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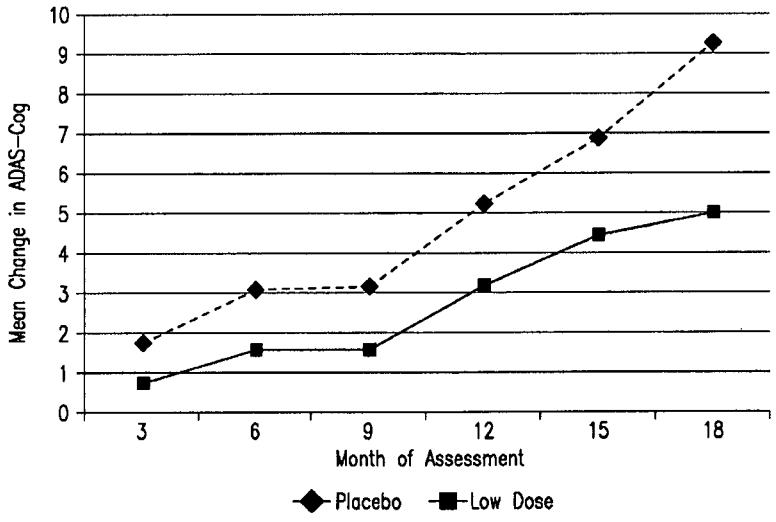

FIG.1

(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.

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.

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 of special interest (fall, confusional state, somnolence, dizziness), by dose group.

FIG. 8 - Kaplan-Meier curves are shown of time for adverse event of special interest (fall, confusional state, somnolence, dizziness), 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).

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 of special interest.

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 of special interest (fall, confusional state, somnolence, dizziness), 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

low dose group (5 mg, indicated by the dashed line) dominates the placebo group (indicated by the intermittent dotted-dashed line) 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 AESI.

FIG. 8 displays Kaplan-Meier curves for time for time to event adverse event of special interest (fall, confusional state, somnolence, dizziness), 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 (indicated by the dashed line) dominates the placebo group (indicated by the solid line) 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 AESI.

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.

CLAIMS

We claim:

1. A method of treating Alzheimer's disease comprising administering to a subject in need thereof an amount less than 20 mg per day 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.

2. The method of claim 1, wherein the [3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl amine is administered in a dose ranging from about 1 mg per day to less than 20 mg per day.

3. The method of claim 2, wherein 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.

4. The method of any of the preceding claims, wherein the method of treatment further comprises administering to the subject an acetylcholinesterase inhibitor (AChEI).

5. The method of claim 4, wherein the AChEI is chosen from the group comprising donepezil hydrochloride, galantamine hydrochloride, rivastigmine tartrate, and tacrine hydrochloride.

6. The method of any of the preceding claims, wherein the method of treatment further comprises administering to the subject memantine hydrochloride.

7. The method of any of the previous claims, wherein the blood serum concentration 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 the 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.

8. The method of claim 7, wherein the blood serum concentration in the subject is between about 8 to about 15 ng/ml.

9. The method of claim 8, wherein the blood serum concentration in the subject is about 12.5 ng/ml.

10. The method of any of the previous claims, wherein the treatment 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 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 Evaluation (MMSE).

11. The method of claim 10, wherein the treatment results in a reduction in the rate of deterioration in ADAS-cog scores.

12. The method of claim 11, wherein the treatment results in a median reduction in the rate of deterioration of ADAS-cog scores of two to five points.

13. A method of treating Alzheimer's disease comprising administering to a subject in need thereof an amount 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 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.

14. The method of claim 13, wherein the treatment is administered in an amount of 1 mg/20 kg per day.

15. 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 [3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl amine or a pharmaceutically acceptable salt thereof.

16. The method of claim 15, wherein the RAGE ligand is selected from the group consisting of soluble β-amyloid, insoluble β-amyloid, s100b, calgranulin, EN-RAGE, HMGB1 (high mobility group box 1), amphoterin, and carboxymethyllysine.

17. The method of claim 15, wherein [3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl amine or a pharmaceutically acceptable salt thereof is administered in a dose ranging from 1 to about 20 mg per day.

18. The method of claim 17, wherein 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.

19. The method of any one of claims 15 to 18, wherein the method of treatment further comprises administering to the subject an acetylcholinesterase inhibitor (AChEI).

20. The method of claim 19, wherein the AChEI is chosen from the group comprising donepezil hydrochloride, galantamine hydrochloride, rivastigmine tartrate, and tacrine hydrochloride.

21. The method of any one of claims 15 to 20, wherein the method of treatment further comprises administering to the subject memantine hydrochloride.

22. The method of any of claims 1-21, wherein the method treats mild Alzheimer's disease.

23. The method of claim 22, wherein mild Alzheimer's disease is defined as a subject that presents with an ADAS-cog score of less than or equal to 23.

24. A method for treating diabetes comprising administering to a subject in need thereof an amount less than 20 mg per day 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.

25. The method of claim 24, wherein the [3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl amine is administered in a dose ranging from about 1 to about 20 mg per day.

26. The method of claim 25, wherein 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.

27. The method of any one of claims 24 to 26, wherein the method of treatment further comprises administering to the subject an acetylcholinesterase inhibitor (AChEI).

28. The method of claim 27, wherein the AChEI is chosen from the group comprising donepezil hydrochloride, galantamine hydrochloride, rivastigmine tartrate, and tacrine hydrochloride.

29. The method of any one of claims 24 to 28, wherein the method of treatment further comprises administering to the subject memantine hydrochloride.

30. 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 [3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl amine or a pharmaceutically acceptable salt thereof.

31. The method of claim 30, wherein 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.

32. The method of any one of claims 30 to 31, wherein the method of treatment further comprises administering to the subject an acetylcholinesterase inhibitor (AChEI).

33. The method of claim 32, wherein the AChEI is chosen from the group comprising donepezil hydrochloride, galantamine hydrochloride, rivastigmine tartrate, and tacrine hydrochloride.

34. The method of any one of claims 30 to 33, wherein the method of treatment further comprises administering to the subject memantine hydrochloride.

35. 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 [3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl amine or a pharmaceutically acceptable salt thereof.

36. The method of claim 35, wherein 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.

37. The method of any one of claims 35 to 36, wherein the method of treatment further comprises administering to the subject an acetylcholinesterase inhibitor (AChEI).

38. The method of claim 37, wherein the AChEI is chosen from the group comprising donepezil hydrochloride, galantamine hydrochloride, rivastigmine tartrate, and tacrine hydrochloride.

39. The method of any one of claims 35 to 38, wherein the method of treatment further comprises administering to the subject memantine hydrochloride.

40. The method of claim 35, wherein the subject is suffering from mild-to-moderate Alzheimer's Disease.

41. The method of claim 35, wherein the subject's blood glucose levels are reduced 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 to 20 mg/dl.

42. The method of claim 35, wherein the subject's naïve glucose level is greater than 100 mg/dl.

43. A method of treating insomnia comprising administering to a subject in need thereof an amount less than 20 mg per day 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.

44. The method of claim 43, wherein 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.

45. The method of any one of claims 43 to 44, wherein the method of treatment further comprises administering to the subject an acetylcholinesterase inhibitor (AChEI).

46. The method of claim 45, wherein the AChEI is chosen from the group comprising donepezil hydrochloride, galantamine hydrochloride, rivastigmine tartrate, and tacrine hydrochloride.

47. The method of any one of claims 43 to 46, wherein the method of treatment further comprises administering to the subject memantine hydrochloride.

48. A method of treating insomnia 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 [3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl amine or a pharmaceutically acceptable salt thereof.

49. The method of claim 48, wherein 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.

50. The method of any one of claims 48 to 49, wherein the method of treatment further comprises administering to the subject an acetylcholinesterase inhibitor (AChEI).

51. The method of claim 50, wherein the AChEI is chosen from the group comprising donepezil hydrochloride, galantamine hydrochloride, rivastigmine tartrate, and tacrine hydrochloride.

52. The method of any one of claims 48 to 51, wherein the method of treatment further comprises administering to the subject memantine hydrochloride.

53. A method of decreasing sleep onset latency comprising administering to a subject in need thereof an amount less than 20 mg per day 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.

54. The method of claim 53, wherein 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.

55. The method of any one of claims 53 to 54, wherein the method of treatment further comprises administering to the subject an acetylcholinesterase inhibitor (AChEI).

56. The method of claim 55, wherein the AChEI is chosen from the group comprising donepezil hydrochloride, galantamine hydrochloride, rivastigmine tartrate, and tacrine hydrochloride.

57. The method of any one of claims 53 to 56, wherein the method of treatment further comprises administering to the subject memantine hydrochloride.

58. A method of decreasing sleep onset latency 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 [3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl amine or a pharmaceutically acceptable salt thereof.

59. The method of claim 58, wherein 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.

60. The method of any one of claims 58 to 59, wherein the method of treatment further comprises administering to the subject an acetylcholinesterase inhibitor (AChEI).

61. The method of claim 60, wherein the AChEI is chosen from the group comprising donepezil hydrochloride, galantamine hydrochloride, rivastigmine tartrate, and tacrine hydrochloride.

62. The method of any one of claims 58 to 61, wherein the method of treatment further comprises administering to the subject memantine hydrochloride.

63. 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 [3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl amine or a pharmaceutically acceptable salt thereof.

64. The method of claim 63, wherein 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.

65. The method of any one of claims 63 to 64, wherein the method of treatment further comprises administering to the subject an acetylcholinesterase inhibitor (AChEI).

66. The method of claim 65, wherein the AChEI is chosen from the group comprising donepezil hydrochloride, galantamine hydrochloride, rivastigmine tartrate, and tacrine hydrochloride.

67. The method of any one of claims 63 to 66, wherein the method of treatment further comprises administering to the subject memantine hydrochloride.

68. The method of claim 63, 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.

69. A method of reducing HbA1C levels in a subject in need thereof comprising administering an amount less than 20 mg per day 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.

70. The method of claim 69, wherein the [3-(4-{2-butyl-1-[4-(4-chloro-phenoxy)-phenyl]-1H-imidazol-4-yl}-phenoxy)-propyl]-diethyl amine or a pharmaceutically acceptable salt thereof is administered in a dose ranging from about 1 mg per day to less than 20 mg per day.

71. The method of claim 70, wherein 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.

72. The method of claim 69, wherein the administration 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 reduces the amount of HbA1C in the 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.

73. The method of claim 69, wherein the administration 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 reduces the amount of HbA1C in the subject in need thereof to less than 7%.

74. The method of any one of claims 69 to 73, wherein the method of treatment further comprises administering to the subject an acetylcholinesterase inhibitor (AChEI).

75. The method of claim 74, wherein the AChEI is chosen from the group comprising donepezil hydrochloride, galantamine hydrochloride, rivastigmine tartrate, and tacrine hydrochloride.

76. The method of any one of claims 69 to 75, wherein the method of treatment further comprises administering to the subject memantine hydrochloride.

77. A pharmaceutical composition comprising between 1 mg and 20 mg 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; and an acetylcholinesterase inhibitor (AChEI).

78. The pharmaceutical composition of claim 77, wherein the AChEI is chosen from the group comprising donepezil hydrochloride, galantamine hydrochloride, rivastigmine tartrate, and tacrine hydrochloride.

79. The pharmaceutical composition of claim 78, wherein the AChEI is donepezil hydrochloride present between 5 and 23 mg.

80. The pharmaceutical composition of claim 78, wherein the AChEI is galantamine hydrochloride present between 16 and 24 mg.

81. The pharmaceutical composition of claim 78, wherein the AChEI is rivastigmine tartrate present between 6 and 12 mg.

82. The pharmaceutical composition of claim 78, wherein the AChEI is tacrine hydrochloride present at 40 mg.

83. A pharmaceutical composition comprising between 1 mg and 20 mg 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; and memantine hydrochloride.

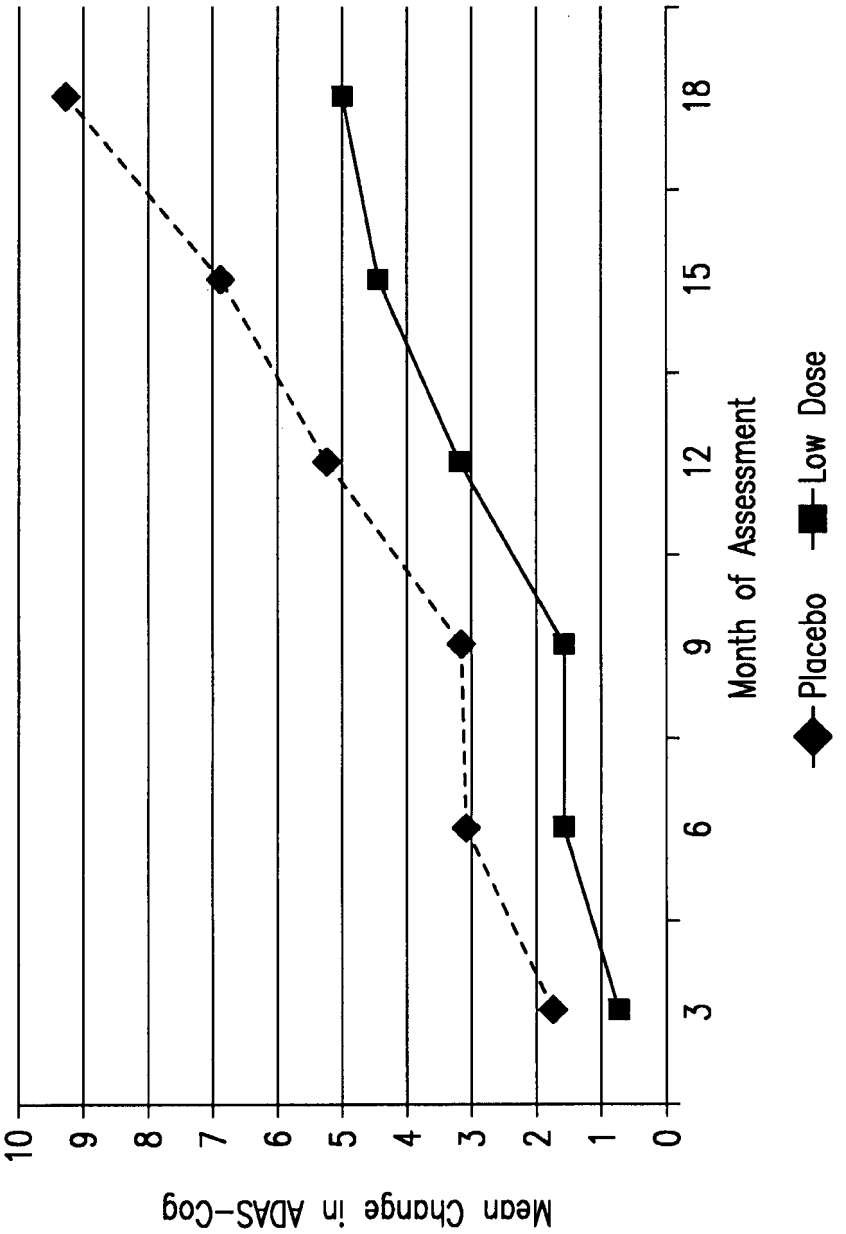
Mean Change in ADAS-Cog
0
1
2
3
4
5
6
7
8
9
10
3
6
9
12
15
18
Month of Assessment
Placebo
Low Dose

FIG.1

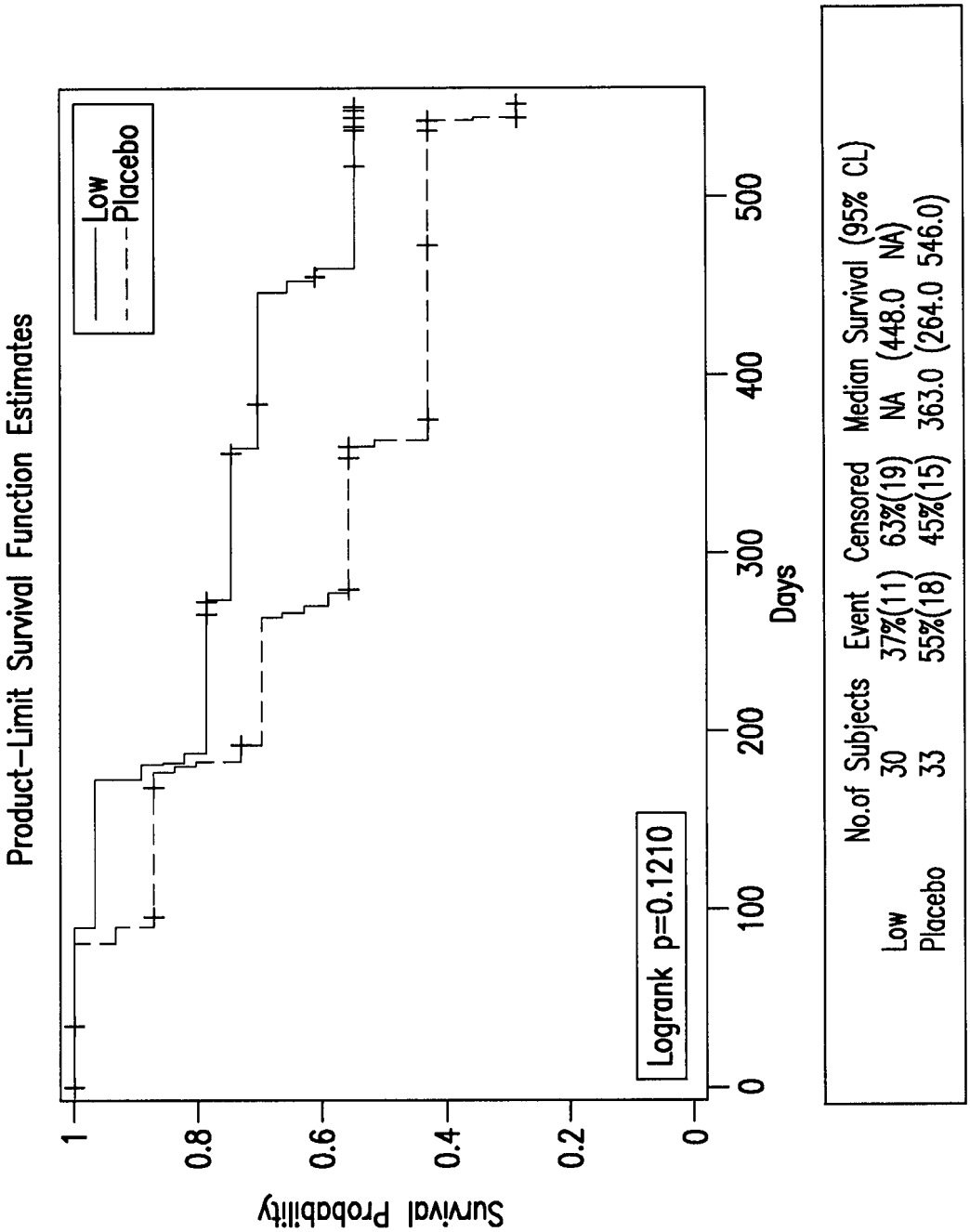
Product-Limit Survival Function Estimates
Low
Placebo
Survival Probability
1
0.8
0.6
0.4
0.2
0
Logrank p=0.1210
0
100
200
300
400
500
Days
No.of Subjects Event Censored Median Survival (95% CL)
Low 30 37%(11) 63%(19) NA (448.0 NA)
Placebo 33 55%(18) 45%(15) 363.0 (264.0 546.0)

FIG.2

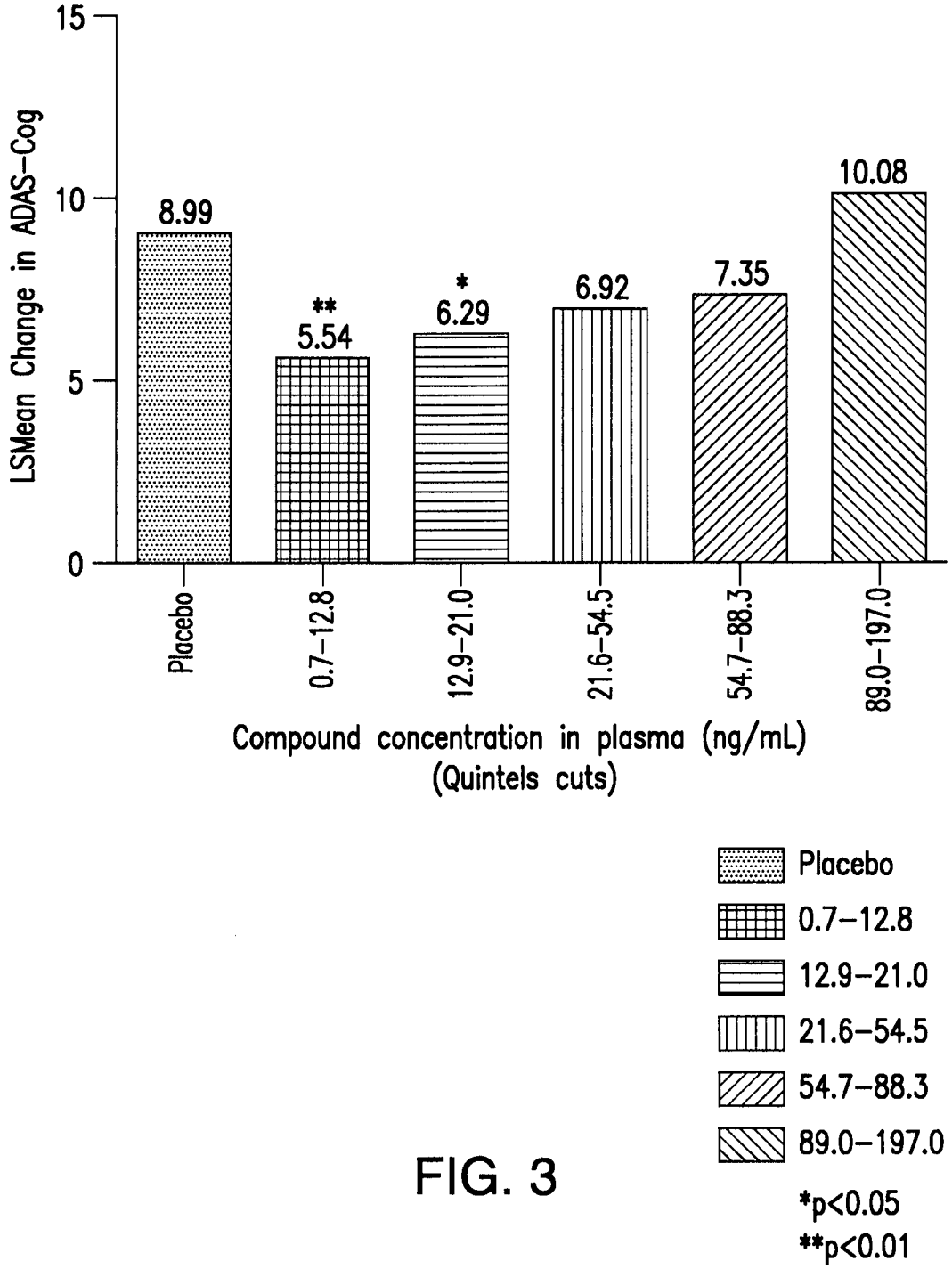
15
10
5
0
LSMean Change in ADAS-Cog
8.99
**
5.54
*
6.29
6.92
7.35
10.08
Placebo
0.7-12.8
12.9-21.0
21.6-54.5
54.7-88.3
89.0-197.0
Compound concentration in plasma (ng/mL)
(Quintels cuts)
Placebo
0.7-12.8
12.9-21.0
21.6-54.5
54.7-88.3
89.0-197.0
*p<0.05
**p<0.01

FIG. 3

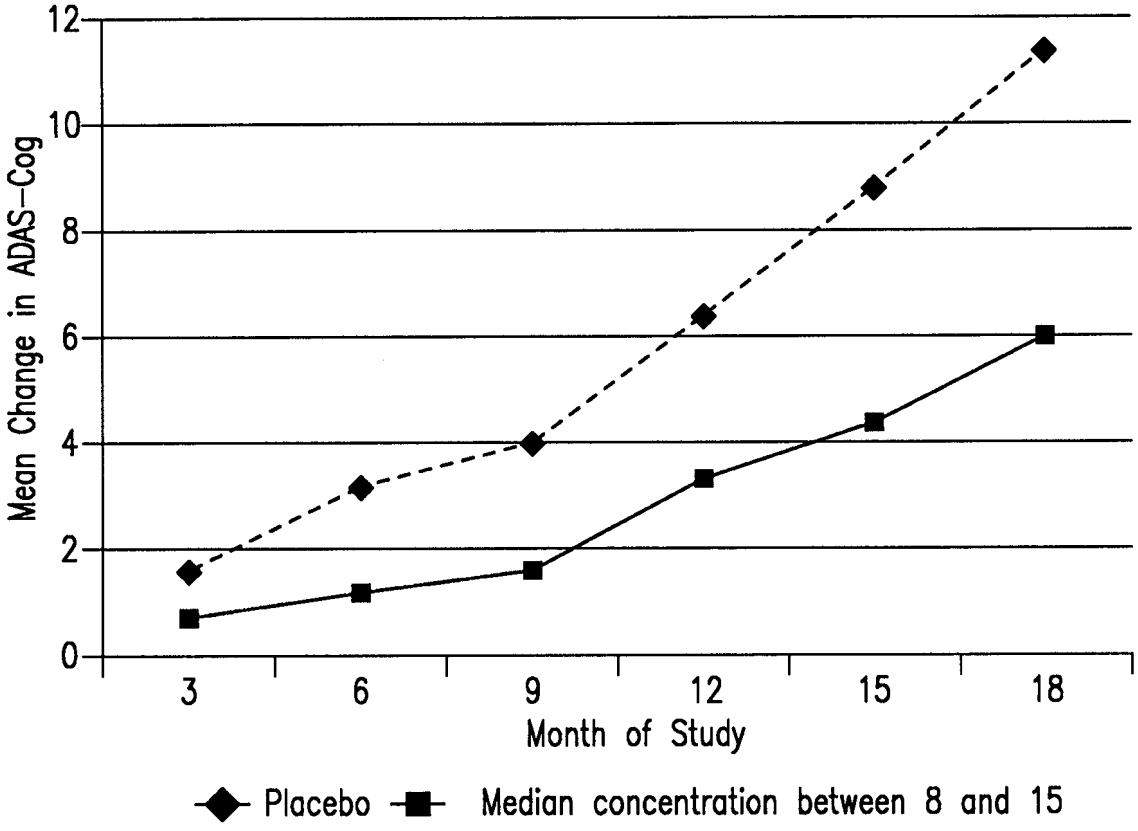
12
10
8
6
4
2
0
Mean Change in ADAS-Cog
3
6
9
12
15
18
Month of Study
Placebo
Median concentration between 8 and 15

FIG.4

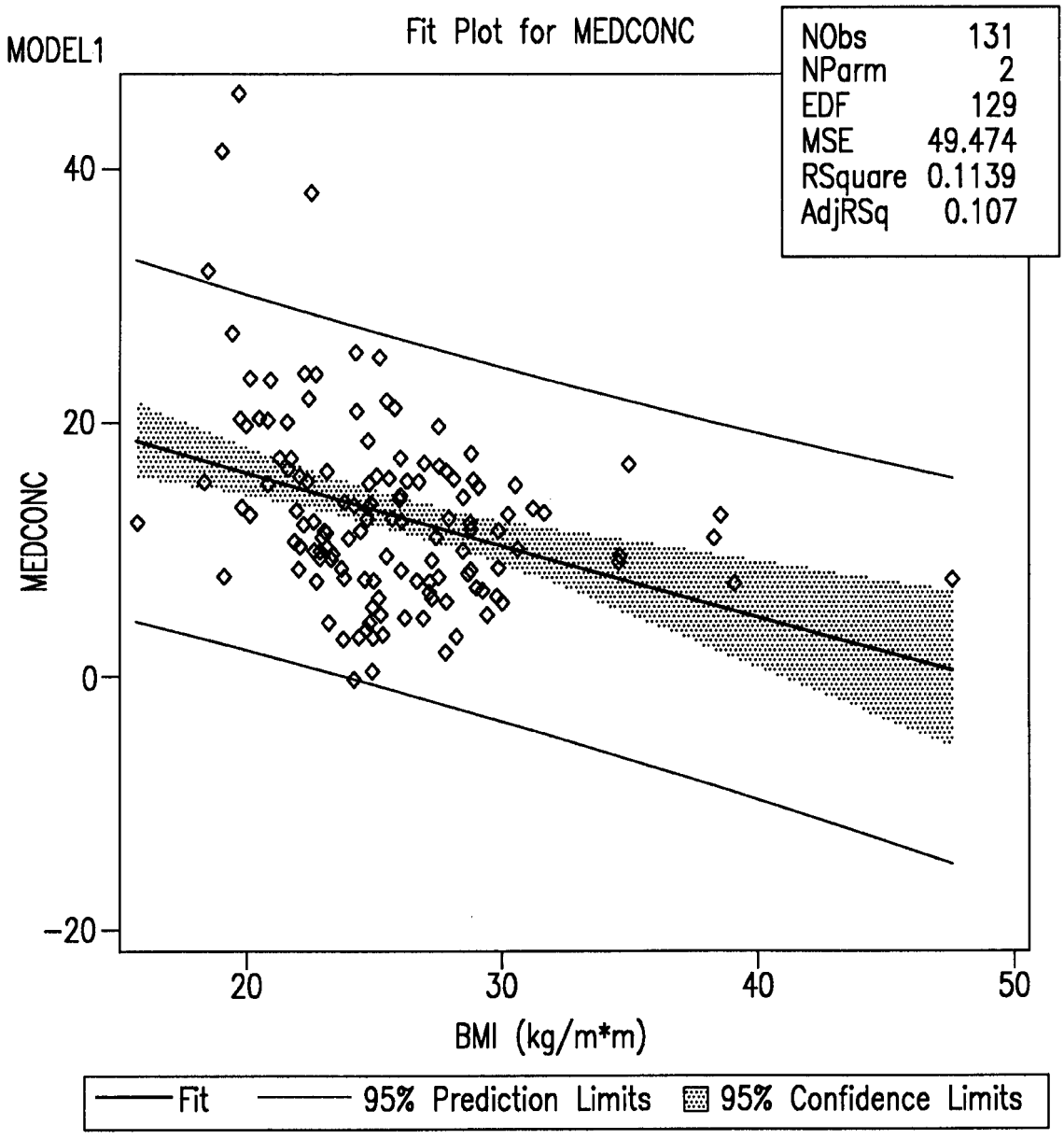
MODEL1
Fit Plot for MEDCONC
NObs 131
NParm 2
EDF 129
MSE 49.474
RSquare 0.1139
AdjRSq 0.107
40
20
0
-20
MEDCONC
20
30
40
50
BMI (kg/m*m)
Fit
95% Prediction Limits
95% Confidence Limits

FIG. 5A

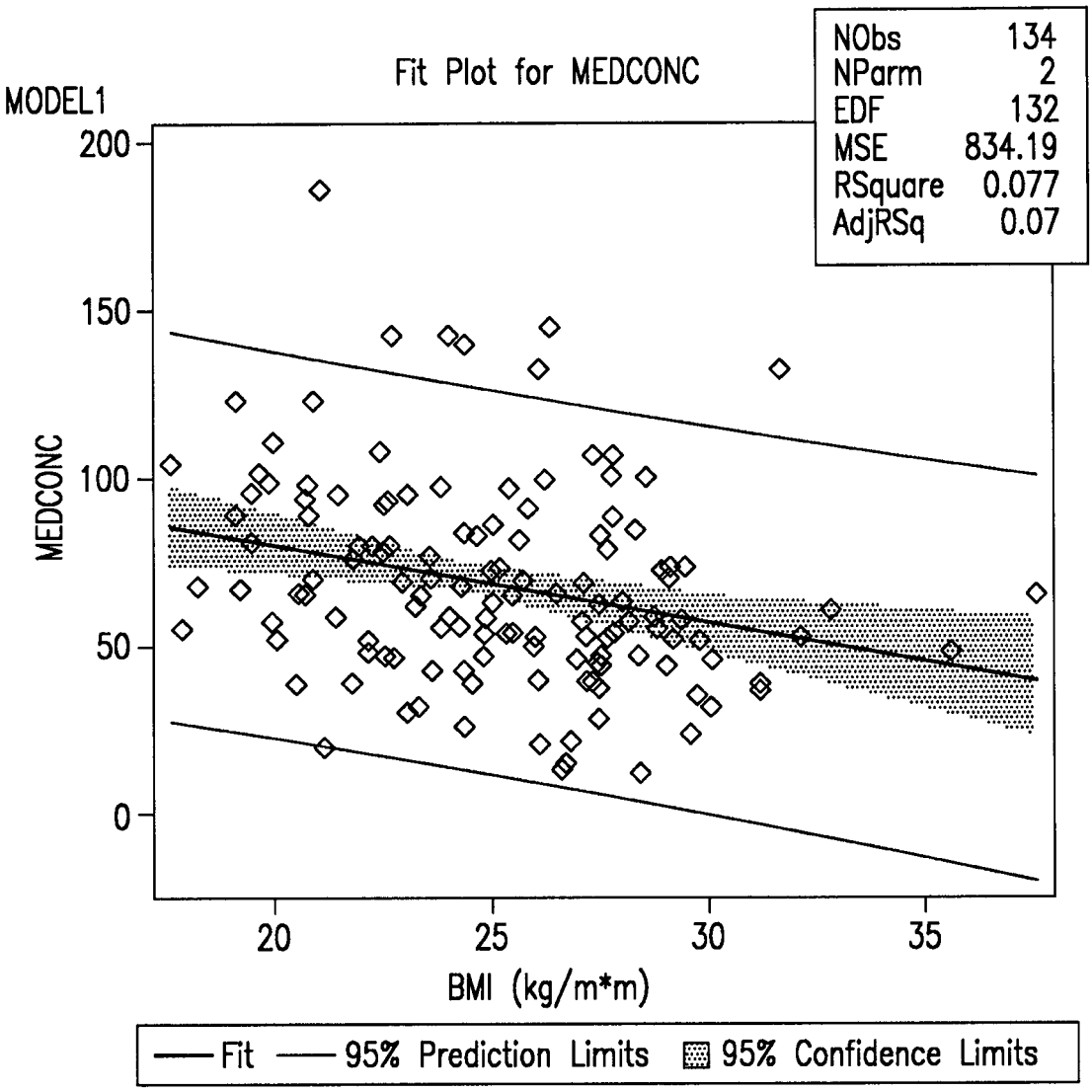
Fit Plot for MEDCONC
MODEL1
NObs 134
NParm 2
EDF 132
MSE 834.19
RSquare 0.077
AdjRSq 0.07
MEDCONC
200
150
100
50
0
20
25
30
35
BMI (kg/m*m)
Fit
95% Prediction Limits
95% Confidence Limits

FIG. 5B

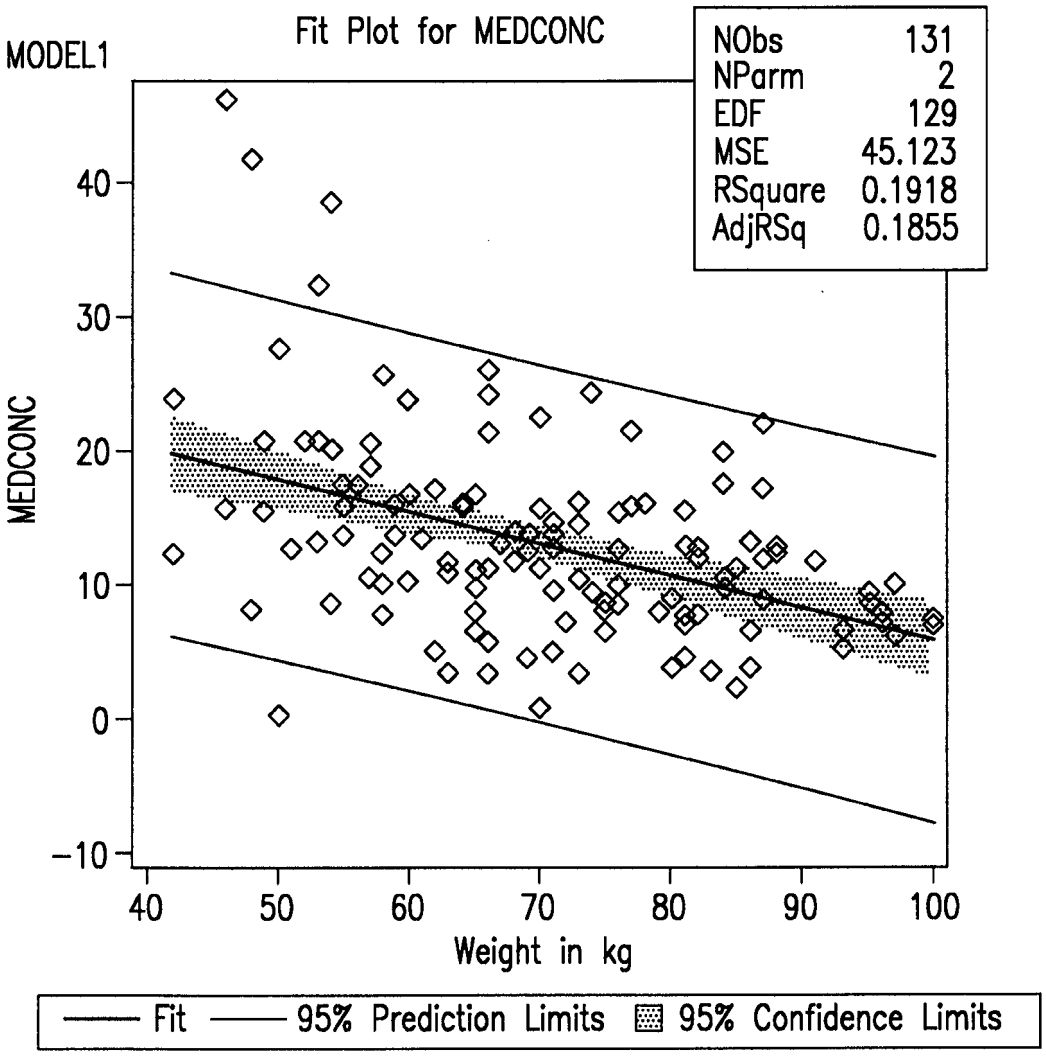
Fit Plot for MEDCONC
MODEL1
NObs 131
NParm 2
EDF 129
MSE 45.123
RSquare 0.1918
AdjRSq 0.1855
MEDCONC
40
30
20
10
0
-10
40
50
60
70
80
90
100
Weight in kg
Fit
95% Prediction Limits
95% Confidence Limits

FIG. 5C

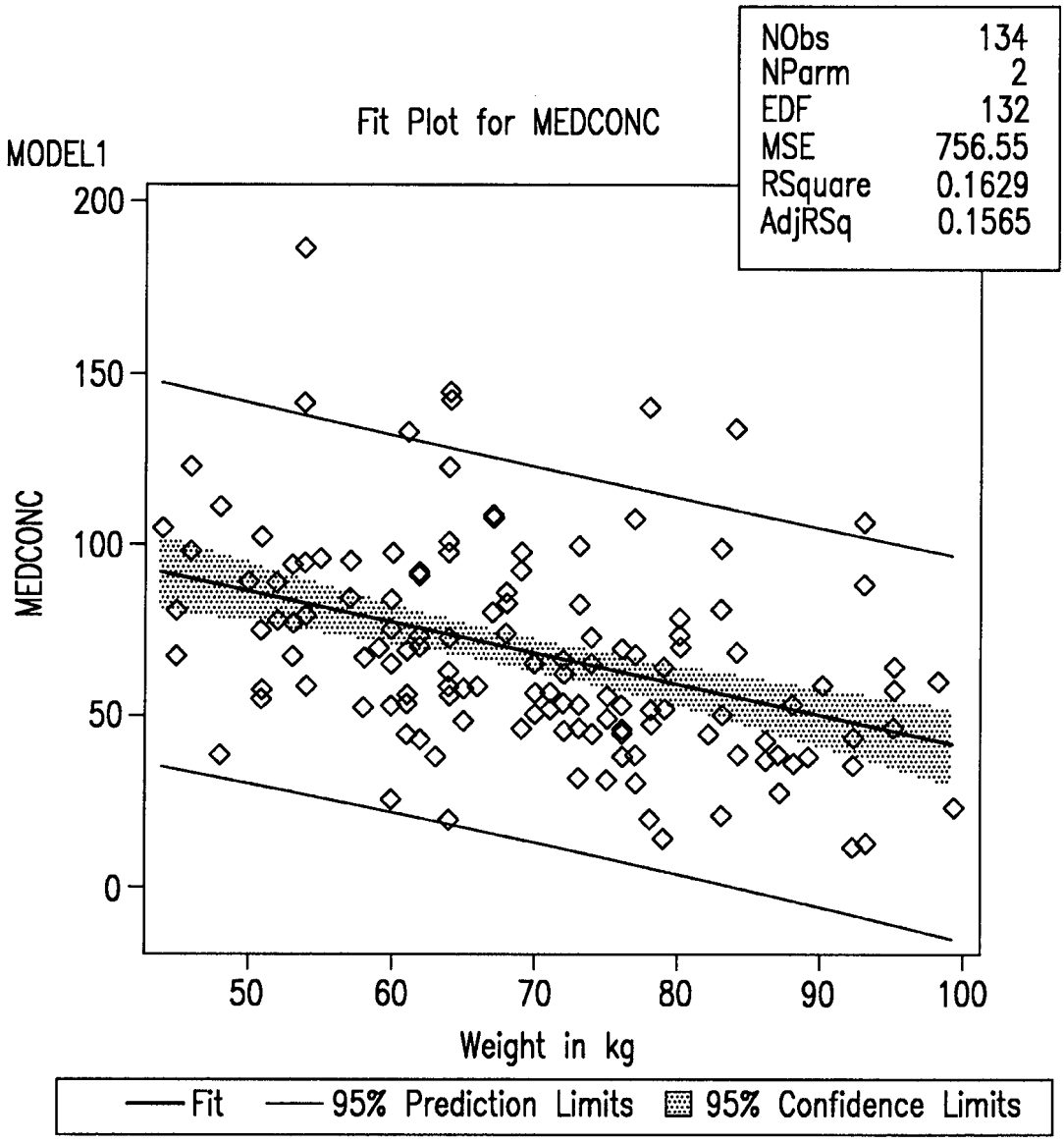
Fit Plot for MEDCONC
MODEL1
NObs 134
NParm 2
EDF 132
MSE 756.55
RSquare 0.1629
AdjRSq 0.1565
MEDCONC
200
150
100
50
0
50
60
70
80
90
100
Weight in kg
Fit
95% Prediction Limits
95% Confidence Limits

FIG. 5D

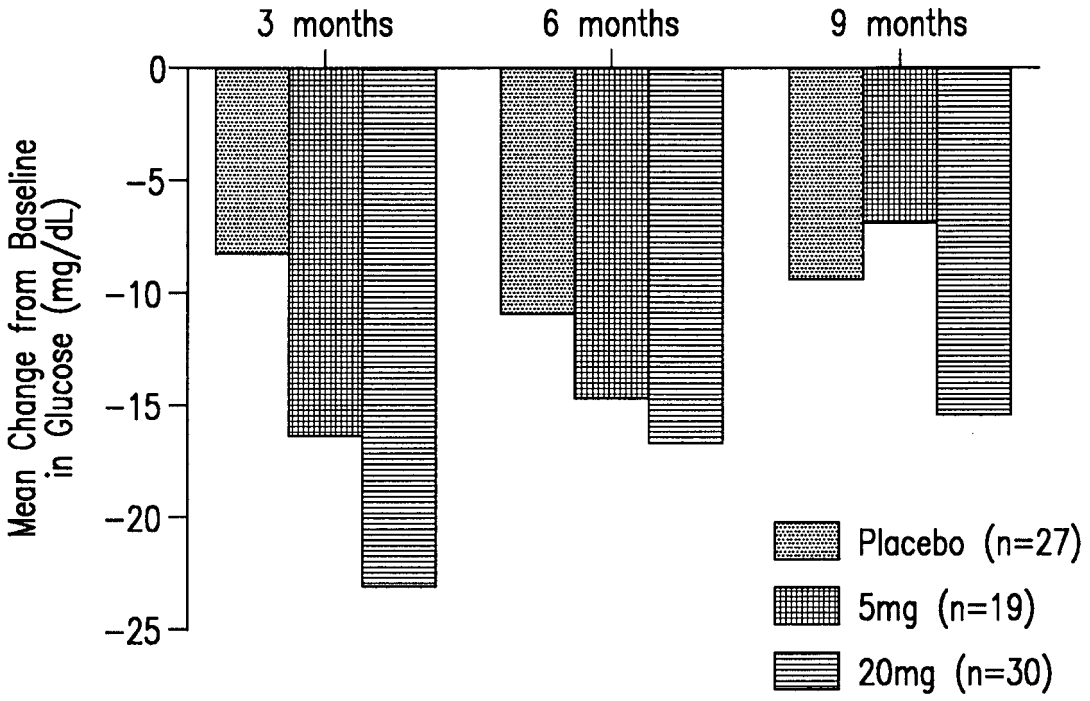
3 months
6 months
9 months
0
-5
-10
-15
-20
-25
Mean Change from Baseline in Glucose (mg/dL)
Placebo (n=27)
5mg (n=19)
20mg (n=30)

FIG. 6A

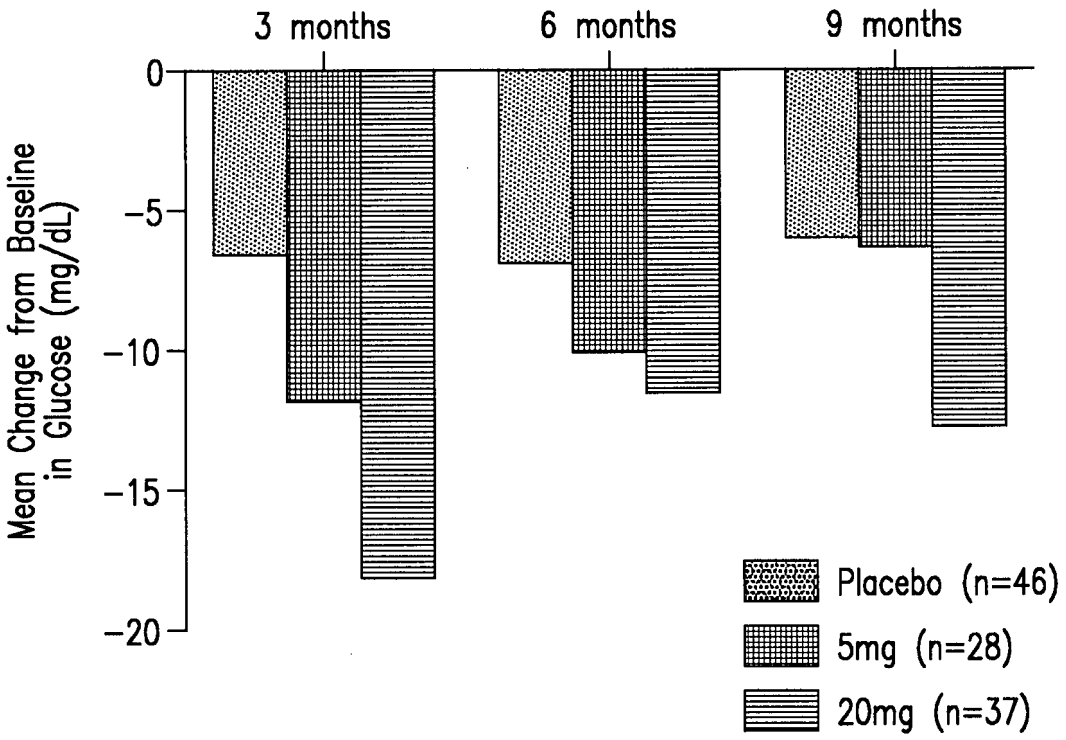
3 months
6 months
9 months
0
−5
−10
−15
−20
Mean Change from Baseline in Glucose (mg/dL)
Placebo (n=46)
5mg (n=28)
20mg (n=37)

FIG. 6B

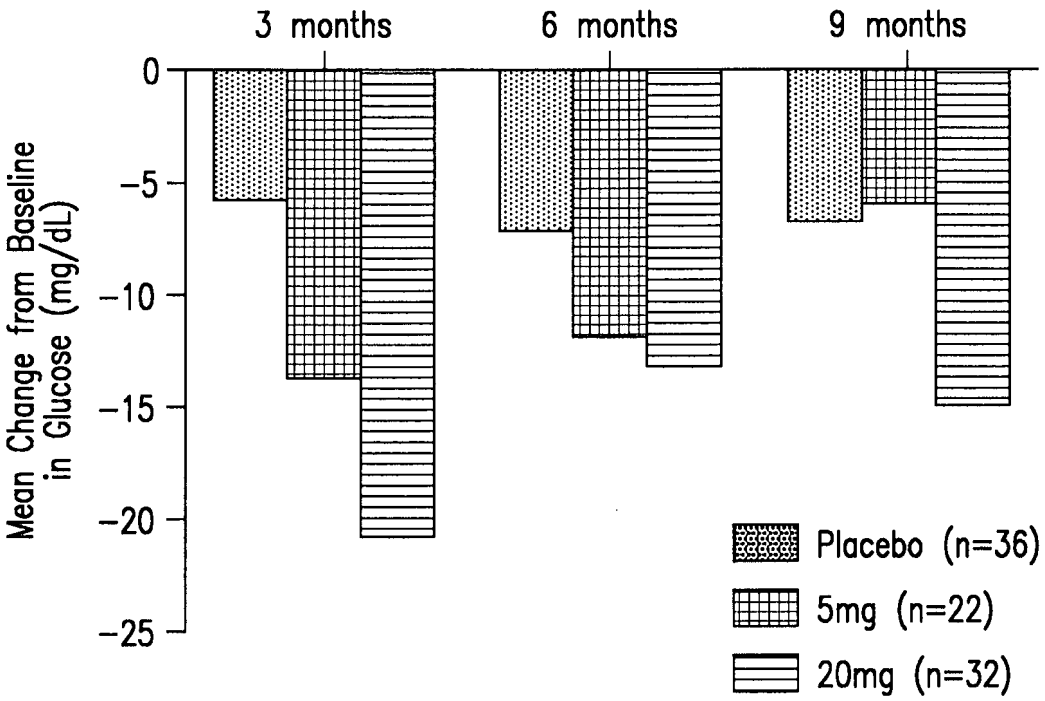
3 months
6 months
9 months
0
-5
-10
-15
-20
-25
Mean Change from Baseline in Glucose (mg/dL)
Placebo (n=36)
5mg (n=22)
20mg (n=32)

FIG. 6C

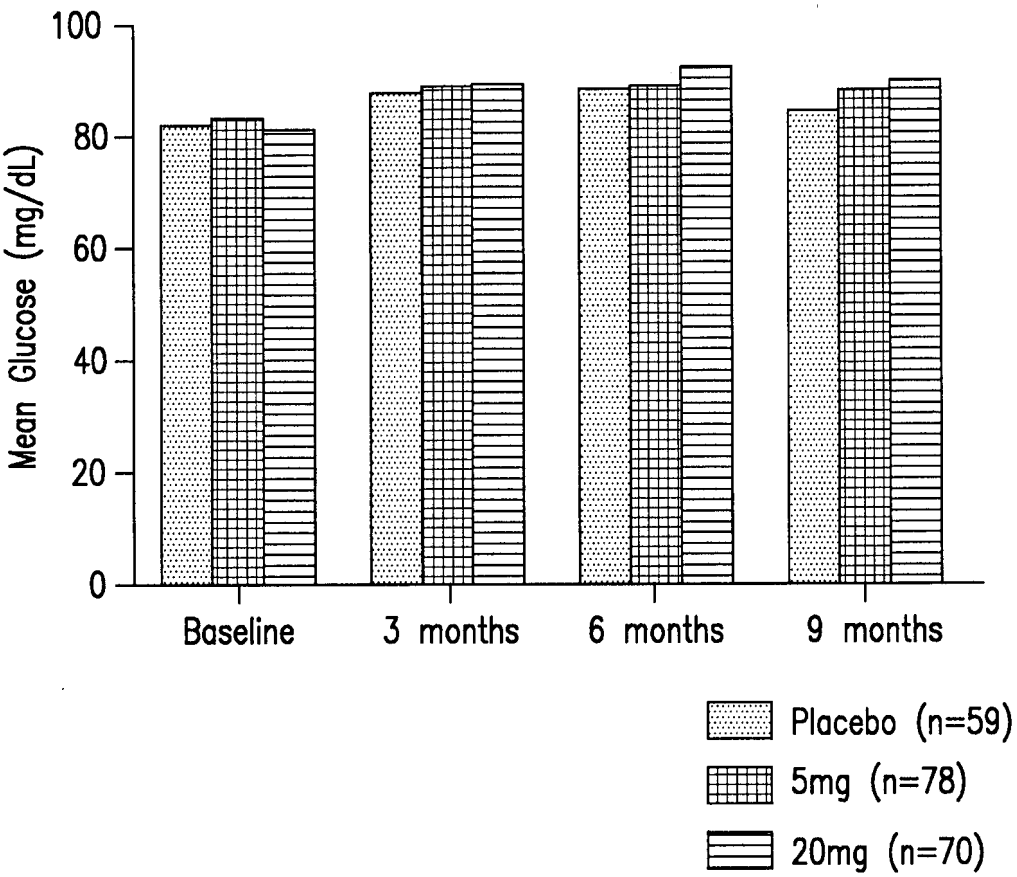
100
80
60
40
20
0
Mean Glucose (mg/dL)
Baseline
3 months
6 months
9 months
Placebo (n=59)
5mg (n=78)
20mg (n=70)

FIG. 6D

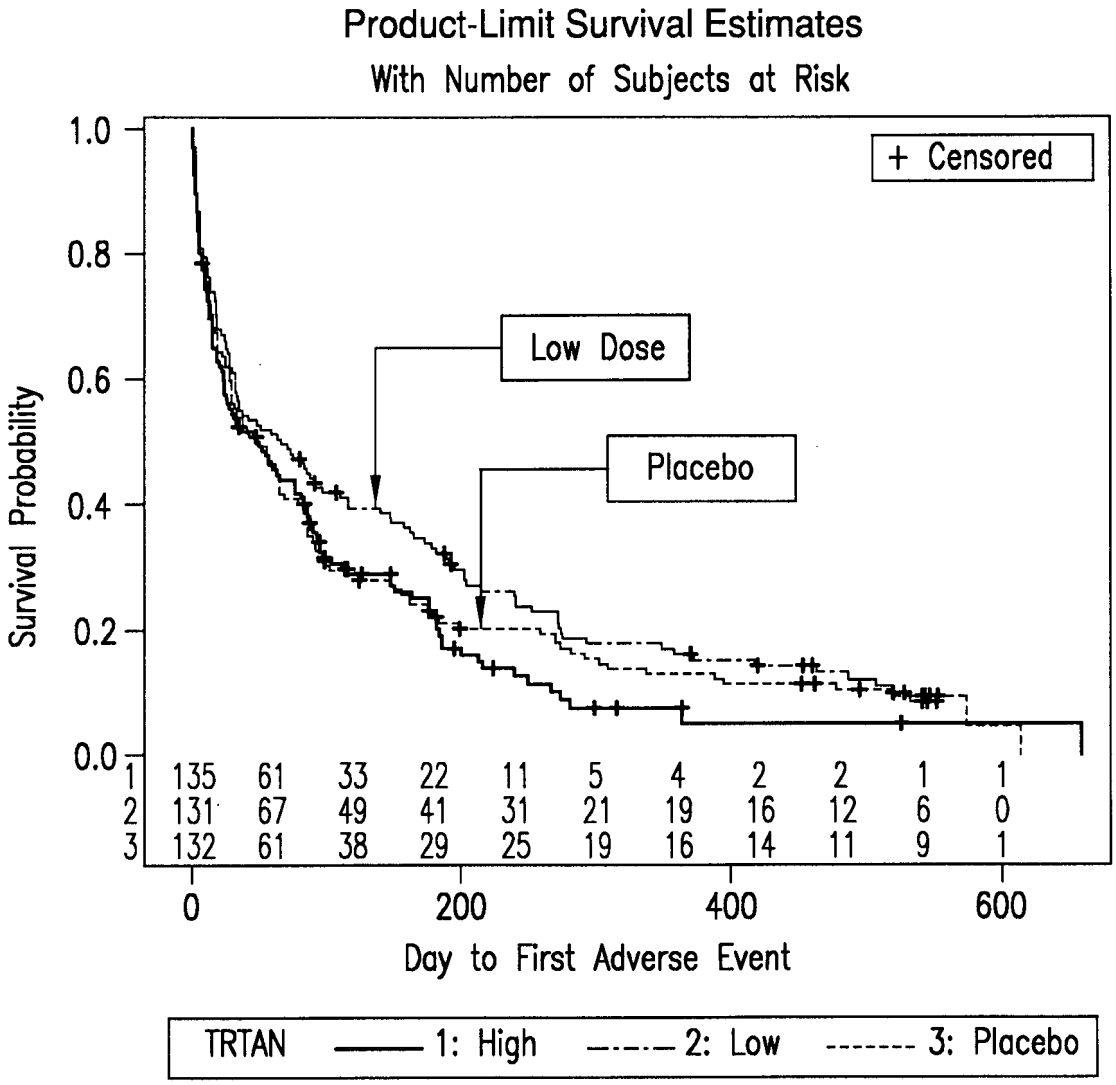
Product-Limit Survival Estimates
With Number of Subjects at Risk
+ Censored
Low Dose
Placebo
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
1 135 61 33 22 11 5 4 2 2 1 1
2 131 67 49 41 31 21 19 16 12 6 0
3 132 61 38 29 25 19 16 14 11 9 1
0
200
400
600
Day to First Adverse Event
TRTAN 1: High 2: Low 3: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

FIG. 7

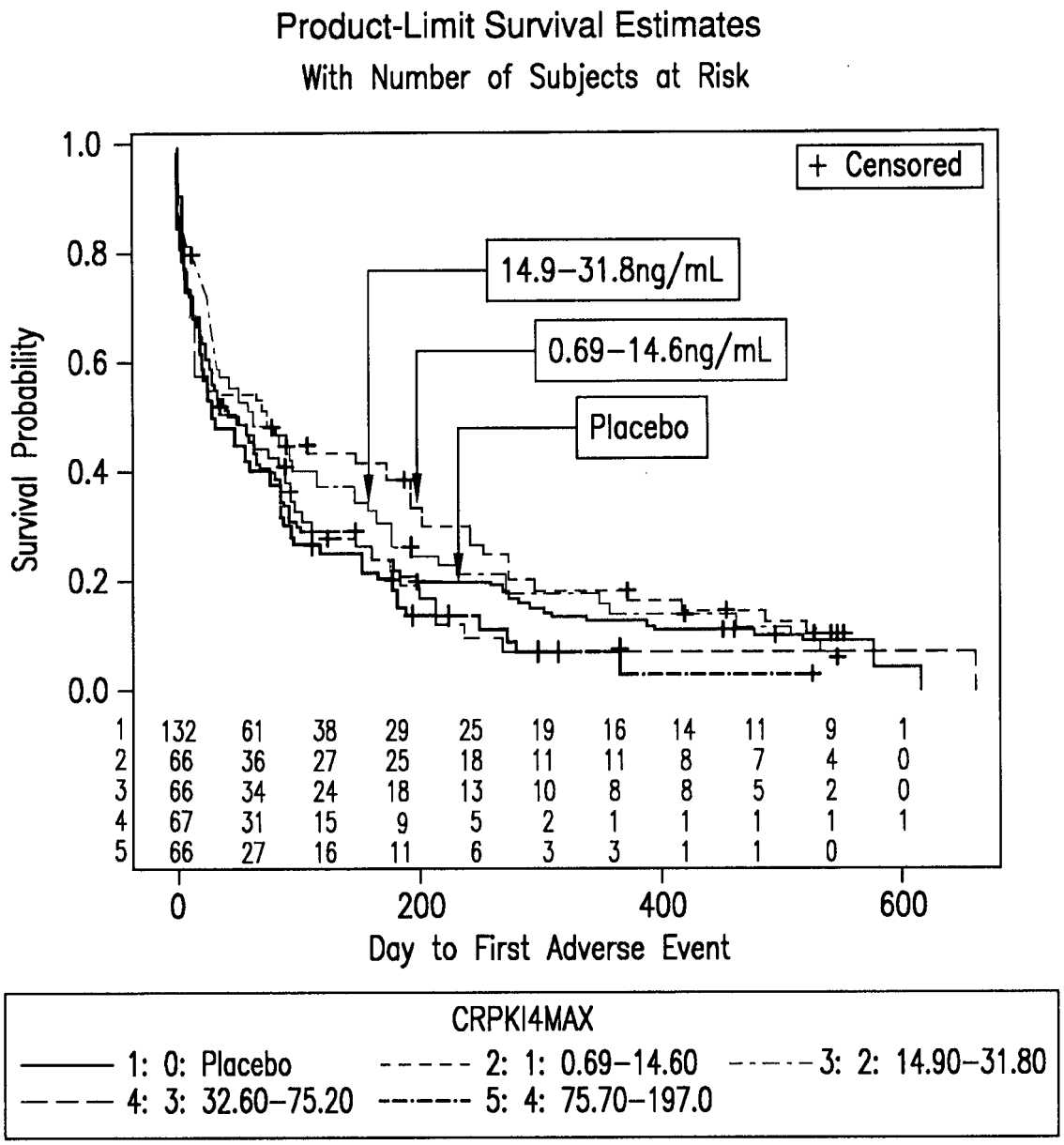
Product-Limit Survival Estimates
With Number of Subjects at Risk
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
+ Censored
14.9–31.8ng/mL
0.69–14.6ng/mL
Placebo
1 132 61 38 29 25 19 16 14 11 9 1
2 66 36 27 25 18 11 11 8 7 4 0
3 66 34 24 18 13 10 8 8 5 2 0
4 67 31 15 9 5 2 1 1 1 1 1
5 66 27 16 11 6 3 3 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

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/062964

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/13 A61K31/4164 A61P25/28 A61P25/20 A61P3/10
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 7 361 678 B2 (MJALLI ADNAN M M [US] ET AL) 22 April 2008 (2008-04-22) cited in the application the whole document column 1, line 15 - column 2, line 60 column 225 - column 226; compound 406 column 513, line 9 - column 517, line 53 column 521, line 6 - line 62 claims 6(3),14 ----- -/--	1-23, 43-68, 77-83

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 November 2013	19/11/2013
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Economou, Dimitrios

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/062964

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/153957 A1 (UNIV COLUMBIA [US]; SCHMIDT ANN MARIE [US]; FERRANTE ANTHONY [US]; SON) 18 December 2008 (2008-12-18) the whole document page 3, lines 16-22 page 6, line 29 page 32, lines 22-24 page 34, line 20 - line 25 page 36, line 5 - page 37, line 29 claim 31; compound 22 claims 32,34	24-39, 69-76
X	US 7 884 219 B2 (HARI ANITHA [US]) 8 February 2011 (2011-02-08) cited in the application the whole document column 1, line 65 - column 2, line 9 column 3, line 39 - line 54	1-3, 7-18, 22-26, 30,31, 35-37, 40-44, 48,49, 53,54, 58,59, 63,64, 68-73
X	WO 2005/000295 A1 (TRANSTECH PHARMA INC [US]; MJALLI ADNAN M M [US]; ANDREWS ROBERT C [US) 6 January 2005 (2005-01-06) the whole document page 1, paragraph 2 page 3, paragraph 1 - paragraph 6 page 5, paragraph 2 - paragraph 5 page 6, paragraph 2 - paragraph 4 page 7, paragraph 3 - page 8, paragraph 4 page 8, paragraph 7 - page 9, paragraph 3 page 10, paragraph 7 - page 11, paragraph 5 page 11, last paragraph - page 12, paragraph 2 page 36, last paragraph - page 37, paragraph 1 page 51, paragraph 3 - page 61, last paragraph page 62; example A examples 1-3,5 claims 1-9,11,23-34,39-42	1-23, 43-68, 77-83

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2013/062964

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 7361678 B2	22-04-2008	AT 529110 T	15-11-2011
		AU 2003217943 A1	22-09-2003
		AU 2007202350 A1	14-06-2007
		AU 2009202814 A1	06-08-2009
		CA 2476594 A1	18-09-2003
		CN 1633290 A	29-06-2005
		CN 101597262 A	09-12-2009
		CN 101613321 A	30-12-2009
		DK 1482931 T3	19-12-2011
		EP 1482931 A2	08-12-2004
		EP 2324830 A1	25-05-2011
		ES 2373875 T3	09-02-2012
		HK 1069549 A1	06-07-2012
		JP 4481011 B2	16-06-2010
		JP 2005525378 A	25-08-2005
		JP 2009096806 A	07-05-2009
		US 2004082542 A1	29-04-2004
		US 2007021386 A1	25-01-2007
		US 2007213347 A1	13-09-2007
		US 2010256119 A1	07-10-2010
		US 2012088778 A1	12-04-2012
		WO 03075921 A2	18-09-2003
WO 2008153957 A1	18-12-2008	US 2010254983 A1	07-10-2010
		WO 2008153957 A1	18-12-2008
US 7884219 B2	08-02-2011	AR 065896 A1	08-07-2009
		CA 2681864 A1	16-10-2008
		CL 9872008 A1	08-08-2008
		EP 2144883 A1	20-01-2010
		JP 2010523559 A	15-07-2010
		PA 8775601 A1	23-04-2009
		PE 08082009 A1	27-06-2009
		TW 200900384 A	01-01-2009
		US 2008249316 A1	09-10-2008
		US 2011166361 A1	07-07-2011
		UY 31004 A1	28-11-2008
		WO 2008123914 A1	16-10-2008
WO 2005000295 A1	06-01-2005	AU 2004251599 A1	06-01-2005
		BR PI0410436 A	30-05-2006
		CA 2522275 A1	06-01-2005
		CN 1805743 A	19-07-2006
		EP 1635823 A1	22-03-2006
		JP 2007503469 A	22-02-2007
		MX PA05012350 A	25-05-2006
		US 2005026811 A1	03-02-2005
		US 2009035302 A1	05-02-2009
		WO 2005000295 A1	06-01-2005
		ZA 200508300 A	28-03-2007

(19)中华人民共和国国家知识产权局

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WO2014/055588 EN 2014.04.10
(71)申请人 转化技术制药有限责任公司
地址 美国北卡罗来纳
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M·C·瓦尔卡西-洛佩兹
M·J·考斯图拉
(74)专利代理机构 中国国际贸易促进委员会专利商标事务所 11038
代理人 张敏
(51)Int.Cl.
A61K 31/13(2006.01)
A61K 31/4164(2006.01)
A61P 25/28(2006.01)
A61P 25/20(2006.01)
A61P 3/10(2006.01)

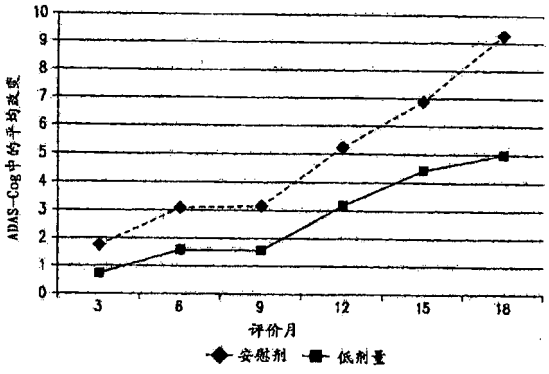
权利要求书5页 说明书19页 附图13页

(54)发明名称

治疗轻度和中度阿尔茨海默病的方法

(57)摘要

本发明涉及使用[3-(4-{2-丁基-1-[4-(4-氯-苯氧基)-苯基]-1H-咪唑-4-基}-苯氧基)-丙基]-二乙胺(“化合物I”)或其药学上可接受的盐的治疗方法。在不同的实施方案中,所述治疗方法包括治疗阿尔茨海默型轻度至中度痴呆、糖尿病、失眠症和其它适应征。本发明还涉及包含化合物I或其药学上可接受的盐的药物组合物。



CN 104703592 A

1. 治疗阿尔茨海默病的方法，包含对有此需要的受试者施用小于 20mg/ 天的用量的 3-(4-{2- 丁基 -1-[4-(4- 氯 - 苯氧基)- 苯基]-1H- 咪唑 -4- 基 }- 苯氧基)- 丙基]- 二乙胺或其药学上可接受的盐。

2. 权利要求 1 的方法，其中以约 1mg/ 天一小于 20mg/ 天范围的剂量施用 [3-(4-{2- 丁基 -1-[4-(4- 氯 - 苯氧基)- 苯基]-1H- 咪唑 -4- 基 }- 苯氧基)- 丙基]- 二乙胺。

3. 权利要求 2 的方法，其中所述剂量为约 5mg/ 天或约 4mg/ 天或约 3mg/ 天或约 2mg/ 天。

4. 上述权利要求任一项的方法，其中该治疗方法还包含对所述受试者施用乙酰胆碱酯酶抑制剂 (AChEI)。

5. 权利要求 4 的方法，其中所述 AChEI 选自盐酸多奈哌齐、盐酸加兰他敏、酒石酸利伐斯的明和盐酸他克林。

6. 上述权利要求任一项的方法，其中该治疗方法还包含对所述受试者施用盐酸美金刚。

7. 上述权利要求任一项的方法，其中 [3-(4-{2- 丁基 -1-[4-(4- 氯 - 苯氧基)- 苯基]-1H- 咪唑 -4- 基 }- 苯氧基)- 丙基]- 二乙胺或其药学上可接受的盐在受试者中的血清浓度为：

约 1ng/ml 一约 65ng/ml、或约 1ng/ml 一约 60ng/ml ；或

约 1ng/ml 一约 55ng/ml、或约 1ng/ml 一约 50ng/ml ；或

约 1ng/ml 一约 45ng/ml、或约 1ng/ml 一约 40ng/ml ；或

约 1ng/ml 一约 35ng/ml、或约 1ng/ml 一约 30ng/ml ；或

约 1ng/ml 一约 25ng/ml、或约 1ng/ml 一约 20ng/ml ；或

约 1ng/ml 一约 15ng/ml、或约 1ng/ml 一约 10ng/ml。

8. 权利要求 7 的方法，其中受试者中的血清浓度为约 8 一约 15ng/ml。

9. 权利要求 8 的方法，其中受试者中的血清浓度为约 12.5ng/ml。

10. 上述权利要求任一项的方法，其中根据在选自如下的评价的至少一种中的改善或无恶化或恶化速率降低确定治疗：阿尔茨海默病评定量表认知分量表 (ADAS-cog)、临床痴呆评级笔盒 (CDR-sb)、阿尔茨海默病协作研究日常生活能力量表 (ADCS-ADL)；神经精神量表 (NPI) 和细微精神状态评价 (MMSE)。

11. 权利要求 10 的方法，其中该治疗导致 ADAS-cog 评分中的恶化速率降低。

12. 权利要求 11 的方法，其中该治疗导致 ADAS-cog 评分的恶化速率平均降低 2 一 5 个点。

13. 治疗阿尔茨海默病的方法，包含对有此需要的受试者施用 1mg/5kg 受试者体重 / 天一 1mg/50kg 受试者体重 / 天的用量的 [3-(4-{2- 丁基 -1-[4-(4- 氯 - 苯氧基)- 苯基]-1H- 咪唑 -4- 基 }- 苯氧基)- 丙基]- 二乙胺或其药学上可接受的盐。

14. 权利要求 13 的方法，其中以 1mg/20kg/ 天的用量施用治疗。

15. 在具有轻度至中度阿尔茨海默病的受试者中抑制高度聚糖化作用终产物的受体 (RAGE) 与 RAGE 配体相互作用的方法，包含对有此需要的受试者施用小于 20mg/ 天的用量的 [3-(4-{2- 丁基 -1-[4-(4- 氯 - 苯氧基)- 苯基]-1H- 咪唑 -4- 基 }- 苯氧基)- 丙基]- 二乙胺或其药学上可接受的盐。

16. 权利要求 15 的方法，其中 RAGE 配体选自可溶性 β - 淀粉样蛋白、不溶性 β - 淀粉样蛋白、s100b、钙粒蛋白、EN-RAGE、HMGB1（高速泳动族框 1）、两性蛋白和羧甲基赖氨酸。

17. 权利要求 15 的方法，其中以 1 一约 20mg/ 天范围的剂量施用 [3-(4-{2- 丁基 -1-[4-(4- 氯 - 苯氧基)- 苯基]-1H- 咪唑 -4- 基 }- 苯氧基)- 丙基]- 二乙胺或其药学上可接受的盐。

18. 权利要求 17 的方法，其中所述剂量为约 5mg/ 天或约 4mg/ 天或约 3mg/ 天或约 2mg/ 天。

19. 权利要求 15 — 18 任一项的方法，其中该治疗方法还包含对所述受试者施用乙酰胆碱酯酶抑制剂 (AChEI)。

20. 权利要求 19 的方法，其中所述 AChEI 选自盐酸多奈哌齐、盐酸加兰他敏、酒石酸利伐斯的明和盐酸他克林。

21. 权利要求 15 — 20 任一项的方法，其中该治疗方法还包含对所述受试者施用盐酸美金刚。

22. 权利要求 1 — 21 任一项的方法，其中该方法治疗轻度阿尔茨海默病。

23. 权利要求 22 的方法，其中将轻度阿尔茨海默病定义为给予小于或等于 23 的 ADAS-cog 评分的受试者。

24. 治疗糖尿病的方法，包含对有此需要的受试者施用小于 20 mg/ 天的用量的 [3-(4-{2- 丁基 -1-[4-(4- 氯 - 苯氧基)- 苯基]-1H- 咪唑 -4- 基 }- 苯氧基)- 丙基]- 二乙胺或其药学上可接受的盐。

25. 权利要求 24 的方法，其中以约 1 一约 20mg/ 天范围的剂量施用 [3-(4-{2- 丁基 -1-[4-(4- 氯 - 苯氧基)- 苯基]-1H- 咪唑 -4- 基 }- 苯氧基)- 丙基]- 二乙胺。

26. 权利要求 25 的方法，其中所述剂量为约 5mg/ 天或约 4mg/ 天或约 3mg/ 天或约 2mg/ 天。

27. 权利要求 24 — 26 任一项的方法，其中该治疗方法还包含对所述受试者施用乙酰胆碱酯酶抑制剂 (AChEI)。

28. 权利要求 27 的方法，其中所述 AChEI 选自盐酸多奈哌齐、盐酸加兰他敏、酒石酸利伐斯的明和盐酸他克林。

29. 权利要求 24 — 28 任一项的方法，其中该治疗方法还包含对所述受试者施用盐酸美金刚。

30. 抑制与具有轻度至中度阿尔茨海默病的受试者的恢复相关的葡萄糖代谢减少的方法，包含对有此需要的受试者施用小于 20 mg/ 天的用量的 [3-(4-{2- 丁基 -1-[4-(4- 氯 - 苯氧基)- 苯基]-1H- 咪唑 -4- 基 }- 苯氧基)- 丙基]- 二乙胺或其药学上可接受的盐。

31. 权利要求 30 的方法，其中所述剂量为约 5mg/ 天或约 4mg/ 天或约 3mg/ 天或约 2mg/ 天。

32. 权利要求 30 — 31 任一项的方法，其中该治疗方法还包含对所述受试者施用乙酰胆碱酯酶抑制剂 (AChEI)。

33. 权利要求 32 的方法，其中所述 AChEI 选自盐酸多奈哌齐、盐酸加兰他敏、酒石酸利伐斯的明和盐酸他克林。

34. 权利要求 30 － 33 任一项的方法，其中该治疗方法还包含对所述受试者施用盐酸美金刚。

35. 降低受试者中血糖水平的方法，包含对有此需要的受试者施用小于 20mg/ 天的用量的 [3-(4-{2- 丁基 -1-[4-(4- 氯 - 苯氧基)- 苯基]-1H- 咪唑 -4- 基 }- 苯氧基)- 丙基]- 二乙胺或其药学上可接受的盐。

36. 权利要求 35 的方法，其中所述剂量为约 5mg/ 天或约 4mg/ 天或约 3mg/ 天或约 2mg/ 天。

37. 权利要求 35 － 36 任一项的方法，其中该治疗方法还包含对所述受试者施用乙酰胆碱酯酶抑制剂 (AChEI)。

38. 权利要求 37 的方法，其中所述 AChEI 选自盐酸多奈哌齐、盐酸加兰他敏、酒石酸利伐斯的明和盐酸他克林。

39. 权利要求 35 － 38 任一项的方法，其中该治疗方法还包含对所述受试者施用盐酸美金刚。

40. 权利要求 35 的方法，其中所述受试者患有轻度至中度阿尔茨海默病。

41. 权利要求 35 的方法，其中所述受试者的血糖水平降低了至少 5mg/dl、或至少 10mg/dl、或至少 15mg/dl、或至少 20mg/dl 或 5 － 20mg/dl。

42. 权利要求 35 的方法，其中所述受试者的初次葡萄糖水平高于 100mg/dl。

43. 治疗失眠症的方法，包含对有此需要的受试者施用小于 20mg/ 天的用量的 [3-(4-{2- 丁基 -1-[4-(4- 氯 - 苯氧基)- 苯基]-1H- 咪唑 -4- 基 }- 苯氧基)- 丙基]- 二乙胺或其药学上可接受的盐。

44. 权利要求 43 的方法，其中所述剂量为约 5mg/ 天或约 4mg/ 天或约 3mg/ 天或约 2mg/ 天。

45. 权利要求 43 － 44 任一项的方法，其中该治疗方法还包含对所述受试者施用乙酰胆碱酯酶抑制剂 (AChEI)。

46. 权利要求 45 的方法，其中所述 AChEI 选自盐酸多奈哌齐、盐酸加兰他敏、酒石酸利伐斯的明和盐酸他克林。

47. 权利要求 43 － 36 任一项的方法，其中该治疗方法还包含对所述受试者施用盐酸美金刚。

48. 治疗具有轻度至中度阿尔茨海默病的受试者的失眠症的方法，包含对有此需要的受试者施用小于 20mg/ 天的用量的 [3-(4-{2- 丁基 -1-[4-(4- 氯 - 苯氧基)- 苯基]-1H- 咪唑 -4- 基 }- 苯氧基)- 丙基]- 二乙胺或其药学上可接受的盐。

49. 权利要求 48 的方法，其中所述剂量为约 5mg/ 天或约 4mg/ 天或约 3mg/ 天或约 2mg/ 天。

50. 权利要求 48 － 49 任一项的方法，其中该治疗方法还包含对所述受试者施用乙酰胆碱酯酶抑制剂 (AChEI)。

51. 权利要求 50 的方法，其中所述 AChEI 选自盐酸多奈哌齐、盐酸加兰他敏、酒石酸利伐斯的明和盐酸他克林。

52. 权利要求 48 － 51 任一项的方法，其中该治疗方法还包含对所述受试者施用盐酸美金刚。

53. 减少睡眠起始潜伏期的方法，包含对有此需要的受试者施用小于 20mg/ 天的用量的 [3-(4-{2- 丁基 -1-[4-(4- 氯 - 苯氧基)- 苯基]-1H- 咪唑 -4- 基 }- 苯氧基)- 丙基]- 二乙胺或其药学上可接受的盐。

54. 权利要求 53 的方法，其中所述剂量为约 5mg/ 天或约 4mg/ 天或约 3mg/ 天或约 2mg/ 天。

55. 权利要求 53 － 54 任一项的方法，其中该治疗方法还包含对所述受试者施用乙酰胆碱酯酶抑制剂 (AChEI)。

56. 权利要求 55 的方法，其中所述 AChEI 选自盐酸多奈哌齐、盐酸加兰他敏、酒石酸利伐斯的明和盐酸他克林。

57. 权利要求 53 － 56 任一项的方法，其中该治疗方法还包含对所述受试者施用盐酸美金刚。

58. 减少具有轻度至中度阿尔茨海默病的受试者的睡眠起始潜伏期的方法，包含对有此需要的受试者施用小于 20mg/ 天的用量的 [3-(4-{2- 丁基 -1-[4-(4- 氯 - 苯氧基)- 苯基]-1H- 咪唑 -4- 基 }- 苯氧基)- 丙基]- 二乙胺或其药学上可接受的盐。

59. 权利要求 58 的方法，其中所述剂量为约 5mg/ 天或约 4mg/ 天或约 3mg/ 天或约 2mg/ 天。

60. 权利要求 58 － 59 任一项的方法，其中该治疗方法还包含对所述受试者施用乙酰胆碱酯酶抑制剂 (AChEI)。

61. 权利要求 60 的方法，其中所述 AChEI 选自盐酸多奈哌齐、盐酸加兰他敏、酒石酸利伐斯的明和盐酸他克林。

62. 权利要求 58 － 61 任一项的方法，其中该治疗方法还包含对所述受试者施用盐酸美金刚。

63. 降低具有轻度至中度阿尔茨海默病的受试者的不良事件频率的方法，包含对有此需要的受试者施用小于 20mg/ 天的用量的 [3-(4-{2- 丁基 -1-[4-(4- 氯 - 苯氧基)- 苯基]-1H- 咪唑 -4- 基 }- 苯氧基)- 丙基]- 二乙胺或其药学上可接受的盐。

64. 权利要求 63 的方法，其中所述剂量为约 5mg/ 天或约 4mg/ 天或约 3mg/ 天或约 2mg/ 天。

65. 权利要求 63 － 64 任一项的方法，其中该治疗方法还包含对所述受试者施用乙酰胆碱酯酶抑制剂 (AChEI)。

66. 权利要求 65 的方法，其中所述 AChEI 选自盐酸多奈哌齐、盐酸加兰他敏、酒石酸利伐斯的明和盐酸他克林。

67. 权利要求 63 － 66 任一项的方法，其中该治疗方法还包含对所述受试者施用盐酸美金刚。

68. 权利要求 63 的方法，其中所述不良事件选自失落、头晕、精神混乱状态和嗜睡 ;或选自激动、抑郁症、焦虑、攻击性和多动。

69. 降低有此需要的受试者中 HbA1C 水平的方法，包含施用小于 20mg/ 天的用量的 [3-(4-{2- 丁基 -1-[4-(4- 氯 - 苯氧基)- 苯基]-1H- 咪唑 -4- 基 }- 苯氧基)- 丙基]- 二乙胺或其药学上可接受的盐。

70. 权利要求 69 的方法，其中以约 1mg/ 天 － 小于 20mg/ 天范围的剂量施用

[3-(4-{2- 丁基 -1-[4-(4- 氯 - 苯氧基)- 苯基]-1H- 咪唑 -4- 基 }- 苯氧基)- 丙基]- 二乙胺或其药学上可接受的盐。

71. 权利要求 70 的方法，其中所述剂量为约 5mg/ 天或约 4mg/ 天或约 3mg/ 天或约 2mg/ 天。

72. 权利要求 69 的方法，其中施用 [3-(4-{2- 丁基 -1-[4-(4- 氯 - 苯氧基)- 苯基]-1H- 咪唑 -4- 基 }- 苯氧基)- 丙基]- 二乙胺或其药学上可接受的盐将有此需要的受试者的 HbA1C 的量减少了至少 0.1 个百分点或 0.2 个百分点或 0.3 个百分点或 0.4 个百分点或 0.5 个百分点或 0.6 个百分点或 0.7 个百分点或 0.8 个百分点或 0.9 个百分点或 1 个百分点。

73. 权利要求 69 的方法，其中施用 [3-(4-{2- 丁基 -1-[4-(4- 氯 - 苯氧基)- 苯基]-1H- 咪唑 -4- 基 }- 苯氧基)- 丙基]- 二乙胺或其药学上可接受的盐将有此需要的受试者的 HbA1C 的量减少至小于 7%。

74. 权利要求 69 — 73 任一项的方法，其中该治疗方法还包含对所述受试者施用乙酰胆碱酯酶抑制剂 (AChEI)。

75. 权利要求 74 的方法，其中所述 AChEI 选自盐酸多奈哌齐、盐酸加兰他敏、酒石酸利伐斯的明和盐酸他克林。

76. 权利要求 69 — 75 任一项的方法，其中该治疗方法还包含对所述受试者施用盐酸美金刚。

77. 药物组合物，包含 1mg — 20mg 的 [3-(4-{2- 丁基 -1-[4-(4- 氯 - 苯氧基)- 苯基]-1H- 咪唑 -4- 基 }- 苯氧基)- 丙基]- 二乙胺或其药学上可接受的盐和乙酰胆碱酯酶抑制剂 (AChEI)。

78. 权利要求 77 的药物组合物，其中所述 AChEI 选自盐酸多奈哌齐、盐酸加兰他敏、酒石酸利伐斯的明和盐酸他克林。

79. 权利要求 78 的药物组合物，其中所述 AChEI 是以 5 — 23mg 存在的盐酸多奈哌齐。

80. 权利要求 78 的药物组合物，其中所述 AChEI 是以 16 — 24mg 存在的盐酸加兰他敏。

81. 权利要求 78 的药物组合物，其中所述 AChEI 是以 6 — 12mg 存在的酒石酸利伐斯的明。

82. 权利要求 78 的药物组合物，其中所述 AChEI 是以 40mg 存在的盐酸他克林。

83. 药物组合物，包含 1mg — 20mg 的 [3-(4-{2- 丁基 -1-[4-(4- 氯 - 苯氧基)- 苯基]-1H- 咪唑 -4- 基 }- 苯氧基)- 丙基]- 二乙胺或其药学上可接受的盐；以及盐酸美金刚。

治疗轻度和中度阿尔茨海默病的方法

发明领域

[0001] 本发明涉及治疗患有轻度至中度阿尔茨海默型痴呆的个体的方法，通过施用有效量的[3-(4-{2-丁基-1-[4-(4-氯-苯氧基)-苯基]-1H-咪唑-4-基}-苯氧基)-丙基]-二乙胺（“化合物I”）来进行。本发明还涉及抑制具有轻度至中度阿尔茨海默病的个体的高级糖基化终产物(RAGE)的受体与RAGE配体的相互作用的方法。本发明还涉及治疗糖尿病和葡萄糖代谢减少、包括患有轻度至中度阿尔茨海默病的个体的糖尿病和葡萄糖代谢减少的方法。另外，本发明涉及治疗个体、包括那些患有轻度至中度阿尔茨海默病的个体的失眠症或睡眠起始潜伏期的方法。

[0002] 发明背景

[0003] RAGE和疾病的治疗

[0004] 高度聚糖化作用终产物的受体(RAGE)是细胞表面分子的免疫球蛋白超家族的成员。RAGE的胞外(N-末端)结构域包括3个免疫球蛋白-型区、1个V(可变)型结构域、随后是2个C-型(恒定)结构域(Neeper等人，J.Biol.Chem.267:14998-15004(1992))。单一跨膜跨度结构域和短的高度带电荷的胞质尾跟随胞外结构域。可以通过使RAGE蛋白水解分离N-末端胞外结构域，生成由V和C结构域组成的可溶性RAGE(sRAGE)。

[0005] RAGE在大多数组织中表达，特别是，可在胚胎发生期间在皮质神经元中找到(Hori等人，(1995))。增加的RAGE水平也在老化组织中发现(Schleicher等人，J.Cl in.Invest.99(3):457-468(1997))和在糖尿病性视网膜、脉管系统和肾中发现(Schmidt等人，Nature Med.1:1002-1004(1995))。在不同组织和器官中的RAGE活化导致许多病理生理后果。RAGE牵涉包括如下的各种病况：急性和慢性炎症(Hofmann等人，Cel l 97:889-901(1999))，糖尿病晚期并发症的发展如增加的血管渗透性(Wautier等人，J.Cl in.Invest.97:238-243(1996))，肾病(Tei l let等人，J.Am.Soc.Nephrol.11:1488-1497(2000))，动脉粥样硬化(VIassara等人，The Finnish Medical Society DUODECIM,Ann.Med.28:419-426(1996))，和视网膜病(Hammes等人，Diabetologia42:603-607(1999))。RAGE也牵涉阿尔茨海默病(Yan等人，Nature 382:685-691(1996))，勃起机能障碍和牵涉肿瘤的侵入和转移(Taguchi等人，Nature 405:354-357(2000))。

[0006] 高级糖基化终产物(AGEs)涉牵各种障碍，包括与糖尿病和正常衰老相关的并发症。将蛋白质或脂质与醛糖糖类一起温育导致非酶的糖化和蛋白质上的氨基氧化，形成Amadori加合物。随着时间推移，这些聚合物进行另外的重排、脱水和与其它蛋白质交联，形成称作AGEs的复合物。促进AGEs形成的因素包括延迟的蛋白质转换(例如作为在淀粉样变性中)、具有高赖氨酸含量的大分子蓄积和高血糖水平(例如作为在糖尿病中)(Hori等人，J.Biol.Chem.270:25752-761,(1995))。

[0007] AGEs展示出与微脉管系统、单核细胞和巨噬细胞、平滑肌细胞、间质细胞和神经元的内皮细胞上的细胞表面受体的特异性和可饱和的结合。

[0008] 除AGEs以外，其它化合物可以结合到RAGE上并抑制生理配体与RAGE的相互作

用。在正常发育中，RAGE 与两性蛋白相互作用，两性蛋白是介导培养的胚胎神经元中轴突生长的多肽 (Hori 等人，(1995))。RAGE 也显示可与 EN-RAGE 相互作用，EN-RAGE 是基本相似于钙粒蛋白的蛋白质 (Hofmann 等人，(1999))。也已经表明，RAGE 可与 β-淀粉状蛋白相互作用 (Yan 等人，Nature 389:689-695(1997) ;Yan 等人，Nature 382:685-691(1996) ; Yan 等人，Proc. Natl. Acad. Sci, 94:5296-5301(1997))。

[0009] 配体如 AGEs、S100/ 钙粒蛋白 /EN-RAGE、β-淀粉状蛋白、CML(N ε-羧甲基赖氨酸)、和两性蛋白对 RAGE 的结合已经表明可用来改进各种基因的表达。例如，在 RAGE 和它的配体之间的许多细胞类型相互作用中，产生氧化应激，该氧化应激因此导致自由基敏感性转录因子 NF-κB 的活化和 NF-κB 调节基因，如细胞因子 IL-Iβ、TNF-a 等的活化。

[0010] 如上所述，RAGE 拮抗剂用于治疗糖尿病并发症。已经证实最终导致高级糖基化终产物 (AGEs) 形成的大分子的非酶糖基化在炎症部位上、在肾衰竭中、高血糖症和其它与全身或局部氧化性应激相关的病症的存在下得以增强 (Dyer, D 等人，J. Clin. Invest., 91:2463-2469(1993) ;Reddy, S. 等人，Biochem., 34:10872-10878(1995) ; Dyer, D. 等人，J. Biol. Chem., 266:11654-11660(1991) ;Degenhardt, T. 等人，Cell Mol. Biol, 44:1139-1145(1998))。AGEs 在脉管系统中蓄积可以在局部发生，如在具有与透析相关的淀粉样变性的患者中发现的 AGE-B2- 免疫球蛋白组成的关节淀粉样蛋白中 (Miyata, T 等人，J. Clin. Invest, 92:1243-1252(1993) ;Miyata, T 等人，J. Clin. Invest, 98:1088-1094(1996))，或一般以具有糖尿病的患者的脉管系统和组织为典型 (Schmidt, A-M 等人 Nature Med, 1:1002-1004(1995))。具有糖尿病的患者中 AGEs 随时间的推移的进行性蓄积启示内源性清除机制不能在 AGE 沉积部位上有效地起作用。这样蓄积的 AGEs 具有通过许多机制改变细胞特性的能力。尽管 RAGE 以低水平在正常组成和脉管系统中表达，但是在其中受体的配体蓄积的环境中，已经证实 RAGE 变成得到增量调节 (Li, J. 等人，J. Biol. Chem., 272:16498-16506(1997) ; Li, J. 等人，J. Biol. Chem., 273:30870-30878(1998) ;Tanaka, N. 等人，J. Biol. Chem,. 275:25781-25790(2000))。RAGE 表达在糖尿病单核吞噬细胞中的内皮、平滑肌细胞和浸润单核吞噬细胞中增加。此外，在细胞培养物中的研究已经证实 AGE-RAGE 相互作用导致血管内平衡中重要的细胞特性改变。

[0011] RAGE 拮抗剂还用于治疗淀粉样变性 (amyloidoses) 和 / 或阿尔茨海默病。RAGE 显然是细胞表面受体，该受体结合 β-折叠原纤维物质，与亚单位的组成无关 (淀粉样蛋白 -β 肽、Aβ、支链淀粉、血清淀粉样蛋白 A、朊病毒 - 衍生的肽)(Yan, S. -D. 等人., Nature, 382:685-691(1996) ;Yan, S-D 等人，Nat. Med, 6:643-651(2000))。已经证实淀粉样蛋白沉积导致 RAGE 表达增强。例如，在具有阿尔茨海默病的患者脑中，RAGE 表达在神经元和神经胶质中增加 (Yan, S. -D 等人 Nature 382:685-691(1996))。Aβ 与 RAGE 相互作用的结果显然在神经元与小神经胶质细胞上十分不同。而作为 Aβ-RAGE 相互作用的结果，小神经胶质细胞变活化，正如细胞因子运动性和表达增强所反映出的，早期 RAGE- 介导的神经元活化在随后的时间被细胞毒性取代 (superceded)。RAGE 在 Aβ 细胞相互作用中的作用的另外的证据涉及抑制 Aβ- 诱导的大脑血管收缩和在该受体被阻断时肽通过血脑屏障转移至脑实质 (Kumar, S 等人，Neurosci. Program, p141(2000))。已经证实抑制 RAGE- 淀粉样蛋白相互作用减少细胞 RAGE 和细胞应激标记表达 (以及 NF-kB 活化)，并且

减少淀粉样蛋白沉积 (Yan, S-D 等人 , Nat. Med, 6:643-651(2000)), 从而启示 RAGE- 淀粉样蛋白相互作用在为淀粉样蛋白富集的环境中细胞特性的干扰 (甚至在早期阶段) 以及在淀粉样蛋白蓄积中的作用。

[0012] 发明概述

[0013] 本发明提供了治疗轻度至中度阿尔茨海默病的方法, 通过对有此需要的受试者施用有效量的 [3-(4-{2- 丁基 -1-[4-(4- 氯 - 苯氧基)- 苯基]-1H- 咪唑 -4- 基 }- 苯氧基)- 丙基]- 二乙胺 (“化合物 I”) 或其药学上可接受的盐来进行。

[0014] 在一个实施方案中, 以小于 20mg/ 天的用量施用化合物 I 或其药学上可接受的盐。

[0015] 在另一个实施方案中, 以 1mg/5kg 受试者体重 / 天 — 1mg/50kg 受试者体重 / 天施用化合物 I 或其药学上可接受的盐。

[0016] 在另一个实施方案中, 本发明提供了抑制具有轻度至中度阿尔茨海默病的受试者的高级糖基化终产物受体 (RAGE) 与 RAGE 配体的相互作用的方法, 包含对有此需要的受试者施用小于 20mg/ 天的用量的化合物 I 或其药学上可接受的盐 .

[0017] 在另一个实施方案中, 本发明提供了治疗糖尿病的方法, 包含对有此需要的受试者施用小于 20mg/ 天的用量的化合物 I 或其药学上可接受的盐。

[0018] 本发明还提供了抑制与具有轻度至中度阿尔茨海默病的受试者的退化 (regression) 相关的葡萄糖代谢减少的方法, 包含对有此需要的受试者施用小于 20mg/ 天的用量的化合物 I 或其药学上可接受的盐。

[0019] 在另一个实施方案中, 本发明提供了降低受试者的血糖水平的方法, 包含对有此需要的受试者施用小于 20mg/ 天的用量的化合物 I 或其药学上可接受的盐。

[0020] 在另一个实施方案中, 本发明还提供了治疗失眠症的方法, 包含对有此需要的受试者施用小于 20mg/ 天的用量的化合物 I 或其药学上可接受的盐。

[0021] 在另一个实施方案中, 治疗失眠症的方法在具有轻度至中度阿尔茨海默病的受试者中进行。

[0022] 本发明还提供了减少睡眠起始潜伏期的方法, 包含对有此需要的受试者施用小于 20mg/ 天的用量的化合物 I 或其药学上可接受的盐。

[0023] 在另一个实施方案中, 治疗睡眠起始潜伏期的的方法在具有轻度至中度阿尔茨海默病的受试者中进行。

[0024] 在另一个实施方案中, 本发明提供了降低具有轻度至中度阿尔茨海默病的受试者的不良事件频率的方法, 包含对有此需要的受试者施用小于 20mg/ 天的用量的化合物 I 或其药学上可接受的盐。

[0025] 在任意上述实施方案的另一个实施方案中, 还可以施用适量的乙酰胆碱酯酶抑制剂 (AChEI) 或美金刚。

[0026] 本发明还提供了药物组合物, 其包含 1mg — 20mg 的化合物 I 或其药学上可接受的盐。

[0027] 在另一个实施方案中, 该药物组合物包括乙酰胆碱酯酶抑制剂 (AChEI)。

[0028] 在另一个实施方案中, 该药物组合物包括美金刚。

[0029] 附图简述

[0030] 图 1 展示对于安慰剂与使用 5mg 化合物 I 治疗之间小于或等于 22.8 的基线处得

到 ADAS-cog 评分的受试者 ADAS-cog 小组的从 ADAS-cog 中的基线改变的示意图。

[0031] 图 2 对于施用安慰剂的组和施用 5mg 化合物 I 的组的卡普兰 - 迈耶曲线，其中将事件定义为，对于目前具有低基线 ADAS-cog 的受试者小组在任意时间时获得的 ADAS-cog 增加为 7 点或 7 点以上，其中低是在最低 25％的研究群体中的受试者中。

[0032] 图 3 显示与施用的化合物 I 剂量无关的受试者的浓度 - 驱动分类的示意图。

[0033] 图 4 显示比较安慰剂治疗的受试者与研究中的受试者随时间变化的分布的示意图，所述研究测量的平均 pk 浓度在 8 — 15ng/ml 化合物 I。

[0034] 图 5a 显示对于 5mg 剂量组将浓度 (ng/ml) 与 BMI (kg/m^2) 回归的回归分析的示意图。

[0035] 图 5b 显示对于 20mg 剂量组将浓度 (ng/ml) 与 BMI (kg/m^2) 回归的回归分析的示意图。

[0036] 图 5c 显示对于 5mg 剂量组将浓度 (ng/ml) 与体重 (kg) 回归的回归分析的示意图。

[0037] 图 5d 显示对于 20mg 剂量组将浓度 (ng/ml) 与体重 (kg) 回归的回归分析的示意图。

[0038] 图 6a 显示从存在高葡萄糖值的受试者的葡萄糖基线的平均改变的示意图，其中将高定义为在基线处为 100mg/ml 或以上。注意与安慰剂比较排除了回归到平均值。

[0039] 图 6b 显示从存在高葡萄糖热值的受试者的葡萄糖基线的平均改变的示意图，其中将高定义为最高为在基线处的葡萄糖热值的三分之一 (33％)。注意与安慰剂比较排除了回归到平均值。

[0040] 图 6c 显示从存在高葡萄糖热值的受试者的葡萄糖基线的平均改变的示意图，其中将高定义为最高为在基线处的葡萄糖热值的 25％。注意与安慰剂比较排除了回归到平均值。

[0041] 图 6d 显示从存在正常或低葡萄糖热值的受试者的葡萄糖平均值的示意图，其中取小组作为在基线处的葡萄糖热值的下半部分 (50％) 中的所有受试者 (使用去掉中间值定义小组)。

[0042] 图 7- 显示使用剂量组的时间与特别关注的不良事件 (失落、精神混乱状态、嗜睡、头晕) 关系的卡普兰 - 迈耶曲线。

[0043] 图 8 显示使用浓度组的时间与特别关注的不良事件 (失落、精神混乱状态、嗜睡、头晕) 关系的卡普兰 - 迈耶曲线。

[0044] 详细描述

[0045] 本发明显示，具有轻度至中度阿尔茨海默病的受试者与安慰剂对比可以得益于使用化合物 I 的剂量依赖性治疗。此外，本发明显示，使用化合物 I 治疗可以降低葡萄糖水平并且可以抑制与具有轻度至中度阿尔茨海默病的受试者退化相关的葡萄糖代谢减少。另外，发明提供了治疗受试者、包括那些具有轻度至中度阿尔茨海默病的受试者的失眠症或睡眠起始潜伏期的方法，通过给受试者提供有效量的化合物 I 或其药学上可接受的盐来进行。

[0046] 本发明基于来自平行三 - 臂阶段 2 的研究结果，以便在具有轻度至中度阿尔茨海默病的受试者中评价与安慰剂对比两种剂量的化合物 I 的安全性、耐受性和效能。该研究在横跨美国的 40 个不同研究地点进行。

[0047] 在本发明的研究中，有 399 位受试者 (133 位 / 组)，将他们随机给予安慰剂或每日 20mg 施用的化合物 I(每日 60mg 的负荷剂量 6 天后) 或每日 5mg 施用的化合物 I(每日 15mg 的负荷剂量 6 天后)。

[0048] 研究探访在筛选、基线 (筛选后 4 周内)、然后是 4 周、3、6、9、12、15、18 个月时进行，其中在 21 个月时进行安全性随访。探访包括临床和安全性评价、为血浆生物标记和药代动力学分析的血液抽取和为评价依从性的药丸计数。在基线和随后 3 次每月探访时得到初步 (临床) 结果测量值，并且在基线和 6 个月间隔时得到二次临床结果测量值。在基线、12 和 18 个月时得到脑 MRIs。在基线和 12 个月时对 1 个小组的受试者进行用于 CSF 生物标记的腰椎穿刺术。

[0049] 关键合格标准包括年龄在 50 岁或以上、具有可能为阿尔茨海默病的诊断、具有 14 － 26 的细微精神状态检查 (MMSE) 评分并且是一般健康状况良好的受试者。受试者可以没有促成痴呆的中风证据。另外的选择标准包括在随机选择前使用稳定剂量的乙酰胆碱酯酶抑制剂和 / 或美金刚治疗至少 4 个月和有可利用的医疗护理提供者充当填报人的角色并且监督研究用药。淘汰标准包括不受控制的高血压、不稳定的心脏病或肺疾病、糖尿病、在过去的 2 年内体重低于 40kg 或 100kg 以上、长期应用非类固醇抗炎药或免疫抑制剂、增加 QTc 或抑制 CYP 34A 的药物、ECG 或 QTc(QTcB 或 QTcF) 显著异常或对于女性任意筛选 12- 导联 ECG 大于 450msec 或对于男性大于 430msec。此外，在过去 5 年内无癌症治疗、药物或酒精滥用或严重精神病史。女性不能有分娩可能性。在筛选前受试者不能服用另一种研究药物 3 个月。

[0050] 初步效能测量值为 70- 点 ADAS-cog。ADAS-cog 用于评价认知缺损的选择区域的严重性 (记忆力、语言、方向、推理和行为)。评分范围从 0 到 70，其中较低的评分表示严重性较低，而 70 的评分代表最为恶化的认知缺损。其在评价和接下来具有轻度至中度阿尔茨海默病的患者中的改变中的应用已经广泛地得到验证。初步安全性测量值包括不良事件报告、血尿检验和 ECG 测量值。二次临床测量值包括临床痴呆评级笔盒 (Clinical Dementia Rating Sum of Boxes)(CDR-sb) ；阿尔茨海默病协作研究日常生活能力量表 (Alzheimer's Disease Cooperative Study Activities of Daily Living Scale)(ADCS-ADL) ；神经精神量表 (Neuropsychiatric Inventory)(NPI) ；和 MMSE。受试者还接受一套神经心理测验，包括 ：数字符号替换测验 (Digit Symbol Substitution Test)、向前和向后数字广度测验 (Forward and Backward Digit Span Test)、对照口述语词联想试验 (Controlled Oral Word Association Test)、Stroop 色 - 词干扰测验 (Stroop Color Word interference Test) 和接龙试验 (Trail-Making Test)(A 和 B 部分)。医疗护理提供者接收生活质量调查表和资源利用计划表。

[0051] 在基线和 12 个月时，使用 1.5T 扫描器，使用基于 ADNI 研究中的那些的标准化获取参数进行脑 MRI，并且用于容量分析。通过在基线和 12 个月后进行腰椎穿刺术得到脑脊髓液，用于分析阿尔茨海默病 - 相关生物标记。进行载脂蛋白 E(APO-E) 基因分型，并且将 DNA 存库用于对所涉及的受试者进行药物基因组研究。在每次探访时检测血浆的研究药物水平并且储存用于生物标记研究。此外，在基线时进行完整的身体和神经系统检查，并且在随访时进行生命体征和简单检查。在每次探访时进行临床实验室研究和尿分析。在全部探访时得到心电图 (ECGs) 并且在中心读取 (由心脏病学家进行 QTc 分析)。由地点研究人员

根据严重性和因果关系分类不良事件并且使用标准方法报告给 ADCS 和资助人。如果受试者决定从本研究中退出或由地点研究人员中断，则早期的终止探访在 14 天内按照计划进行，包括与基线探访类似的临床和安全性评价。

[0052] 定义

[0053] 尽管本发明宽范围内举出的数值范围和参数是近似值，但是具体实施例中举出的数值可尽可能地以精确方式报道。然而，任意的数值自身因在其相应试验测量值中发现的标准偏差而导致必然包含误差。

[0054] 所谓重量百分比是指用组合物中的一种成分的具体重量除以该组合物中所有成分的总重。重量百分比可以互换地使用且是指与重量 / 重量百分比或％（重量 / 重量）或按质量计的百分比或质量百分比近似相同。

[0055] 还应注意，作为在本说明书中使用的，除非特别地和明确地限于一种指示物，否则单数形式 " 一种 (a)"、" 一种 (an)" 和 " 该 (the)" 包括复数指示物。

[0056] 在另一个实施方案中，化合物 I 或其药学上可接受的盐的剂量或血液水平可以是在以足够水平治疗阿尔茨海默病的足够时间下足以抑制 RAGE 的生物功能。

[0057] 化合物 I 是指 [3-(4-{2- 丁基 -1-[4-(4- 氯 - 苯氧基)- 苯基]-1H- 咪唑 -4- 基 }- 苯氧基)- 丙基]- 二乙胺。化合物 I 是美国专利 US7,361,678 和 US7,884,219 的主题。

[0058] 可以使用化合物 I 的不同盐和异构体。术语 " 盐 " 可以包括游离碱的酸加成盐或加成盐。可以用于形成药学上可接受的酸加成盐的酸的实例包括 :无机酸，例如盐酸、硫酸或磷酸 ;和有机酸，例如乙酸、马来酸、琥珀酸或柠檬酸等。可以通过常规方式制备所有这些盐（或其它类似的盐）。盐的性质并不关键，只要它是无毒性的且基本上不会干扰期望的药理学活性。用于本发明方法的优选盐是盐酸盐。

[0059] 术语 " 药学上可接受的 " 在与本发明组合物结合使用时是指这样的组合物的分子本体和其它成分，它们是生理学可耐受的且在施用于哺乳动物（例如人）时典型地不会产生不需要的反应（毒性或副作用）。优选地，本文所用的术语 " 药学上可接受的 " 是指由联邦或州政府管理局批准的或美国药典或用于哺乳动物且更具体地是用于人的一般公认的药典中列出的。Berge 等人 Journal of Pharmaceutical Science, Vol. 66(1), pp. 1-19(1977)。

[0060] 适用于本发明的药物组合物的术语 " 载体 " 是指与活性化合物（例如 1- 氨基环己烷衍生物）一起施用的稀释剂、赋形剂或媒介物。这样的药用载体可以是无菌液体，例如水、盐水溶液、葡萄糖水溶液、甘油水溶液和油，包括凡士林、动物、植物或合成来源的油，例如花生油、大豆油、矿物油、矿物油等。适合的药用载体描述在 E. W. Martin 的 "Remington's Pharmaceutical Sciences", 第 18 版中。

[0061] 本文所用的术语 " 受试者 " 或 " 有此需要的受试者 " 是指哺乳动物。在一个实施方案中，该术语是指被诊断为轻度至中度阿尔茨海默病的人。

[0062] " 轻度至中度阿尔茨海默病 " 可以通过诊断、根据神经和交流障碍和中风国家研究所 / 阿尔茨海默病和相关障碍协会 (National Institute of Neurological and Communicative Disorders and Stroke/the Alzheimer's Disease and Related Disorders Association)(NINCDS-ADRDA) 标准评价为 " 可能的阿尔茨海默病 "。

[0063] ″轻度至中度″的诊断充分属于使用标准依据的本领域普通技术人员的范围，包括上下文中公开的临床评价等级。作为实例，下列有关标准化细微精神状态检查（MMSE；0-30 等级）的数值范围已经用于诊断轻度至中度、中度和中度至重度阿尔茨海默病。

[0064] 在本研究中如通过 10 — 22 的 MMSE 评分并且还根据来自使用治疗轻度至中度阿尔茨海默病的其它治疗剂（例如多奈哌齐）的研究中的 10-26 所确定的诊断轻度至中度阿尔茨海默病。在具有小于 10 的 MMSE 评分的受试者中诊断严重阿尔茨海默病。

[0065] 因此，对于具有上述范围内的较高评分、例如 MMSE 上的约 21 — 26 的受试者诊断为″轻度″阿尔茨海默病。

[0066] 应注意，MMSE 等级并非诊断轻度阿尔茨海默病的唯一方式，而是代表一种便利性。也不应将权利要求视为需要使用所进行的 MMSE 分级对受试者″进行分级″的步骤。在一个实施方案中，如果该患者根据 MMSE 评分进行评分，具有轻度阿尔茨海默病的受试者是评分为 21 或以上的患者。如果使用不同的等级，则″轻度″阿尔茨海默病可以被定义为基于评分诊断为阿尔茨海默病或可能为阿尔茨海默病，所述评分显然不与为同一等级建立的中度至重度阿尔茨海默病的评分范围重叠。

[0067] 在一个实施方案中，将轻度阿尔茨海默病定义为具有小于或等于 23 的 ADAS-cog 评分的个体。

[0068] 术语“意向性治疗原则（intent to treat principle）”是指推定可以通过基于治疗受试者的意向（即计划的治疗方案）而不是实际给出的治疗方案评价来最佳地评价治疗方针的效果的原理。所产生的结果是应随访、评价和分析分入治疗组的作为该组成员的受试者，而与他们对计划的疗程的依从性无关。注意 ITT 原则是指一种方法（如何），而不是分析群体（是谁）。还应注意，ITT 分析一般被接受为最确实的分析，即它们得到随机选择的支持，且基于受试者行为特征排除受试者（例如与试验药物的依从性）与 ITT 原则不一致，因为得不到随机选择支持。还应注意，基于群体特征的小组分析（例如基线处的 AD 严重性）得到随机选择支持并且被视为是确实的。

[0069] 术语“全分析组（FAS）”是指尽可能地接近意向性治疗原则所指的理念的受试者组。它来源于通过最小化并且消除两端的受试者的全部随机选择的受试者组。FAS 包括接受至少一种剂量的试验药物并且具有至少一种基线后评价的全部受试者。FAS 的数据组包括无论是使用治疗还是脱离治疗的全部采集的数据（与治疗的依从性无关）。注意治疗中断后受试者的观察结果仍然包括在 ITT 纯分析中，认为所接受的、特别是使用具有长半衰期的化合物治疗影响治疗后采集的评价，与受试者是否仍然采取积极的疗法无关。

[0070] 术语“治疗中（on treatment）”是指在最终剂量的 28 天内采集的数据。首次剂量的试验药物治疗与最终剂量的试验药物治疗之间采集的全部数据以及在最终剂量的试验药物治疗的 28 天内采集的全部数据被视为治疗中。”

[0071] 术语“脱离治疗”是指在最终剂量的试验药物治疗后 29 天或之后的数据采集。

[0072] 术语“试验药物治疗”是指在无论是活性成分还是安慰剂的临床试验中的全盲式药物治疗。

[0073] 术语“基线后”是指在基线后采集的全部数据，与是在治疗中还是脱离治疗无关。

[0074] 术语“每一方案组（确认的病例，有效样本，可评价的受试者样本）”或“每一治疗组”是指依从所述方案的受试者小组生成的数据组，根据基础科学模型，足以确保这些数据

能够显示治疗作用。依从性覆盖例如暴露于治疗、测量值的可利用性和不存在主要的方案违背性这样的考量。注意每一治疗分析基于行为特征排除受试者并且一般得不到随机选择支持。这样的分析可能是有用的，但一般不与 ITT 分析同样确切。

[0075] 术语“统计学分析计划 (SAP)”是指包含在截断保护 α 之前计划的分析的文件。它更具有专业性且详细阐述了方案中描述的分析的主要特征，且包括用于执行主要和次要变量和其它数据的统计学分析的详细程序。SAP 一般是在截断前标记，并且在截断后修改 SAP，例如基于受试者的因果行为的未计划的分析（例如治疗依从性）。

[0076] 术语“失控”是指临床试验中因任何原因不能继续进行试验他 / 她需要根据研究方案进行最终探访的受试者。特别地，在这些研究中，受试者是失控的，此时该受试者的最后一次探访在第 18 个月之前进行。

[0077] 术语“治疗效果”是指归因于临床试验中治疗的效果。在大部分临床试验中，所关注的治疗效果是两种或多种治疗的对比（或差别）。注意治疗效果不包括安慰剂效果。随机化活性成分治疗组与安慰剂组之间的差别一般被视为对照临床试验中的治疗效果。

[0078] 术语“治疗突发事件”是指在未进行预治疗或相对于预治疗状态恶化的治疗过程中突发的观察结果或事件。

[0079] 术语“治疗突发不良事件”是指在首次剂量的试验药物（在首次剂量的试验药物之前不存在）后观察到或报告的任何不利事件或代表预先存在的病情加剧的任何不利事件。加剧包括严重性或频度的任何增加。

[0080] 术语“泛化、一般化”是指可以从参与本试验的受试者到更宽泛的患者群体和更宽泛的临床情况中合理地推断临床试验发现的程度。

[0081] 本文所用的术语 ″ 治疗 (treatment)″ 是指针对受试者所患有的指定病症或障碍的治疗全谱，包括缓解或改善因该障碍导致的症状的一种或多种，到延缓该障碍发作或进展。

[0082] 本文所用的术语 ″ 治疗 (treat)″ 是指减轻或缓解受试者的疾病的至少一种症状。例如，术语 ″ 治疗 ″ 可以包含减轻或缓解认知缺损（例如记忆力和 / 或方向受损）或总体功能缺损（日常生活活动）和 / 或减缓或逆转 ADL 中的进行性恶化或具有轻度至中度阿尔茨海默病的个体的认知缺损。

[0083] 在本发明含义范围内，术语 ″ 治疗 (treat)″ 还可以指延缓存在与阿尔茨海默病相关的另外的症状的患者的疾病进展，例如、但不限于使用上述定义的 ADAS-cog、MMSE、ADCS-ADL 标准、CDR-sb 或 NPI 总体标准的一种或多种鉴定的那些。本文所用的术语 ″ 延缓进展 ″ 是指与未治疗的受试者相比比预期的受试者疾病的发展或持续或恶化减缓。例如，可以通过与未治疗的患者（代表预期的疾病进展）中的那些措施相比，得到比例如在治疗患者中的认知性能措施中的预期的恶化减缓，确定针对阿尔茨海默病的这种延缓进展。可以使用例如阿尔茨海默病评定量表 (Alzheimer's Disease Assessment Scale(ADAS-cog) 或阿尔茨海默病协同研究 - 日常生活活动 (Alzheimer's Disease Cooperative Study-Activities of Daily Living)(ADCS-ADL) 确定认知性能。例如，具有轻度阿尔茨海默病的受试者中的典型疾病进展在约 6 个月的时间期限内在 ADAS-cog 上有约 1 一约 3 个点的增加。然而，疾病进展是高度个体化的且还依赖于例如患者初始病情这样的因素。

[0084] 在一个具体的实施方案中，术语 ″ 治疗 ″ 还可以指增加具有轻度至中度阿尔茨海

默病的患者的葡萄糖代谢率或抑制代谢率的进一步下降，这与退化（regression）相关。还可以通过比较治疗患者中的葡萄糖代谢与未治疗患者中的葡萄糖代谢评价这一点。与未治疗患者相比治疗患者中的葡萄糖代谢下降的减少或比治疗患者中预期的葡萄糖代谢下降减慢或稳定预示伴随治疗的有益性。

[0085] 在另一个具体的实施方案中，术语“治疗”还可以指改善与具有轻度至中度阿尔茨海默病的患者中的失眠症或睡眠起始潜伏期相关的症状，这与退化相关。

[0086] 本文所用的术语＂治疗有效量＂是指有效地改善或延缓与轻度至中度阿尔茨海默病相关的症状、行为或事件的化合物 I 的用量或剂量。或者，治疗有效量足以导致有此需要的个体中与阿尔茨海默病相关的临床显著的情况或参数改善（根据使用上述标准组的一种或多种的主治医师的判断）。在另一个实施方案中，本文所用的治疗有效量表示所寻求的引起受试者治疗应答的化合物 I 或其药学上可接受的盐的用量。在一个实施方案中，治疗应答可以是拮抗 RAGE。

[0087] 将＂应答者＂定义为未进展且 ADAS-cog 中从基线至 18 个月的改变小于或等于 7 的患者。

[0088] 术语＂约＂和＂近似地＂一般应指对于指定测量值的性质或精确度确定的用量的可接受的误差或变异程度。典型地，误差或变异程度在指定数值或数值范围的 20 百分比（％）、优选 10％且更优选在 5％范围内。除非另有描述，否则本文给出的数量是近似值，即，如果没有特别地描述，则可以推定术语＂约＂或＂近似地＂。

[0089] 制剂、剂量和施用

[0090] 本发明还提供了包含化合物 I 的化合物或其药学上可接受的盐和药学上可接受的载体的药物组合物。本文所用的术语＂药物组合物＂表示可以施用于哺乳动物宿主的组合物，例如通过口服、局部、胃肠外、通过吸入喷雾剂或通过直肠，以包含常用无毒性载体、稀释剂、佐剂、媒介物等的单位剂型的形式。本文所用的术语＂胃肠外＂包括皮下注射、静脉内、肌内、胸骨内注射（intraci sternal）或通过输注技术。

[0091] 包含本发明化合物的药物组合物可以是适合于口服应用的形式，例如，为片剂、药片、锭剂、水或油混悬液、可分散粉末或颗粒、乳剂、硬胶囊或软胶囊或糖浆剂或酏剂。

[0092] 欲用于口服应用的组合物可以根据任意公知方法制备且这样的组合物可以包含选自甜味剂、矫味剂、着色剂和防腐剂的一种或多种试剂，以便提供药学上美观和适口的制剂。片剂可以包含活性成分与适合于制备片剂的无毒性药学上可接受的赋形剂的混合物。这些赋形剂可以是，例如惰性稀释剂，例如碳酸钙、碳酸钠、乳糖、磷酸钙或磷酸钠；成粒剂和崩解剂，例如玉米淀粉或藻酸；粘合剂，例如淀粉、明胶或阿拉伯胶；和润滑剂，例如硬脂酸镁、硬脂酸或滑石粉。片剂可以是不包衣的或可以通过公知技术将它们包衣，以延缓在胃肠道中崩解和吸收，且由此在较长期限内提供持续作用。例如，可以使用延时材料，例如单硬脂酸甘油酯或二硬脂酸甘油酯。还可以通过美国专利 US 4,356,108；和 US4,265,874 中所述的技术将它们包衣，以形成用于控释的渗透治疗片剂。

[0093] 还可以将用于口服应用的制剂制成硬胶囊，其中将活性成分与惰性固体稀释剂例如碳酸钙、磷酸钙或高岭土混合；或制成软胶囊，其中将活性成分与水或油介质例如花生油、液体石蜡或橄榄油混合。

[0094] 水性混悬液可以包含活性化合物与适合于制备水性混悬液的赋形剂的混合物。这

样的赋形剂是助悬剂，例如羧甲基纤维素钠、甲基纤维素、羟丙基甲基纤维素、藻酸钠、聚乙烯吡咯烷酮、黄蓍树胶和阿拉伯树胶；分散剂或湿润剂可以是天然存在的磷脂，例如卵磷脂或烯化氧与脂肪酸的缩合产物，例如聚氧乙烯硬脂酸酯；或环氧乙烷与长链脂族醇的缩合产物，例如十七乙烯氧基鲸蜡醇；或环氧乙烷与衍生自脂肪酸和己糖醇的偏酯的缩合产物，例如聚氧乙烯山梨醇单油酸酯；或环氧乙烷与衍生自脂肪酸和己糖醇酸酐的偏酯的缩合产物，例如聚乙烯脱水山梨糖醇单油酸酯。水性混悬液还可以包含一种或多种着色剂、一种或多种矫味剂和一种或多种甜味剂，例如蔗糖或糖精。

[0095] 可以通过将活性成分混悬于植物油例如花生油、橄榄油、芝麻油或矿物油例如液体石蜡配制油性混悬液。油性混悬液可以包含增稠剂，例如蜂蜡、硬石蜡或鲸蜡醇。可以加入例如上述举出的那些甜味剂和环烷基，以提供适口的口服制剂。可以通过添加抗氧化剂例如抗坏血酸对这些组合物防腐。

[0096] 适合于通过添加水制备水性混悬液的可分散粉末和颗粒提供了活性化合物于分散剂或湿润剂、助悬剂和一种或多种防腐剂的混合物。适合的分散剂或湿润剂以上述已经举出的那些为示例。还可以存在另外的赋形剂，例如甜味剂、矫味剂和着色剂。

[0097] 本发明的药物组合物还可以是水包油型乳剂形式。油相可以是植物油，例如橄榄油或花生油或矿物油，例如液体石蜡或其混合物。适合的乳化剂可以是天然存在的树胶，例如阿拉伯树胶或黄蓍树胶；天然存在的磷脂类，例如大豆、卵磷脂和衍生自脂肪酸和己糖醇酸酐的酯或偏酯，例如去水山梨糖醇单油酸酯；和所述偏酯于环氧乙烷的缩合产物，例如聚氧乙烯脱水山梨糖醇单油酸酯。乳剂还可以包含甜味剂和矫味剂。

[0098] 可以用甜味剂例如甘油、病二醇、山梨醇或蔗糖配制糖浆剂和酏剂。这样的制剂还可以包含缓和剂、防腐剂和矫味剂和着色剂。药物组合物可以是无菌可注射水或油混悬液的形式。可以根据公知方法、使用适合的分散剂或湿润剂和上述助悬剂配制这种混悬液。无菌可注射制剂还可以是在无毒性胃肠外可接受的稀释剂或溶剂中的无菌可注射溶液或混悬液，例如，为在1,3-丁二醇中的溶液。在可接受的媒介物和溶剂中，可以使用的有林格液和等渗氯化钠溶液。此外，可以将无菌的固定油便利地用作溶剂或助悬介质。为了这一末端，可以使用合成的单酸甘油酯类或二脂酰甘油酯类应用任意温和的固定油。此外，脂肪酸例如油酸应用于制备可注射制剂。

[0099] 组合物还可以是用于本发明化合物直肠施用的栓剂形式。可以通过混合药物于适合的无刺激性赋形剂制备这些组合物，其在常温下为固体，而在直肠温度下为液体，且由此可以在直肠中熔化以释放药物。例如，这样的材料包括可可脂和聚乙二醇。

[0100] 对于局部应用而言，关注包含本发明化合物的霜剂、软膏剂、凝胶剂、溶液或混悬液、洗剂、眼膏剂和滴眼液或滴耳剂、浸渍的敷料和气雾剂等。这些局部用制剂可以包含适合的常用添加剂，例如防腐剂、辅助药物渗透的溶剂和在软膏剂和霜剂中的软化剂。这些制剂还可以包含相容性常用载体，例如霜剂或软膏剂基质和用于洗剂的乙醇或油醇。这样的载体可以以占制剂约.1%—约99%存在。更通常地，其构成制剂的至多约80%。为了这一应用目的，局部施用应包括口腔洗剂和含漱液。

[0101] 为了通过吸入施用，便利地以气雾剂形式从加压药包或喷雾器中递送本发明的化合物，其中使用适合的抛射剂，例如二氯二氟甲烷、三氯氟甲烷、二氯四氟乙烷、四氟乙烷、七氟丙烷、二氧化碳或其它适合的气体。

[0102] 在加压气雾剂的情况中，可以通过安装阀门以递送计量的用量确定剂量单位。可以配制包含本发明化合物和适合的粉末基质例如乳糖或淀粉的粉末混合物的例如用于吸入器或吹入器的明胶胶囊和药筒。

[0103] 下列制备描述中列出的设备和参数是可以用于制备药物制剂的设备和参数的代表。用于制备药物制剂的实际设备和参数可变。

[0104] 可以将化合物（游离碱形式）过筛并且于近似等量的微晶纤维素一起称出。以几何学方式用微晶纤维素稀释该混合物。可以将该混合物、任意其余的微晶纤维素、一水合乳糖、交联羧甲基纤维素钠、胶体二氧化硅和淀粉 1500 加入到搅拌机中并且混合。可以取出少部分混合物，与硬脂酸镁合并，并且返回到搅拌机中且混合。可以包囊得到的混合物并且施用。可以调整化合物、微晶纤维素和 / 或一水合乳糖的重量百分比，以制备具有较高或较低用量化合物的剂量。例如，下表中的配方 A 可以用于制备 5mg/ 剂量的胶囊剂，而配方 B 可以用于制备 20mg/ 剂量的胶囊剂。

[0105]

成分名称	配方 A (wt%)	配方 B (wt%)
化合物(游离碱)	2.4	9.5
微晶纤维素	54.2	50.6
一水合乳糖	27.9	24.4
预胶化淀粉	8.0	8.0
交联羧甲基纤维素钠	6.4	6.4
胶体二氧化硅	0.4	0.4
硬脂酸镁	0.8	0.8

[0106] 在一个实施方案中，治疗阿尔茨海默病的方法包含对有此需要的受试者施用小于 20mg/ 天的用量的化合物 I 或其药学上可接受的盐。可以以约 1mg/ 天一小于 20mg/ 天范围的剂量施用化合物 I 或其药学上可接受的盐。在一些实施方案中，所述剂量约为 1mg/ 天一约 19mg/ 天、或约 1mg/ 天一约 18mg/ 天、或约 1mg/ 天一约 17mg/ 天、或约 1mg/ 天一约 16mg/ 天、或约 1mg/ 天一约 15mg/ 天、或约 1mg/ 天一约 14mg/ 天、或约 1mg/ 天一约 13mg/ 天、或约 1mg/ 天一约 12mg/ 天、或约 1mg/ 天一约 11mg/ 天、或约 1mg/ 天一约 10mg/ 天、或约 1mg/ 天一约 9mg/ 天、或约 1mg/ 天一约 8mg/ 天、或约 1mg/ 天一约 7mg/ 天、或约 1mg/ 天一约 6mg/ 天、或约 1mg/ 天一约 5mg/ 天、或约 1mg/ 天一约 4mg/ 天、或约 1mg/ 天一约 3mg/ 天、或约 1mg/ 天一约 2mg/ 天。在其它实施方案中，所述剂量约为 5mg/ 天或约 4mg/ 天或约 3mg/ 天或约 2mg/ 天。

[0107] 在一些实施方案中，化合物 I 或其药学上可接受的盐在受试者中的血清浓度约为 1ng/ml 一约 65ng/ml、或约 1ng/ml 一约 60ng/ml、或约 1ng/ml 一约 55ng/ml、或约 1ng/ml 一约 50ng/ml、或约 1ng/ml 一约 45ng/ml、或约 1ng/ml 一约 40ng/ml、或约 1ng/ml 一约 35ng/

ml、或约 1ng/ml 一约 30ng/ml、或约 1ng/ml 一约 25ng/ml、或约 1ng/ml 一约 20ng/ml、或约 1ng/ml 一约 15ng/ml、或约 1ng/ml 一约 10ng/ml。在其它实施方案中，在受试者中的血清浓度为 8 一约 15ng/ml。在其它实施方案中，在受试者中的血清浓度约为 12.5ng/ml。

[0108] 在另一个实施方案中，根据在选自如下的评价的至少一种中的改善或无恶化或恶化速率降低确定治疗阿尔茨海默病的方法：阿尔茨海默病评价量表 - 认知分量表 (ADAS-cog)；临床痴呆评级笔盒 (CDR-sb)；阿尔茨海默病协作研究日常生活能力量表 (ADCS-ADL)；神经精神量表 (NPI)；和细微精神状态检查 (MMSE)。在一些实施方案中，治疗导致 ADAS-cog 评分中的恶化速率降低。在其它实施方案中，治疗导致 ADAS-cog 评分的恶化速率平均降低 2 一 5 个点。

[0109] 在其它实施方案中，治疗阿尔茨海默病的方法包含对有此需要的受试者施用 1mg/5kg 受试者体重 / 天一 1mg/50kg 受试者体重 / 天的用量的化合物 I 或其药学上可接受的盐。施用化合物 I 或其药学上可接受的盐的施用量约为 1mg/10kg/ 天或 1mg/15kg/ 天或 1mg/20kg/ 天或 1mg/25kg/ 天或 1mg/30kg/ 天或 1mg/35kg/ 天或 1mg/40kg/ 天或 1mg/45kg/ 天。在其它实施方案中，化合物 I 或其药学上可接受的盐的施用量为 1mg/20kg/ 天。在其它实施方案中，化合物 I 或其药学上可接受的盐的施用量约为 0.2mg/kg/ 天一 0.02mg/kg/ 天。在其它实施方案中，化合物 I 或其药学上可接受的盐的施用量约为 0.1mg/kg/ 天或约 0.09mg/kg/ 天或约 0.08mg/kg/ 天或约 0.07mg/kg/ 天或约 0.06mg/kg/ 天或约 0.05mg/kg/ 天或约 0.04mg/kg/ 天或约 0.03mg/kg/ 天。

[0110] 在一些实施方案中，提供了抑制具有轻度至中度阿尔茨海默病的受试者的高级糖基化终产物 (RAGE) 的受体与 RAGE 配体相互作用的方法，通过对有此需要的受试者施用小于 20mg/ 天的用量的化合物 I 或其药学上可接受的盐来进行。在一个实施方案中，RAGE 配体可以是可溶性 β - 淀粉样蛋白、不溶性 β - 淀粉样蛋白、s100b, 钙粒蛋白、EN-RAGE、HMGB1 (高速泳动族框 1)、aphoterin 或羧甲基赖氨酸之一。化合物 I 或其药学上可接受的盐的施用剂量范围约为 1mg/ 天一小于 20mg/ 天。在一些实施方案中，所述剂量约为 1mg/ 天一约 19mg/ 天、或约 1mg/ 天一约 18mg/ 天、或约 1mg/ 天一约 17mg/ 天、或约 1mg/ 天一约 16mg/ 天、或约 1mg/ 天一约 15mg/ 天、或约 1mg/ 天一约 14mg/ 天、或约 1mg/ 天一约 13mg/ 天、或约 1mg/ 天一约 12mg/ 天、或约 1mg/ 天一约 11mg/ 天、或约 1mg/ 天一约 10mg/ 天、或约 1mg/ 天一约 9mg/ 天、或约 1mg/ 天一约 8mg/ 天、或约 1mg/ 天一约 7mg/ 天、或约 1mg/ 天一约 6mg/ 天、或约 1mg/ 天一约 5mg/ 天、或约 1mg/ 天一约 4mg/ 天、或约 1mg/ 天一约 3mg/ 天、或约 1mg/ 天一约 2mg/ 天。在其它实施方案中，所述剂量约为 5mg/ 天或约 4mg/ 天或约 3mg/ 天或约 2mg/ 天。

[0111] 在一个实施方案中，施用化合物 I 或其药学上可接受的盐治疗轻度阿尔茨海默病。在一些实施方案中，可以将轻度阿尔茨海默病定义为存在 ADAS-cog 评分小于或等于 23 的受试者。

[0112] 在其它实施方案中，用化合物 I 或其药学上可接受的盐治疗用于治疗糖尿病，通过对有此需要的受试者施用小于 20mg/ 天的用量来进行。在其它实施方案中，化合物 I 或其药学上可接受的盐的施用剂量约为 1 一约 20mg/ 天。化合物 I 或其药学上可接受的盐的施用剂量范围可以约为 1mg/ 天一小于 20mg/ 天。在一些实施方案中，所述剂量约为 1mg/ 天一约 19mg/ 天、或约 1mg/ 天一约 18mg/ 天、或约 1mg/ 天一约 17mg/ 天、或约 1mg/ 天一约

16mg/ 天、或约 1mg/ 天一约 15mg/ 天、或约 1mg/ 天一约 14mg/ 天、或约 1mg/ 天一约 13mg/ 天、或约 1mg/ 天一约 12mg/ 天、或约 1mg/ 天一约 11mg/ 天、或约 1mg/ 天一约 10mg/ 天、或约 1mg/ 天一约 9mg/ 天、或约 1mg/ 天一约 8mg/ 天、或约 1mg/ 天一约 7mg/ 天、或约 1mg/ 天一约 6mg/ 天、或约 1mg/ 天一约 5mg/ 天、或约 1mg/ 天一约 4mg/ 天、或约 1mg/ 天一约 3mg/ 天、或约 1mg/ 天一约 2mg/ 天。在其它实施方案中，所述剂量约为 5mg/ 天或约 4mg/ 天或约 3mg/ 天或约 2mg/ 天。在其它实施方案中，该方法包括治疗具有轻度至中度阿尔茨海默病的患者的糖尿病。

[0113] 在一些实施方案中，施用化合物 I 或其药学上可接受的盐可以降低有此需要的受试者的 HbA1C 水平。在其它实施方案中，施用化合物 I 或其药学上可接受的盐可以将有此需要的受试者的 HbA1C 的量降低至少 0.1 个百分点或 0.2 个百分点或 0.3 个百分点或 0.4 个百分点或 0.5 个百分点或 0.6 个百分点或 0.7 个百分点或 0.8 个百分点或 0.9 个百分点或 1 个百分点。在其它实施方案中，施用化合物 I 或其药学上可接受的盐可以将有此需要的受试者的 HbA1C 水平降低至 7% 以下。在其它实施方案中，HbA1C 水平可以降至 5 — 6.5% 的水平。

[0114] 在一些实施方案中，本发明提供了抑制与具有轻度至中度阿尔茨海默病的受试者的退化 (regression) 相关的葡萄糖代谢减少的方法，通过对有此需要的受试者施用小于 20mg/ 天的用量的化合物 I 或其药学上可接受的盐来进行。化合物 I 的施用剂量范围可以约为 1mg/ 天一小于 20mg/ 天。在一些实施方案中，所述剂量约为 1mg/ 天一约 19mg/ 天、或约 1mg/ 天一约 18mg/ 天、或约 1mg/ 天一约 17mg/ 天、或约 1mg/ 天一约 16mg/ 天、或约 1mg/ 天一约 15mg/ 天、或约 1mg/ 天一约 14mg/ 天、或约 1mg/ 天一约 13mg/ 天、或约 1mg/ 天一约 12mg/ 天、或约 1mg/ 天一约 11mg/ 天、或约 1mg/ 天一约 10mg/ 天、或约 1mg/ 天一约 9mg/ 天、或约 1mg/ 天一约 8mg/ 天、或约 1mg/ 天一约 7mg/ 天、或约 1mg/ 天一约 6mg/ 天、或约 1mg/ 天一约 5mg/ 天、或约 1mg/ 天一约 4mg/ 天、或约 1mg/ 天一约 3mg/ 天、或约 1mg/ 天一约 2mg/ 天。

[0115] 在其它实施方案中，所述剂量约为 5mg/ 天或约 4mg/ 天或约 3mg/ 天或约 2mg/ 天。在其它实施方案中，施用化合物 I 或其药学上可接受的盐用于降低血糖水平。在其它实施方案中，受试者患有轻度至中度阿尔茨海默病。在其它实施方案中，受试者血糖水平降低了至少 5mg/dl、或至少 10mg/dl、或至少 15mg/dl、或至少 20mg/dl 或 5mg/dl — 20mg/dl。在其它实施方案中，受试者初次 (naive) 血糖水平高于 100ng/dl。

[0116] 在其它实施方案中，施用化合物 I 或其药学上可接受的盐用于治疗失眠症，通过对有此需要的受试者施用小于 20mg/ 天的用量的化合物 I 或其药学上可接受的盐来进行。化合物 I 的施用剂量范围可以约为 1mg/ 天一小于 20mg/ 天。在一些实施方案中，所述剂量约为 1mg/ 天一约 19mg/ 天、或约 1mg/ 天一约 18mg/ 天、或约 1mg/ 天一约 17mg/ 天、或约 1mg/ 天一约 16mg/ 天、或约 1mg/ 天一约 15mg/ 天、或约 1mg/ 天一约 14mg/ 天、或约 1mg/ 天一约 13mg/ 天、或约 1mg/ 天一约 12mg/ 天、或约 1mg/ 天一约 11mg/ 天、或约 1mg/ 天一约 10mg/ 天、或约 1mg/ 天一约 9mg/ 天、或约 1mg/ 天一约 8mg/ 天、或约 1mg/ 天一约 7mg/ 天、或约 1mg/ 天一约 6mg/ 天、或约 1mg/ 天一约 5mg/ 天、或约 1mg/ 天一约 4mg/ 天、或约 1mg/ 天一约 3mg/ 天、或约 1mg/ 天一约 2mg/ 天。在其它实施方案中，所述剂量约为 5mg/ 天或约 4mg/ 天或约 3mg/ 天或约 2mg/ 天。在其它实施方案中，来自失眠症的受试者患有轻度至中

度阿尔茨海默病。在其它实施方案中，施用化合物 I 或其药学上可接受的盐用于减少睡眠起始潜伏期。在其它实施方案中，具有睡眠起始潜伏期的受试者还具有轻度至中度阿尔茨海默病。在另一个实施方案中，睡眠起始潜伏期减少了 1-5 分钟或 5-10 分钟。

[0117] 在一些实施方案中，使用化合物 I 或其药学上可接受的盐治疗降低了具有轻度至中度阿尔茨海默病的受试者的不良事件频率。在一些实施方案中，所述不良事件包括失落、头晕、精神混乱状态和嗜睡。在其它实施方案中，所述不良事件可以是精神病的不良事件。精神病不良事件可以包括激动、抑郁症、焦虑、攻击行为和多动。化合物 I 或其药学上可接受的盐的施用剂量范围可以约为 1mg/ 天－小于 20mg/ 天。在一些实施方案中，所述剂量约为 1mg/ 天－约 19mg/ 天、或约 1mg/ 天－约 18mg/ 天、或约 1mg/ 天－约 17mg/ 天、或约 1mg/ 天－约 16mg/ 天、或约 1mg/ 天－约 15mg/ 天、或约 1mg/ 天－约 14mg/ 天、或约 1mg/ 天－约 13mg/ 天、或约 1mg/ 天－约 12mg/ 天、或约 1mg/ 天－约 11mg/ 天、或约 1mg/ 天－约 10mg/ 天、或约 1mg/ 天－约 9mg/ 天、或约 1mg/ 天－约 8mg/ 天、或约 1mg/ 天－约 7mg/ 天、或约 1mg/ 天－约 6mg/ 天、或约 1mg/ 天－约 5mg/ 天、或约 1mg/ 天－约 4mg/ 天、或约 1mg/ 天－约 3mg/ 天、或约 1mg/ 天－约 2mg/ 天。在其它实施方案中，所述剂量约为 5mg/ 天或约 4mg/ 天或约 3mg/ 天或约 2mg/ 天。

[0118] 在任意上述实施方案中，施用化合物 I 或其药学上可接受的盐还可以额外包括使用乙酰胆碱酯酶抑制剂 (AChEI) 治疗。所述 AChEI 可以包括盐酸多奈哌齐 (donepezil)、盐酸加兰他敏 (galantamine)、酒石酸利伐斯的明 (rivastigmine) 或盐酸他克林 (tacrine)。在其它实施方案中，施用化合物 I 或其药学上可接受的盐还可以包括施用美金刚治疗。在一些实施方案中，受试者在施用化合物 I 或其药学上可接受的盐前已经接受使用 AChEI 或美金刚治疗至少 4 个月。

[0119] 本发明的另一个实施方案包括药物组合物，其包括 1mg － 20mg 的化合物 I 或其药学上可接受的盐和 AChEI。在其它实施方案中，该药物组合物可以包括 1mg － 20mg 的化合物 I 或其药学上可接受的盐和美金刚。所述 AChEI 可以包括盐酸多奈哌齐、盐酸加兰他敏、酒石酸利伐斯的明或盐酸他克林。在一些实施方案中，所述 AChEI 是盐酸多奈哌齐，其存在量为 5mg － 23mg。在其它实施方案中，所述 AChEI 是盐酸加兰他敏，其存在量为 16mg － 24mg。在其它实施方案中，所述 AChEI 为酒石酸利伐斯的明，其存在量为 6mg － 12mg。在其它实施方案中，所述 AChEI 为盐酸他克林，其存在量为 40mg。在其它实施方案中，美金刚以 5mg － 20mg 存在。所述药物组合物可以包括约 1mg/ 天－约 19mg/ 天、或约 1mg/ 天－约 18mg/ 天、或约 1mg/ 天－约 17mg/ 天、或约 1mg/ 天－约 16mg/ 天、或约 1mg/ 天－约 15mg/ 天、或约 1mg/ 天－约 14mg/ 天、或约 1mg/ 天－约 13mg/ 天、或约 1mg/ 天－约 12mg/ 天、或约 1mg/ 天－约 11mg/ 天、或约 1mg/ 天－约 10mg/ 天、或约 1mg/ 天－约 9mg/ 天、或约 1mg/ 天－约 8mg/ 天、或约 1mg/ 天－约 7mg/ 天、或约 1mg/ 天－约 6mg/ 天、或约 1mg/ 天－约 5mg/ 天、或约 1mg/ 天－约 4mg/ 天、或约 1mg/ 天－约 3mg/ 天、或约 1mg/ 天－约 2mg/ 天的化合物 I。

[0120] 在其它实施方案中，使用化合物 I 或其药学上可接受的盐治疗减少了在脑脊髓液 (CSF) 中发现的可溶性 Aβ 的量。在一些实施方案中，Aβ 的可溶性形式为同种型 1-40。在其它实施方案中，Aβ 的可溶性形式为同种型 1-42。在其它实施方案中，Aβ 的可溶性形式为同种型 1-38。在其它实施方案中，使用化合物 I 或其药学上可接受的盐治疗改变了 CSF

中同种型 1-40 与同种型 1-42 的量之间的比例。

[0121] 在一些实施方案中，观察结果为，当 20-mg- 剂量组中的受试者中断治疗时，其 ADAS-cog 评分显示改善。众所周知阿尔茨海默病是变性疾病，且患者无法自主缓和。探索分析证实使用 20mg 化合物 I 治疗的受试者在终点探访（停止治疗后）时显示从基线改变，这些改变优于安慰剂组中从基线的改变。这一发现与化合物 I 对患者的潜在疾病状态具有有益作用的推断一致。与较高浓度化合物 I 相关的症状可能掩蔽了所述改善，而当药物浓度降至更有益的范围时，治疗的有益作用可以突显。

实施例

[0122] 实施例 1

[0123] 评价具有轻度至中度阿尔茨海默病的参与者中使用化合物 I 治疗 18 个月的效能和安全性的双盲、安慰剂对照、随机选择的多中心研究

[0124] 使用三臂设计本研究：60mg/ 天的负荷剂量持续 6 天后 20mg/ 天；15mg/ 天的负荷剂量持续 6 天后 5mg/ 天；和安慰剂。本研究以平衡比例 (1:1:1) 随机选择具有轻度 - 中度阿尔茨海默病的 N = 399 患者。20-mg- 剂量组在间断分析时终止。随后基于在原始方案中计划的无用分析提早终止本研究。

[0125] 本研究的统计学分析包括在方案和统计学分析计划中计划的分析且还包括探查和研究分析。在患者的研究治疗的终止后，指示该患者继续参与研究探访并且持续采集数据。统计学分析包括数据组，其包括全部可得到的数据（治疗中和脱离治疗）和治疗中数据，其中将“治疗中”定义为在最终剂量当日的 28 天内。脱离治疗数据反映出根据随机选择方案指定的治疗；因此，基于随机选择群体并且遵循意向性原则的治疗中和脱离治疗分析是有效的。

[0126] 统计学分析比较了 5-mg- 剂量组 (n = 131；平均年龄 = 74 岁；53% 女性）与安慰剂组 (n = 132；平均年龄 = 72 岁；57% 女性）。不完全研究中的失控率对于 5mg 化合物 I 和安慰剂分别为 48% 和 52%。使用针对具有治疗中数据的全部随机选择的患者的末次观测值转结 (last-observation-carried-forward) 对 ADAS-cog 中从基线到终点进行标准意向性治疗进行协方差分析（针对基线调整），导致最小二乘法平均值为 6.4 和 8.7（标称 p = 0.03）。对于施用 5mg 化合物 I 和安慰剂的组的从基线的实际改变平均值分别为 6.59 (SD = 7.91) 和 9.00 (SD = 9.21)。未调整的分析同样产生了标称 p = 0.03，有利于使用 5mg 化合物 I 治疗。

[0127] 对通过探访观察的病例、ADAS-cog 中从基线的改变百分比和显示 ADAS-cog 中增加为 7 或 7 以上点（应答者分析）的患者比例的另外的分析同样具有标称 p- 值，这使得在趋势水平上 5-mg 化合物 I 优于安慰剂或更佳。

[0128] 下表概括了计划的效能分析，将其命名为初步和支持性分析，以确保初步分析结论的可靠。这些分析是在本研究方案中计划的，在统计学分析计划中计划的，并且遵循 ICH E9 中所述的意向性原则。有关 18 个月时 ADAS-cog 的关键结果概述如下：

[0129] 表 1：研究方案中所述的计划的 ITT 统计学分析概述

[0130]

分析	统计	治疗组		统计学分析	
		5-mg 剂量化合物 I	安慰剂	方法	p-值
方案中所述的初步分析和 SAP: mITT 报告编号: 2011-06-23-001	样本大小	69	68	具有 MI 对策的 ANCOVA (方案中的初步值和 SAP)	0.008
	到第 18 个月的改变平均值	8.84	11.94	完全病例 ANCOVA	0.02

[0131]

	到第 18 个月的改变中间值	6.76	10.34	LOCF ANCOVA	0.03
	平均值的 δ	3.1		GEE	0.03
	中间值的 δ	3.58		混合模型重复测量值(随机效应)	0.04

[0132] 实施例 2

[0133] 基于基线处的 ADAS-cog,在严重性较低的阿尔茨海默病患者中的药物效果比在严重性较高的阿尔茨海默病患者中更显著

[0134] 进入本研究基于 MMSE ;基于 ADAS-cog 不存在合格标准。因果分析检验了具有比其他个体更显著有益性的个体的特征。判别分析启示一些患者小组对化合物 I 的应答优于其他小组患者。

[0135] 对分析的观察结果揭示出研究中阿尔茨海默病严重性较低的患者显示,基于 ADAS-cog,来自安慰剂的示意图优于进入时具有更严重疾病的那些。

[0136] 图 1 展示出在基线处 ADAS-cog 评分小于或等于 23 的受试者小组的 ADAS-cog 中从基线的改变。

[0137] 存在轻度痴呆的使用安慰剂治疗的受试者 (虚线) 显示 ADAS-cog 中从基线更大的增加,表明阿尔茨海默病的恶化比例高于存在轻度阿尔茨海默病的使用 5-mg 化合物 I 治疗的受试者 (实线)。样本大小随时间改变,因为患者脱离了本研究。这种分析包括治疗中的全数据,其中将治疗中定义为最终剂量日 +28 天。使用容纳漏失数据的末次观测值转结,安慰剂组与使用 5mg 化合物 I 治疗的组之间的差别在第 18 个月时具有统计学显著性。

[0138] 应答者是未进展且在 18 个月内的进展在 ADAS-cog 上增加 7 或 7 以上的点的受试者。

[0139] 图 2 展示出使用安慰剂施药的组和使用 5mg 化合物 I 施药的组的卡普兰 - 迈耶曲线,其中将事件定义为在任意时间点实现 ADAS-cog 增加为 7 或 7 以上。图 2 中的卡普兰 - 迈耶曲线显示根据 ADAS-cog、通过在 ADAS-cog 增加 7 个点时将受试者分类为具有“事件”确定的阿尔茨海默病下降的受试者比例 (7 个点为进展的参考文献 :Vellas 等

人的出版物，“Long-term changes in ADAS-cog:What is clinically relevant for disease modifying trails in Alzheimer？”（第 11 卷，第 4 期，2007；Journal of Nutrition,Health&Aging)）。该分析使用具有实现事件作为吸收状态的马尔科夫链模型公约。低剂量组（5mg，由实线表示）在所有点处均优于安慰剂组（由虚线表示），且线之间的距离表示使用化合物 I 治疗在减缓基线处存在轻度阿尔茨海默病的患者中阿尔茨海默病进展方面优于安慰剂。

[0140] 实施例 3

[0141] 鉴定范围内浓度在患者中的药物效果更显著。浓度水平与体重和 BMI 高度相关。最佳施药方式是浓度 - 驱动的。

[0142] 在每次研究探访时取血样以测定药物水平的波谷浓度。药物浓度分析与通过 ADAS-cog 评价的应答相关。

[0143] 使用波谷浓度和 ADAS-cog 中从基线的改变进行鉴定优化化合物效能的浓度范围的统计学模型化。初步的结果显示 7-20ng/ml 的范围，其中在本研究中所有其他组中，化合物 I- 治疗的受试者具有最大应答（在 ADAS-cog 中从基线的改变最小）。其它分析产生了 8 — 15ng/ml 的范围。当将分析扩展以包括 4 个支持性效能测量值以及 ADAS-cog(MMSE、ADL、CDR-sb 和 NPI) 时，鉴定的最佳范围是 8-13ng/ml。

[0144] 为了进行分析，根据在 18 个月试验期限期间的波谷水平最大值将受试者分入暴露组。使用二分位数截止 (tertile cuts)、四分位数截止 (quartile cuts)、五分位数截止 (quintile cuts) 和十分位数截止 (decile cut) 分析是一致的。PK/PD 模型化持续进行以鉴定最佳施药方式。

[0145] 图 3 展示出的棒形图显示与施用剂量无关的浓度驱动的受试者分类。在图 3 中，显示 0.7 — 12.8ng/ml 范围内的浓度在从 ADAS-cog 的基线的 LOCF LSMEAN 改变中与安慰剂存在标称统计学显著性差异，其中较高评分表示更晚期的阿尔茨海默病。针对 12.9 — 21.0ng/ml 的 pk 浓度的第三个棒形图中的浓度范围在延迟阿尔茨海默病进展方面在统计学意义上也优于安慰剂。

[0146] 分析结论：当给受试者施用 5mg 或 20mg 的化合物 I 并且由此得到具有 8 — 13ng/ml（包括）的范围的浓度时，显示化合物 I 优于安慰剂。

[0147] 当施药方式 (dosing paradigm) 是浓度驱动的而非使用固定施药时，化合物 I 的效能在阿尔茨海默病中更为显著。分析显示，如果浓度过低，则效能不明显。然而，如果浓度过高，则显然效能可能被副作用掩盖。当浓度在目标区间时，化合物 I 优于安慰剂是明显的。

[0148] 图 4 显示随时间变化分布的线性示意图，比较安慰剂治疗的受试者与本研究中的受试者，其测定的平均 pk 浓度在 8 — 15ng/ml 的范围。

[0149] 用安慰剂治疗的受试者（虚线）显示在 ADAS-cog 中从基线开始较大的增加，表明阿尔茨海默病的恶化比例高于使用具有平均 pk 浓度范围在 8 — 15ng/ml 的化合物 I 治疗的受试者（实线）。样本大小随时间改变，因为患者脱离本研究。这种分析包括治疗中的全部数据，其中将治疗中定义为最终剂量日 +28 天。使用容纳漏失数据的末次观测值转结，安慰剂组与使用化合物 I 这些浓度治疗的组之间的差异在第 18 个月时具有标称统计学显著性。

[0150] 表 2 提供了描述从第 6 个月开始并且在 18- 个月研究其余期间维持的安慰剂与使用化合物 I 治疗之间的统计概括。

[0151] 表 2

[0152] 使用安慰剂治疗的受试者和使用具有 8 — 15ng/ml 平均波谷浓度的化合物 I 治疗的受试者随时间在 ADAS-cog 中的平均值和中间值改变的

[0153] 概括

[0154]

时间	统计	安慰剂	8 - 15 ng/ml 的浓度	平均差	P-值 (2-样本 t-检验)
基线	平均值	24.11	24.22	0.11	0.9
	中间值	22.3	22.0		
3	改变平均值	1.57	0.73	0.84	0.3
	改变中间值	2.0	2.3		
6	改变平均值	3.16	1.16	2.00	0.03
	改变中间值	2.7	1.3		
9	改变平均值	3.95	1.52	2.43	0.04
	改变中间值	2.2	1.3		
12	改变平均值	6.34	3.31	3.03	0.02
	改变中间值	5.5	2.3		
15	改变平均值	8.74	4.39	4.35	0.008
	改变中间值	7.8	4.7		
18	改变平均值	11.32	6.04	5.28	0.01
	改变中间值	10.3	4.7		

[0155] 表 2 中的数据显示在其测定的平均波谷浓度为 8 — 15ng/ml 的受试者中使用化合物 I 治疗从第 6 个月开始在统计学上被描述为标称统计学显著性。分析结论表明，在一些浓度范围内，使用化合物 I 治疗的有益性是明显的。浓度变化分析导致了如下结论 :体重和 BMI 影响浓度。这些分析支持了对于并入体重或 BMI 的浓度 - 驱动的治疗的需求。

[0156] 图 5 显示浓度对 BMI 回归的回归分析。将浓度（因变量）针对 BMI 和体重回归的回归分析显示在全部 4 种分析中具有统计学显著性的负相关性 :具有较低体重或较低 BMI 的受试者对于同一施用剂量倾向于具有高于具有较高体重或较高 BMI 值的受试者的浓度。结果对于每种剂量水平都是真实的 ;因此，这种发现适合于两种剂量水平。这些分析基于所有治疗中可得到的分析，其中将治疗中定义为最终剂量日 +28 天。这一发现转变成在所述施用剂量中并入体重或 BMI 的施药方式，从而产生了期望的浓度水平。这些发现与浓度驱动效能且体重或 BMI 驱动浓度的要求一致。该发现启示在低体重和低 BMI 下，较低剂量能够比较高剂量更有效。

[0157] 实施例 4

[0158] 当受试者存在升高的葡萄糖值时用高剂量的化合物 I 治疗观察到葡萄糖减少

[0159] 来自使用化合物 I 的研究的数据的统计学分析得出结论 :在葡萄糖值方面存在下

降，特别是对于进入具有升高的葡萄糖水平的研究的受试者而言。降低升高的葡萄糖有益于患者，而降低正常或较低水平的葡萄糖值可能具有有害作用。

[0160] 统计学分析显示，在本研究中，具有较高葡萄糖值的受试者在使用 20mg 化合物 I 治疗时与安慰剂相比下降。在基线具有较低葡萄糖值的受试者未显示葡萄糖的明显下降。

[0161] 图 6a-d 显示在葡萄糖方面从基线的平均改变由使用在第 3、6 和 9 个月时可得到的全部数据的治疗组展示。通过取具有 100mg/dl 或以上的基线值的全部受试者、在上三分之一中的全部受试者（俩分位数截止）、在最上面 25％中的全部受试者（四分位数截止）和在最上面 20％中的全部受试者（五分位数截止（未显示））确定小组。图 6-d 展示出具有较低或正常值的受试者，其中通过中间值截止的组确定小组，且该小组是具有基线值低于组中间值（下半部分）的全部受试者。在第 9 个月后，退出率导致数据对于有意义的分析而言过于稀疏。使用高 - 剂量 (20mg) 化合物 I 治疗的组显示葡萄糖明显下降，这在治疗组中具有统计学显著性 ($p<0.05$)，且使用 2- 样本 t- 检验显示与安慰剂相比也具有统计学显著性差异 ($p<0.05$)。对于具有正常或具有低基线葡萄糖值的受试者而言，不存在与使用化合物 I 治疗相关的下降。在治疗组中在基线处的差异不具有统计学显著性。在进入具有低于研究群体中间值的葡萄糖值的研究的受试者小组中研究与使用化合物 I 治疗相关的下降的对比不具有统计学显著性 ($p>0.15$)。

[0162] 实施例 5

[0163] 使用 5mg 化合物 I 治疗延迟或降低了特别关注的不良事件发生率

[0164] 不良事件

[0165] 特别关注的不良事件 (AESI) 涉及潜在的认知缺损：失落、头晕、精神混乱状态和嗜睡。针对使用 20mg、5mg 和安慰剂治疗的组的至少一种 AESI 的报告频率分别为 50(37％)、49(37％) 和 44(33％)。具体的 AESI 未显示与化合物 I 剂量相关的可辨别模式。

[0166] 图 7 展示出使用剂量组的时间与特别关注的不良事件事件关系的卡普兰 - 迈耶曲线（失落、精神混乱状态、嗜睡、头晕）。

[0167] 图 7 显示时间与事件关系曲线，其展示出当受试者从无事件的研究中退出时，使用 Kaplan-Meier 检查在截止到研究当天时受试者无事件的比例。该分析使用具有实现作为吸收状态的事件的马尔科夫链模型公约。低剂量组 (5mg，由虚线表示）在所有点处均优于安慰剂组（表示为间断的点 - 虚线）且线之间的距离表示相对于安慰剂使用 5mg 化合物 I 治疗在减少具有 AESI 的可能性方面的有益性。

[0168] 图 8 展示出使用浓度组的时间与特别关注的不良事件事件关系的卡普兰 - 迈耶曲线（失落、精神混乱状态、嗜睡、头晕）。时间与事件关系曲线展示出当受试者从无事件的研究中退出时，使用 Kaplan-Meier 检查在截止到研究当天时受试者无事件的比例。该分析使用具有完成作为吸收状态的事件的马尔科夫链模型公约。在第 3 个月后的所有点处，具有小于 14.6ng/dl 的浓度的组（表示为虚线）优于安慰剂组（表示为实线），且线之间的距离表示相对于安慰剂使用低浓度的化合物 I 治疗在减少具有 AESI 的可能性方面的有益性。

[0169] 在完成本发明不同目的中描述了本发明的不同实施方案。应认为这些实施方案仅是本发明原理的示例。可以在不脱离本发明精神和范围的情况下进行大量变型混及其修改，这对本领域技术人员而言是显而易见的。

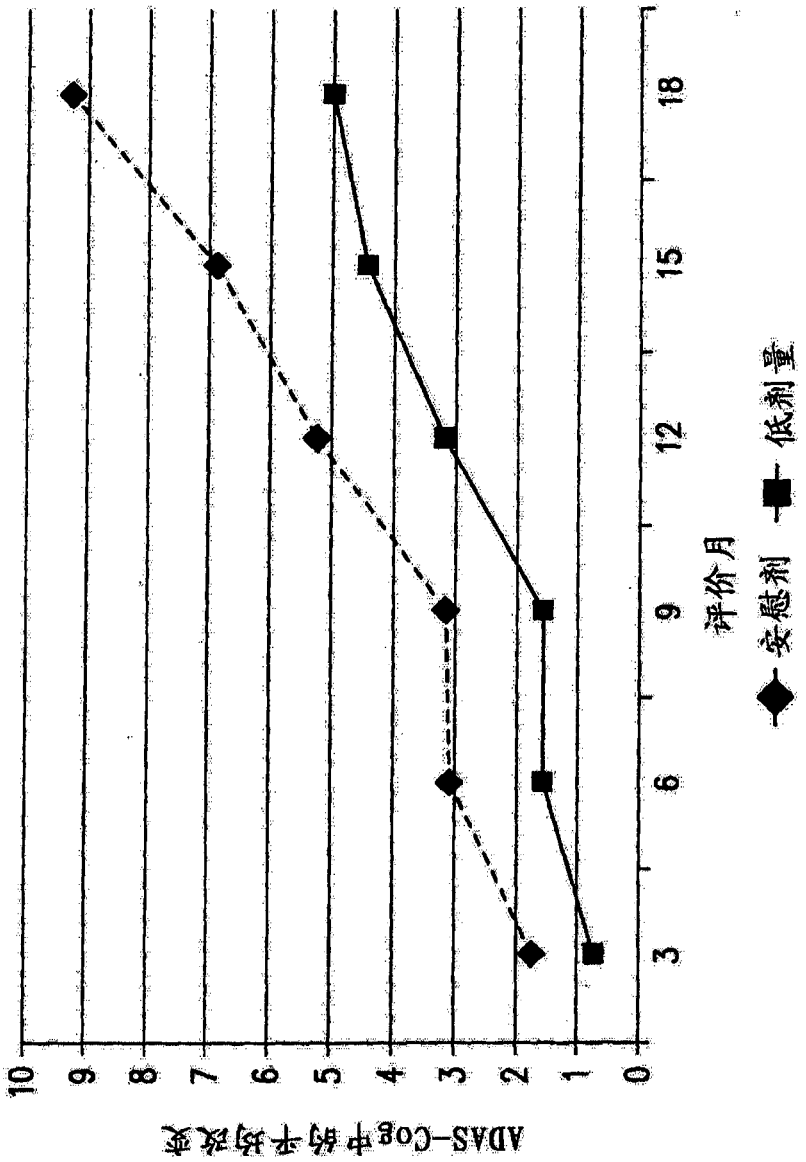


图 1

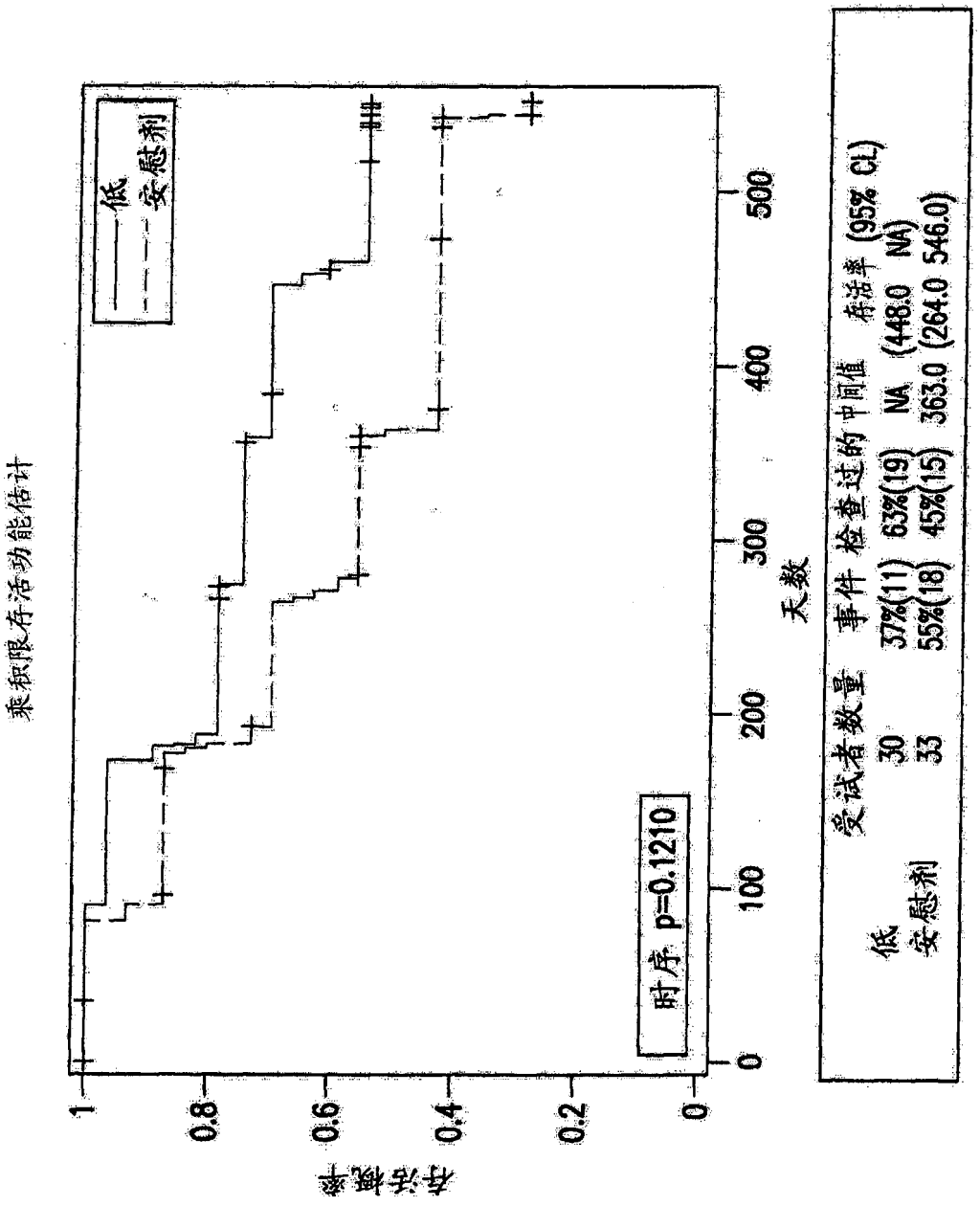

乘积限存活功能估计
存活概率
天数
低
安慰剂
时序 p=0.1210
受试者数量 事件 检查过的 中间值 存活率 (95% CL)
低 30 37%(11) 63%(19) NA (448.0 NA)
安慰剂 33 55%(18) 45%(15) 363.0 (264.0 546.0)

图 2

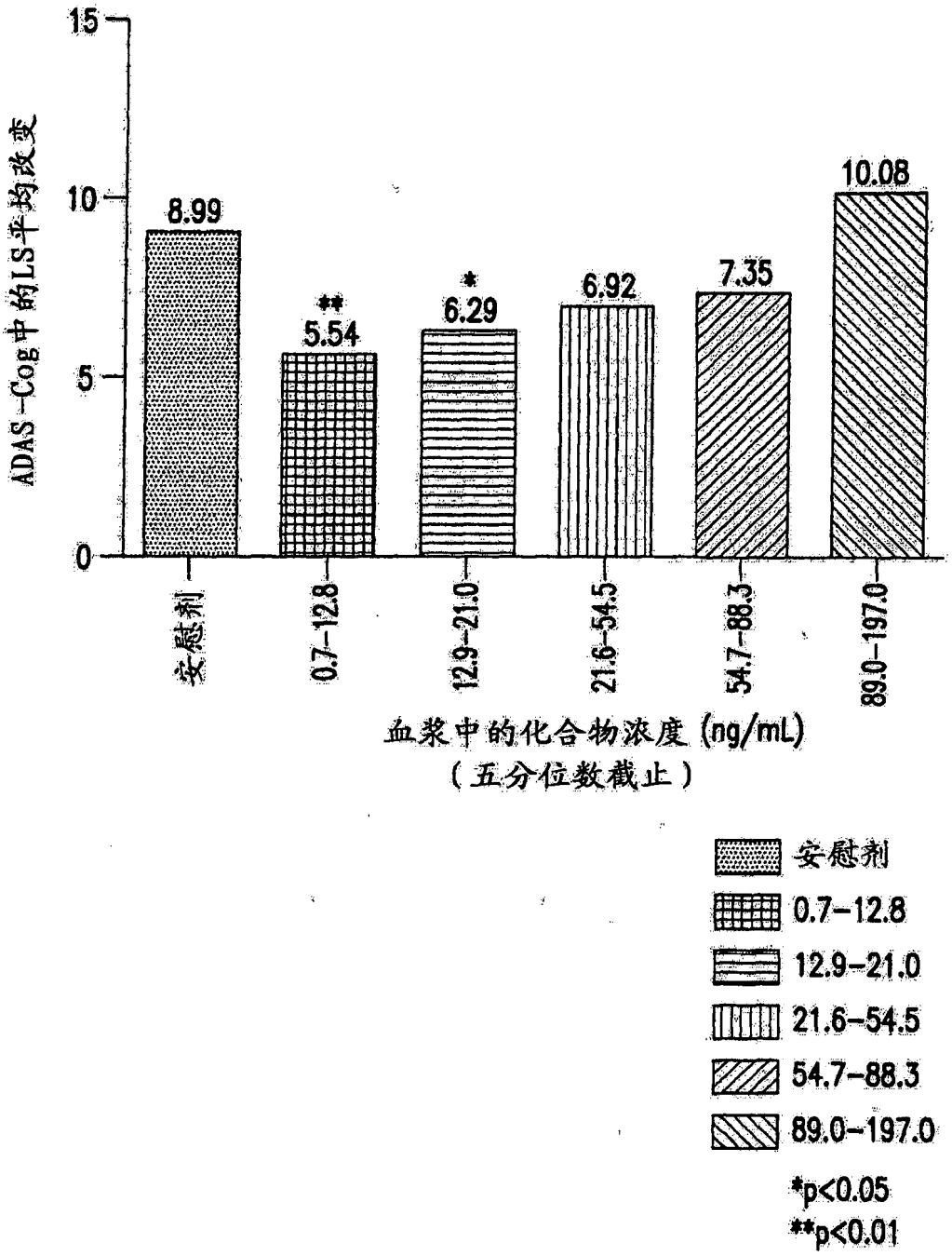

15
10
5
0
ADAS-Cog中的LS平均改变
8.99
**
5.54
*
6.29
6.92
7.35
10.08
安慰剂
0.7-12.8
12.9-21.0
21.6-54.5
54.7-88.3
89.0-197.0
血浆中的化合物浓度 (ng/mL)
(五分位数截止)
安慰剂
0.7-12.8
12.9-21.0
21.6-54.5
54.7-88.3
89.0-197.0
*p<0.05
**p<0.01

图 3

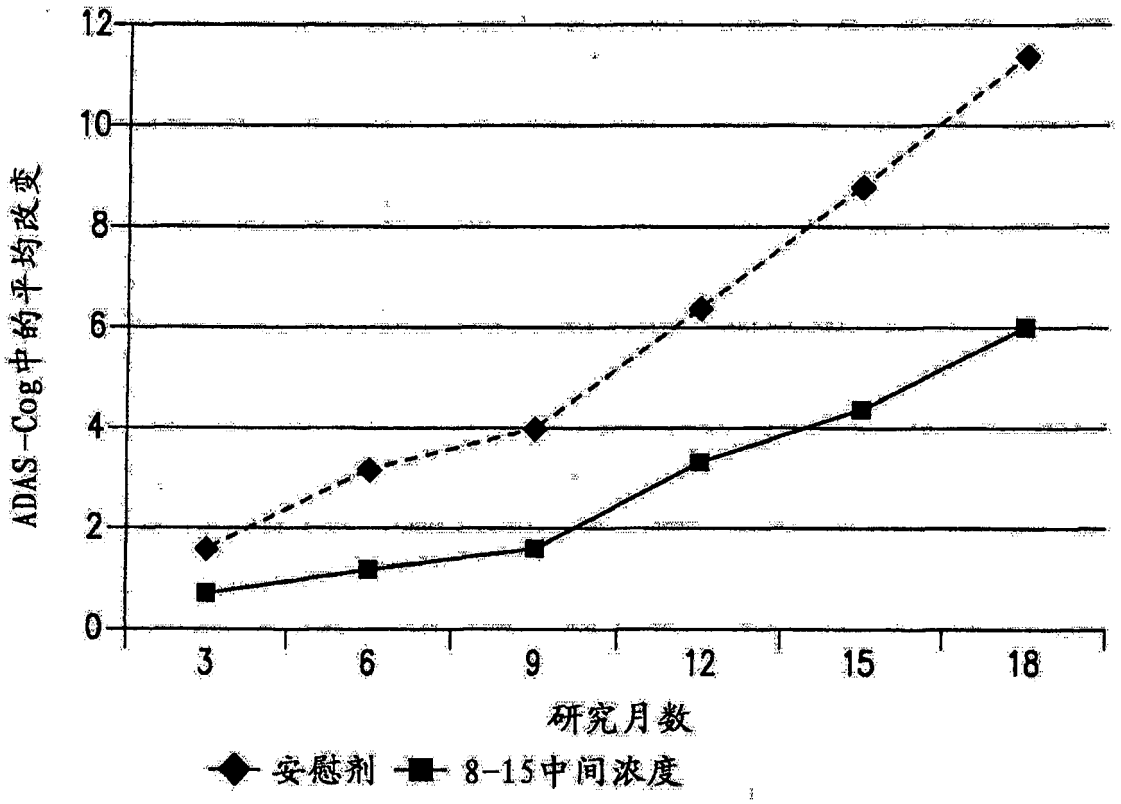


图 4

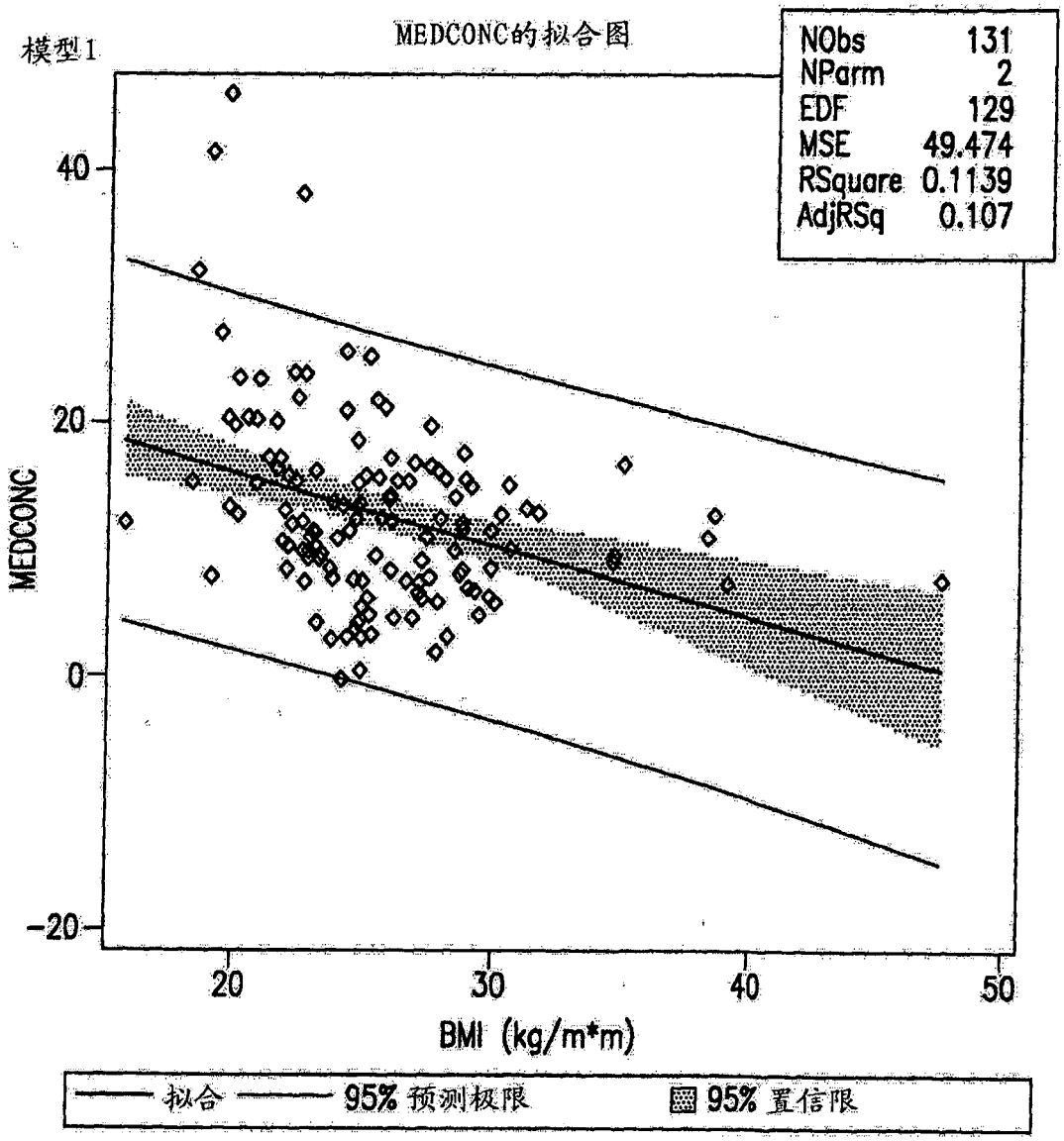

模型1
MEDCONC的拟合图
NObs 131
NParm 2
EDF 129
MSE 49.474
RSquare 0.1139
AdjRSq 0.107
MEDCONC
40
20
0
-20
20
30
40
50
BMI (kg/m*m)
拟合
95% 预测极限
95% 置信限

图 5A

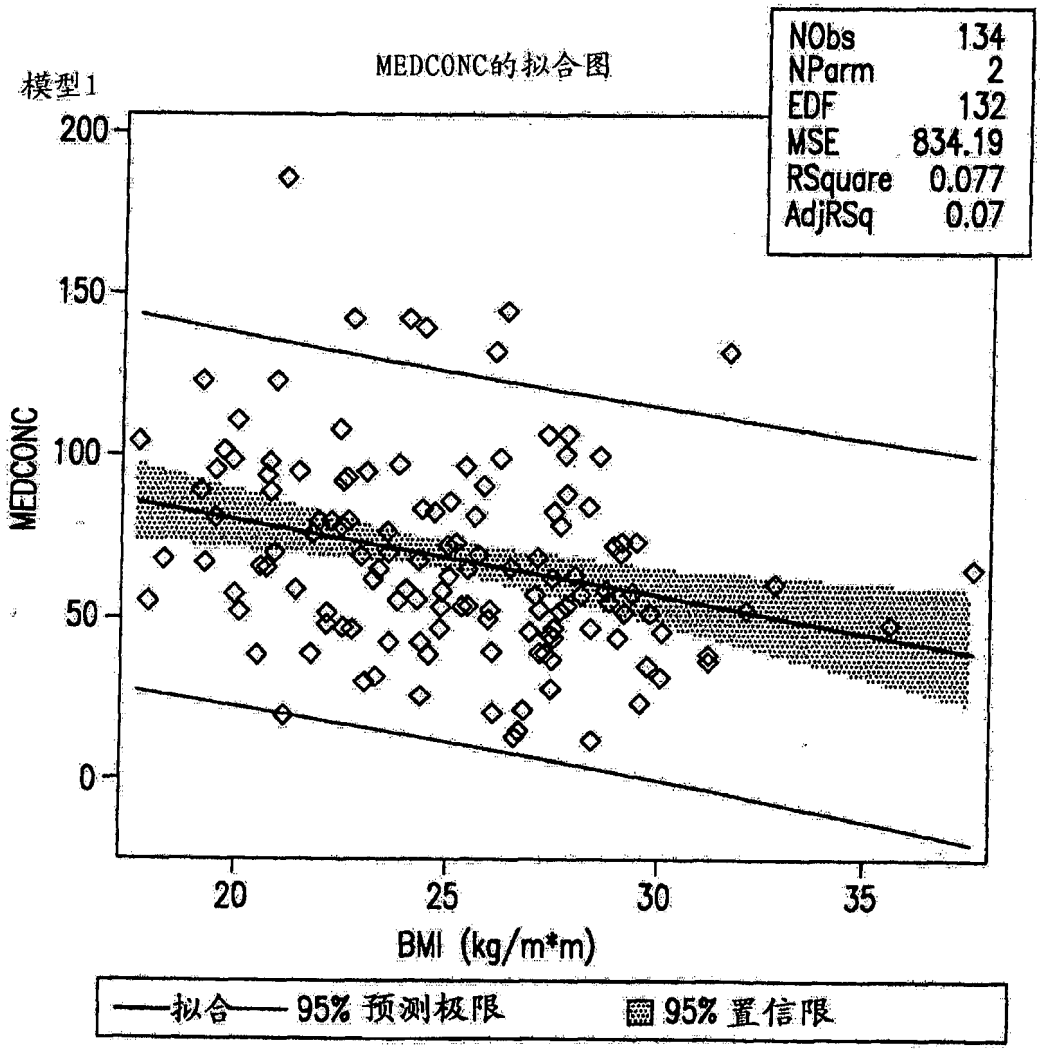


图 5B

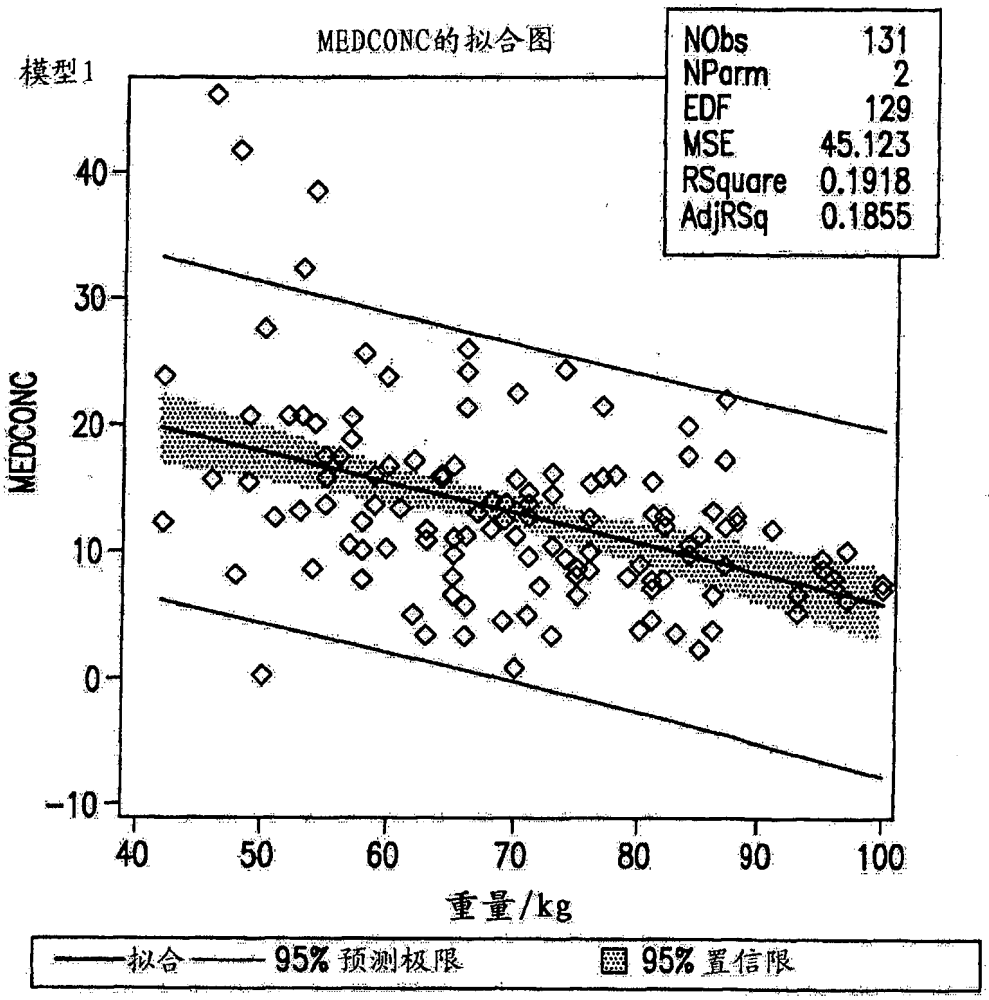

MEDCONC的拟合图
模型1
NObs 131
NParm 2
EDF 129
MSE 45.123
RSquare 0.1918
AdjRSq 0.1855
MEDCONC
40
30
20
10
0
-10
40
50
60
70
80
90
100
重量/kg
拟合
95% 预测极限
95% 置信限

图 5C

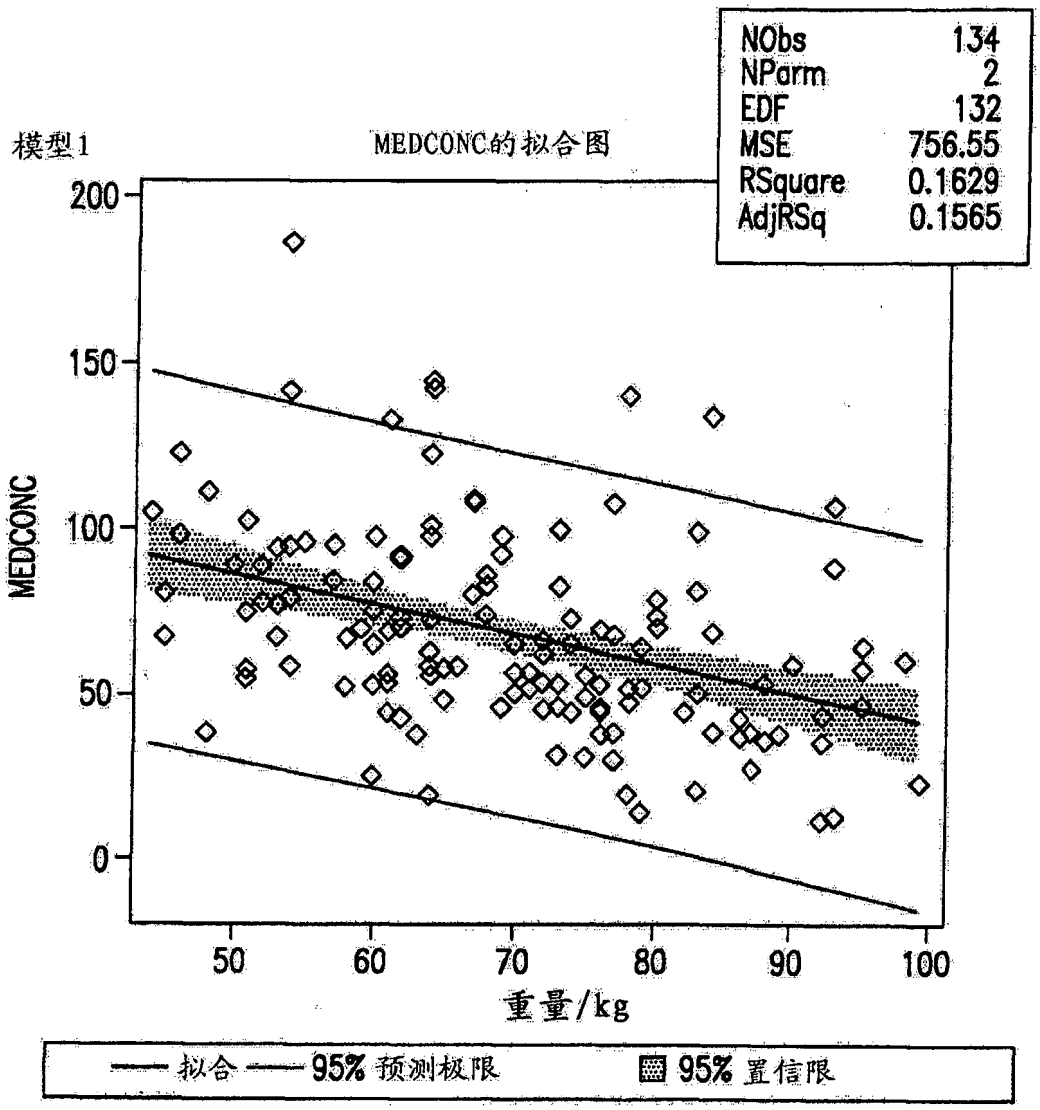

模型1
MEDCONC的拟合图
NObs 134
NParm 2
EDF 132
MSE 756.55
RSquare 0.1629
AdjRSq 0.1565
MEDCONC
200
150
100
50
0
50
60
70
80
90
100
重量/kg
拟合
95% 预测极限
95% 置信限

图 5D

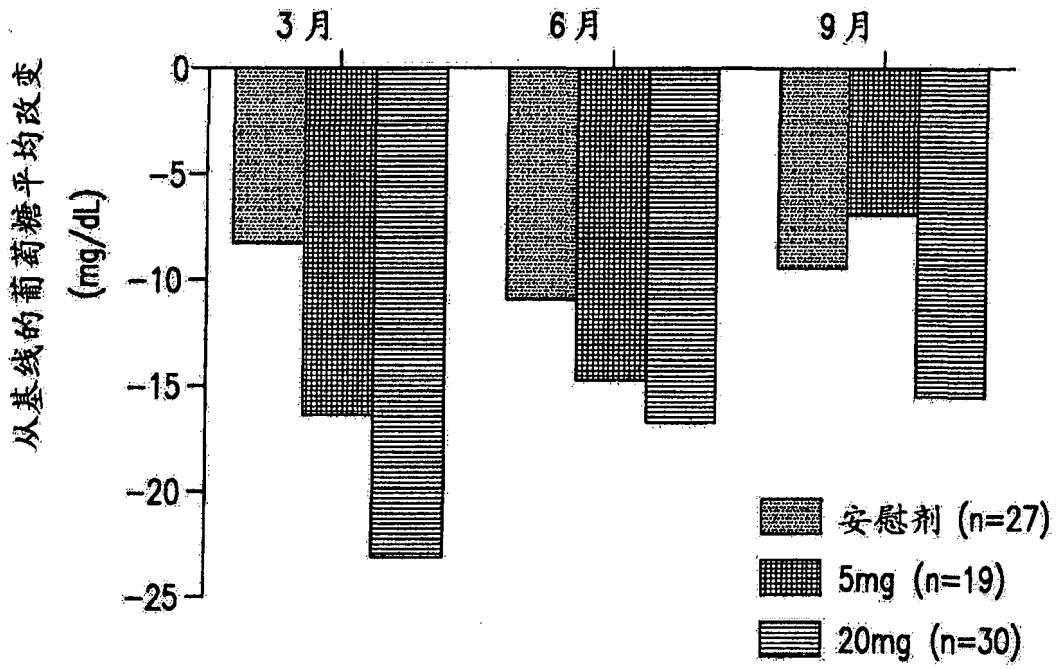

3月
6月
9月
从基线的葡萄糖平均改变
(mg/dL)
0
-5
-10
-15
-20
-25
安慰剂 (n=27)
5mg (n=19)
20mg (n=30)

图 6A

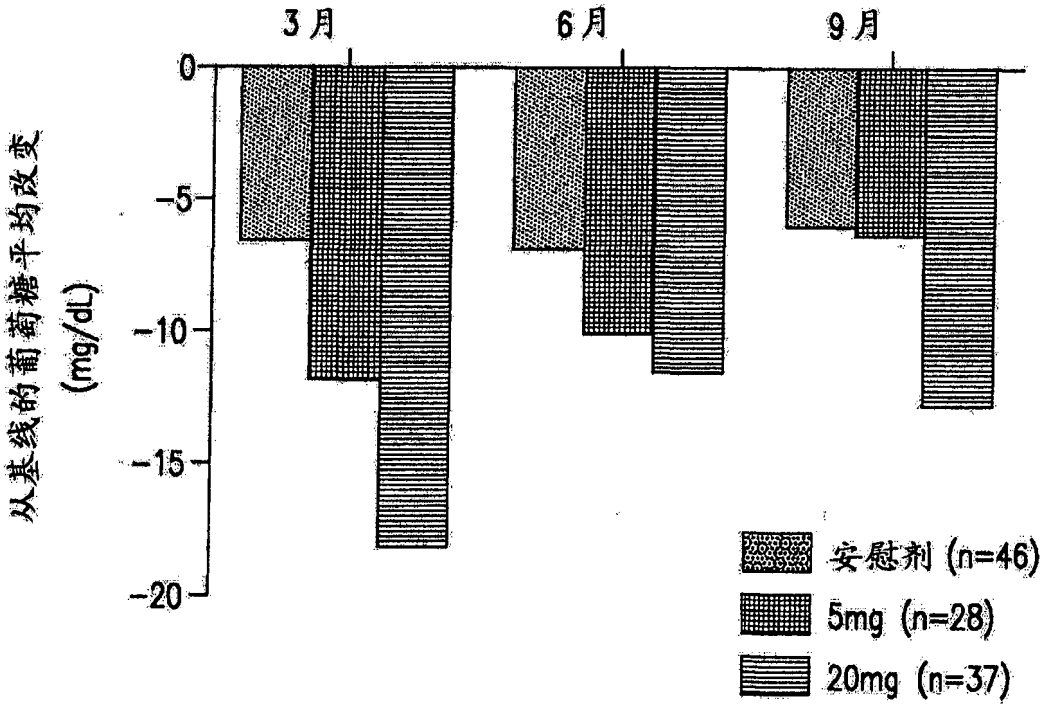

3月
6月
9月
从基线的葡萄糖平均改变
(mg/dL)
0
-5
-10
-15
-20
安慰剂 (n=46)
5mg (n=28)
20mg (n=37)

图 6B

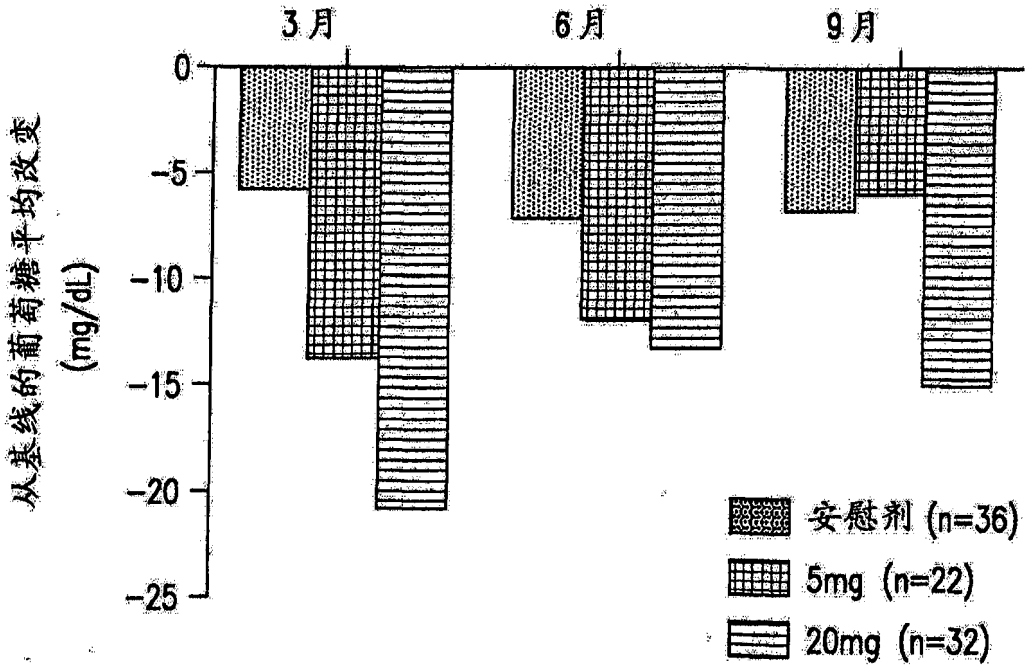

3月
6月
9月
0
-5
-10
-15
-20
-25
从基线的葡萄糖平均改变
(mg/dL)
安慰剂 (n=36)
5mg (n=22)
20mg (n=32)

图 6C

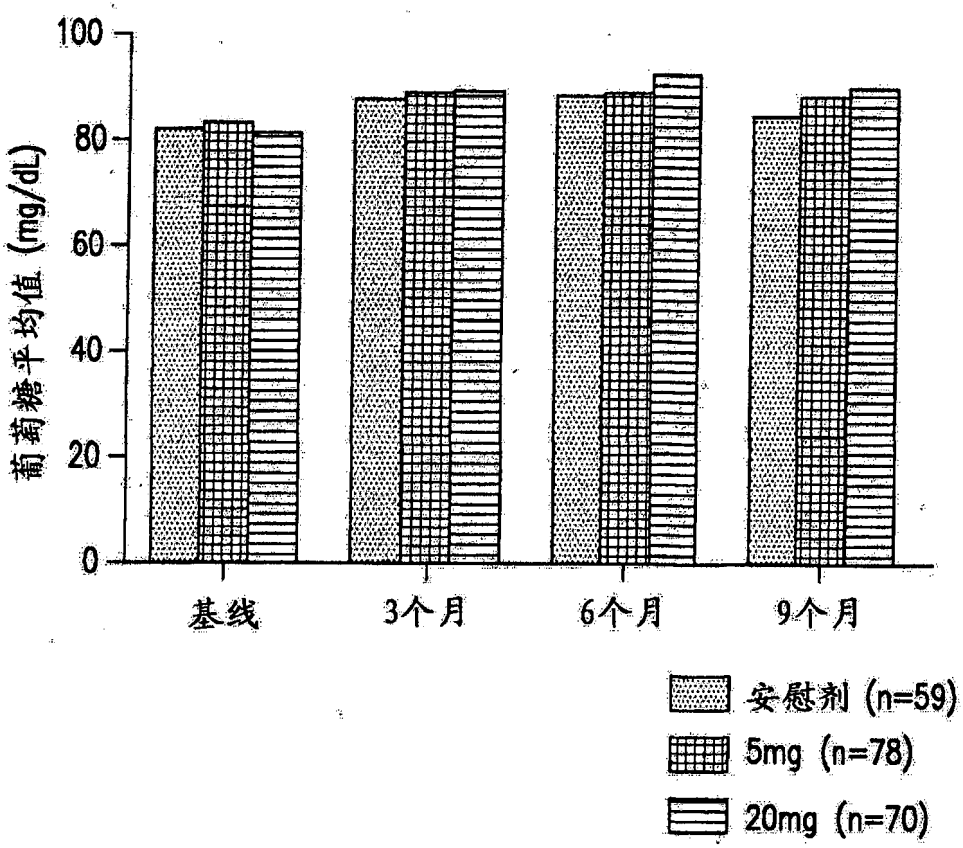


图 6D

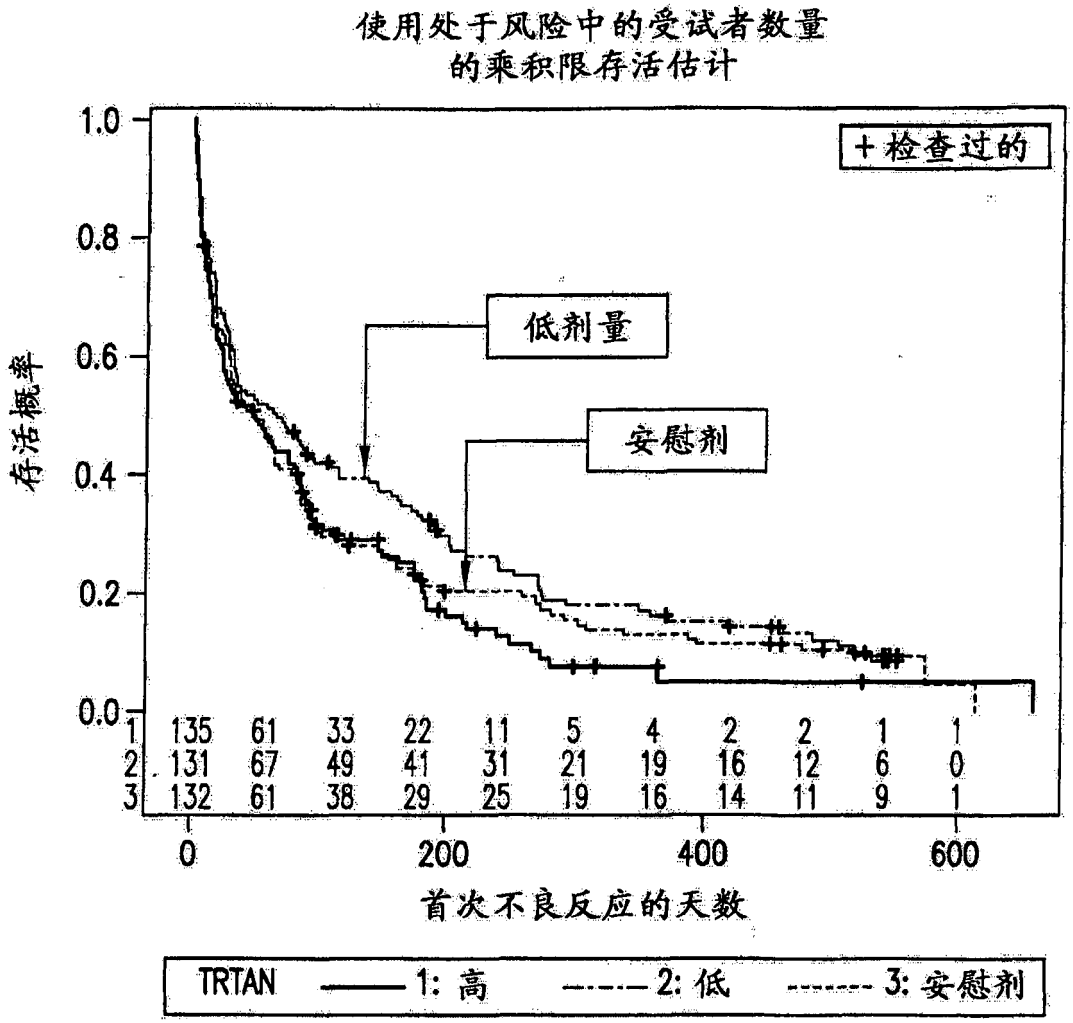


图 7

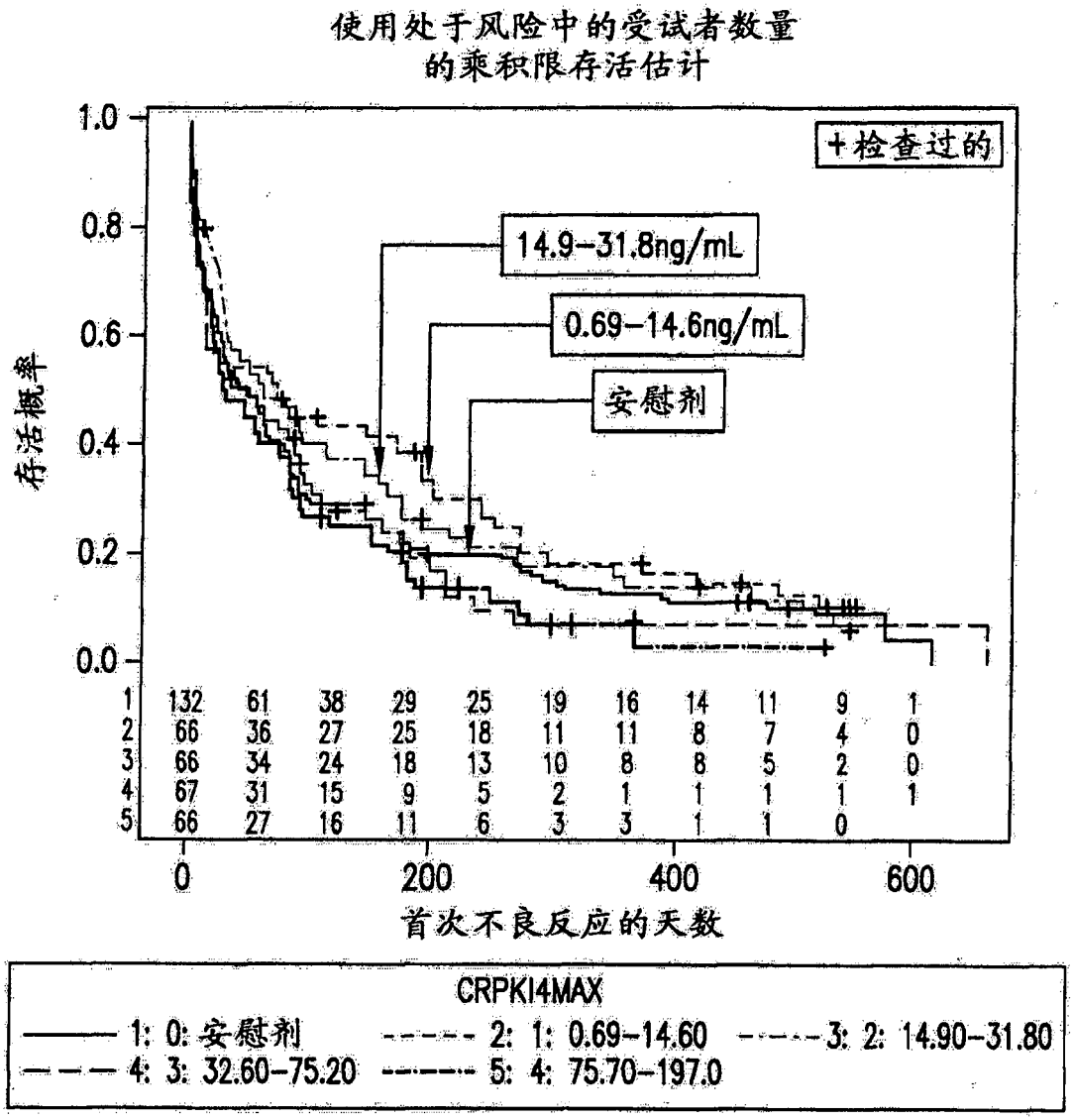

使用处于风险中的受试者数量
的乘积限存活估计
1.0
0.8
0.6
0.4
0.2
0.0
存活概率
+检查过的
14.9–31.8ng/mL
0.69–14.6ng/mL
安慰剂
1 132 61 38 29 25 19 16 14 11 9 1
2 66 36 27 25 18 11 11 8 7 4 0
3 66 34 24 18 13 10 8 8 5 2 0
4 67 31 15 9 5 2 1 1 1 1 1
5 66 27 16 11 6 3 3 1 1 0
0
200
400
600
首次不良反应的天数
CRPKI4MAX
1: 0: 安慰剂
2: 1: 0.69–14.60
3: 2: 14.90–31.80
4: 3: 32.60–75.20
5: 4: 75.70–197.0

图 8