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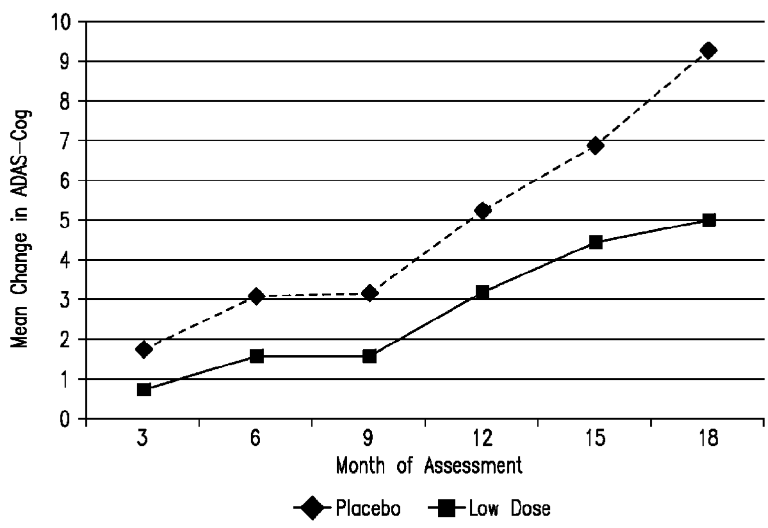

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The present invention relates to methods of treatment using [3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl amine ("COMPOUND I") or a pharmaceutically acceptable salt thereof. In various embodiments, the methods of treatment include treatment of mild-to-moderate dementia of Alzheimer's type, diabetes, insomnia, and other indications. The present invention also relates to pharmaceutical compositions comprising COMPOUND I or a pharmaceutically acceptable salt thereof.

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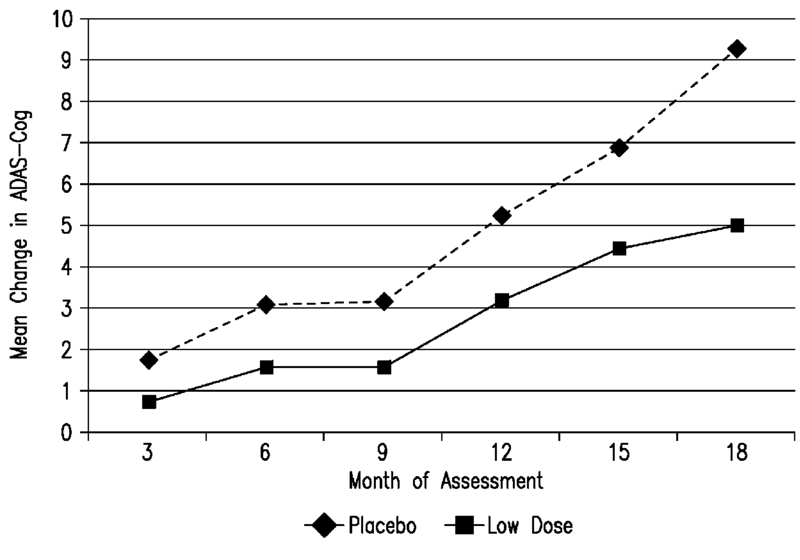

FIG.1

(57) **Abstract**: The present invention relates to methods of treatment using [3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl amine ("COMPOUND I") or a pharmaceutically acceptable salt thereof. In various embodiments, the methods of treatment include treatment of mild-to-moderate dementia of Alzheimer's type, diabetes, insomnia, and other indications. The present invention also relates to pharmaceutical compositions comprising COMPOUND I or a pharmaceutically acceptable salt thereof.

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TREATMENT OF MILD AND MODERATE ALZHEIMER'S DISEASE

FIELD OF THE INVENTION

The present invention relates to a method of treating individuals suffering from mild-to-moderate dementia of Alzheimer's type by administering an effective amount of [3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl amine ("COMPOUND I"). The present invention also relates to a method of inhibiting the interaction of the receptor for advanced glycation end products (RAGE) with a RAGE ligand in individuals with mild-to-moderate Alzheimer's disease. The present invention also relates to a method for treating diabetes and the reduction of glucose metabolism, including in individuals suffering from mild-to-moderate Alzheimer's disease. Additionally, the present invention relates to a method for treating insomnia or sleep onset latency in individuals, including those suffering from mild-to-moderate Alzheimer's disease.

BACKGROUND OF THE INVENTION

RAGE and the Treatment of Disease

The Receptor for Advanced Glycation Endproducts (RAGE) is a member of the immunoglobulin super family of cell surface molecules. The extracellular (N-terminal) domain of RAGE includes three immunoglobulin-type regions, one V (variable) type domain followed by two C-type (constant) domains (Neeper et al ., J. Biol. Chem. 267:14998-15004 (1992)). A single transmembrane spanning domain and a short, highly charged cytosolic tail follow the extracellular domain. The N-terminal, extracellular domain can be isolated by proteolysis of RAGE to generate soluble RAGE (sRAGE) comprised of the V and C domains.

RAGE is expressed in most tissues, and in particular, is found in cortical neurons during embryogenesis (Hori et al. (1995)). Increased levels of RAGE are also found in aging tissues (Schleicher et al., J. Clin. Invest. 99 (3): 457-468 (1997)), and the diabetic retina, vasculature and kidney (Schmidt et al., Nature Med. 1 :1002-1004 (1995)). Activation of RAGE in different tissues and organs leads to a number of pathophysiological consequences. RAGE has been implicated in a variety of conditions including: acute and chronic inflammation (Hofmann et al ., Cell 97:889-901 (1999)), the development of diabetic late complications such as increased vascular permeability (Wautier et al., J. Clin. Invest. 97:238-243 (1996)), nephropathy (Teillet et al., J. Am. Soc. Nephrol. 11 :1488-1497 (2000)), atherosclerosis (Vlassara et. al., The Finnish Medical Society DUODECIM, Ann. Med. 28:419-426 (1996)), and retinopathy (Hammes et al, Diabetologia 42:603-607 (1999)). RAGE has also been implicated in Alzheimer's disease (Yan et al . Nature 382: 685-691 (1996)), erectile dysfunction, and in tumor invasion and metastasis (Taguchi et al. Nature 405: 354-357 (2000)).

Advanced glycation endproducts (AGEs) have been implicated in a variety of disorders including complications associated with diabetes and normal aging. Incubation of proteins or lipids with aldose sugars results in nonenzymatic glycation and oxidation of amino groups on proteins to form Amadori adducts. Over time, the adducts undergo additional rearrangements, dehydrations, and cross-linking with other proteins to form complexes known as AGEs. Factors which promote formation of AGEs include delayed protein turnover (e.g. as in amyloidoses), accumulation of macromolecules having high lysine content, and high blood glucose levels (e.g. as in diabetes) (Hori et al, J. Biol. Chem. 270: 25752-761 , (1995)).

AGEs display specific and saturable binding to cell surface receptors on endothelial cells of the microvasculature, monocytes and macrophages, smooth muscle cells, mesengial cells, and neurons.

In addition to AGEs, other compounds can bind to, and inhibit the interaction of physiological ligands with RAGE. In normal development, RAGE interacts with amphoterin, a polypeptide which mediates neurite outgrowth in cultured embryonic neurons (Hori et al, (1995)). RAGE has also been shown to interact with EN-RAGE, a protein having substantial similarity to calgranulin (Hofmann et al . (1999)). RAGE has also been shown to interact with β-amyloid (Yan et al. Nature 389:689-695 (1997); Yan et al. Nature 382:685-691 (1996); Yan et al, Proc. Natl. Acad. Sci, 94:5296-5301 (1997)).

Binding of ligands such as AGEs, S100/calgranulin/EN-RAGE, β-amyloid, CML (Nε-Carboxymethyl lysine), HMGB1 (high mobility group box 1) and amphoterin to RAGE has been shown to modify expression of a variety of genes. For example, in many cell types interaction between RAGE and its ligands generates oxidative stress, which thereby results in activation of the free radical sensitive transcription factor NF-κB, and the activation of NF-κB regulated genes, such as the cytokines IL-I β, TNF-a, and the like.

As noted above, RAGE antagonists are useful in the treatment of the complications of diabetes. It has been shown that nonenzymatic glycoxidation of macromolecules ultimately resulting in the formation of advanced glycation endproducts (AGEs) is enhanced at sites of inflammation, in renal failure, in the presence of hyperglycemia and other conditions associated with systemic or local oxidant stress (Dyer, D, et al., J. Clin. Invest., 91 :2463-2469 (1993); Reddy, S., et al., Biochem., 34:10872-10878 (1995); Dyer, D., et al., J. Biol . Chem., 266: 11654-1 1660 (1991); Degenhardt, T., et al., Cell Mol. Biol, 44: 1139-1 145 (1998)). Accumulation of AGEs in the vasculature can occur focally, as in the joint amyloid composed of AGE-B2-microglobulin found in patients with dialysis-related amyloidosis (Miyata, T, et al , J. Clin. Invest, 92: 1243-1252 (1993); Miyata, T, et al , J. Clin. Invest, 98:1088-1094 (1996)), or generally, as exemplified by the vasculature and tissues of patients with diabetes (Schmidt, A-M, et al. Nature Med, 1 :1002-1004 (1995)). The progressive accumulation of AGEs over time in patients with diabetes suggests that endogenous clearance mechanisms are not able to function effectively at sites of AGE deposition. Such accumulated AGEs have the capacity to alter cellular properties by a number of mechanisms. Although RAGE is expressed at low levels in normal tissues and vasculature, in an environment where the receptor's ligands accumulate, it has been shown that RAGE becomes upregulated (Li, J. et al., J. Biol. Chem., 272: 16498-16506 (1997); Li, J., et al., J. Biol. Chem., 273:30870-30878 (1998); Tanaka, N., et al., J. Biol . Chem,. 275:25781-25790(2000)). RAGE expression is increased in endothelium, smooth muscle cells and infiltrating mononuclear phagocytes in diabetic vasculature. Also, studies in cell culture have demonstrated that AGE-RAGE interaction caused changes in cellular properties important in vascular homeostasis.

RAGE antagonists are also useful in treating amyloidoses and/or Alzheimer's disease. RAGE appears to be a cell surface receptor which binds β-sheet fibrillar material regardless of the composition of the subunits (amyloid-β peptide, Aβ, amylin, serum amyloid A, prion-derived peptide) (Yan, S. -D., et al ., Nature, 382:685-691 (1996); Yan, S-D, et al, Nat. Med, 6:643-651

(2000)). Deposition of amyloid has been shown to result in enhanced expression of RAGE. For example, in the brains of patients with Alzheimer's disease, RAGE expression increases in neurons and glia (Yan, S. -D, et al. Nature 382:685-691 (1996)). The consequences of Aβ interaction with RAGE appear to be quite different on neurons versus microglia. Whereas microglia become activated as a consequence of Aβ-RAGE interaction, as reflected by increased motility and expression of cytokines, early RAGE-mediated neuronal activation is superceded by cytotoxicity at later times. Further evidence of a role for RAGE in cellular interactions of Aβ concerns inhibition of Aβ-induced cerebral vasoconstriction and transfer of the peptide across the blood-brain barrier to brain parenchyma when the receptor was blocked (Kumar, S, et al, Neurosci. Program, p141 (2000)). Inhibition of RAGE-amyloid interaction has been shown to decrease expression of cellular RAGE and cell stress markers (as well as NF-kB activation), and diminish amyloid deposition (Yan, S-D, et al, Nat. Med, 6:643-651 (2000)) suggesting a role for RAGE-amyloid interaction in both perturbation of cellular properties in an environment enriched for amyloid (even at early stages) as well as in amyloid accumulation.

SUMMARY OF THE INVENTION

The present invention provides a method for the treatment of mild-to-moderate Alzheimer's disease by administering to a subject in need thereof an effective amount of [3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl amine ("COMPOUND I") or a pharmaceutically acceptable salt thereof.

In one embodiment, COMPOUND I or a pharmaceutically acceptable salt thereof is administered in an amount of less than 20 mg per day.

In another embodiment, COMPOUND I or a pharmaceutically acceptable salt thereof is administered between 1 mg/5 kg of the subject's body weight per day to 1 mg/50 kg of the subject's body weight per day.

In yet another embodiment, the present invention provides a method for inhibiting the interaction of the receptor for advanced glycation end products (RAGE) with a RAGE ligand in subjects with mild-to-moderate Alzheimer's disease, comprising administering to a subject in need thereof an amount less than 20 mg per day of COMPOUND I or a pharmaceutically acceptable salt thereof.

In a further embodiment, the present invention provides a method of treating diabetes comprising administering to a subject in need thereof an amount less than 20 mg per day of COMPOUND I or a pharmaceutically acceptable salt thereof.

The present invention also provides a method for inhibiting the reduction of glucose metabolism associated with the regression of subjects with mild-to-moderate Alzheimer's disease, comprising administering to a subject in need thereof an amount less than 20 mg per day of COMPOUND I or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a method of lowering blood glucose levels in a subject comprising administering to a subject in need thereof an amount less than 20 mg per day of COMPOUND I or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the present invention also provides of treating insomnia comprising administering to a subject in need thereof an amount less than 20 mg per day of COMPOUND I or a pharmaceutically acceptable salt thereof.

In another embodiment, the treatment of insomnia is in a subject with mild-to-moderate Alzheimer's disease.

The present invention also provides a method of decreasing sleep onset latency comprising administering to a subject in need thereof an amount less than 20 mg per day of COMPOUND I or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the method of decreasing sleep onset latency is in a subject with mild-to-moderate Alzheimer's disease.

In another embodiment, the present invention provides a method of reducing the frequency of adverse events in a subject with mild-to-moderate Alzheimer's disease comprising administering to a subject in need thereof an amount less than 20 mg per day of COMPOUND I or a pharmaceutically acceptable salt thereof.

In another embodiment of any of the previous embodiments, a suitable amount of an acetylcholinesterase inhibitor (AChEI) or memantine may also be administered.

The present invention also provides a pharmaceutical composition comprising between 1 mg and 20 mg of COMPOUND I or a pharmaceutically acceptable salt thereof.

In another embodiment, the pharmaceutical composition includes an acetylcholinesterase inhibitor (AChEI).

In still another embodiment, the pharmaceutical composition includes memantine.

In a further embodiment, the present invention provides oral use of [3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl amine, or a pharmaceutically acceptable salt thereof, in an amount of about 5 mg per day for the treatment of Alzheimer's disease in a human suffering from mild Alzheimer's disease.

In a further embodiment, the present invention provides oral use of [3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl amine, or a pharmaceutically acceptable salt thereof, for reducing the frequency of adverse events in a subject with mild-to-moderate Alzheimer's disease, wherein the [3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl amine, or pharmaceutically acceptable salt thereof, is for use in a daily dose of about 5 mg per day.

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BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 – Graph displaying the change from baseline in ADAS-cog for ADAS-cog subgroup of subjects presenting with ADAS-cog scores at baseline of less than or equal to 22.8 between placebo and treatment with 5 mg of COMPOUND I.

FIG. 2 - Kaplan-Meier curves for the group dosed with placebo and the group dosed with 5 mg of COMPOUND I where an event is defined as achievement of an increase in ADAS-cog of 7 or more points at any time for the subgroup of subjects with low baseline ADAS-cog at presentation where low is among subjects in the lowest 25% of the study population.

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FIG. 3 – Graph showing concentration-driven classification of subjects regardless of dose of COMPOUND I administered.

FIG. 4 – Graph showing profile over time comparing placebo-treated subjects to subjects in study whose measured median pk concentrations were in the range of 8 to 15 ng/ml of COMPOUND I.

FIG. 5a – Graph showing a regression analysis regressing concentration (ng/ml) on BMI (kg/m^2) for the 5 mg dose group.

FIG. 5b – Graph showing a regression analysis regressing concentration (ng/ml) on BMI (kg/m^2) for the 20 mg dose group.

FIG. 5c – Graph showing a regression analysis regressing concentration (ng/ml) on body weight (kg) for the 5 mg dose group.

FIG. 5d – Graph showing a regression analysis regressing concentration (ng/ml) on body weight (kg) for the 20 mg dose group.

FIG. 6a – Graph showing that mean change from baseline in glucose for subjects who present with high glucose values where high is defined as being 100 mg/ml or greater at baseline. It is noted that comparison with placebo rules out regression to the mean.

FIG. 6b – Graph showing that mean change from baseline in glucose for subjects who present with high glucose values where high is defined as being in the highest one third (33%) of glucose values at baseline. It is noted that comparison with placebo rules out regression to the mean.

FIG. 6c – Graph showing that mean change from baseline in glucose for subjects who present with high glucose values where high is defined as being in the highest 25% of glucose values at baseline. It is noted that comparison with placebo rules out regression to the mean.

FIG. 6d – Graph showing that mean glucose for subjects who present with normal or low glucose values where subgroup is taken as all subjects in the lower half (50%) of glucose values at baseline (subgroup is defined with a median cut).

FIG. 7 - Kaplan-Meier curves are shown of time for adverse event by dose group.

FIG. 8 - Kaplan-Meier curves are shown of time for adverse event by concentration group.

DETAILED DESCRIPTION

The present invention demonstrates that subjects with mild-to-moderate Alzheimer's disease may benefit from dose-dependent treatment with COMPOUND I compared with placebo. Further, the present invention demonstrates that treatment with COMPOUND I may lower glucose levels and may inhibit reduction in glucose metabolism that is associated with the regression of subjects with mild-to-moderate Alzheimer's disease. Additionally, the present invention provides a treatment for insomnia or sleep onset latency in subjects, including those with mild-to-moderate Alzheimer's disease by providing subjects with an effective amount of COMPOUND I or a pharmaceutically acceptable salt thereof.

The present invention is based on results from a parallel three-arm phase 2 study to evaluate the safety, tolerability, and efficacy of two doses of COMPOUND I compared to placebo in subjects with mild-to-moderate Alzheimer's disease. The study was conducted at forty different study sites across the United States.

In the study of the present invention, there were 399 subjects (133 per group), who were randomized to placebo or to COMPOUND I administered at 20 mg daily (after a loading dose of 60 mg daily for 6 days), or to COMPOUND I administered at 5 mg daily (after a loading dose of 15 mg daily for 6 days).

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Study visits occurred at screening, baseline (within four weeks after screening), then at four weeks, 3, 6, 9, 12, 15, 18 months, with a safety follow-up visit at 21 months. Visits included clinical and safety evaluations, blood draw for plasma biomarker and pharmacokinetic analysis, and pill counts to assess compliance. Primary (clinical) outcome measures were obtained at baseline and at subsequent three monthly visits, and secondary clinical outcome measures at baseline and at six monthly intervals. Brain MRIs were obtained at baseline, 12 and 18 months. Lumbar punctures for CSF biomarkers were performed at baseline and 12 months on a subgroup of subjects.

Key eligibility criteria included subjects who were aged 50 or older; had a diagnosis of probable Alzheimer's disease; had a Mini-Mental State Examination (MMSE) score between 14 and 26; and were in good general health. Subjects could have no evidence of stroke contributing to dementia. Further inclusion criteria included treatment with a stable dose of an acetylcholinesterase inhibitor and/or memantine for at least four months prior to randomization, and an available caregiver to act as informant and supervise study medications. Exclusion criteria included uncontrolled hypertension, unstable cardiac or pulmonary disease, diabetes, weight less than 40 kg or greater than 100 kg within the past two years, chronic use of non-steroidal anti-inflammatory drugs or immunosuppressive agents, drugs that increase QTc or inhibit CYP 34A, markedly abnormal ECG or QTc (QTcB or QTcF) or any screening 12-lead ECG greater than 450 msec for females or greater than 430 msec for males. There also could be no history of treatment for cancer within the past five years, drug or alcohol abuse, or major psychiatric illness. Women could not be of child-bearing potential. Subjects could not have taken another investigational drug for three months before screening.

The primary efficacy measure was the 70-point ADAS-cog. The ADAS-cog is used to assess the severity of selected areas of cognitive impairment (memory, language, orientation, reason and praxis). Scores range from 0 to 70 with lower scores indicating lesser severity and a score of 70 representing the worst cognitive impairment. Its use in assessing and following changes in patients with mild to moderate Alzheimer's disease has been extensively validated. Primary safety measures included reports of adverse events, blood and urine tests, and ECG measures. Secondary clinical measures included Clinical Dementia Rating Sum of Boxes (CDR-sb);

Alzheimer's Disease Cooperative Study Activities of Daily Living Scale (ADCS-ADL); Neuropsychiatric Inventory (NPI); and MMSE. Subjects also received a neuropsychological test battery, including: Digit Symbol Substitution Test, Forward and Backward Digit Span Test, Controlled Oral Word Association Test, Stroop Color Word interference Test, and Trail-Making Test (Parts A and B). Caregivers received a Quality of Life questionnaire and a Resource Utilization Schedule.

A brain MRI was performed at baseline and 12 months, on 1.5T scanners, using standardized acquisition parameters based on those in the ADNI study, and used for volumetric analysis. Cerebrospinal fluid was obtained by lumbar puncture, at baseline and after 12 months, for analysis of Alzheimer's disease-related biomarkers. Apolipoprotein E (APO-E) genotyping was performed and DNA was banked for pharmacogenomic studies on subjects who consented. Plasma was assayed for study drug levels at each visit and was stored for biomarker studies. Further, complete physical and neurological examinations were performed at baseline, and vital signs and brief examinations at subsequent visits. Clinical laboratory studies and urinalysis were performed at every visit. Electrocardiograms (ECGs) were obtained at all visits and centrally read (QTc analysis by a cardiologist). Adverse events were classified according to severity and causality by site investigators and reported to the ADCS and sponsors using standard methods. If subjects decided to withdraw from the study or were discontinued by site investigators, an early termination visit was scheduled within 14 days, including clinical and safety evaluations similar to the baseline visit.

Definitions

Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements.

By percent by weight it is meant that a particular weight of one ingredient in a composition is divided by the total weight of all of the ingredients in that composition. Percent by weight may be used interchangeably and means approximately the same as weight/weight percent or % (weight/weight) or percent by mass or mass percent.

It is further noted that, as used in this specification, the singular forms "a," "an," and "the" include plural referents unless expressly and unequivocally limited to one referent.

In another embodiment, the dosage or blood level of COMPOUND I or a pharmaceutically acceptable salt thereof and administration may be sufficient for inhibition of the biological function of RAGE at a sufficient level for sufficient time to treat Alzheimer's disease.

COMPOUND I refers to [3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl amine. COMPOUND I is the subject matter of U.S. Patent Nos. 7,361,678 and 7,884,219.

Various salts and isomers of COMPOUND I can be used. The term "salts" can include acid addition salts or addition salts of free bases. Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include inorganic acids such as hydrochloric, sulfuric, or phosphoric acid, and organic acids such as acetic, maleic, succinic, or citric acid, etc. All of these salts (or other similar salts) may be prepared by conventional means. The nature of the salt is not critical, provided that it is non-toxic and does not substantially interfere with the desired pharmacological activity. A preferred salt for the method of the present invention is the hydrochloride salt.

The phrase "pharmaceutically acceptable", as used in connection with compositions of the invention, refers to molecular entities and other ingredients of such compositions that are physiologically tolerable and do not typically produce untoward reactions (toxicity or side effects) when administered to a mammal (e.g., human). Preferably, as used herein, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in mammals, and more particularly in humans. Berge, et al. Journal of Pharmaceutical Science, Vol. 66(1), pp. 1-19 (1977).

The term "carrier" applied to pharmaceutical compositions of the invention refers to a diluent, excipient, or vehicle with which an active compound (e.g., an 1-aminocyclohexane derivative) is administered. Such pharmaceutical carriers can be sterile liquids, such as water, saline solutions, aqueous dextrose solutions, aqueous glycerol solutions, and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin, 18th Edition.

The term "subject" or "subject in need thereof" as used herein refers to a mammal. In an embodiment, the term refers to humans diagnosed with mild-to-moderate Alzheimer's disease.

"Mild-to-moderate Alzheimer's disease" can be diagnostically assessed as "probable Alzheimer's" according to the National Institute of Neurological and Communicative Disorders and Stroke/the Alzheimer's Disease and Related Disorders Associations (NINCDS-ADRDA) criteria.

The diagnosis of "mild-to-moderate" is well within the purview of the ordinary skilled physician using standard criteria, including the clinical assessment scales disclosed above and below. By way of example, the following numerical ranges on the standardized Mini-Mental State Examination (MMSE; 0-30 scale) have been used to diagnose mild-to-moderate, moderate, and moderate-to-severe Alzheimer's.

Mild-to-moderate Alzheimer's disease has been diagnosed as determined by MMSE scores of 10 to 22 in the present study, and also from 10-26 in studies using other therapeutics for treating mild-to-moderate Alzheimer's (e.g., donepezil). Severe Alzheimer's has been diagnosed in subjects having MMSE scores of less than 10.

Accordingly, a diagnosis of "mild" Alzheimer's disease could be made for subjects having the higher scores within the above-described ranges, e.g., about 21 to 26 on the MMSE.

It should be noted that the MMSE scale is not the only way to diagnose mild Alzheimer's disease, but represents a convenience. Nor should the claims be construed as requiring the step of "grading" a subject on the MMSE scale to be performed. In an embodiment, a subject having mild Alzheimer's disease is a patient who would score 21 or higher if the patient were scored according to MMSE scale. If a different scale were to be used, "mild" Alzheimer's disease would be defined as a diagnosis of Alzheimer's disease or probable Alzheimer's disease which is made based on a score that clearly does not overlap with the score range for moderate-to-severe Alzheimer's disease established for the same scale.

In an embodiment, mild Alzheimer's disease is defined as individuals having an ADAS-cog score of less than or equal to 23.

The term "intent to treat principle" refers to the principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (i.e. the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed and analyzed as members of that group irrespective of their compliance to the planned course of treatment. It is noted that the ITT principle refers to a methodology (how), not a population of analysis (who). It is also noted that the ITT analyses are generally accepted as the most valid analyses in that they are supported by randomization, and exclusion of a subject based on behavior characteristics of the subject (e.g., compliance with trial medication) is not consistent with the ITT principle because it is not supported by randomization. It is also noted that subgroup analyses based on population characteristics (e.g., severity of AD at baseline) are supported by randomization and considered valid.

The term "Full Analysis Set (FAS)" refers to the set of subjects that is as close as possible to the ideal implied by the intention-to-treat principle. It is derived from the set of all randomized subjects by minimal and justified elimination of subjects. The FAS includes all subjects who receive at least one dose of trial medication and have at least one post-baseline assessment. The dataset for the FAS includes all collected data whether on treatment or off-treatment (it is irrelevant to treatment compliance). It is noted that observations of subjects after treatment has discontinued are still included in a pure ITT analysis recognizing that the treatment that was received, particularly with a compound with a long half-life, affects assessments collected after treatment, regardless of whether or not the subject is still taking active treatment.

The term "on treatment" refers to data collected within 28 days of last dose. All data collected between the first dose of trial medication and the last dose of trial medication and all data collected within 28 days of the last dose of trial medication are considered to be on-treatment."

The term "off treatment" refers to data collection 29 days or later following the final dose of trial medication.

The term "trial medication" refers to all blinded medication within a clinical trial whether active or placebo.

The term "post baseline" refers to all data collected after baseline regardless of whether it is on treatment or off treatment.

The term "Per Protocol Set (Valid Cases, Efficacy Sample, Evaluable Subjects Sample)" or "per-treatment set" refers to the set of data generated by the subset of subjects who complied with the protocol sufficiently to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of major protocol violations. It is noted that a per-treatment analysis excludes subjects based on behavior characteristics and is not generally supported by randomization. Such analyses can be useful, but are not generally as valid as ITT analyses.

The term "Statistical Analysis Plan (SAP)" refers to a document that contains the analyses planned in advance of unblinding to protect alpha. It is a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data. The SAP is generally signed prior to unblinding, and modifications to the SAP after unblinding, such as unplanned analyses based on post-hoc behavior of a subject (e.g., treatment compliance).

The term “dropout” refers to a subject in a clinical trial who for any reason fails to continue in the trial until the last visit required of him/her by the study protocol. In particular, in these studies, a subject is a dropout when the subject’s last visit occurred prior to Month 18.

The term “Treatment Effect” refers an effect attributed to a treatment in a clinical trial. In most clinical trials the treatment effect of interest is a comparison (or contrast) of two or more treatments. It is noted that the treatment effect does not include the placebo effect. Differences between randomized active treatment groups and placebo groups are generally recognized as treatment effects in controlled clinical trials.

The term “treatment-emergent” refers to an observation or event that emerges during treatment having been absent pre-treatment, or worsens relative to the pre-treatment state.

The term “treatment-emergent adverse event” refers to any untoward event that is observed or reported after the first dose of trial medication that was not present prior to the first dose of trial medication or any untoward event that represents the exacerbation of a pre-existing condition. Exacerbation includes any increase in severity or frequency.

The term “Generalisability, Generalisation” refers to the extent to which the findings of a clinical trial can be reliably extrapolated from the subjects who participated in the trial to a broader patient population and a broader range of clinical settings.

The term "treatment" as used herein, refers to the full spectrum of treatments for a given condition or disorder from which a subject is suffering, including alleviation or amelioration of one or more of the symptoms resulting from that disorder, to the delaying of the onset or progression of the disorder.

The term "treat" is used herein to mean to relieve or alleviate at least one symptom of a disease in a subject. For example, the term "treat" may mean to relieve or alleviate cognitive impairment (such as impairment of memory and/or orientation) or impairment of global functioning (activities of daily living) and/or slow down or reverse the progressive deterioration in ADL or cognitive impairment in individuals having mild-to-moderate Alzheimer's disease.

Within the meaning of the present invention, the term "treat" may also mean delay of the progression of a disease in the patients presenting with additional symptoms associated with Alzheimer's disease, such as but not limited to those identified using one or more of the ADAS-cog, the MMSE, the ADCS-ADL criteria, the CDR-sb, or the NPI total criteria, defined above. The term "delay the progression" is used herein to mean slower than expected development or continuance or aggravation of a disease in a subject compared to an untreated subject. This can be determined for Alzheimer's disease, for example, by obtaining slower than expected deterioration in measures such as cognitive performance in treated patients, compared with those measures in untreated patients (who represent the expected progression of the disease). Cognitive performance can be measured using, e.g., the Alzheimer's Disease Assessment Scale (ADAS-cog), or the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL). For example, the typical disease progression in subjects with mild Alzheimer's disease is an increase of about 1 to about 3 points on the ADAS-cog over a time period of about 6 months. However, disease progression is highly individualized, and also depends on factors such as the initial condition of the patient.
In a specific embodiment, the term "treat" may also mean to increase the glucose metabolic rate, or to inhibit further reduction in the metabolic rate in patients with mild-to-moderate Alzheimer's disease, which is associated with regression. This can also be assessed by comparing the glucose metabolism in treated patients with that in untreated patients. A reduction in the decrease of glucose metabolism in the treated patients, or a slower than expected decrease, or stability of glucose metabolism in treated patients, compared with untreated patients, is indicative of a benefit accompanying the treatment.

In another specific embodiment, the term "treat" may also mean to improve symptoms associated with insomnia or decrease sleep onset latency in patients with mild-to-moderate Alzheimer's disease, which is associated with regression.

The term "therapeutically effective amount" is used herein to mean an amount or dose of COMPOUND I that is effective to ameliorate or delay a symptom, behavior or event associated with mild-to-moderate Alzheimer's disease. Alternatively, a therapeutically effective amount is sufficient to cause an improvement in a clinically significant condition or parameter (according to the attending physician employing one or more of the foregoing sets of criteria) associated with Alzheimer's disease in an individual in need thereof. In still another embodiment, a therapeutically effective amount is used herein to denote the amount of COMPOUND I or a pharmaceutically acceptable salt thereof that will elicit the therapeutic response of a subject that is being sought. In an embodiment, the therapeutic response may be antagonizing RAGE.

A "responder" is defined as a patient who has not progressed and for whom the change from baseline to 18 months in ADAS-cog is less than or equal to 7.

The terms "about" and "approximately" shall generally mean an acceptable degree of error or variation for the quantity measured given the nature or precision of the measurements. Typically, degrees of error or variation are within 20 percent (%), preferably within 10%, and more preferably within 5% of a given value or range of values. Numerical quantities given herein are approximate unless stated otherwise, meaning that the term "about" or "approximately" can be inferred when not expressly stated.

Formulation, Dosage, and Administration

The invention further provides pharmaceutical compositions comprising a compound of COMPOUND I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. The term "pharmaceutical composition" is used herein to denote a composition that may be administered to a mammalian host, e.g., orally, topically, parenterally, by inhalation spray, or rectally, in unit dosage formulations containing conventional non-toxic carriers, diluents, adjuvants, vehicles and the like. The term "parenteral" as used herein, includes subcutaneous injections, intravenous, intramuscular, intraci sternal injection, or by infusion techniques.

The pharmaceutical compositions containing a compound of the invention may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous, or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any known method, and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents, and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with non-toxic pharmaceutically-acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in U.S. Patent Nos. 4,356,108; and 4,265,874, to form osmotic therapeutic tablets for controlled release.

Formulations for oral use may also be presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or a soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil .

Aqueous suspensions may contain the active compounds in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide such as lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyl-eneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as a liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active compound in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring, and coloring agents may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example a liquid paraffin, or a mixture thereof. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known methods using suitable dispersing or wetting agents and suspending agents described above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1 ,3-butanediol . Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conveniently employed as solvent or suspending medium. For this purpose, any bland fixed oil may be employed using synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compositions may also be in the form of suppositories for rectal administration of the compounds of the invention. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will thus melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols, for example.

For topical use, creams, ointments, jellies, solutions or suspensions, lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols etc., containing the compounds of the invention are contemplated. These topical formulations may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams. The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about .1 % up to about 99% of the formulation. More usually they will form up to about 80% of the formulation. For the purpose of this application, topical applications shall include mouth washes and gargles.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, tetrafluoroethane, heptafluoropropane, carbon dioxide or other suitable gas.

In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

The equipment and parameters listed in the following manufacturing description are representative of the equipment and parameters that may be used to prepare a pharmaceutical formulation. The actual equipment and parameters used in the manufacture of a pharmaceutical formulation may vary.

The compound (in free base form) may be sifted and weighed out with an approximately equal amount of microcrystalline cellulose. The mixture may be geometrically diluted with microcrystalline cellulose. The mixture, any remaining microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, colloidal silicon dioxide, and Starch 1500 may be added into a blender and mixed. A small portion of the mixture may be removed, combined with magnesium stearate, and returned to the blender and mixed. The resulting mixed may be encapsulated and administered. The weight percent of the compound, microcrystalline cellulose, and/or lactose monohydrate may be adjusted to prepare dosages with higher or lower amounts of the compound. For example, Formulation A in the table below may be used to prepare a capsule formulation of 5 mg per dose, and Formula B may be used to prepare a capsule formulation of 20 mg per dose.

Name of Ingredients	**Formulation A (wt%)**	**Formulation B (wt%)**
Compound (free base)	2.4	9.5
Microcrystalline Cellulose	54.2	50.6
Lactose Monohydrate	27.9	24.4
Pregelatinized Starch	8.0	8.0
Croscarmellose Sodium	6.4	6.4
Colloidal Silicon Dioxide	0.4	0.4
Magnesium Sterarate	0.8	0.8

In one embodiment, a method of treating Alzheimer's disease comprises administering to a subject in need thereof an amount less than 20 mg per day of COMPOUND I or a pharmaceutically acceptable salt thereof. COMPOUND I or a pharmaceutically acceptable salt thereof may be administered in a dose ranging from about 1 mg per day to less than 20 mg per day. In some embodiments, the dose is from about 1 mg per day to about 19 mg per day, or from about 1 mg per day to about 18 mg per day, or from about 1 mg per day to about 17 mg per day, or from about 1 mg per day to about 16 mg per day, or from about 1 mg per day to about 15 mg per day, or from about 1 mg per day to about 14 mg per day, or from about 1 mg per day to about 13 mg per day, or from about 1 mg per day to about 12 mg per day, or from about 1 mg per day to about 11 mg per day, or from about 1 mg per day to about 10 mg per day, or from about 1 mg per day to about 9 mg per day, or from about 1 mg per day to about 8 mg per day, or from about 1 mg per day to about 7 mg per day, or from about 1 mg per day to about 6 mg per day, or from about 1 mg per day to about 5 mg per day, or from about 1 mg per day to about 4 mg per day, or from about 1 mg per day to about 3 mg per day, or from about 1 mg per day to about 2 mg per day. In other embodiments, the dose is about 5 mg per day or about 4 mg per day or about 3 mg per day or about 2 mg per day.

In some embodiments, the serum blood concentration of COMPOUND I or a pharmaceutically acceptable salt thereof in a subject is between about 1 ng/ml to about 65 ng/ml, or between about 1 ng/ml to about 60 ng/ml, or between about 1 ng/ml to about 55 ng/ml, or between about 1 ng/ml to about 50 ng/ml, or between about 1 ng/ml to about 45 ng/ml, or between about 1 ng/ml to about 40 ng/ml, or between about 1 ng/ml to about 35 ng/ml, or between about 1 ng/ml to about 30 ng/ml, or between about 1 ng/ml to about 25 ng/ml, or between about 1 ng/ml to about 20 ng/ml, or between about 1 ng/ml to about 15 ng/ml, or between about 1 ng/ml to about 10 ng/ml. In other embodiments, the serum blood concentration in the subject is between 8 to about 15 ng/ml. In still other embodiments, the serum blood concentration in the subject is about 12.5 ng/ml.

In another embodiment, the method of the treatment of Alzheimer's disease is determined by the improvement, or no deterioration, or a reduction in the rate of deterioration in at least one of the assessments selected from the group consisting of Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), the Clinical Dementia Rating Sum of Boxes (CDR-sb), the Alzheimer's Disease Cooperative Study Activities of Daily Living Scale (ADCS-ADL), the Neuropsychiatric Inventory (NPI), and the Mini-Mental State Evaluation (MMSE). In some embodiments, the treatment results in a reduction in the rate of deterioration in ADAS-cog scores. In other embodiments, the treatment results in a median reduction in the rate of deterioration of ADAS-cog scores of two to five points.

In other embodiments, a method of treating Alzheimer's disease comprises administering to a subject in need thereof an amount of COMPOUND I or a pharmaceutically acceptable salt thereof between 1 mg/5 kg of the subject's body weight per day and 1 mg/50 kg of the subject's body weight per day. The administration of COMPOUND I or a pharmaceutically acceptable salt thereof may be administered in an amount of about 1 mg/10 kg per day, or 1 mg/15 kg per day, or 1 mg/20 kg per day, or 1 mg/25 kg per day, or 1 mg/30 kg per day, or 1 mg/35 kg per day, or 1 mg/40 kg per day, or 1 mg/45 kg per day. In yet other embodiments, COMPOUND I or a pharmaceutically acceptable salt thereof is administered in an amount of 1 mg/20 kg per day. In yet other embodiments, COMPOUND I or a pharmaceutically acceptable salt thereof is administered in an amount between about 0.2 mg/kg per day and 0.02 mg/kg per day. In yet other embodiments, COMPOUND I or a pharmaceutically acceptable salt thereof is administered in an amount between about 0.1 mg/kg per day, or about 0.09 mg/kg per day, or about 0.08 mg/kg per day, or about 0.07 mg/kg per day, or about 0.06 mg/kg per day, or about 0.05 mg/kg per day, or about 0.04 mg/kg per day, or about 0.03 mg/kg per day.

In some embodiments, a method is provided to inhibit the interaction of the receptor for advanced glycation end products (RAGE) with a RAGE ligand in subjects with mild-to-moderate Alzheimer's disease, by administering to a subject in need thereof an amount less than 20 mg per day of COMPOUND I or a pharmaceutically acceptable salt thereof. In an embodiment, the RAGE ligand may be one of soluble β-amyloid, insoluble β-amyloid, s100b, calgranulin, EN-RAGE, HMGB1 (high mobility group box 1), aphoterin, or carboxymethyllysine. COMPOUND I or a pharmaceutically acceptable salt thereof may be administered in a dose ranging from about 1 mg per day to less than 20 mg per day. In some embodiments, the dose is from about 1 mg per day to about 19 mg per day, or from about 1 mg per day to about 18 mg per day, or from about 1 mg per day to about 17 mg per day, or from about 1 mg per day to about 16 mg per day, or from about 1 mg per day to about 15 mg per day, or from about 1 mg per day to about 14 mg per day, or from about 1 mg per day to about 13 mg per day, or from about 1 mg per day to about 12 mg per day, or from about 1 mg per day to about 11 mg per day, or from about 1 mg per day to about 10 mg per day, or from about 1 mg per day to about 9 mg per day, or from about 1 mg per day to about 8 mg per day, or from about 1 mg per day to about 7 mg per day, or from about 1 mg per day to about 6 mg per day, or from about 1 mg per day to about 5 mg per day, or from about 1 mg per day to about 4 mg per day, or from about 1 mg per day to about 3 mg per day, or from about 1 mg per day to about 2 mg per day. In other embodiments, the dose is about 5 mg per day or about 4 mg per day or about 3 mg per day or about 2 mg per day.

In an embodiment, the administration of COMPOUND I or a pharmaceutically acceptable salt thereof treats mild Alzheimer's disease. In some embodiments, mild Alzheimer's disease may be defined as a subject that presents with an ADAS-cog score of less than or equal to23.

In other embodiments, treatment with COMPOUND I or a pharmaceutically acceptable salt thereof is used to treat diabetes by administering to a subject in need thereof an amount less than 20 mg per day. In other embodiments, COMPOUND I or a pharmaceutically acceptable salt thereof is administered in a dose from about 1 to about 20 mg per day. COMPOUND I or a pharmaceutically acceptable salt thereof may be administered in a dose ranging from about 1 mg per day to less than 20 mg per day. In some embodiments, the dose is from about 1 mg per day to about 19 mg per day, or from about 1 mg per day to about 18 mg per day, or from about 1 mg per day to about 17 mg per day, or from about 1 mg per day to about 16 mg per day, or from about 1 mg per day to about 15 mg per day, or from about 1 mg per day to about 14 mg per day, or from about 1 mg per day to about 13 mg per day, or from about 1 mg per day to about 12 mg per day, or from about 1 mg per day to about 11 mg per day, or from about 1 mg per day to about 10 mg per day, or from about 1 mg per day to about 9 mg per day, or from about 1 mg per day to about 8 mg per day, or from about 1 mg per day to about 7 mg per day, or from about 1 mg per day to about 6 mg per day, or from about 1 mg per day to about 5 mg per day, or from about 1 mg per day to about 4 mg per day, or from about 1 mg per day to about 3 mg per day, or from about 1 mg per day to about 2 mg per day. In other embodiments, the dose is about 5 mg per day or about 4 mg per day or about 3 mg per day or about 2 mg per day. In still other embodiments, the method includes treating diabetes in patients with mild-to-moderate Alzheimer's disease.

In some embodiments, the administration of COMPOUND I or a pharmaceutically acceptable salt thereof may reduce the levels of HbA1C in a subject in need thereof. In other embodiments, the administration of COMPOUND I or a pharmaceutically acceptable salt thereof may reduce the amount of HbA1C in a subject in need thereof by at least 0.1 of a percentage point, or 0.2 of a percentage point, or 0.3 of a percentage point, or 0.4 of a percentage point, or 0.5 of a percentage point, or 0.6 of a percentage point, or 0.7 of a percentage point, or 0.8 of a percentage point, or 0.9 of a percentage point, or one percentage point. In still other embodiments, the administration of COMPOUND I or a pharmaceutically acceptable salt thereof may reduce the level of HbA1C in a subject in need thereof to less than 7%. In other embodiments, the level of HbA1C may be reduced to a level between 5 and 6.5%.

In some embodiments, the present invention provides a method for inhibiting the reduction of glucose metabolism associated with the regression of subjects with mild-to-moderate Alzheimer's disease by administering to a subject in need thereof an amount less than 20 mg per day of COMPOUND I or a pharmaceutically acceptable salt thereof. COMPOUND I may be administered in a dose ranging from about 1 mg per day to less than 20 mg per day. In some embodiments, the dose is from about 1 mg per day to about 19 mg per day, or from about 1 mg per day to about 18 mg per day, or from about 1 mg per day to about 17 mg per day, or from about 1 mg per day to about 16 mg per day, or from about 1 mg per day to about 15 mg per day, or from about 1 mg per day to about 14 mg per day, or from about 1 mg per day to about 13 mg per day, or from about 1 mg per day to about 12 mg per day, or from about 1 mg per day to about 11 mg per day, or from about 1 mg per day to about 10 mg per day, or from about 1 mg per day to about 9 mg per day, or from about 1 mg per day to about 8 mg per day, or from about 1 mg per day to about 7 mg per day, or from about 1 mg per day to about 6 mg per day, or from about 1 mg per day to about 5 mg per day, or from about 1 mg per day to about 4 mg per day, or from about 1 mg per day to about 3 mg per day, or from about 1 mg per day to about 2 mg per day.

In other embodiments, the dose is about 5 mg per day or about 4 mg per day or about 3 mg per day or about 2 mg per day. In other embodiments, the administration of COMPOUND I or a pharmaceutically acceptable salt thereof is used to lower blood glucose levels. In still other embodiments, the subject is suffering from mild-to-moderate Alzheimer's disease. In other embodiments, a subject's blood glucose levels are lowered by at least 5 mg/dl, or at least 10 mg/dl, or at least 15 mg/dl, or at least 20 mg/dl or between 5 mg/dl to 20 mg/dl. In other embodiments, the subject's naïve glucose level is greater than 100 ng/dl.

In other embodiments, the administration of COMPOUND I or a pharmaceutically acceptable salt thereof is used to treat insomnia by the administration to a subject in need thereof of an amount less than 20 mg per day of COMPOUND I or a pharmaceutically acceptable salt thereof. COMPOUND I may be administered in a dose ranging from about 1 mg per day to less than 20 mg per day. In some embodiments, the dose is from about 1 mg per day to about 19 mg per day, or from about 1 mg per day to about 18 mg per day, or from about 1 mg per day to about 17 mg per day, or from about 1 mg per day to about 16 mg per day, or from about 1 mg per day to about 15 mg per day, or from about 1 mg per day to about 14 mg per day, or from about 1 mg per day to about 13 mg per day, or from about 1 mg per day to about 12 mg per day, or from about 1 mg per day to about 11 mg per day, or from about 1 mg per day to about 10 mg per day, or from about 1 mg per day to about 9 mg per day, or from about 1 mg per day to about 8 mg per day, or from about 1 mg per day to about 7 mg per day, or from about 1 mg per day to about 6 mg per day, or from about 1 mg per day to about 5 mg per day, or from about 1 mg per day to about 4 mg per day, or from about 1 mg per day to about 3 mg per day, or from about 1 mg per day to about 2 mg per day. In other embodiments, the dose is about 5 mg per day or about 4 mg per day or about 3 mg per day or about 2 mg per day. In other embodiments, the subject with from insomnia suffers from mild-to-moderate Alzheimer's disease. In other embodiments, the administration of COMPOUND I or a pharmaceutically acceptable salt thereof is used to decrease sleep onset latency. In still other embodiments, the subject with sleep onset latency also has mild-to-moderate Alzheimer's disease. In another embodiment, sleep onset latency is decrease by 1-5 minutes or by 5-10 minutes.

In some embodiments, treatment with COMPOUND I or a pharmaceutically acceptable salt thereof reduces the frequency of adverse events in a subject with mild-to-moderate Alzheimer's disease. In some embodiments, the adverse event may include falling, dizziness, confusional state, and somnolence. In other embodiments, the adverse events may be psychiatric adverse events. Psychiatric adverse events may include agitation, depression, anxiety, aggression, and restlessness. COMPOUND I or a pharmaceutically acceptable salt thereof may be administered in a dose ranging from about 1 mg per day to less than 20 mg per day. In some embodiments, the dose is from about 1 mg per day to about 19 mg per day, or from about 1 mg per day to about 18 mg per day, or from about 1 mg per day to about 17 mg per day, or from about 1 mg per day to about 16 mg per day, or from about 1 mg per day to about 15 mg per day, or from about 1 mg per day to about 14 mg per day, or from about 1 mg per day to about 13 mg per day, or from about 1 mg per day to about 12 mg per day, or from about 1 mg per day to about 11 mg per day, or from about 1 mg per day to about 10 mg per day, or from about 1 mg per day to about 9 mg per day, or from about 1 mg per day to about 8 mg per day, or from about 1 mg per day to about 7 mg per day, or from about 1 mg per day to about 6 mg per day, or from about 1 mg per day to about 5 mg per day, or from about 1 mg per day to about 4 mg per day, or from about 1 mg per day to about 3 mg per day, or from about 1 mg per day to about 2 mg per day. In other embodiments, the dose is about 5 mg per day or about 4 mg per day or about 3 mg per day or about 2 mg per day.

In any of the preceding embodiments, the administration of COMPOUND I or a pharmaceutically acceptable salt thereof may additionally include treatment with an acetylcholinesterase inhibitor (AChEI). The AChEI may include donepezil hydrochloride, galantamine hydrochloride, rivastigmine tartrate, or tacrine hydrochloride. In still other embodiments, the administration of COMPOUND I or a pharmaceutically acceptable salt thereof may additionally include treatment with memantine. In some embodiments, the subjects may have been receiving treatment with an AChEI or memantine for at least four months prior to the administration of COMPOUND I or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention includes a pharmaceutical composition including between 1 mg and 20 mg of COMPOUND I or a pharmaceutically acceptable salt thereof, and an AChEI. In other embodiments, the pharmaceutical composition may include between 1 mg and 20 mg of COMPOUND I or a pharmaceutically acceptable salt thereof, and memantine. The

AChEI may include donepezil hydrochloride, galantamine hydrochloride, rivastigmine tartrate, or tacrine hydrochloride. In some embodiments, the AChEI is donepezil hydrochloride present between 5 mg and 23 mg. In other embodiments, the AChEI is galantamine hydrochloride present between 16 mg and 24 mg. In yet other embodiments, the AChEI is rivastigmine tartrate present between 6 mg and 12 mg. In still other embodiments, the AChEI is tacrine hydrochloride present at 40 mg. In still other embodiments, memantine is present between 5 mg and 20 mg. The pharmaceutical composition may include COMPOUND I from about 1 mg per day to about 19 mg per day, or from about 1 mg per day to about 18 mg per day, or from about 1 mg per day to about 17 mg per day, or from about 1 mg per day to about 16 mg per day, or from about 1 mg per day to about 15 mg per day, or from about 1 mg per day to about 14 mg per day, or from about 1 mg per day to about 13 mg per day, or from about 1 mg per day to about 12 mg per day, or from about 1 mg per day to about 11 mg per day, or from about 1 mg per day to about 10 mg per day, or from about 1 mg per day to about 9 mg per day, or from about 1 mg per day to about 8 mg per day, or from about 1 mg per day to about 7 mg per day, or from about 1 mg per day to about 6 mg per day, or from about 1 mg per day to about 5 mg per day, or from about 1 mg per day to about 4 mg per day, or from about 1 mg per day to about 3 mg per day, or from about 1 mg per day to about 2 mg per day.

In other embodiments, treatment with COMPOUND I or a pharmaceutically acceptable salt thereof reduces the amount of soluble Aβ found in the cerebral spinal fluid (CSF). In some embodiments, the soluble form of Aβ is isoform 1-40. In other embodiments, the soluble form of Aβ is isoform 1-42. In still other embodiments, the soluble form of Aβ is isoform 1-38. In still other embodiment, treatment with COMPOUND I or a pharmaceutically acceptable salt thereof alters the ratio between the amounts of isoform 1-40 to isoform 1-42 in the CSF.

In some embodiments, an observation was that when subjects in the 20-mg-dose group were discontinued from treatment, their ADAS-cog scores showed improvement. It is well known that Alzheimer's disease is a degenerative disease, and patients do not spontaneously remit. Exploratory analyses confirmed that subjects treated with 20 mg of COMPOUND I showed changes from baseline at endpoint visits (after treatment was stopped) that were superior to changes from baseline in the placebo group. This finding is consistent with the hypothesis that

COMPOUND I had beneficial effects on the underlying disease state of the patients. The symptoms associated with higher concentrations of COMPOUND I, may have masked the improvement, and when the drug concentrations reduced to more beneficial ranges, the beneficial effects of the treatment could emerge.

Examples

Example 1

A Double-Blind, Placebo-Controlled, Randomized, Multicenter Study Evaluating the Efficacy and Safety of Eighteen Months of Treatment with COMPOUND I in Participants with Mild-to-Moderate Alzheimer's Disease

The study was designed with three arms: 20 mg/day after a loading dose of 60 mg/day for 6 days; 5 mg/day after a loading dose of 15 mg/day for 6 days, and placebo. The study randomized N=399 patients with mild-moderate Alzheimer's disease in balanced ratios (1:1:1). The 20-mg-dose group was terminated at an interim analysis. Subsequently, the study was terminated prematurely based on a futility analysis that was planned in the original protocol.

Statistical analysis of the study included analyses that were planned in the protocol and statistical analysis plan and also exploratory and investigative analyses. Subsequent to a patient's termination of study treatment, the patient was instructed to continue attending study visits, and data continued to be collected. Statistical analysis included datasets that included all available data (on-treatment and off-treatment) and on-treatment data, where "on-treatment" was defined as within 28 days of the date of last dose. Off-treatment data reflect the treatment that was given according to the randomization schedule; therefore, on-treatment and off-treatment analyses that are based on the randomized population and follow the intent-to-treat principles are valid.

Statistical analysis compared the 5-mg-dose group (n=131; mean age=74 yr; 53% female) with the placebo group (n=132; mean age 72 yr; 57% female). Dropout rates in the incomplete study were 48% and 52% for 5 mg COMPOUND I and placebo, respectively. Performing a standard intent-to-treat analysis of covariance (adjusting for baseline) on change from baseline to endpoint in ADAS-cog using last-observation-carried-forward on all randomized patients with on-treatment data resulted in least-squares means of 6.4 and 8.7 (nominal p=0.03). Actual mean changes from baseline were 6.59 (SD=7.91) and 9.00 (SD=9.21) for groups dosed with 5 mg COMPOUND I and placebo, respectively. The unadjusted analysis likewise yielded nominal p=0.03 favoring treatment with 5 mg COMPOUND I.

Additional analysis on observed cases by visit, on percent change from baseline in ADAS-cog, and proportion of patients showing an increase in ADAS-cog of 7 or more points (responder analysis) likewise had nominal p-values favoring 5-mg COMPOUND I over placebo at the trend level or better.

The following table summarizes the planned efficacy analysis designated as primary and the supportive analyses to ensure robustness of the conclusions of the primary analysis. These analyses were planned in the study protocol, planned in the statistical analysis plan, and follow the intent-to-treat principles depicted in ICH E9. A summary of the key results on ADAS-cog at 18 months follows:

Table 1: Summary of planned ITT statistical analysis described in the study protocol

Analysis	Statistic	Treatment Group		Statistical Analysis	
		5-mg dose COMPOUND I	Placebo	Methodology	p-value
Primary analysis described in protocol and SAP: mITT Report number: 2011-06-23-001	Sample size	69	68	ANCOVA with MI imputation (primary in protocol and SAP)	0.008
	Mean change to month 18	8.84	11.94	Complete Cases ANCOVA	0.02
	Median change to month 18	6.76	10.34	LOCF ANCOVA	0.03
	Delta in mean	3.1		GEE	0.03
	Delta in median	3.58		Mixed models repeated measures (random effects)	0.04

Example 2

Drug effects were more pronounced among patients who presented with less severity of Alzheimer's disease than those who presented with greater severity of Alzheimer's disease, based on the ADAS-cog at baseline.

Entry into the study was based on the MMSE; there was no eligibility criterion based on the ADAS-cog. Post-hoc analysis examined characteristics of individuals who may have more pronounced benefit than others. Discriminant analysis suggested that some subgroups of patients may respond better than others to COMPOUND I.

An observation of the analysis revealed that patients in Study who presented with less severe Alzheimer's showed better delineation from placebo than those who had more severe disease at entry, based on the ADAS-cog.

FIG. 1 displays the change from baseline in ADAS-cog for an ADAS-cog subgroup of subjects presenting with ADAS-cog scores at baseline of less than or equal to 23.
The subjects presenting with mild dementia treated with placebo (dashed line) show greater increases from baseline in ADAS-cog, indicating worsening of Alzheimer's disease at a greater rate than subjects presenting with mild Alzheimer's disease who were treated with 5-mg COMPOUND I (solid line). The sample size varies over time as patients leave the study. This analysis includes all data on-treatment where on-treatment is defined as date of last dose plus 28 days. The difference between the placebo group and the group treated with COMPOUND I at 5 mg is statistically significant at Month 18 using last-observation-carried-forward to accommodate missing data.

A responder is one who has not progressed, and progression is an increase of 7 or more points on the ADAS-cog within 18 months.

FIG. 2 displays Kaplan-Meier curves for the group dosed with placebo and the group dosed with COMPOUND I at 5 mg where an event is defined as achievement of an increase in ADAS-cog of 7 or more points at any time. The Kaplan-Meier curves in FIG. 2 show the proportions of subjects declining in Alzheimer's disease as measured by the ADAS-cog by classifying a subject as having an "event" at the time of an increase in ADAS-cog of 7 points (reference for 7 points being progression: Publication by Vellas, et al., "Long-term changes in ADAS-cog: What is clinically relevant for disease modifying trails in Alzheimer?" (Volume 11, Number 4, 2007; *Journal of Nutrition, Health & Aging*)). The analysis uses Markov-Chain model conventions with achievement of an event as an absorbing state. The low dose group (5 mg, indicated by the solid line) dominates the placebo group (indicated by the dotted line) at all points, and the distance between the lines indicates superiority of treatment with COMPOUND I relative to placebo to retard the progression of Alzheimer's disease in patients who present with mild Alzheimer's disease at baseline.

Example 3

Drug effects were more pronounced among patients with concentrations within identified ranges. Concentration levels were highly correlated with bodyweight and with BMI. The optimal dosing paradigm is concentration-driven.

Blood samples were taken at each study visit to measure trough concentrations of drug levels. Analysis of drug concentrations correlated with response as assessed by ADAS-cog. Statistical modeling to identify the concentration range that optimizes the efficacy of the compound was done using the trough concentrations and the change from baseline in ADAS-cog. Preliminary results showed a range of 7-20 ng/ml where COMPOUND I-treated subjects had maximal response (smallest changes from baseline in ADAS-cog) among all other groups in the study. Other analyses resulted in a range of 8 to 15 ng/ml. When analysis was expanded to include 4 supportive efficacy measures in addition to the ADAS-cog, (MMSE, ADL, CDR-sb, and NPI), the identified optimal range was 8-13 ng/ml.

For analysis, subjects were categorized into exposure groups by the maximum of the trough levels during the 18-month trial period. Analysis using tertile cuts, quartile cuts, quintile cuts, and decile cuts were consistent. PK/PD modeling is ongoing to identify an optimal dosing paradigm.

FIG. 3 displays bar graphs showing concentration-driven classification of subjects regardless of dose administered. In FIG. 3, it is shown that concentrations in the range of 0.7 to 12.8 ng/ml show a nominally statistically significant difference from placebo in the LOCF LSMEAN change from baseline in ADAS-cog, where higher scores indicate more advanced Alzheimer's disease. The concentration range in the third bar, which is for pk concentrations of 12.9 to 21.0 ng/ml, is also statistically superior to placebo in delaying the progression of Alzheimer's disease.
A conclusion of the analysis is that when subjects are dosed with COMPOUND I at either 5 mg or 20 mg and have a resulting concentration in the range from 8 to 13 ng/ml, inclusive, the superiority of COMPOUND I over placebo is evident.

The efficacy of COMPOUND I is more pronounced in Alzheimer's disease when the dosing paradigm is concentration-driven than when fixed dosing is used. Analysis shows that if the concentrations are too low, the efficacy is not evident. However, if the concentrations are too high, it appears that efficacy may be masked by side effects. When the concentrations are in the target interval, the superiority of COMPOUND I over placebo is evident.

FIG. 4 shows line graphs of the profile over time comparing placebo-treated subjects to subjects in the study whose measured median pk concentrations were in the range 8 to 15 ng/ml.
The subjects treated with placebo (dashed line) show greater increases from baseline in ADAS-cog, indicating worsening of Alzheimer's disease at a greater rate than subjects who were treated with COMPOUND I with median pk concentrations in the range of 8 and 15 ng/ml (solid line). The sample size varies over time as patients leave the study. This analysis includes all data on-treatment where on-treatment is defined as date of last dose plus 28 days. The difference between the placebo group and the group treated with COMPOUND I these concentrations has nominal statistical significance at Month 18 using last-observation-carried-forward to accommodate missing data.

Table 2 provides a summary of statistics delineating between placebo and treatment with COMPOUND I beginning with Month 6 and being maintained over the course of the remainder of the 18-month study.

Table 2

Summary of Mean and Median changes in ADAS-cog over time for subjects treated with placebo and those treated with COMPOUND I with median trough concentrations between 8 and 15 ng/ml.

Time	Statistic	Placebo	Concentration between 8 and 15 ng/ml	Mean Difference	P-value (2-sample t-test)
Baseline	Mean	24.11	24.22	0.11	0.9
	Median	22.3	22.0		
3	Mean change	1.57	0.73	0.84	0.3
	Median change	2.0	2.3		
6	Mean change	3.16	1.16	2.00	0.03
	Median change	2.7	1.3		
9	Mean change	3.95	1.52	2.43	0.04
	Median change	2.2	1.3		
12	Mean change	6.34	3.31	3.03	0.02
	Median change	5.5	2.3		
15	Mean change	8.74	4.39	4.35	0.008
	Median change	7.8	4.7		
18	Mean change	11.32	6.04	5.28	0.01
	Median change	10.3	4.7		

The data in Table 2 shows that treatment with COMPOUND I in subjects whose measured median trough concentrations are between 8 and 15 ng/ml are statistically delineated with nominal statistical significance beginning at Month 6. Analysis conclusions indicate that, in certain concentration ranges, the benefits of treatment with COMPOUND I are clear. Analysis of variations in concentrations resulted in conclusions that bodyweight and BMI affected concentrations. These analyses support the need for concentration-driven treatment that incorporates bodyweight or BMI.

FIG. 5 shows the regression analysis regressing concentration on BMI. Regression analysis regressing concentration (dependent variable) onto BMI and onto bodyweight showed statistically significant negative correlations in all 4 analyses: subjects who have lower bodyweight or lower BMI tend to have higher concentration values for the same administered dose than subjects who have higher bodyweight or higher BMI values. The result was true for each dose level; therefore, the finding applies to both dose levels. These analyses are based on all available on-treatment where on-treatment is defined as date of last dose plus 28 days. This finding translates to a dosing paradigm that incorporates bodyweight or BMI in the dose administered to produce the desired concentration levels. These findings are consistent with claims that concentration drives efficacy and bodyweight or BMI drives concentration. This finding suggests that at low bodyweight and low BMI, lower doses are likely to be more effective than higher doses.

Example 4

Decreases in glucose are observed when treated with COMPOUND I at high doses when subjects present with elevated glucose values.

Statistical analysis of data from the study with COMPOUND I concluded that there were declines in glucose values, particularly for subjects entering the studies with elevated glucose levels. Lowering elevated glucose benefits patients, while lowering normal or lower level glucose values could have a detrimental effect.

Statistical analysis showed that in the study, subjects who presented with higher glucose values had declines when treated with 20 mg of COMPOUND I compared with placebo. Subjects with lower glucose values at baseline did not show significant decreases in glucose.

FIG. 6a-d demonstrates the mean change from baseline in glucose is displayed by treatment group using all data available at Months 3, 6, and 9. Subgroups were defined by taking all subjects with a baseline value of 100 mg/dl or greater, all subjects in the upper third (tertile cut), all subjects in the uppermost 25% (quartile cut), and all subjects in the uppermost 20% (quintile cut (not shown)). FIG. 6-d displays subjects with lower or normal values, where the subgroup is defined by a group median cut, and the subgroup is all subjects with baseline values less than the group median (lower half). After Month 9, withdrawal rates resulted in data too sparse for meaningful analysis. The group treated with high-dose (20 mg) of COMPOUND I showed marked declines in glucose which were statistically significant within the treatment group ($p<0.05$) and also statistically significantly different from placebo using 2-sample t-tests ($p<0.05$). For subjects who are normal or have low baseline glucose values, there is not a decline associated with treatment with COMPOUND I.. The differences among treatment groups at baseline are not statistically significant. Comparisons investigating the decreases in glucose associated with treatment with COMPOUND I in the subgroups of subjects who presented into the study with glucose values below the population median for the study are not statistically significant ($p>0.15$).

Example 5

Treatment with 5 mg COMPOUND I delays or reduces the incidence of adverse events.

Adverse Events

Adverse events of special interest (AESI) were related to potential cognitive impairment: fall, dizziness, confusional state, and somnolence. Reported frequencies for at least one AESI for the groups treated with 20 mg, 5 mg, and placebo, respectively, were 50 (37%), 49 (37%), and 44 (33%). Specific AESI showed no discernible pattern related to dose of COMPOUND I. FIG. 7 displays Kaplan-Meier curves for time to event for adverse event by dose group.

FIG. 7 shows the time to event curves display the proportions of subjects event-free by study day with Kaplan-Meier censoring when subjects withdraw from the study event-free. The analysis uses Markov-Chain model conventions with achievement of an event as an absorbing state. The

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low dose group dominates the placebo group at all points, and the distance between the lines indicates benefit of treatment with COMPOUND I at 5 mg relative to placebo to reduce the likelihood of having an adverse event.

FIG. 8 displays Kaplan-Meier curves for time for time to event adverse event by concentration group. The time to event curves display the proportions of subjects event-free by study day with Kaplan-Meier censoring when subjects withdraw from the study event-free. The analysis uses Markov-Chain model conventions with achievement of an event as an absorbing state. The group with concentrations less than 14.6 ng/dl dominates the placebo group at all points after month 3, and the distance between the lines indicates benefit of treatment with COMPOUND I at low concentrations relative to placebo to reduce the likelihood of having an adverse event.

Various embodiments of the invention have been described in fulfillment of the various objects of the invention. It should be recognized that these embodiments are merely illustrative of the principles of the present invention. Numerous modifications and adaptations thereof will be readily apparent to those skilled in the art without departing from the spirit and scope of the present invention.

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CLAIMS:

1. Oral use of [3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl amine, or a pharmaceutically acceptable salt thereof, in an amount of about 5 mg per day for the treatment of Alzheimer's disease in a human suffering from mild Alzheimer's disease.

2. Use according to claim 1, further comprising use of an acetylcholinesterase inhibitor (AChEI).

3. Use according to claim 2, wherein the AChEI is selected from the group consisting of donepezil hydrochloride, galantamine hydrochloride, rivastigmine tartrate, and tacrine hydrochloride.

4. Use according to claim 3, wherein the AChEI is donepezil hydrochloride, and wherein the donepezil hydrochloride is for use in an amount between 5 mg and 23 mg per day.

5. Use according to claim 3, wherein the AChEI is galantamine hydrochloride, and wherein the galantamine hydrochloride is for use in an amount between 16 mg to 24 mg per day.

6. Use according to claim 3, wherein the AChEI is rivastigmine tartrate, and wherein the rivastigmine tartrate is for use in an amount between 6 mg to 12 mg per day.

7. Use according to claim 3, wherein the AChEI is tacrine hydrochloride, and wherein the tacrine hydrochloride is for use in an amount of 40 mg per day.

8. Use according to any one of claims 1 to 7, further comprising use of memantine hydrochloride.

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9. Use according to claim 8, wherein the memantine hydrochloride is for use in an amount between 5 mg to 20 mg per day.

10. Use according to any one of claims 1 to 9, wherein the treatment is determined by (i) the improvement, (ii) no deterioration or (iii) a reduction in the rate of deterioration, in at least one of the assessments selected from the group consisting of the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), the Clinical Dementia Rating Sum of Boxes (CDR-sb), the Alzheimer's Disease Cooperative Study Activities of Daily Living Scale (ADCS-ADL), the Neuropsychiatric Inventory (NPI), and the Mini-Mental State Examination (MMSE).

11. Use according to any one of claims 1 to 9, wherein the human suffering from mild Alzheimer's disease presents with an ADAS-cog score of less than or equal to 23.

12. Use according to any one of claims 1 to 9, wherein the human suffering from mild Alzheimer's disease presents with a Mini-Mental State Examination score of greater than or equal to 21.

13. Use according to any one of claims 1 to 9, wherein the human suffering from mild Alzheimer's disease presents with a Mini-Mental State Examination score of between about 21 to about 26.

14. Use according to claim 10, wherein the treatment results in a reduction in the rate of deterioration in at least one of the assessments selected from the group consisting of the Alzheimer's Disease Assessment Scale-cognitive sub scale (ADAS-cog), the Clinical Dementia Rating Sum of Boxes (CDR-sb), the Alzheimer's Disease Cooperative Study Activities of Daily Living Scale (ADCS-ADL), the Neuropsychiatric Inventory (NPI), and the Mini-Mental State Examination (MMSE).

15. Use according to claim 10, wherein the treatment results in a reduction in the rate of deterioration in ADAS-cog scores.

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16. Use according to claim 15, wherein the treatment results in a median reduction in the rate of deterioration of ADAS-cog scores of two to five points.

17. Use according to claim 15, wherein the treatment results in a mean reduction in the rate of deterioration of ADAS-cog scores of 3.1.

18. Oral use of [3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl amine, or a pharmaceutically acceptable salt thereof, for reducing the frequency of adverse events in a subject with mild-to-moderate Alzheimer's disease,
wherein the [3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl amine, or pharmaceutically acceptable salt thereof, is for use in a daily dose of about 5 mg per day.

19. Use according to claim 18, further comprising use of an acetylcholinesterase inhibitor (AChEI).

20. Use according to claim 19, wherein the AChEI is selected from the group consisting of donepezil hydrochloride, galantamine hydrochloride, rivastigmine tartrate, and tacrine hydrochloride.

21. Use according to any one of claims 18 to 20, further comprising use of memantine hydrochloride.

22. Use according to any one of claims 18 to 21 wherein the subject presents with an ADAS-cog score of less than or equal to 23.

23. Use according to any one of claims 18 to 21, wherein the adverse events are selected from the group consisting of falling, dizziness, confusional state, and somnolence, or from the group consisting of agitation, depression, anxiety, aggression, and restlessness.

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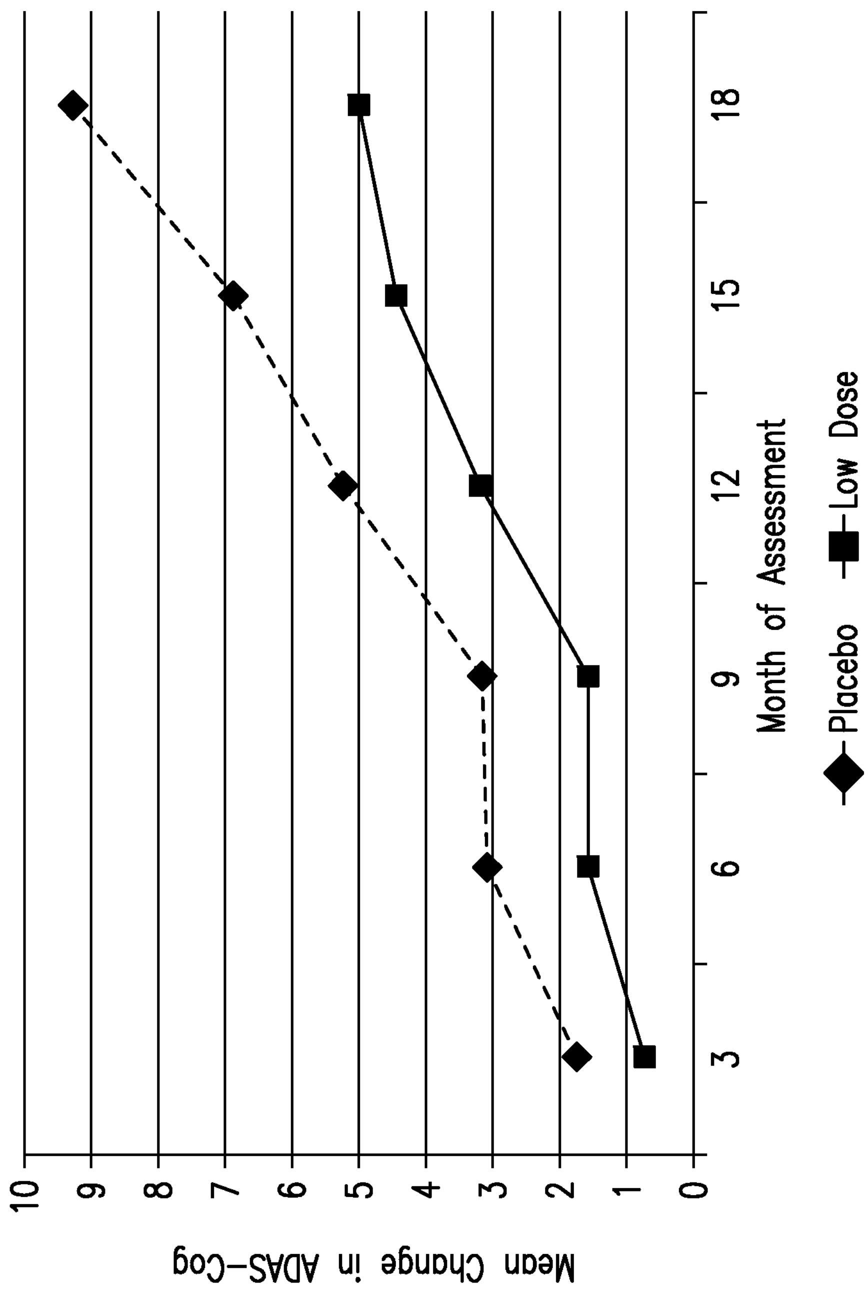
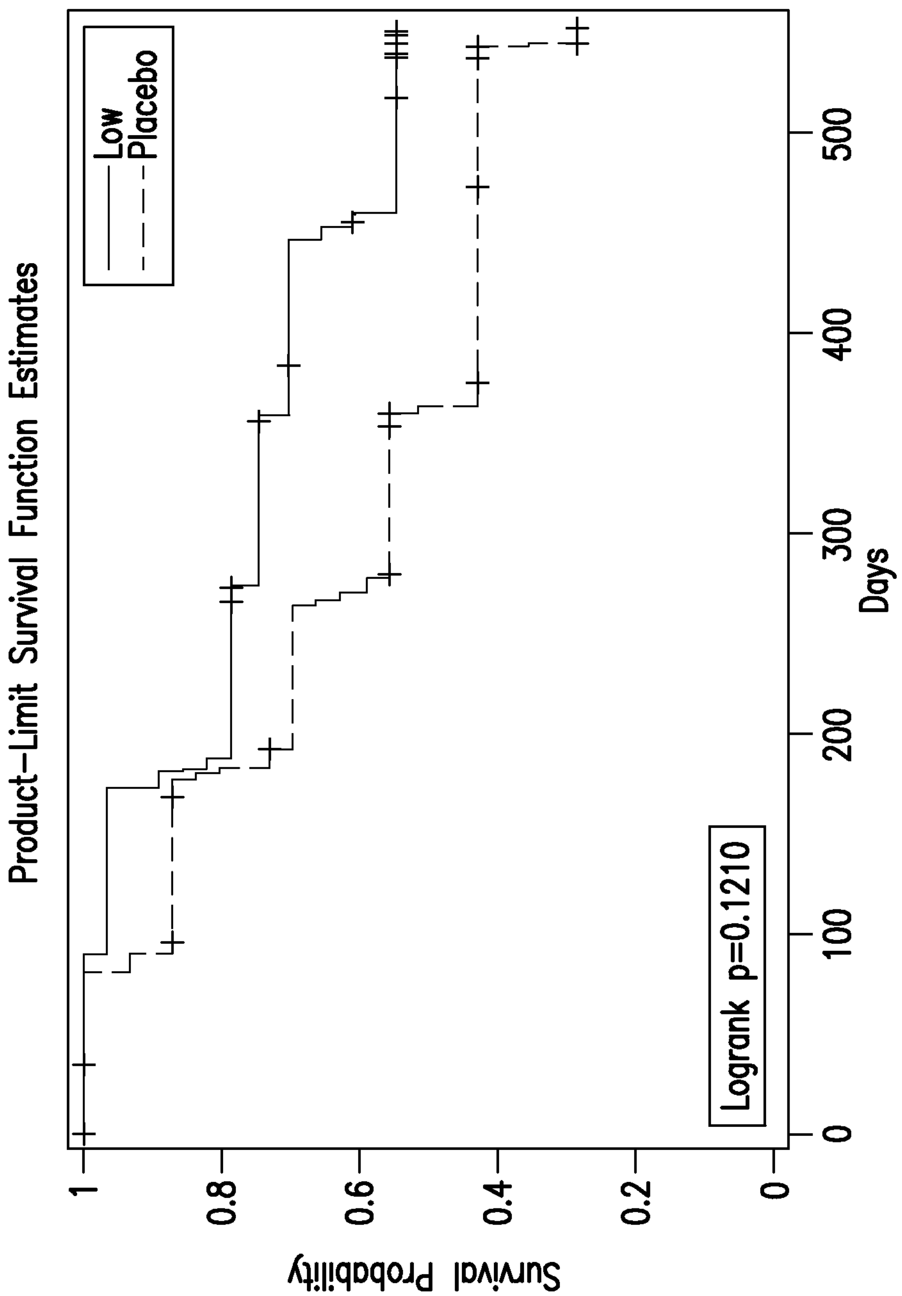

Mean Change in ADAS−Cog
10
9
8
7
6
5
4
3
2
1
0
3
6
9
12
15
18
Month of Assessment
Placebo
Low Dose

FIG.1



	No.of Subjects	Event	Censored	Median Survival (95% CL)
Low	30	37%(11)	63%(19)	NA (448.0 NA)
Placebo	33	55%(18)	45%(15)	363.0 (264.0 546.0)

FIG.2

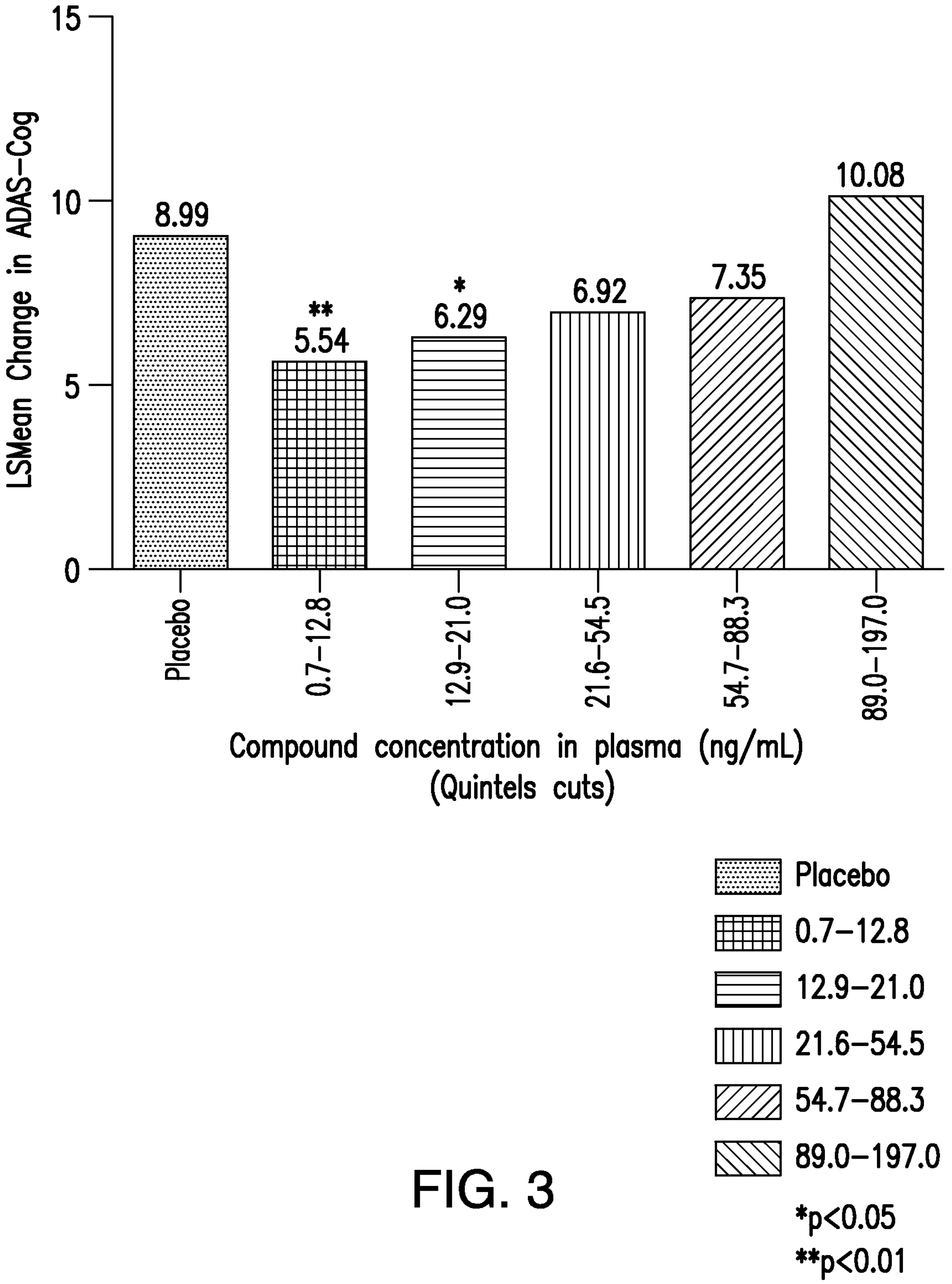

15
10
5
0
LSMean Change in ADAS-Cog
8.99
**
5.54
*
6.29
6.92
7.35
10.08
Placebo
0.7-12.8
12.9-21.0
21.6-54.5
54.7-88.3
89.0-197.0
Compound concentration in plasma (ng/mL)
(Quintels cuts)
Placebo
0.7-12.8
12.9-21.0
21.6-54.5
54.7-88.3
89.0-197.0
*p<0.05
**p<0.01

FIG. 3

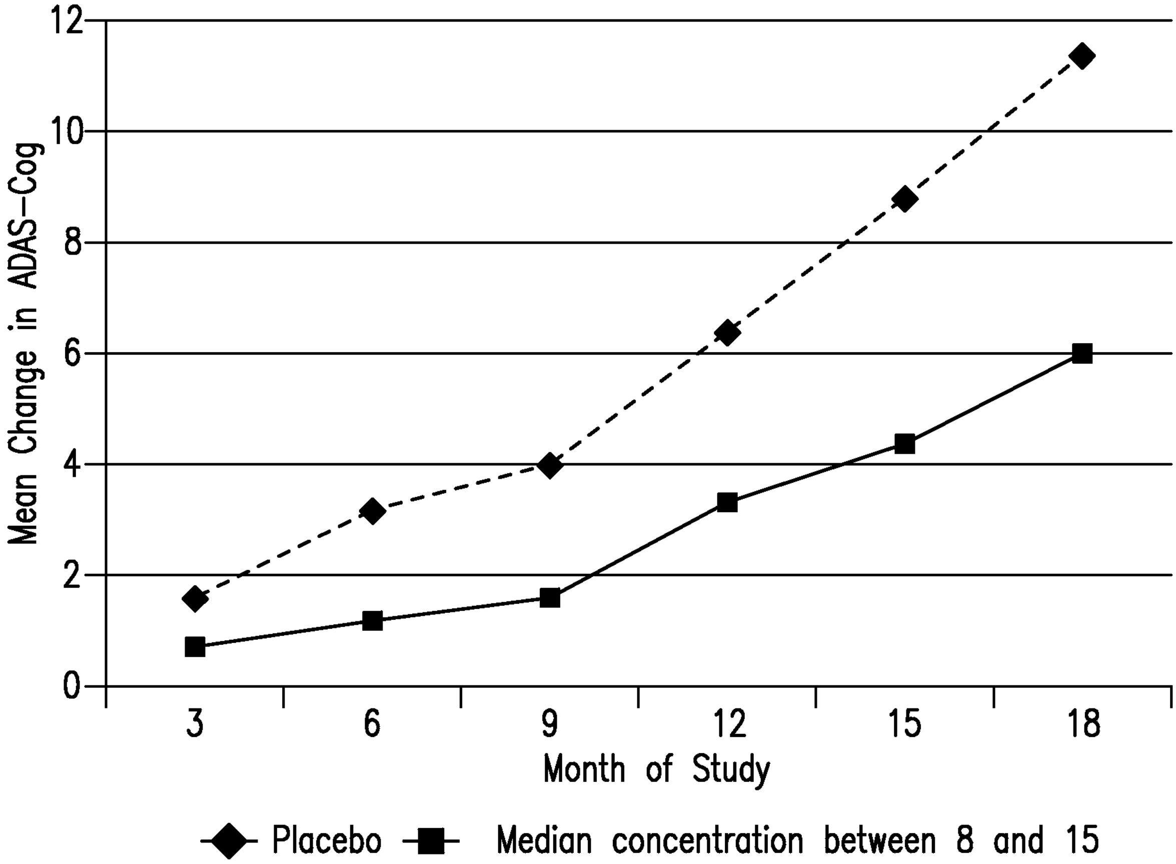

12
10
8
6
4
2
0
Mean Change in ADAS-Cog
3
6
9
12
15
18
Month of Study
Placebo
Median concentration between 8 and 15

FIG.4

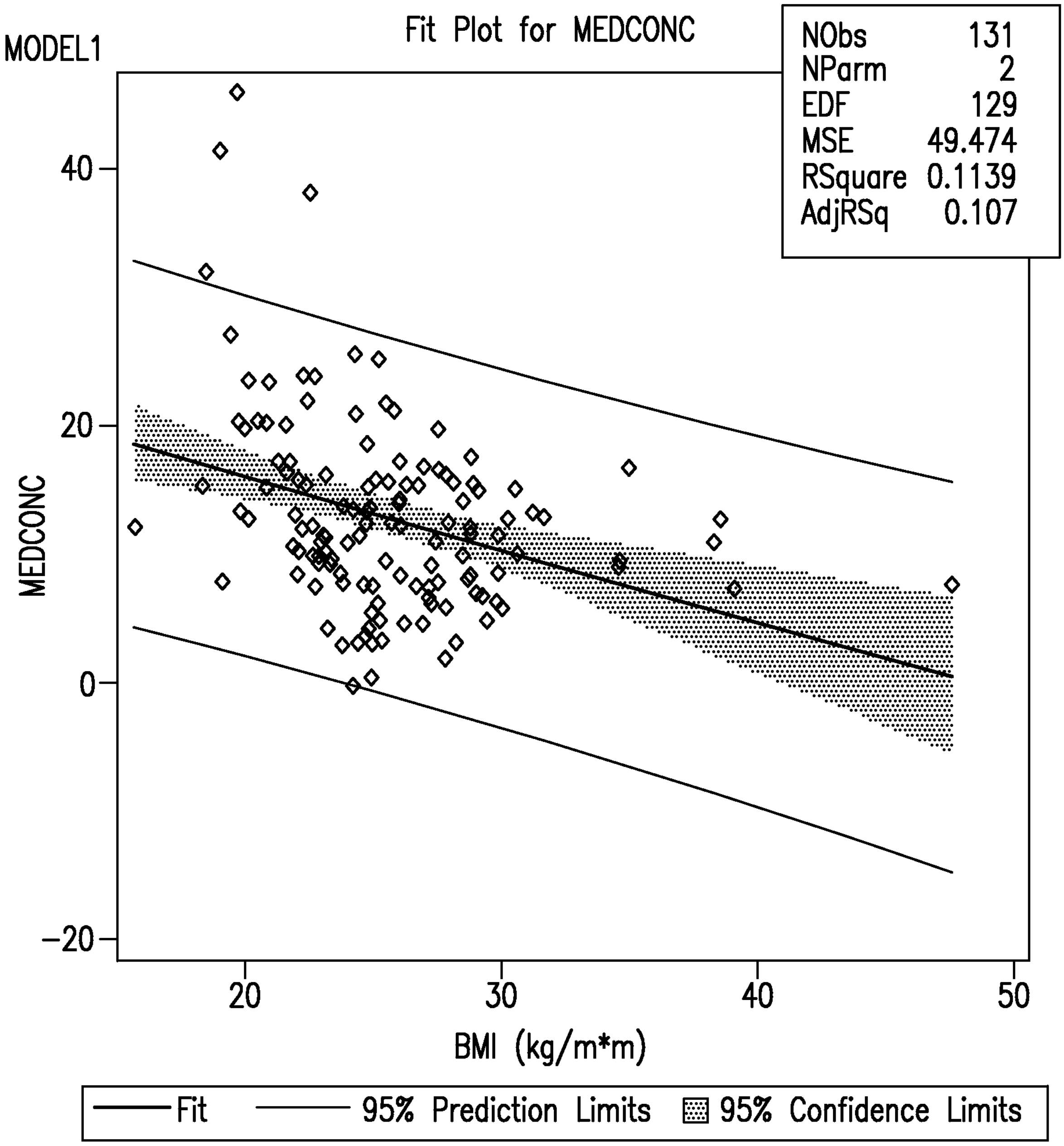

MODEL1
Fit Plot for MEDCONC
NObs 131
NParm 2
EDF 129
MSE 49.474
RSquare 0.1139
AdjRSq 0.107
40
20
0
−20
MEDCONC
20
30
40
50
BMI (kg/m*m)
Fit
95% Prediction Limits
95% Confidence Limits

FIG. 5A

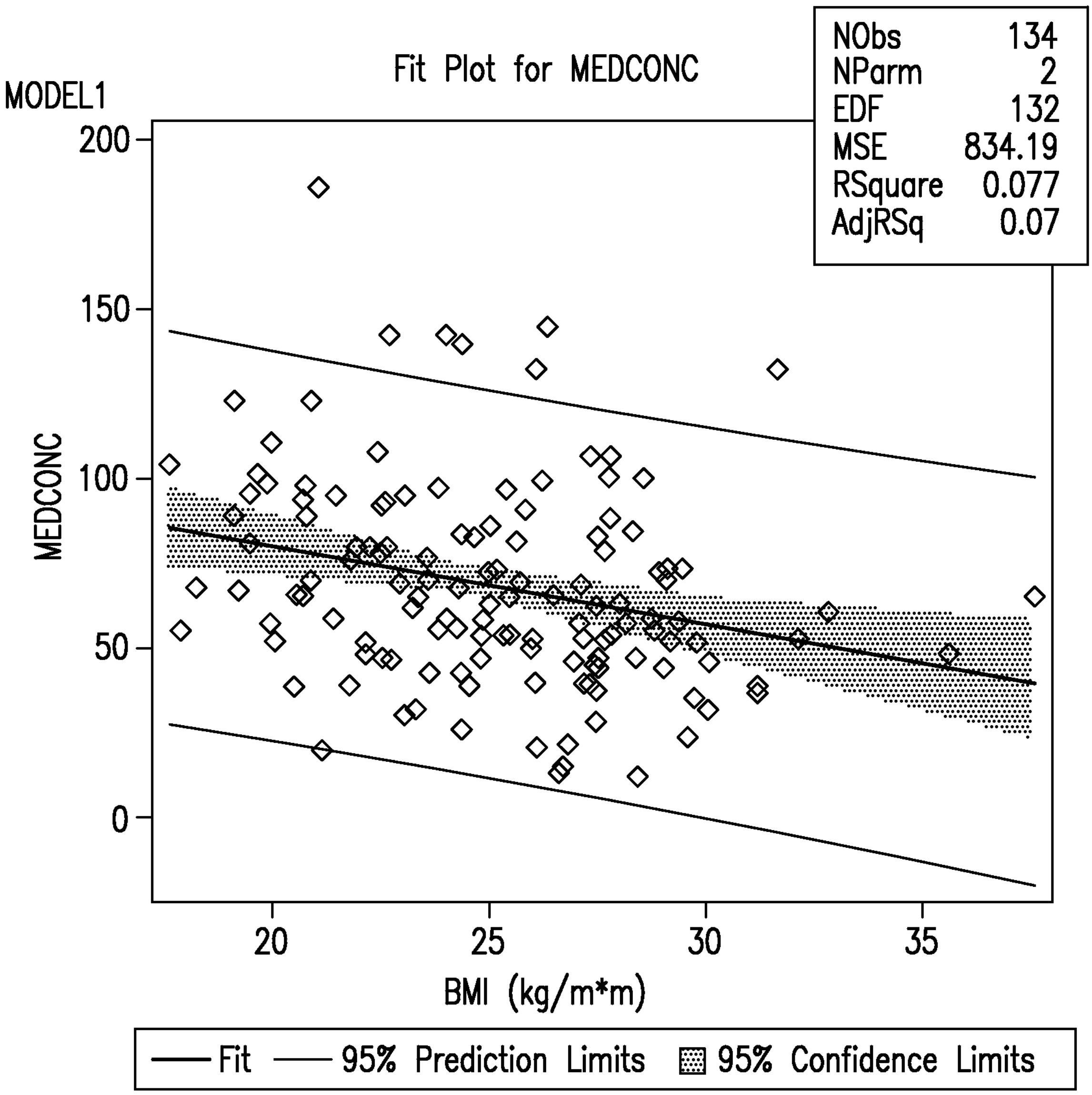

Fit Plot for MEDCONC
MODEL1
NObs 134
NParm 2
EDF 132
MSE 834.19
RSquare 0.077
AdjRSq 0.07
MEDCONC
200
150
100
50
0
20
25
30
35
BMI (kg/m*m)
Fit
95% Prediction Limits
95% Confidence Limits

FIG. 5B

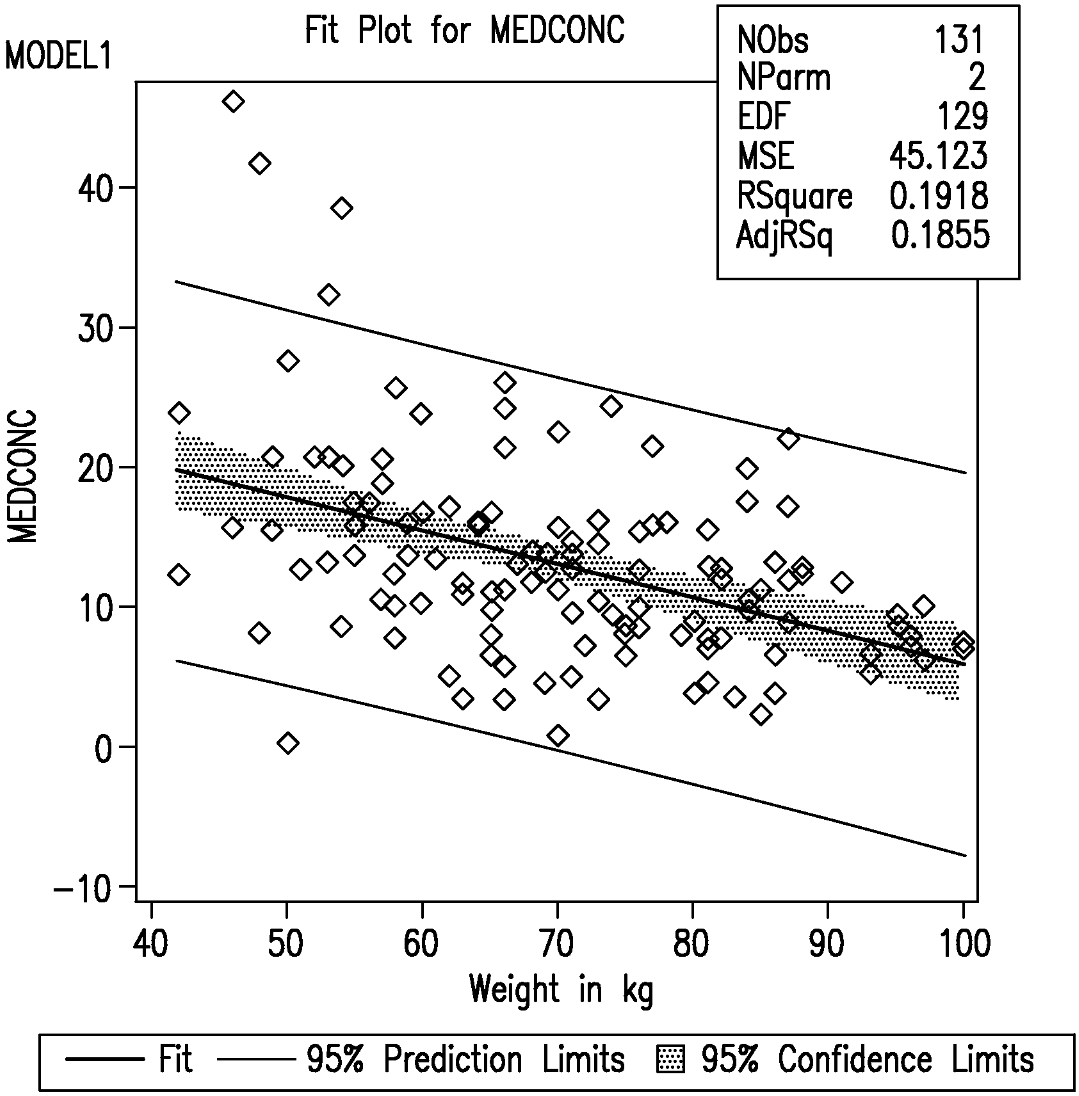

Fit Plot for MEDCONC
MODEL1
NObs 131
NParm 2
EDF 129
MSE 45.123
RSquare 0.1918
AdjRSq 0.1855
MEDCONC
40
30
20
10
0
−10
40
50
60
70
80
90
100
Weight in kg
Fit
95% Prediction Limits
95% Confidence Limits

FIG. 5C

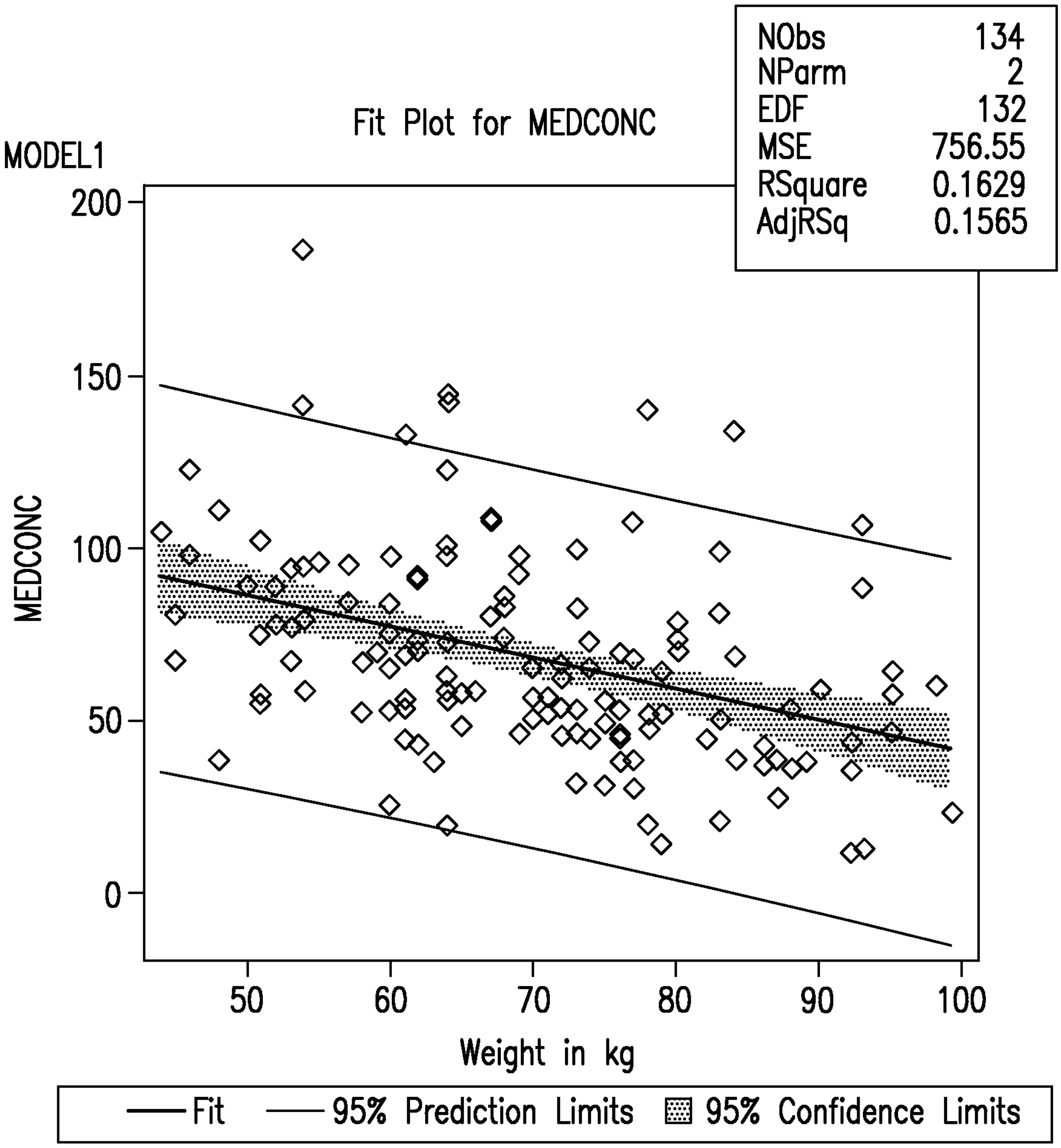

Fit Plot for MEDCONC
MODEL1
NObs 134
NParm 2
EDF 132
MSE 756.55
RSquare 0.1629
AdjRSq 0.1565
MEDCONC
200
150
100
50
0
50
60
70
80
90
100
Weight in kg
Fit
95% Prediction Limits
95% Confidence Limits

FIG. 5D

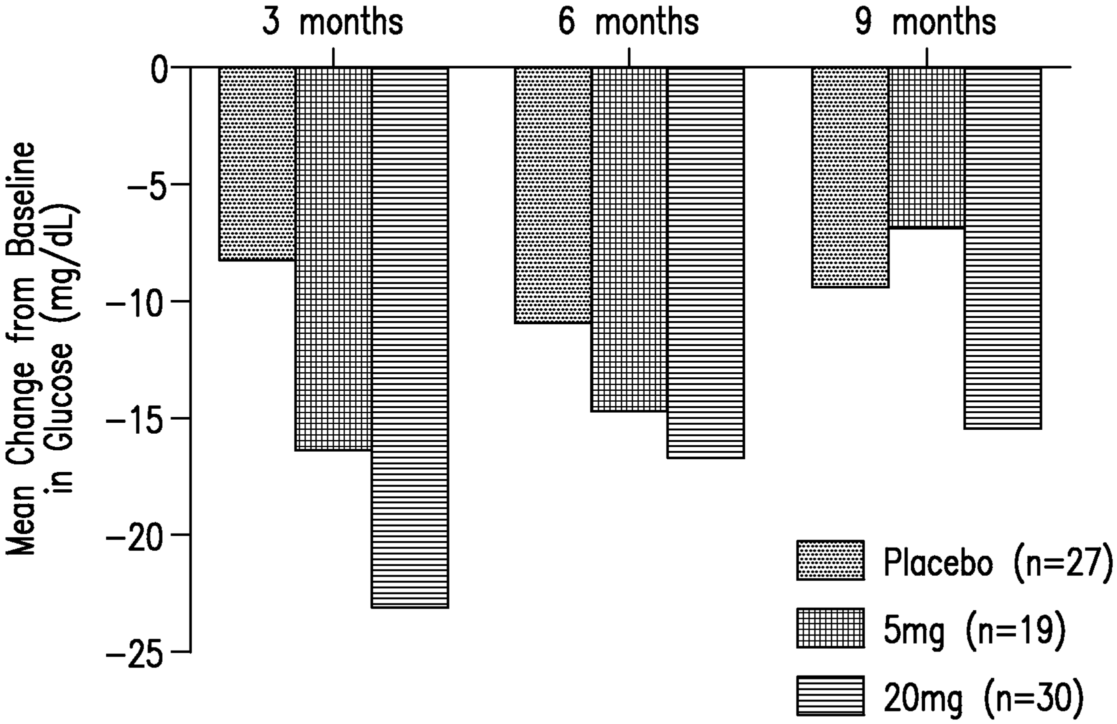

3 months
6 months
9 months
0
-5
-10
-15
-20
-25
Mean Change from Baseline in Glucose (mg/dL)
Placebo (n=27)
5mg (n=19)
20mg (n=30)

FIG. 6A

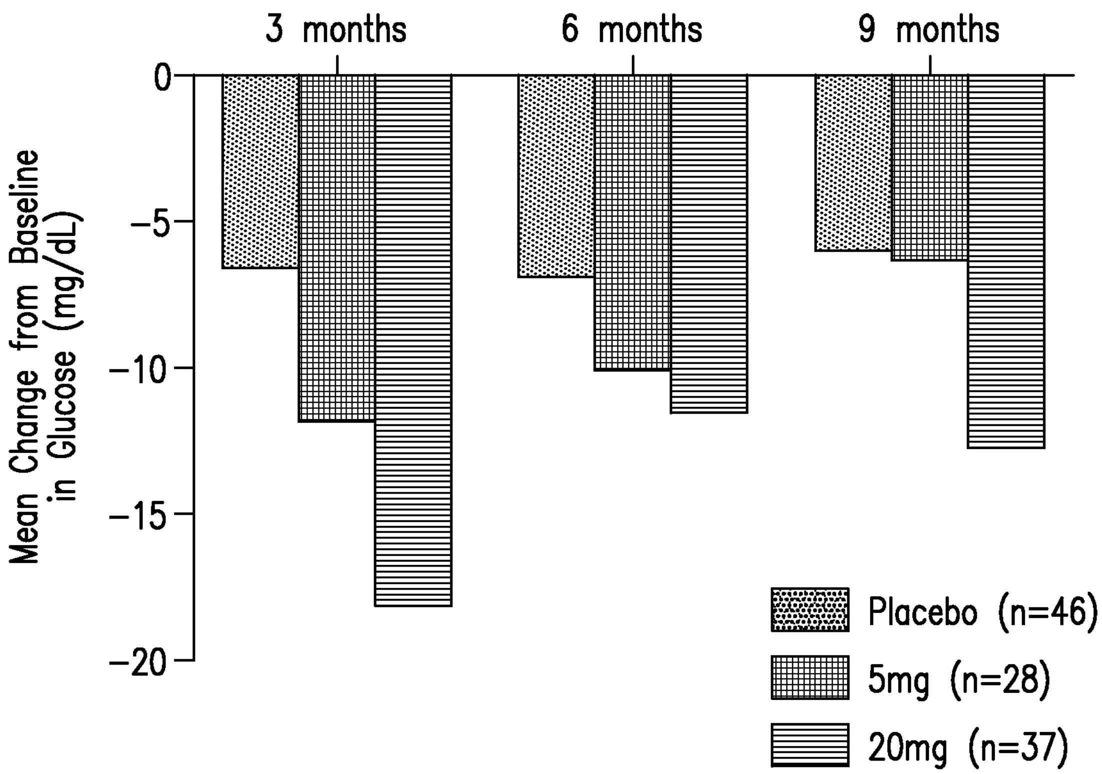

3 months
6 months
9 months
0
-5
-10
-15
-20
Mean Change from Baseline in Glucose (mg/dL)
Placebo (n=46)
5mg (n=28)
20mg (n=37)

FIG. 6B

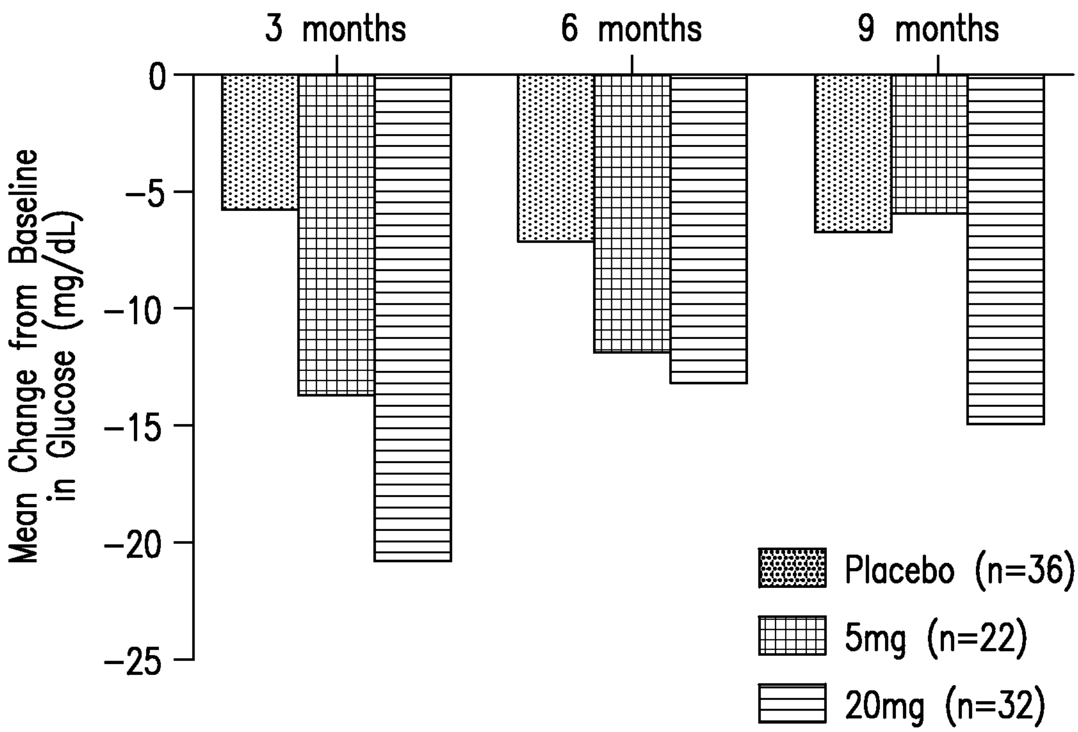

3 months
6 months
9 months
0
-5
-10
-15
-20
-25
Mean Change from Baseline in Glucose (mg/dL)
Placebo (n=36)
5mg (n=22)
20mg (n=32)

FIG. 6C

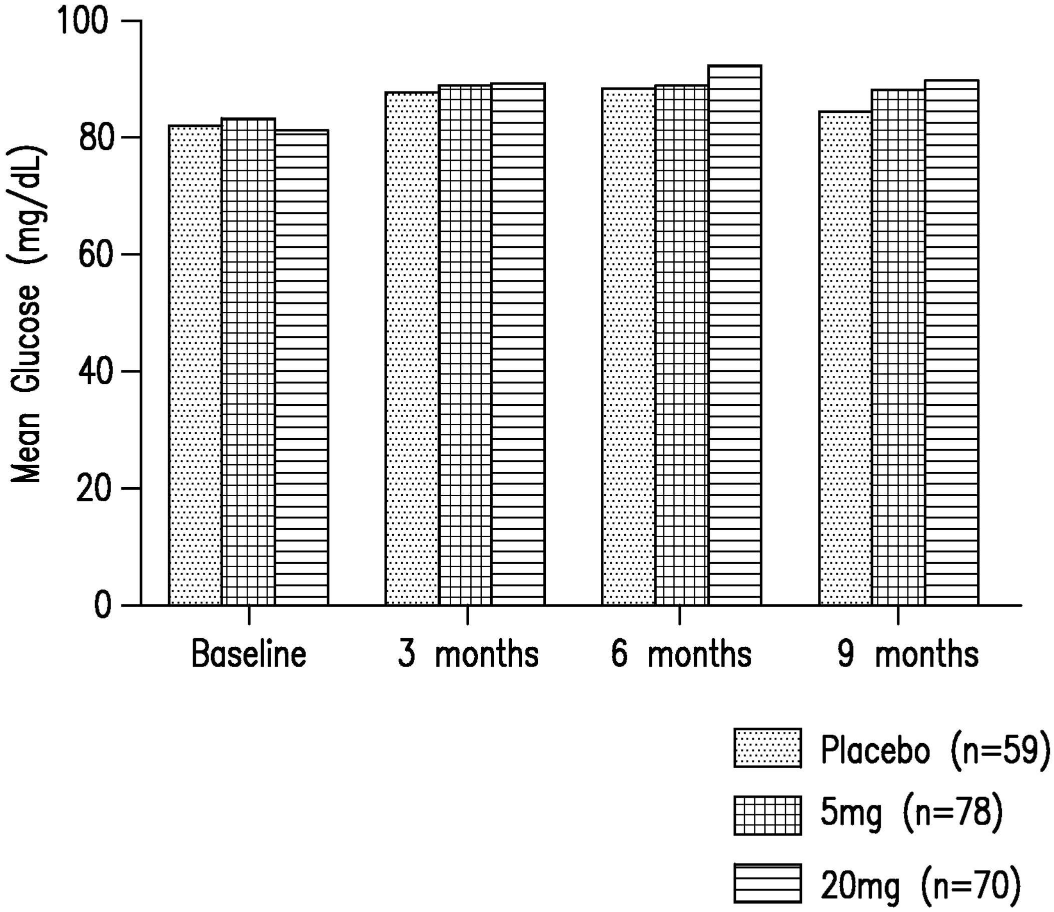

100
80
60
40
20
0
Mean Glucose (mg/dL)
Baseline
3 months
6 months
9 months
Placebo (n=59)
5mg (n=78)
20mg (n=70)

FIG. 6D

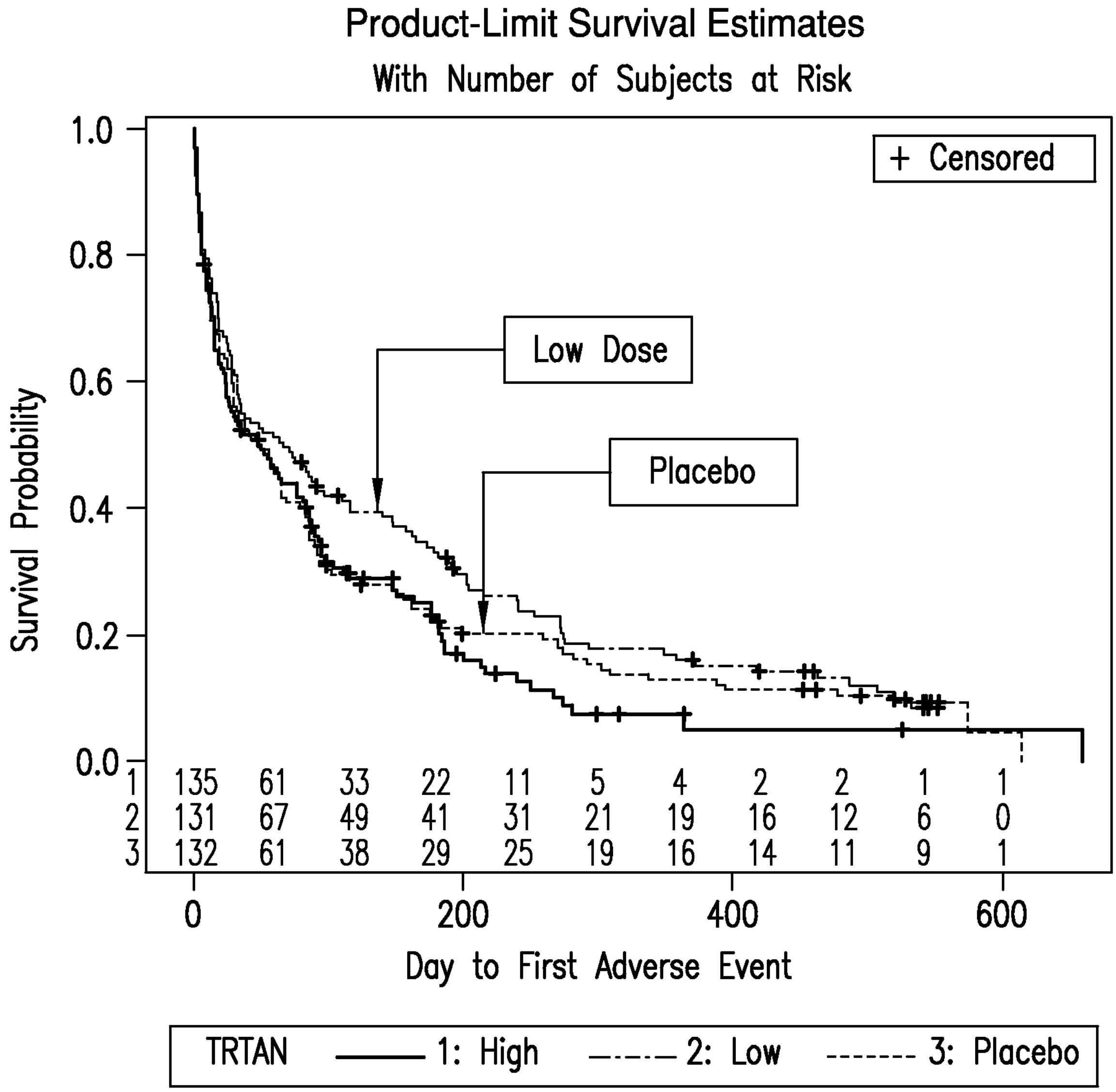

Product-Limit Survival Estimates
With Number of Subjects at Risk
+ Censored
Low Dose
Placebo
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
1 135 61 33 22 11 5 4 2 2 1 1
2 131 67 49 41 31 21 19 16 12 6 0
3 132 61 38 29 25 19 16 14 11 9 1
0
200
400
600
Day to First Adverse Event
TRTAN 1: High 2: Low 3: Placebo

FIG. 7

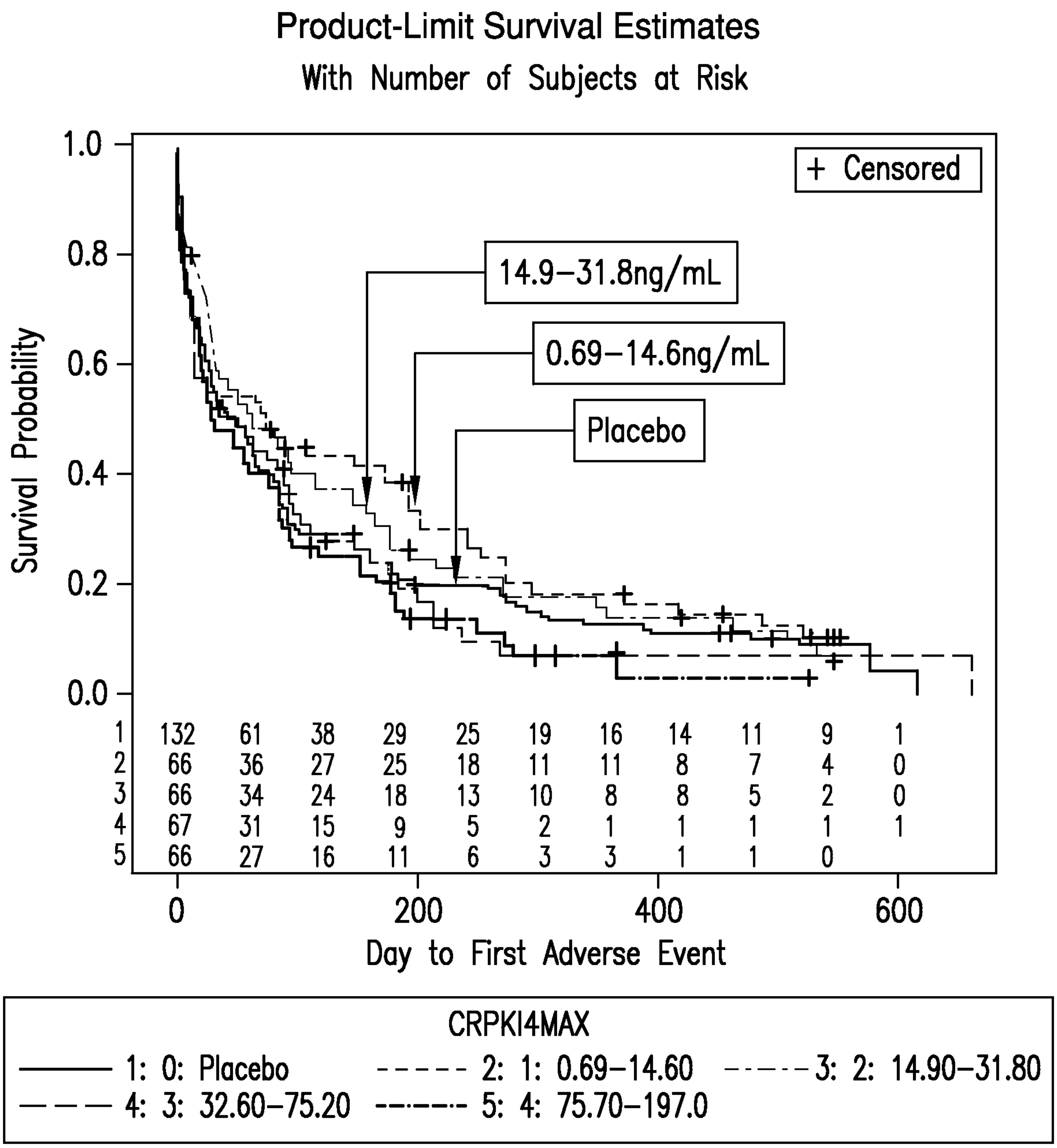
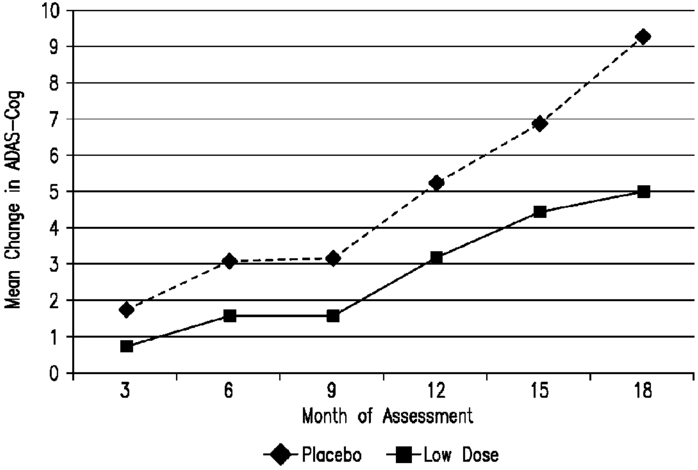

Product-Limit Survival Estimates
With Number of Subjects at Risk
+ Censored
14.9–31.8ng/mL
0.69–14.6ng/mL
Placebo
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
1 132 61 38 29 25 19 16 14 11 9 1
2 66 36 27 25 18 11 11 8 7 4 0
3 66 34 24 18 13 10 8 8 5 2 0
4 67 31 15 9 5 2 1 1 1 1 1
5 66 27 16 11 6 3 3 1 1 0
0
200
400
600
Day to First Adverse Event
CRPKI4MAX
1: 0: Placebo
2: 1: 0.69–14.60
3: 2: 14.90–31.80
4: 3: 32.60–75.20
5: 4: 75.70–197.0

FIG. 8



Mean Change in ADAS-Cog
0
1
2
3
4
5
6
7
8
9
10
3
6
9
12
15
18
Month of Assessment
Placebo
Low Dose