on a scale of 0 (no impairment) to 4 (very severe impairment), giving a basic ADL total score of 0-24. Each of the instrumental ADL items is scored on a scale of 0 (no impairment) to 3 (severe impairment) giving an instrumental ADL total score of 0-30. The overall 16 item ADFACS therefore has a total score range of 0 -54.The ADFACS will be performed at Baseline, Months 6, 12 and 18.

Disease Modification

Withdrawal Phase:

At the completion of Month 18, subjects randomized to receive an acetycholinesterase inhibitor, for example, (donepezil) plus for example, atorvastatin will either continue to receive an acetycholinesterase inhibitor, for example, (donepezil) plus atorvastatin until completion of the trial or be

withdrawn from active atorvastatin therapy and complete the study while taking only donepezil therapy. This predetermined second stage randomization will be decided prior to study start. Approximately 75% of subjects on active atorvastatin therapy will be re-randomized to withdraw from active atorvastatin therapy. Thus, subjects will be randomized at Baseline so that at Month 18 they either:

a. Continue with matching placebo plus an acetylcholinesterase inhibitor, for example, (donepezil 10 mg) or
b. Continue with atorvastatin 80 mg plus an acetylcholinesterase inhibitor, for example, (donepezil 10 mg) or
a. Withdrawal from treatment with atorvastatin 80 mg so that the subjects receive 8 weeks of matching placebo plus an acetylcholinesterase inhibitor, for example, (donepezil 10 mg)

Two study designs have been proposed (Leber 1996, 1997) that would indirectly assess changes in the disease process[57, 58].

MRI / MRS Substudy: Neuroimaging: Magnetic Resonance Imaging (MRI) / Magnetic Resonance Spectroscopy (MRS)

In this MRI / MRS Substudy, Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS) will be used as secondary efficacy variables to assess effects of treatment on measures of disease progression in the brain. MRI is performed at Baseline and at Month 18 to assess brain volumetric changes (global and regional atrophy). MRS is performed at the same visits to assess endogenous brain metabolites, including N–acetyl L-aspartate (NAA) and Myoinositol (MI).

The measures of interest from the MRI are global brain atrophy and regional brain atrophy (hippocampal atrophy) as defined by the rate of change in the global or regional volumes, Δvolume/time. The measures of interest for the MRS are the change in N-acetylaspartate to creatine (NAA/Cr) and normalized NAA levels in the frontal cortex and occipital cortex, as well as MI/Cr and MI/NAA and normalized MI levels. Given the logistical complexity of obtaining neuroimaging studies, these are performed in a subgroup of 200 subjects.

Apolipoproteins (ApoE and ApoB). Assay of the serum samples for lipids and Plasma Biomarkers

Plasma biomarkers of interest include plasma β-amyloid peptide (Aβ1-40, Aβ1-42), S 100b and 24-hydroxycholesterol (cerebrosterol). Plasma biomarkers are collected at Baseline, Months 3, 6, 12, 18 and 20 for analysis.

S 100b is an intercellular signaling molecule, involved in the regulation of calcium levels. Mrak RE, Griffin WS. The role of activated astrocytes and of the neurotrophic cytokine S100B in the pathogenesis of Alzheimer's disease. *Neurobiol Aging*, 22(6):915-22. Review; Nov-Dec 2001. Activated astrocytes have elevated levels of S 100b resulting from brain injury and inflammation. The level of S 100b in CSF of mild to moderate AD patients is elevated relative to age-matched control subjects. Peskind ER, Griffin WS, Akama KT, Raskind MA, Van Eldik LJ. Cerebrospinal fluid S100B is elevated in the earlier stages of Alzheimer's disease. *Neurochem Int.*, 39(5-6):409-413; Nov-Dec 2001.

An increase in S 100b in brain can also result in elevated levels of S 100b in blood. Thus, the level of S 100b in plasma and the impact of medication on S 100b levels are assessed.

Inclusion/Exclusion Criteria:

Inclusion Criteria:

- Written informed consent must be obtained from the subject, the caregiver, and the subject's legal guardian (if applicable), prior to beginning any screening activities. Should the subject not be capable of providing written informed consent, verbal assent must be obtained from the subject in the presence of the authorized representative and witness. Documentation of the verbal assent and identity of those present must be made in both the source document as well as on the consent form.
- Subjects and caregivers must be sufficiently proficient in their local language and be capable of reliably completing study assessments at Screening and Baseline.
- Male and female outpatients, any race, with age range 50 to 90 inclusive.

- Women must have undergone the onset of spontaneous or surgical menopause prior to the start of the study and have been amennorrheic for at least 6 months. Spontaneous menopause is defined as the natural cessation of ovarian function. Surgical menopause is defined as bilateral oophorectomy with an intact uterus.
- Diagnostic evidence of probable Alzheimer's disease consistent with NINCDS/ADRDA and DSM IV criteria made by the site physician at the time of Screening. This evidence must be fully documented in the subject's source document prior to Baseline. The investigator must consider the severity of the AD to be mild to moderate and the subject to be otherwise in good health.
- CT or MRI within the last 12 months consistent with a diagnosis of probable Alzheimer's disease and without any other clinically significant comorbid pathologies. A copy of the report will be required and should be appended to the CRF. If there has been a significant clinical change suggestive of stroke or other possible neurological disease with onset between the time of the last CT or MRI and the Screening evaluation, the scan may be repeated with the Sponsors approval.

  MRI / MRS substudy: Subjects participating in the MRI substudy must be able to undergo a study-specific MRI at Baseline and at Visit 9 / Month 18 (or Early Termination if at least 9 months post-Baseline), regardless of the timing of any prior neuroimaging studies. The MRI at Baseline also serves as the Screening MRI to support the diagnosis of probable AD (including in those subjects for whom there has been a clinical change suggesting the possibility of comorbid pathology and for whom a repeat neuroimaging scan is required).
- Subject's Mini-Mental Status Examination Score (MMSE) must be in the range of 13 – 25 (inclusive) at Screening.
- Subjects must have been taking a stable dose of 10 mg donepezil for ≥ 3 months prior to Screening.
- Subjects not taking any antihyperlipidemic medication.

Subjects' Rosen Modified Hachinski Ischemia (Rosen WG, Terry RD, Fuld PA, Karzman R, Peck A. Pathological Verification of Ischemic Score in Differentiation of Dementias. *Ann. Neurol.*, 7:486-488; 1980) scale ≤ 4. [Exceptions may be made on a case-by-case basis in conjunction with the Sponsor for selected subjects who fail to meet the Hachinski score criteria, but who, in the clinical opinion of the investigator, do not have multi-infarct dementia or dementia associated with cerebrovascular disease (e.g., no focal neurological signs or symptoms and no history of CVA)].

- Subjects' laboratory findings must be within normal limits, or if abnormal, judged clinically insignificant at Screening. (Any abnormalities must be documented by the investigator as "not clinically significant", i.e., not likely to cause cognitive impairment or medical instability.)
- Subjects must have LDL-C levels ≥ 100 mg/dL and ≤ 190 mg/dL, and not require treatment for dyslipidemia with any lipid-lowering drug in the opinion of the investigator.
- Subjects with history or evidence of cornorary artery disease should be approved by the Medical Monitor.

Subjects with diabetes on a stable regimen of diet and/or oral hypoglycemic agents and/or insulin are eligible provided they are monitored regularly to ensure adequacy of diabetes control and approved by the Medical Monitor. Subjects with known diabetes should have an HbA_1c level of < 10% and a fasting serum glucose value of ≤ 170 mg/dL. Subjects who meet the above criteria must also have LDL-C values ≥ 100 mg/dL and ≤ 130 mg/dL.

- Subjects must be able to swallow oral medication (tablets). Tablets are not to be crushed.
- Subjects' vital signs must be considered normal for age. Subjects' Screening 12-lead ECG must demonstrate predominantly normal sinus rhythm. Minor abnormalities (including sinus bradycardia ≤ 50 beats per minute) documented as clinically insignificant by the investigator will be allowed. Subjects with clinically significant but stable ECG abnormalities may enter the trial only with documented (e.g., telephone, written) permission of the Sponsor.

- Subjects with right bundle branch block (complete or partial) and pacemakers may be included in the study, if considered clinically stable.
- Subjects must have the same reliable caregiver or family member who agrees to accompany the subject to all scheduled visits, provide information about the subject as required by this protocol, and ensure compliance with the medication schedule. The caregiver must be a constant and reliable informant and must have contact at least 5 days per week with the subject and for a minimum of 10 waking hours per week. This contact should be judged by the investigator to be adequate to ensure accurate reporting of the subject's behavior and his/her ability to perform activities of daily living.
- Subjects will be without sensory (e.g., impaired hearing or vision) or motor difficulties preventing their participation in all aspects of the study. [A cane (walking stick) or walker is permitted.]
- Subjects in assisted living situations where, in the opinion of the investigator and with approval from the Medical Monitor, he/she has the opportunity to perform and be assessed for all activities of daily living as specified in the ADFACS. This living situation is expected to be maintained over the course of the study.
- Putative non-prescription/prescription cognitive enhancers (e.g. gingko, high dose vitamin E, lecithin, estrogen, NSAIDS) are not excluded but should be discouraged. If a putative cognitive enhancer is allowed, the dosage should have been stable for at least 3 months prior to randomization and should not change during the course of the study.

Exclusion Criteria:

- Subjects who have received treatment with any cholinesterase inhibitor other than the test acetylcholine estrase inhibitor within 3 months of Screening.
- Subjects who may not be able to comply with the protocol or perform the outcome measures.

- Subjects with any active or clinically significant conditions affecting absorption, distribution or metabolism of the study drugs (e.g., inflammatory bowel disease, gastric or duodenal ulcers, severe lactose intolerance).
- Subjects who currently or have within the past five years met DSM IV criteria for drug or alcohol abuse or dependence.
- Subjects with significant allergies to or significant intolerance of donepezil or piperidine derivatives or known hypersensitivity or intolerance to HMG-CoA Reductase Inhibitors.
- Subjects that are on any other lipid lowering agents.
- Subjects who have not tolerated 10 mg per day of donepezil treatment within 3 months prior to Screening.
- Participation in any other studies involving investigational or marketed products concomitantly or within 30 days or 5 half-lives prior to Screening, whichever is longer.
- Subjects with likelihood of requiring treatment during the study period with drugs not permitted by the study protocol.
- Subjects who have donated blood or blood products during the 30 days prior to Screening, or who plan to donate blood while participating in the study or within four weeks after completion of the study.

Subjects with a current DSM-IV diagnosis of Major Depressive Disorder (MDD), MDD in partial remission, or any current primary psychiatric diagnosis other than Alzheimer's disease (as per DSM-IV).

- Subjects with dementia complicated by other organic disease or Alzheimer's disease with delirium (DSM 290.30 or 290.11) are excluded. Psychiatric symptoms (e.g., depression, anxiety, delusions) are common in AD, but subjects with pronounced severe symptoms such that they warrant an alternative concurrent diagnosis, should be excluded.
- Subjects who, in the judgment of the investigator, currently represent a significant suicide risk.

- Subjects who, in the judgment of the investigator, would require treatment with electro-convulsive therapy (ECT).
- Subjects with unstable psychiatric symptoms who, in the opinion of the investigator, are likely to require major adjustments or modifications in psychotropic medication.
- Subjects with history or presence of seizure disorders or encephalitis.
- Subjects with a CT or MRI scan consistent with the diagnosis of stroke, intracranial bleeding, mass lesion, or normal pressure hydrocephalus (NPH).

MRI / MRS Substudy:

All potential subjects for the MRI/MRS Substudy will be screened for contraindications for MR examination. Any subject with contraindications for MR examination (e.g., pacemaker, neurostimulators, aneurysm clips, etc.) will be excluded from the substudy. Screening will occur for both the Baseline and Month 18 scanning.

- Subjects with dementia due to causes other than Alzheimer's disease. These include toxic, alcoholic or vascular etiologies, and medical disorders such as HIV, Parkinson's disease, Lewy Body Dementia, Huntington's disease, Pick's disease, Creutzfeld-Jacob disease and neurosyphilis.
- Subjects with a history of cognitive deficits immediately following head trauma. Subjects with serious head trauma with loss of consciousness require that the investigator make a judgment. (Note: Remote history of head trauma without cognitive sequelae is not exclusionary.)
- Subjects who are hospitalized or residing in a skilled nursing facility or subjects who are anticipated to enter a nursing home over the course of the study.
- Subjects with a history of deep venous thrombosis, pulmonary embolus or any other thrombo-embolic disorder.
- Subjects who have taken prohibited concomitant medications prior to Screening

- Subjects currently experiencing any clinically significant or unstable medical condition including: dermatologic disease, hematologic disease, pulmonary disease, cardiovascular disease, renal disease, hepatic disease, gastrointestinal disease, genitourinary disease, endocrine disease, neurological disease (other than Alzheimer's disease).
- Subjects who have suffered severe infections or a major surgical operation within 3 months prior to Screening (e.g., sepsis, coronary angioplasty, coronary artery bypass graft, hip replacement).
- Subjects with a history of malignant neoplasms treated within 5 years prior to study entry (other than basal or squamous cell carcinoma of the skin) or where there is current evidence of recurrent or metastatic disease.
- Subjects with a vitamin B_{12} deficiency. However, subjects on a stable dose of medication for at least 3 months prior to Screening, and who have normal serum B_{12} levels at Screening, will be eligible. The stable dose must be maintained throughout the study.
- Subjects with uncontrolled hypothyroidism and hyperthyroidism. Subjects on a stable dose of medication for at least 3 months prior to Screening with normal TSH and free T_4 at Screening are considered euthyroid and will be eligible. The stable dose must be maintained throughout the study.
- Subjects with impaired hepatic function, as shown by but not limited to AST (SGOT) or ALT (SGPT) $\geq$ 3.0 times the upper limit of normal at Screening.
- Subjects with a BUN of $\geq$ 30 mg/dL at Screening.
- Subjects with serum creatinine $\geq$ 3.0 mg/dL or any proteinuria greater than "trace" present on urinalysis at Screening.
- Subjects with CPK (creatinine phosphokinase) > 5 times the upper limit of normal range at Screening.
- Subjects on lipid lowering therapy within the last 6 months.
- Subjects with serum triglyceride level $\geq$ 500 mg/dL.

- Subjects with uncontrolled hypertension (sitting diastolic BP > 95 mmHg and systolic > 160 mmHg), as assessed by the investigator, regardless of taking or not taking a concurrent antihypertensive medication.
- Any other condition, which, in the investigator's judgment might increase the risk to the subject or decrease the reliability of the data required to meet the objectives of the study.

The following medications/therapies are prohibited during the study:

- All antilipidemic medications [e.g. niacin, probucol, fibrates and derivatives, bile acid sequestering resins, Xenical, HMG-CoA reductase inhibitors, psyllium derivatives including Metamucil (>2 tablespoons per day) or fish oil].
- Drugs known to be associated with rhabdomyolysis in combination with HMG-CoA reductase inhibitors (e.g., cyclosporine, erythromycin, etc). If these drugs are needed temporarily during the study, study medication should be interrupted appropriately.
- Azole antifungals.
- Any immunosuppressive agents (e.g. cyclosporine, mycophenlate mofetil).
- Drugs known to have significant adverse effects on lipid levels such as all retinoids including isotretinoin.
- If antacids are to be utilized, do not take at the same time as study drug. It is permissible to take at least 2 hours before or 2 hours after study drug.

The following medications are NOT ALLOWED as concomitant medications during the study.

ANALGESICS

Tramadol	Ultram

ANTICHOLINERGICS

GENERIC NAME	MARKET NAME®
Amantadine	Symmetrel
Benztropine	Cogentin
Cyproheptadine	Periactin
Dicyclomine	Bentyl
Diphenhydramine	Benadryl, Sominex 2, Benylin
Diphenoxylate with atropine	Lomotil
Hydroxyzine	Vistaril, Atarax
Meclizine	Antivert, Bonine
Orphenadrine citrate	Norflex
Oxybutynin	Ditropan
Prochlorperazine	Compazine
Promethazine	Phenergan
Trihexyphenidyl	Artane
Trimethobezamide	Tigan

ANTICONVULSANTS

GENERIC NAME	MARKET NAME®
Carbamazepine	Tegretol
Clonazepam	Klonopin
Clozabazam	
Ethosuximide	Zarontin

PROHIBITED MEDICATIONS LIST

Felbamate	Felbatol
Levitiracetam	Kepra
Lamotrigine	Lamictal
Phenobarbital	
Phenytoin	Dilantin

Primidone	Mysoline
Topiramate	Topamax
Valproate	Depakene, Depakote
Vigabatrin	Sabril

ANTIDEPRESSANTS

GENERIC NAME	MARKET NAME®
Amitriptyline	Elavil
Amoxapine	Asendin
Bupropion	Welbutrin, Zyban
Clomipramine	Anafranil
Desipramine	Norpramin, Pertofrane
Doxepin	Sinequan
Imipramine	Tofranil
Isocarboxazide	Marplan
Lithium	
Maprotiline	Ludiomil
Mirtazapine	Remeron
Nefazodone	Serzone
Nortriptyline	Aventyl, Pamelor
Phenelzine	Nardil
Protriptyline	Vivactil
Tranylcypromine	Parnate
Trimipramine	Surmontil

PROHIBITED MEDICATIONS LIST

ANTIPSYCHOTICS

Chlorpromazine	Thorazine
Fluphenazine	Prolixin, Permitil
Thioridazine	Mellaril
Loxapine	Loxitane
Clozapine	Clozaril
Molindone	Moban

ANTIFUNGAL AGENTS

GENERIC NAME	MARKET NAME®
Flucytosine	Ancobon
Amphotericin B	Fungizone Intravenous, Amphotec, AmBisome, Abelcet
Ketoconazole	Nizoral
Fluconazole	Diflucan
Griseofulvin	Fulvicin U/F, Grifulvin V, Grisactin
Nystatin	Nystatin, Mycostatin, Nilstat
Itraconazole	Sporanox

ANTI-PARKINSONIAN AGENTS

GENERIC NAME	MARKET NAME®
Biperiden	Akineton
Bromocriptine	Parlodel
Levodopa	Larodopa, Sinemet
Pergolide	Permax
Ropinerol	Requip
Selegiline	Deprenyl, Eldepryl
Tolcapone	Tasmar

PROHIBITED MEDICATIONS LIST

ANXIOLYTICS

GENERIC NAME	MARKET NAME®
Alprazolam	Xanax
Chlorazepate	Tranxene
Chlordiazepoxide	Librium
Diazepam	Valium
Estrazolam	ProSom
Flurazepam	Dalmane
Meprobamate	Equanil, Equagesic, Miltown
Oxazepam	Serax
Temazepam	Restoril
Triazolam	Halcion

CHOLINOMIMETIC AGENTS

GENERIC NAME	MARKET NAME®
Bethanecol	Duvoid, Urecholine
Galantamine	Reminyl
Physostigmine	
Pyridostigmine	Mestinon
Rivastigmine	Exelon
Tetrahydroaminoacidine (tacrine)	Cognex

*Unless the subject test acetylcholine esterase inhibitor compound.

****CYTOCHROME P450-3A4 INHIBITOR AGENTS

GENERIC NAME	MARKET NAME®
Amiodarone	Cordarone, Pacerone
Cannabinoids	
Cimetidine	Tagamet
Clarithromycin	Biaxin

PROHIBITED MEDICATIONS LIST

Clotrimazole	Lotrimin, Mycelex
Cyclosporine	Gengraf, Neoral, Sandimmune
Danazol	Danocrine
Erythromycin	Ery-Tab
Fluconazole	Diflucan
Indinavir	Crixivan
Itraconazole	Sporanox
Ketoconazole	Nizoral
Miconazole	
Nelfinavir	Viracept
Nicardipine	
Norfloxacin	
Omeprazole	Prilosec

Propoxyphene	Darvon, Darvon Pulvule
Quinidine	Quinidex Extentab, Quinaglute Dura-
Tab	
Ritonavir	Kaletra, Norvir
Saquinavir	Fortovase, Invarise
Troleandomycin	Tao
Zafirlukast	
Zileuton	

ERYTHROMYCIN

GENERIC NAME	MARKET NAME®
Erythromycin Base	E-Mycin, Ery-Tab, ERYC, Erythromycin, Erythromcin Delayed Release, PCE Dispertab
Erythromycin Ethyl Succinate, Acetyl Sulfisoxazole	Pedi azole

PROHIBITED MEDICATIONS LIST

IMMUNOSUPPRESSIVE AGENTS

GENERIC NAME	MARKET NAME®
Lymphocyte Immune Globulin	Atgom
Rho (D) Immune Globulin	HypRho-D, MICRhoGAM, Rohm
Azathiopane Sodium	Imuran
Basiliximab	Simulect
Muromonab-CD3	Orto clone OKT3
Cyclosporine	Gengraf, Neoral, Sandimmune
Mycophenolate Mofetil	CellCept
Daclizumab	Zenapax
Glatiramer Acetate	Copaxone
Tacrolimus	Prograf
Sirolimus	Rapamune

LIPID-REGULATING DRUGS

GENERIC NAME	MARKET NAME®
Niacin/Nicotinic-Acid	Niacor, Nicobid, Nicolar, Slo-Niacin
Probucol	Lorelco
Clofibrate	Atromid-5
Cholestyramine	Cholybar, Questran, Questran (Light), Prevalite, LoCHOLEST
Colesevelam	WelChol
Colestipol Hydrochloride	Colestid
Gemfibrozil	Lopid
Fish Oils (omega-3 fatty acids – prescription only)	
Fluvastatin	Lescol
Lovastatin	Mevacor
Pravastatin	Pravachol
Simvastatin	Zocor
Cerivastatin	Baychol
Orlistat	Xenical

PROHIBITED MEDICATIONS LIST

Fenofibrate	Tricor
Dextrothyroxine Sodium	Choloxin
Rosuvastatin	Crestor

STIMULANTS

GENERIC NAME	MARKET NAME®
Amphetamine	Dexedrine
Methylphenidate	Ritalin
Pemoline	Cylert

OTHER AGENTS

GENERIC NAME	MARKET NAME®
Cyclobenzaprine	Flexeril
Ergoloid Mesylates	Hydergine
Isotretinoin	Accutane
Isoxsuprine	Vasodilan
Memantine	Ebixa
Methocarbamol	Robaxin
Mibefradil dihydrochloride	Posicor
Mitoxantrone	Novantrone
Nimodipine	Nimotop
Oxybutynin	Ditropan
Papaverine	Pavabid

MEDICATIONS ALLOWED WITH RESTRICTIONS:

PUTATIVE COGNITIVE ENHANCERS

Putative non-prescription/prescription cognitive enhancers (e.g. gingko, high dose vitamin E, lecithin, estrogen, NSAIDS) are not excluded but should be discouraged. If a putative cognitive enhancer is allowed, the dosage should have been stable for at least 3 months prior to randomization and should not change during the course of the study.

CLINICAL LABORATORY PARAMETERS

1. COMPLETE CLINICAL LABORATORY

Hematology
- *RBC*
- *Hemoglobin*
- *Hematocrit*
- *WBC*
- *Platelet Count*
- *Differential (if WBC is abnormal)*
  - *Neutrophils*
  - *Lymphocytes*
  - *Monocytes*
  - *Eosinophils*
  - *Basophils*

Chemistry
- *SGOT (AST)*
- *SGPT (ALT)*
- *Alkaline Phosphatase*
- *LDH*
- *CPK (CPK-MB if CPK elevated above 5 times the upper reference limit)*
  - *Blood Urea Nitrogen*
  - *Chloride*
  - *Creatinine*
  - *Uric Acid*
  - *Total Protein*
  - *Albumin*
  - *Sodium*
  - *Potassium*
  - *Glucose*
  - *Globulin*
  - *Phosphorus*
  - *Calcium*
  - *$HbA1_c$ (at Visit 1 only)*
  - *Total Bilirubin*
  - *C-Reactive Protein*
  - *TSH Level (at Visit 1 only)*
  - *Free T_4 (at Visit 1 only)*
  - *B_{12} (at Visit 1 only)*
  - *RBC Folate (at Visit 1 only)*

Serology
- *Hepatitis C (at Visit 1 only)*

RPR (at Visit 1 only)

Lipid Profile
Total Cholesterol
LDL-C
VLDL-C
Triglycerides
HDL-C
ApoB
ApoE

Plasma Sampling
ß-amyloid (Aß 1-40, Aß 1-42)
S-100b
24 S-hydroxycholesterol (cerebrosterol)
RBC AChE-I

2. *URINALYSIS*

Determinations by dipstick Leukocytes
Nitrite
Urobilinogen
Protein
PH
Blood
Specific Gravity
Ketone

Glucose

Table I., below, summarizes the experimental method described in detail above.

APPENDIX L – Study Flow Chart / Schedule of Observations

Protocol A2581078

Study Procedure/ Assessment	Screening Visit 1 Days - 14 to −1 ± 7	Baseline / Randomization Visit 2 Day 0^	Week 6 Visit 3 Day 42 ± 7	Month 3 Visit 4 Day 84 ± 7	Month 6 Visit 5 Day 168 ± 7	Month 9 Visit 6 Day 252 ± 7	Month 12 Visit 7 Day 336 ± 7	Month 15 Visit 8 Day 420 ± 7	Month 18 Visit 9 Double-Blind Early Termination Day 504 ± 7^	Month 20 Visit 10 Final Visit/Early Termination Visit Day 560 ± 7
Informed Consents	X									
Medical History	X									
Physical Examination	X[1]	X[1]					X[1]		X[1]	X[1]
Physical Status Assessment				X[2]		X[2]				
Neurological Examination	X	X					X		X	
Vital Signs	X	X		X	X	X	X	X	X	X
Laboratory Assessments (Chemistry/Hematology)	X[3]	X	X	X	X		X		X	X
Urinalysis	X	X			X		X		X	X
Serum Lipid Profile	X			X	X		X		X	X
Plasma Biomarkers[6]		X		X	X		X		X	X
Anonymized Genotyping Sample[7]		X								
Archived Serum Sample	X								X	
Donepezil and RBC AChE-I Levels		X							X	
ECG	X				X				X	X

MRI / MRS Substudy Subjects Only		X^							X[4^]	
*MRI/CT Scan (only at Screen)**	X									
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X
Mini-Mental State Examination (MMSE)	X	X		X	X	X	X	X	X	X
Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)	X	X		X	X	X	X	X	X	X
Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change scale (ADCS-CGIC)		X[3]		X	X	X	X	X	X	X
Neuropsychiatric Inventory (NPI)		X			X		X		X	
Clinical Dementia Rating-Sum of Boxes (CDR-SB)		X					X		X	X
Rosen Modified Hachinski	X									
Alzheimer's Disease Functional Assessment and Change Scale (ADFACS)		X			X		X		X	
Caregiver Burden Questionnaire		X			X		X		X	
Patient Healthcare Resource Utilization Questionnaire		X			X		X		X	
Dispense Donepezil		X		X	X	X	X	X	X[5]	
Dispense Double-Blind Study Medication		X		X	X	X	X	X	X[5]	
Drug Compliance Check				X	X	X	X	X	X	X

[1] Complete Physical Examination

[2] Modified Physical Examination

[3] Baseline interview and videotape for subject and caregiver.

[4] Perform MRI / MRS at Month 18 / Early Termination Visit only if subject discontinues at Month 9 or later.

^ Baseline MRI / MRS Scan should be –10 days of the initiation of study medication and for Month 18 +/- 10 days of the scheduled visit.

[5] Dispense Withdrawal Maneuver Medication

* Previous MRI/CT scan must diagnose probable AD within 12 months prior to the Screen visit.

[6] Visits with Peripheral Biomarkers include ß-amyloid (Aß 1-40, Aß 1-42), S 100b and cerebrosterol.

[7] Includes ApoE

[8] Serology at Screening only

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising:
   a. an amount of an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof;
   b. an amount of a statin or a pharmaceutically acceptable salt thereof; and
   c. a pharmaceutically acceptable carrier or diluent.

2. The pharmaceutical composition of claim 1 comprising a fixed combination selected from the group consisting of:
a statin, 5 mg active and an acetylcholine esterase inhibitor, 10 mg active;
a statin, 10 mg active and an acetylcholine esterase inhibitor, 10 mg active;
a statin, 20 mg active and an acetylcholine esterase inhibitor, 10 mg active;
atorvastatin calcium, 40 mg active and an acetylcholine esterase inhibitor, 10 mg active;
a statin, 80 mg active and an acetylcholine esterase inhibitor, 10 mg active;
a statin, 5 mg active and an acetylcholine esterase inhibitor, 5 mg active;
a statin, 10 mg active and an acetylcholine esterase inhibitor, 5 mg active;
a statin, 20 mg active and an acetylcholine esterase inhibitor, 5 mg active;
a statin, 40 mg active and an acetylcholine esterase inhibitor, 5 mg active; and
a statin, 80 mg active and an acetylcholine esterase inhibitor, 5 mg active.

3. The pharmaceutical composition of Claim 1 or Claim 2 comprising an amount of atorvastatin or a pharmaceutically acceptable salt thereof.

4. The pharmaceutical composition of Claim 3 comprising an amount of donepezil or a pharmaceutically acceptable salt thereof

5. A pharmaceutical composition comprising from about 0.20 mg. to about 20 mg. of donepezil or a pharmaceutically acceptable salt thereof; about 5 mg. to about 80 mg. of atorvastatin or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier or diluent.

6. A first pharmaceutical composition for use with a second pharmaceutical compostion for achieving an Alzheimer's Disease-modifying effect in a mammal suffering from Alzheimer's Disease, which Alzheimer's Disease-modifying effect is greater than the sum of the effects achieved by administering said first and second pharmaceutical compositions separately wherein said first pharmaceutical composition comprises an amount of atorvastatin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, and wherein said second pharmaceutical composition comprises and an amount of donepezil or a pharmaceutically acceptable carrier or diluent.

7. The use of the pharmaceutical composition as defined in any one of claims 1-6 respectively, for the manufacture of a medicament to treat Alzheimer's Disease.

8. The use of the pharmaceutical composition as defined in any one of claims 1-6 respectively, for the manufacture of a medicament for stabilizing symptoms of Alzheimer's Disease in a mammal requiring stabilization.

9. The use as defined in claim 8 wherein said stabilization is assessed by the Alzheimer's Disease Assessment Scale-Cognitive Subscale, (ADAS-Cog), or by the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change Scale, (ADCS-CGIC).

10. A method for treating or preventing a mammal which has been diagnosed as suffering from Alzheimer's Disease or the risk of Alzheimer's Disease, which would benefit from therapy by the combined administration of both (a) and (b) below, and therefore administration of both (a) and (b) has been

prescribed, which comprises administering to said mammal so diagnosed and prescribed

1. an amount of a first active ingredient (a), said first active ingredient (a) being an acetylcholine esterase inhibitor or a pharmaceutically acceptable salt thereof; and
2. an amount of a second active ingredient (b), said second active ingredient (b) being atorvastatin or a pharmaceutically acceptable salt thereof.

wherein said first active ingredient (a) and said second active ingredient (b) are administered together in a single pharmaceutical composition with a pharmaceutically acceptable carrier or diluent.