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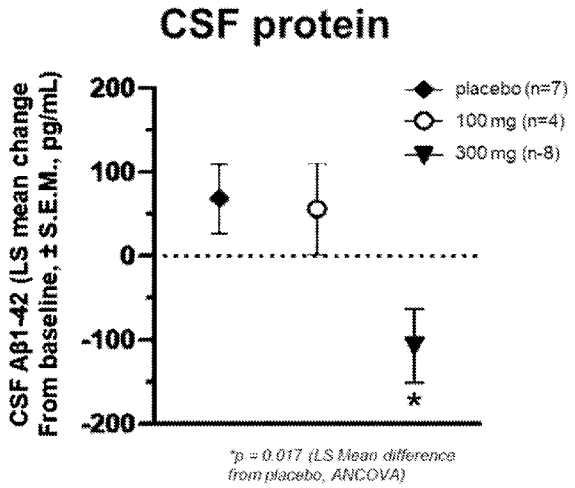

Figure 8

(57) Abstract: The present disclosure relates to methods of decreasing amyloid β monomers and methods of treating cognitive decline in a subject, wherein the treatment results in an increase in amyloid β oligomers and a reduction in cognitive decline. The present disclosure relates to treating cognitive decline, wherein target engagement can be measured in the clinic after treating.

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METHOD OF DECREASING AMYLOID BETA MONOMER LEVELS IN PATIENTS WITH COGNITIVE DECLINE

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 62/976,325 entitled "Method of Decreasing Amyloid Beta Monomer Levels in Patients with Cognitive Decline," filed February 13, 2020, which is incorporated herein by reference in its entirety.

GOVERNMENT INTERESTS

[0002] This invention was made with government support under R43NS083175 awarded by National Institute of Neurological Disorders and Stroke and R43AG037337, R44AG055247, R01AG051593, R01AG054176, R01AG057780, and R01AG058660 awarded by National Institute on Aging. The government has certain rights in the invention.

SUMMARY OF THE INVENTION

[0003] Summary of the Invention: The present disclosure relates to methods of decreasing amyloid β monomers and methods of treating cognitive decline in a subject, wherein the treatment results in an increase in amyloid β oligomers and a reduction in cognitive decline. The present disclosure relates to treating cognitive decline, wherein target engagement can be measured in the clinic after treating.

DESCRIPTION OF THE DRAWINGS:

[0004] Figure 1 describes percent change in levels of Aβ oligomers in patients measured by microimmunoelectrode.

[0005] Figure 2 describes percent change in levels of Aβ oligomers in CSF from patients, measured by Western Blot.

[0006] Figure 3 describes the correlation between measurement of Aβ oligomers measured by microimmunoelectrode and by Western Blot, calculated by Spearman correlation analysis.

[0007] Figure 4 describes CT1812 related increase in Aβ oligomers in patient CSF over time as measured by microimmunoelectrode.

[0008] Figure 5 describes CT1812 related increase in Aβ oligomers in patient CSF over time as measured by Western Blot.

[0009] Figure 6 describes the concentrations of CT1812 in the plasma and CSF of patients after treatment.

[0010] Figure 7 describes a three-point difference in Alzheimer's Disease Assessment Scale (ADAS-COG) score between treated and untreated patients after 185 days of treatment.

[0011] Figure 8 describes the decrease in Aβ monomer (Aβ 1-42) levels in patients treated with a total daily dose of 300 mg CT1812 for 185 days.

DETAILED DESCRIPTION

DEFINITIONS

[0012] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art.

[0013] The articles "a" and "an" as used herein mean "one or more" or "at least one," unless otherwise indicated. That is, reference to any element of the present invention by the indefinite article "a" or "an" does not exclude the possibility that more than one of the element is present.

[0014] As used herein, the term "about" means plus or minus 10% of the numerical value of the number with which it is being used. Therefore, about 50% means in the range of 45%-55%.

[0015] "Administering," or "administration" and the like, when used in conjunction with the compounds of the disclosure refers to providing the compounds or pharmaceutical compositions according to any of the embodiments described herein, to a subject in need of treatment. Preferably the subject is a mammal, more preferably a human. The present invention comprises administering the compound or pharmaceutical composition of the invention alone or in conjunction with another therapeutic agent. When a compound or pharmaceutical composition of the invention is administered in conjunction

with another therapeutic agent, the compound or pharmaceutical composition of the invention and the other therapeutic agent can be administered at the same time or different times, and by the same routes of administration or by different routes of administration. A compound may be administered by oral administration, intravenous administration, intraperitoneal administration, or any other route of administration known in the art.

[0016] The term “amyloid β levels” as used herein includes any measurement of the amount of amyloid β measured in a sample collected from a subject. The sample may include, but is not limited to, cerebral spinal fluid, hippocampal interstitial fluid, and plasma. The amyloid β levels may be measured using any method to measure the concentration or amount of a protein, which may include, but it not limited to, use of microimmunoelectrodes or Western Blot.

[0017] The term "animal" as used herein includes, but is not limited to, humans and non-human vertebrates such as wild, domestic and farm animals.

[0018] As used herein, “cognitive decline” can be any negative change in an animal’s cognitive function. For example cognitive decline, includes but is not limited to, memory loss (e.g. behavioral memory loss), failure to acquire new memories, confusion, impaired judgment, personality changes, disorientation, or any combination thereof. A compound that is effective to treat cognitive decline can be thus effective by restoring long term neuronal potentiation (LTP) or long term neuronal depression (LTD) or a balance of synaptic plasticity measured electrophysiologically; inhibiting, treating, and/or abatement of neurodegeneration; inhibiting, treating, and/or abatement of general amyloidosis; inhibiting, treating, abatement of one or more of amyloid production, amyloid assembly, amyloid aggregation, and amyloid oligomer binding; inhibiting, treating, and/or abatement of a nonlethal effect of one or more of Aβ species on a neuron cell (such as synapse loss or dysfunction and abnormal membrane trafficking); and any combination thereof. Additionally, that compound can also be effective in treating Aβ related neurodegenerative diseases and disorders including, but not limited to dementia, including but not limited to Alzheimer’s Disease (AD) including mild Alzheimer’s disease, Down’s syndrome, vascular dementia (cerebral amyloid angiopathy and stroke), dementia with Lewy bodies, HIV dementia, Mild Cognitive Impairment (MCI); Age-Associated Memory Impairment

(AAMI); Age-Related Cognitive Decline (ARCD), preclinical Alzheimer's Disease (PCAD); and Cognitive Impairment No Dementia (CIND).

[0019] The phrase "pharmaceutically acceptable" refers to those compounds, materials, pharmaceutical compositions, and/or dosage forms that are, within the scope of sound medical judgment, generally regarded as safe and nontoxic. In particular, pharmaceutically acceptable carriers, diluents or other excipients used in the pharmaceutical compositions of this disclosure are physiologically tolerable, compatible with other ingredients, and do not typically produce an allergic or similar untoward reaction (for example, gastric upset, dizziness and the like) when administered to a patient. Preferably, as used herein, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal government or a state government or listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly in humans.

[0020] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; and alkali or organic salts of acidic groups such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile

are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Company, Easton, PA, 1990, the disclosure of which is hereby incorporated by reference.

[0021] The terms "subject," "individual" or "patient" are used interchangeably and as used herein are intended to include human and non-human animals. Non-human animals includes all vertebrates, e.g. mammals and non-mammals, such as non-human primates, sheep, dogs, cats, cows, horses, chickens, amphibians, and reptiles, although mammals are preferred, such as non-human primates, sheep, dogs, cats, cows and horses. Preferred subjects include human patients. The methods are particularly suitable for treating human patients having a condition, disease or disorder described herein.

[0022] As used herein, the term "therapeutic" means an agent utilized to treat, combat, ameliorate, prevent or improve an unwanted condition or disease of a patient.

[0023] A "therapeutically effective amount" of a compound, pharmaceutically acceptable salt thereof or pharmaceutical composition according to any embodiment described herein, is an amount sufficient to produce a selected effect on at least one symptom or parameter of a specific disease or disorder. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect or physician observes a change). The effect contemplated herein, includes both medical therapeutic and/or prophylactic treatment, as appropriate. The specific dose of a compound administered according to this disclosure to obtain therapeutic and/or prophylactic effects is determined by the particular circumstances surrounding the case, including, for example, the compound administered, the route of administration, the co-administration of other active ingredients, the condition being treated, the activity of the specific compound employed, the specific composition employed, the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed and the duration of the treatment;. The therapeutically effective amount administered will be determined by the physician in the light of the foregoing relevant circumstances and the exercise of sound medical judgment. A therapeutically effective amount of a compound, according to any embodiment described herein, is typically an amount such that when it is administered in a physiologically tolerable excipient

composition, it is sufficient to achieve an effective systemic concentration or local concentration in the tissue.

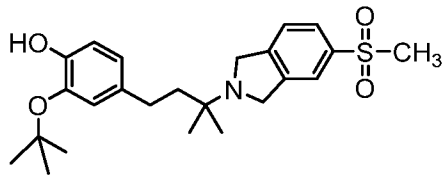
[0024] The terms "treat," "treated," or "treating" as used herein, refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to protect against (partially or wholly) or slow down (e.g., lessen or postpone the onset of) an undesired physiological condition, disorder or disease, or to obtain beneficial or desired clinical results such as partial or total restoration or inhibition in decline of a parameter, value, function or result that had or would become abnormal. For the purposes of this disclosure, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent or vigor or rate of development of the condition, disorder or disease; stabilization (i.e., not worsening) of the state of the condition, disorder or disease; delay in onset or slowing of the progression of the condition, disorder or disease; amelioration of the condition, disorder or disease state; and remission (whether partial or total), whether or not it translates to immediate lessening of actual clinical symptoms, or enhancement or improvement of the condition, disorder or disease. Treatment seeks to elicit a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment.

METHODS

[0025] The present disclosure relates to clinical results in human, the results of which were surprising and unexpected in light of the information available to a skilled artisan. The animal models and preclinical data suggested that CT1812 can selectively displace oligomers and increase their concentration in cerebral spinal fluid and in brain interstitial fluid but had not effect on the concentration of monomers. This was supported by data in human subjects treated with CT1812 for 28 days, which resulted in no change in amyloid β monomer concentration in the cerebral spinal fluid or interstitial fluid (*See* 62/976,325, which is included herein by reference). The results presented here are

surprising and unexpected as in some embodiments of the present disclosure describe a method of reducing amyloid β in a human subject. In some embodiments of the present disclosure, a method of elevating amyloid β oligomer levels in a human subject is described.

[0026] In some embodiments the present disclosure describes a method of reducing amyloid β monomer levels in a subject comprising administering to the subject a therapeutically effective amount of a compound of formula:



, CT1812

or a pharmaceutically acceptable salt thereof.

[0027] In some embodiments described herein, the subject is a human. In some embodiments described herein, the subject is a subject with cognitive decline. In some embodiments described herein, the subject is a subject with cognitive decline wherein the cognitive decline is Alzheimer's disease. In some embodiments described herein, the subject is a subject with Alzheimer's disease.

[0028] In some embodiments the compound is administered orally. In some embodiments, the compound is administered by a route selected from the group comprising oral administration, intravenous administration, intramuscular administration, subcutaneous administration, intranasal administration, intradermal administration, topical administration, In some embodiments, the compound may be formulated as a tablet, as a capsule, as a powder, in a solution, in a suspension, and in an emulsion,

[0029] In some embodiments a total daily dose of 10 mg to 2000 mg, of the compound is administered. The total daily dose of the compounds of this disclosure can be administered to a subject in single dose or in divided doses. In some embodiments the dose is 100 mg per day, in some embodiments the dose is 300 mg per day, in some embodiments the dose is 560 mg. In some embodiments a total daily dose of 100 mg of the compound is administered for at least about 6 months. In some embodiments a total daily dose of 300 mg of the compound is administered for at least about 6 months. In some embodiments a

total daily dose of 560 mg is administered for at least about 6 months. In some embodiments the total daily does is about 10mg to about 2000 mg, about 100 mg to about 2000 mg, about 200 mg to about 2000 mg, about 300 mg to about 2000 mg, about 400 mg to about 2000 mg, about 500 mg to about 2000 mg, about 600 mg to about 2000 mg, about 700 mg to about 2000 mg, about 800 mg to about 2000 mg, about 900 mg to about 2000 mg, about 1000 mg to about 2000 mg, about 1200 mg to about 2000 mg, about 1400 mg to about 2000 mg, about 1600 mg to about 2000 mg, about 1800 mg to about 2000 mg, or a value within these ranges. Specific examples may include about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, about 1600 mg, about 1700 mg, about 1800 mg, about 1900 mg, about 2000 mg, or a range between any two of these values.

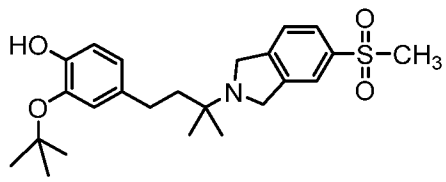
[0030] In some embodiments CT1812 is administered for at least 6 months. In some embodiments, some embodiments CT1812 is administered for about 1 day to about 50 years. In some embodiments CT1812 is administered for about 1 day to about 1 year. In some embodiments CT1812 is administered for about 1 day to about 6 months, about 3 days to about 6 months, about 1 week to about 6 months, about 2 weeks to about 6 months, about 3 weeks to about 6 months, about 1 month to about 6 months, about 2 months to about 6 months, about 3 months to about 6 months, about 4 months to about 6 months, about 5 months to about 6 months, or a value within these ranges. Specific examples may include about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 2 weeks, about 3 weeks, about 4 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 7 months, about 8 months, about 9 months, about 10 months, about 11 months, about 12 months, about 1 year or a range between any two of these values.

[0031] In some embodiments the administration of CT1812 results in a change in amyloid β levels in the cerebral spinal fluid (CSF), hippocampal interstitial fluid, plasma, or a combination thereof. In some embodiments the administration of CT1812 results in a reduction of amyloid β monomer levels. In some embodiments, the amyloid β monomer is selected from Aβ 1-40 and Aβ 1-42. In some embodiments the administration

of CT1812 results in an elevation of amyloid β oligomers in the cerebral spinal fluid (CSF), hippocampal interstitial fluid, plasma, or a combination thereof. In some embodiments the level of amyloid β after administration of CT1812 is relative to the level of amyloid β before administration of CT1812. In some embodiments, the amyloid β levels are measured using microimmunoelectrodes. In some embodiments, the amyloid β levels are measured using Western Blot. In some embodiments, the amyloid β levels are measured using ELISA (enzyme-linked immunosorbent assay).

[0032] In some embodiments, the administration of CT1812 results in a reduction in cognitive decline. In some embodiments, the administration of CT1812 blocks cognitive decline. In some embodiments, the administration of CT1812 results in a reduction in the Alzheimer's Disease Assessment Score (ADAS-COG) score of a subject as compared to the ADAS-COG score of the subject before treatment. In some embodiments the administration of CT1812 results in a subject maintaining the Alzheimer's Disease Assessment Score (ADAS-COG) score of a subject as compared to the ADAS-COG score of the subject before treatment. In some embodiments, the administration of CT1812 results in an at least 3 point reduction in the Alzheimer's Disease Assessment Score (ADAS-COG) score of a subject as compared to the ADAS-COG score of the subject before treatment.

[0033] In some embodiments, the present disclosure describes a method of reducing amyloid β monomer levels in a subject comprising administering to the subject a therapeutically effective amount of a pharmaceutical composition comprising a compound of formula:



, CT1812

or a pharmaceutically acceptable salt thereof,

wherein the pharmaceutical composition comprises at least one pharmaceutically acceptable excipient.

[0034] In some embodiments, the subject is a human. In some embodiments described herein, the subject is a subject with cognitive decline. In some embodiments

described herein, the subject is a subject with cognitive decline wherein the cognitive decline is Alzheimer's disease. In some embodiments described herein, the subject is a subject with Alzheimer's disease.

[0035] In some embodiments the compound is administered orally. In some embodiments, the compound is administered by a route selected from the group comprising oral administration, intravenous administration, intramuscular administration, subcutaneous administration, intranasal administration, intradermal administration, topical administration, In some embodiments, the compound may be formulated as a tablet, as a capsule, as a powder, in a solution, in a suspension, and in an emulsion,

[0036] In some embodiments a total daily dose of 10 mg to 2000 mg, of the compound in a pharmaceutical composition is administered. The total daily dose of the compounds of this disclosure can be administered to a subject in single dose or in divided doses. In some embodiments the dose of the compound in a pharmaceutical composition is 100 mg per day, in some embodiments the dose of the compound in a pharmaceutical composition is 300 mg per day, in some embodiments the dose of the compound in a pharmaceutical composition is 560 mg per day. In some embodiments a total daily dose of 100 mg of the compound in a pharmaceutical composition is administered for at least about 6 months. In some embodiments a total daily dose of 300 mg of the compound in a pharmaceutical composition is administered for at least about 6 months. In some embodiments a total daily dose of about 560 mg of the compound in a pharmaceutical composition is administered for at least about 6 months. In some embodiments the total daily dose is about 10mg to about 2000 mg, about 100 mg to about 2000 mg, about 200 mg to about 2000 mg, about 300 mg to about 2000 mg, about 400 mg to about 2000 mg, about 500 mg to about 2000 mg, about 600 mg to about 2000 mg, about 700 mg to about 2000 mg, about 800 mg to about 2000 mg, about 900 mg to about 2000 mg, about 1000 mg to about 2000 mg, about 1200 mg to about 2000 mg, about 1400 mg to about 2000 mg, about 1600 mg to about 2000 mg, about 1800 mg to about 2000 mg, or a value within these ranges. Specific examples may include about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, about 1600 mg,

about 1700 mg, about 1800 mg, about 1900 mg, about 2000 mg, or a range between any two of these values.

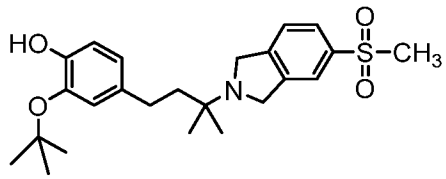
[0037] In some embodiments the pharmaceutical composition is administered for at least 6 months. In some embodiments, some embodiments the pharmaceutical composition is administered for about 1 day to about 50 years. In some embodiments the pharmaceutical composition is administered for about 1 day to about 1 year. In some embodiments the pharmaceutical composition is administered for about 1 day to about 6 months, about 3 days to about 6 months, about 1 week to about 6 months, about 2 weeks to about 6 months, about 3 weeks to about 6 months, about 1 month to about 6 months, about 2 months to about 6 months, about 3 months to about 6 months, about 4 months to about 6 months, about 5 months to about 6 months, or a value within these ranges. Specific examples may include about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 2 weeks, about 3 weeks, about 4 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 7 months, about 8 months, about 9 months, about 10 months, about 11 months, about 12 months, about 1 year or a range between any two of these values.

[0038] In some embodiments the administration of CT1812 results in a change in amyloid β levels in the cerebral spinal fluid (CSF), hippocampal interstitial fluid, plasma, or a combination thereof. In some embodiments the administration of CT1812 results in a reduction of amyloid β monomer levels. In some embodiments, the amyloid β monomer is selected from Aβ 1-40 and Aβ 1-42. In some embodiments the administration of CT1812 results in an elevation of amyloid β oligomers in the cerebral spinal fluid (CSF), hippocampal interstitial fluid, plasma, or a combination thereof. In some embodiments the level of amyloid β after administration of CT1812 is relative to the level of amyloid β before administration of CT1812. In some embodiments, the amyloid β levels are measured using microimmunoelectrodes. In some embodiments, the amyloid β levels are measured using Western Blot. In some embodiments, the amyloid β levels are measured using ELISA (enzyme-linked immunosorbent assay).

[0039] In some embodiments, the administration of the pharmaceutical composition results in a reduction in cognitive decline. In some embodiments, the administration of the pharmaceutical composition blocks cognitive decline. In some

embodiments, the administration of the pharmaceutical composition results in a reduction in the Alzheimer's Disease Assessment Score (ADAS-COG) score of a subject as compared to the ADAS-COG score of the subject before treatment. In some embodiments the administration of the pharmaceutical composition results in a subject maintaining the Alzheimer's Disease Assessment Score (ADAS-COG) score of a subject as compared to the ADAS-COG score of the subject before treatment. In some embodiments, the administration of the pharmaceutical composition results in an at least 3 point reduction in the Alzheimer's Disease Assessment Score (ADAS-COG) score of a subject as compared to the ADAS-COG score of the subject before treatment.

[0040] In some embodiments, the present disclosure describes a method of elevating amyloid β oligomer levels in a subject comprising administering to the subject a therapeutically effective amount of a compound of formula:



, CT1812

or a pharmaceutically acceptable salt thereof.

[0041] In some embodiments described herein, the subject is a human. In some embodiments described herein, the subject is a subject with cognitive decline. In some embodiments described herein, the subject is a subject with cognitive decline wherein the cognitive decline is Alzheimer's disease. In some embodiments described herein, the subject is a subject with Alzheimer's disease.

[0042] In some embodiments the compound is administered orally. In some embodiments, the compound is administered by a route selected from the group comprising oral administration, intravenous administration, intramuscular administration, subcutaneous administration, intranasal administration, intradermal administration, topical administration, In some embodiments, the compound may be formulated as a tablet, as a capsule, as a powder, in a solution, in a suspension, and in an emulsion,

[0043] In some embodiments a total daily dose of 10 mg to 2000 mg, of the compound is administered. The total daily dose of the compounds of this disclosure can be administered to a subject in single dose or in divided doses. In some embodiments the dose

is 100 mg per day, in some embodiments the dose is 300 mg per day, in some embodiments the dose is about 560 mg per day. In some embodiments a total daily dose of 100 mg of the compound is administered one time. In some embodiments a total daily dose of 300 mg of the compound is administered one time. In some embodiments a total daily dose of 560 mg of the compound is administered one time. In some embodiments the total daily does is about 10mg to about 2000 mg, about 100 mg to about 2000 mg, about 200 mg to about 2000 mg, about 300 mg to about 2000 mg, about 400 mg to about 2000 mg, about 500 mg to about 2000 mg, about 600 mg to about 2000 mg, about 700 mg to about 2000 mg, about 800 mg to about 2000 mg, about 900 mg to about 2000 mg, about 1000 mg to about 2000 mg, about 1200 mg to about 2000 mg, about 1400 mg to about 2000 mg, about 1600 mg to about 2000 mg, about 1800 mg to about 2000 mg, or a value within these ranges. Specific examples may include about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, about 1600 mg, about 1700 mg, about 1800 mg, about 1900 mg, about 2000 mg, or a range between any two of these values.

[0044] In some embodiments CT1812 is administered one time. In some embodiments CT1812 is administered for at least 6 months. In some embodiments, CT1812 is administered for about 1 day to about 50 years. In some embodiments, CT1812 is administered for about 1 day to about 1 year. In some embodiments, CT1812 is administered for about 1 day to about 6 months, about 3 days to about 6 months, about 1 week to about 6 months, about 2 weeks to about 6 months, about 3 weeks to about 6 months, about 1 month to about 6 months, about 2 months to about 6 months, about 3 months to about 6 months, about 4 months to about 6 months, about 5 months to about 6 months, or a value within these ranges. Specific examples may include about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 2 weeks, about 3 weeks, about 4 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 7 months, about 8 months, about 9 months, about 10 months, about 11 months, about 12 months, about 1 year or a range between any two of these values.

[0045] In some embodiments the amyloid β oligomers levels are measured within 24 hours of CT1812 administration. In some embodiments the amyloid β oligomer levels are measured within 1 week of CT1812 administration. In some embodiments the amyloid β oligomers levels are measured within 1 month of CT1812 administration. In some embodiments the amyloid β oligomers levels are measured within 6 months of CT1812 administration. In some embodiments the amyloid β oligomers levels are measured at a time point from about 15 minutes to about 12 months after CT1812 administration, about 15 minutes to about 24 hours after CT1812 administration, about 30 minutes to about 24 hours after CT1812 administration, about 45 minutes to about 24 hours after CT1812 administration, about 1 hour to about 24 hours after CT1812 administration, about 2 hours to about 24 hours after CT1812 administration, about 3 hours to about 24 hours after CT1812 administration, about 4 hours to about 24 hours after CT1812 administration, about 6 hours to about 24 hours after CT1812 administration, about 8 hours to about 24 hours after CT1812 administration, about 10 hours to about 24 hours after CT1812 administration, about 12 hours to about 24 hours after CT1812 administration, about 16 hours to about 24 hours after CT1812 administration, about 20 hours to about 24 hours after CT1812 administration, about 1 day to about 7 days after CT1812 administration, about 2 days to about 7 days after CT1812 administration, about 1 week to about 4 weeks after CT1812 administration, about 2 weeks to about 4 weeks after CT1812 administration, about 3 weeks to about 4 weeks after CT1812 administration, about 1 month to about 12 months after CT1812 administration, about 2 months to about 12 months after CT1812 administration, about 3 months to about 12 months after CT1812 administration, about 4 months to about 12 months after CT1812 administration, about 5 months to about 12 months after CT1812 administration, about 6 months to about 12 months after CT1812 administration, about 7 months to about 12 months after CT1812 administration, about 8 months to about 12 months after CT1812 administration, about 9 months to about 12 months after CT1812 administration, about 10 months to about 12 months after CT1812 administration, about 11 months to about 12 months after CT1812 administration.

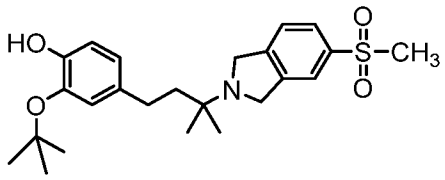
[0046] In some embodiments, the amyloid β levels are indicative of target engagement after administration of CT1812. In some embodiments, the amyloid β levels

increase after administration of CT1812, wherein the increase in amyloid β levels is indicative of target engagement.

[0047] In some embodiments the administration of CT1812 results in a change in amyloid β levels in the cerebral spinal fluid (CSF), hippocampal interstitial fluid, plasma, or a combination thereof. In some embodiments the administration of CT1812 results in a reduction of amyloid β monomer levels. In some embodiments, the amyloid β monomer is selected from Aβ 1-40 and Aβ 1-42. In some embodiments the administration of CT1812 results in an elevation of amyloid β oligomers in the cerebral spinal fluid (CSF), hippocampal interstitial fluid, plasma, or a combination thereof. In some embodiments the level of amyloid β after administration of CT1812 is relative to the level of amyloid β before administration of CT1812. In some embodiments, the amyloid β levels are measured using micorimmunoelectrodes. In some embodiments, the amyloid β levels are measured using Western Blot. In some embodiments, the amyloid β levels are measured using ELISA (enzyme-linked immunosorbent assay).

[0048] In some embodiments, the administration of CT1812 results in a reduction in cognitive decline. In some embodiments, the administration of CT1812 blocks cognitive decline. In some embodiments, the administration of CT1812 results in a reduction in the Alzheimer's Disease Assessment Score (ADAS-COG) score of a subject as compared to the ADAS-COG score of the subject before treatment. In some embodiments the administration of CT1812 results in a subject maintaining the Alzheimer's Disease Assessment Score (ADAS-COG) score of a subject as compared to the ADAS-COG score of the subject before treatment. In some embodiments, the administration of CT1812 results in an at least 3 point reduction in the Alzheimer's Disease Assessment Score (ADAS-COG) score of a subject as compared to the ADAS-COG score of the subject before treatment.

[0049] In some embodiments, the present disclosure describes a method of treating cognitive decline in a subject comprising administering to the subject a therapeutically effective amount of a compound of formula:

[0050]  , CT1812

[0051] or a pharmaceutically acceptable salt thereof.

[0052] In some embodiments described herein, the subject is a human. In some embodiments described herein, the subject is a subject with cognitive decline. In some embodiments described herein, the subject is a subject with cognitive decline wherein the cognitive decline is Alzheimer's disease. In some embodiments described herein, the subject is a subject with Alzheimer's disease.

[0053] In some embodiments the compound is administered orally. In some embodiments, the compound is administered by a route selected from the group comprising oral administration, intravenous administration, intramuscular administration, subcutaneous administration, intranasal administration, intradermal administration, topical administration, In some embodiments, the compound may be formulated as a tablet, as a capsule, as a powder, in a solution, in a suspension, and in an emulsion,

[0054] In some embodiments a total daily dose of 10 mg to 2000 mg, of the compound is administered. The total daily dose of the compounds of this disclosure can be administered to a subject in single dose or in divided doses. In some embodiments the dose is 100 mg per day, in some embodiments the dose is 300 mg per day, in some embodiments the dose is about 560 mg. In some embodiments a total daily dose of 100 mg of the compound is administered for at least about 6 months. In some embodiments a total daily dose of 300 mg of the compound is administered for at least about 6 months. In some embodiments a total daily dose of about 560 mg of the compound is administered for at least about 6 months. In some embodiments the total daily does is about 10mg to about 2000 mg, about 100 mg to about 2000 mg, about 200 mg to about 2000 mg, about 300 mg to about 2000 mg, about 400 mg to about 2000 mg, about 500 mg to about 2000 mg, about 600 mg to about 2000 mg, about 700 mg to about 2000 mg, about 800 mg to about 2000 mg, about 900 mg to about 2000 mg, about 1000 mg to about 2000 mg, about 1200 mg to about 2000 mg, about 1400 mg to about 2000 mg, about 1600 mg to about 2000 mg, about 1800 mg to about 2000 mg, or a value within these ranges. Specific examples may include

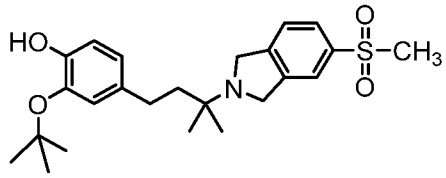
about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, about 1600 mg, about 1700 mg, about 1800 mg, about 1900 mg, about 2000 mg, or a range between any two of these values.

[0055] In some embodiments CT1812 is administered for at least 6 months. In some embodiments, some embodiments CT1812 is administered for about 1 day to about 50 years. In some embodiments CT1812 is administered for about 1 day to about 1 year. In some embodiments CT1812 is administered for about 1 day to about 6 months, about 3 days to about 6 months, about 1 week to about 6 months, about 2 weeks to about 6 months, about 3 weeks to about 6 months, about 1 month to about 6 months, about 2 months to about 6 months, about 3 months to about 6 months, about 4 months to about 6 months, about 5 months to about 6 months, or a value within these ranges. Specific examples may include about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 2 weeks, about 3 weeks, about 4 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 7 months, about 8 months, about 9 months, about 10 months, about 11 months, about 12 months, about 1 year or a range between any two of these values.

[0056] In some embodiments the administration of CT1812 results in a change in amyloid β levels in the cerebral spinal fluid (CSF), hippocampal interstitial fluid, plasma, or a combination thereof. In some embodiments the administration of CT1812 results in a reduction of amyloid β monomer levels. In some embodiments, the amyloid β monomer is selected from Aβ 1-40 and Aβ 1-42. In some embodiments the administration of CT1812 results in an elevation of amyloid β oligomers in the cerebral spinal fluid (CSF), hippocampal interstitial fluid, plasma, or a combination thereof. In some embodiments the level of amyloid β after administration of CT1812 is relative to the level of amyloid β before administration of CT1812. In some embodiments, the amyloid β levels are measured using microimmunoelectrodes. In some embodiments, the amyloid β levels are measured using Western Blot. In some embodiments, the amyloid β levels are measured using ELISA (enzyme-linked immunosorbent assay).

[0057] In some embodiments, the administration of CT1812 results in a reduction in cognitive decline. In some embodiments, the administration of CT1812 blocks cognitive decline. In some embodiments, the administration of CT1812 results in a reduction in the Alzheimer's Disease Assessment Score (ADAS-COG) score of a subject as compared to the ADAS-COG score of the subject before treatment. In some embodiments the administration of CT1812 results in a subject maintaining the Alzheimer's Disease Assessment Score (ADAS-COG) score of a subject as compared to the ADAS-COG score of the subject before treatment. In some embodiments, the administration of CT1812 results in an at least 3 point reduction in the Alzheimer's Disease Assessment Score (ADAS-COG) score of a subject as compared to the ADAS-COG score of the subject before treatment.

[0058] In some embodiments, the present disclosure describes method of treating Alzheimer's disease in a subject comprising administering to the subject a therapeutically effective amount of a compound of formula:



, CT1812

or a pharmaceutically acceptable salt thereof.

[0059] In some embodiments described herein, the subject is a human. In some embodiments described herein, the subject is a subject with cognitive decline. In some embodiments described herein, the subject is a subject with cognitive decline wherein the cognitive decline is Alzheimer's disease. In some embodiments described herein, the subject is a subject with Alzheimer's disease.

[0060] In some embodiments the compound is administered orally. In some embodiments, the compound is administered by a route selected from the group comprising oral administration, intravenous administration, intramuscular administration, subcutaneous administration, intranasal administration, intradermal administration, topical administration, In some embodiments, the compound may be formulated as a tablet, as a capsule, as a powder, in a solution, in a suspension, and in an emulsion,

[0061] In some embodiments a total daily dose of 10 mg to 2000 mg, of the compound is administered. The total daily dose of the compounds of this disclosure can be administered to a subject in single dose or in divided doses. In some embodiments the dose is 100 mg per day, in some embodiments the dose is 300 mg per day, in some embodiments the dose is about 560 mg. In some embodiments a total daily dose of 100 mg of the compound is administered for at least about 6 months. In some embodiments a total daily dose of 300 mg of the compound is administered for at least about 6 months. In some embodiments a total daily dose of 560 mg of the compound is administered for at least about 6 months. In some embodiments the total daily does is about 10mg to about 2000 mg, about 100 mg to about 2000 mg, about 200 mg to about 2000 mg, about 300 mg to about 2000 mg, about 400 mg to about 2000 mg, about 500 mg to about 2000 mg, about 600 mg to about 2000 mg, about 700 mg to about 2000 mg, about 800 mg to about 2000 mg, about 900 mg to about 2000 mg, about 1000 mg to about 2000 mg, about 1200 mg to about 2000 mg, about 1400 mg to about 2000 mg, about 1600 mg to about 2000 mg, about 1800 mg to about 2000 mg, or a value within these ranges. Specific examples may include about 50 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, about 1600 mg, about 1700 mg, about 1800 mg, about 1900 mg, about 2000 mg, or a range between any two of these values.

[0062] In some embodiments CT1812 is administered for at least 6 months. In some embodiments, some embodiments CT1812 is administered for about 1 day to about 50 years. In some embodiments CT1812 is administered for about 1 day to about 1 year. In some embodiments CT1812 is administered for about 1 day to about 6 months, about 3 days to about 6 months, about 1 week to about 6 months, about 2 weeks to about 6 months, about 3 weeks to about 6 months, about 1 month to about 6 months, about 2 months to about 6 months, about 3 months to about 6 months, about 4 months to about 6 months, about 5 months to about 6 months, or a value within these ranges. Specific examples may include about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 2 weeks, about 3 weeks, about 4 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 7 months,

about 8 months, about 9 months, about 10 months, about 11 months, about 12 months, about 1 year or a range between any two of these values.

[0063] In some embodiments the administration of CT1812 results in a change in amyloid β levels in the cerebral spinal fluid (CSF), hippocampal interstitial fluid, plasma, or a combination thereof. In some embodiments the administration of CT1812 results in a reduction of amyloid β monomer levels. In some embodiments, the amyloid β monomer is selected from Aβ 1-40 and Aβ 1-42. In some embodiments the administration of CT1812 results in an elevation of amyloid β oligomers in the cerebral spinal fluid (CSF), hippocampal interstitial fluid, plasma, or a combination thereof. In some embodiments the level of amyloid β after administration of CT1812 is relative to the level of amyloid β before administration of CT1812. In some embodiments, the amyloid β levels are measured using microimmunoelectrodes. In some embodiments, the amyloid β levels are measured using Western Blot. In some embodiments, the amyloid β levels are measured using ELISA (enzyme-linked immunosorbent assay).

[0064] In some embodiments, the administration of CT1812 results in a reduction in cognitive decline. In some embodiments, the administration of CT1812 blocks cognitive decline. In some embodiments, the administration of CT1812 results in a reduction in the Alzheimer's Disease Assessment Score (ADAS-COG) score of a subject as compared to the ADAS-COG score of the subject before treatment. In some embodiments the administration of CT1812 results in a subject maintaining the Alzheimer's Disease Assessment Score (ADAS-COG) score of a subject as compared to the ADAS-COG score of the subject before treatment. In some embodiments, the administration of CT1812 results in an at least 3 point reduction in the Alzheimer's Disease Assessment Score (ADAS-COG) score of a subject as compared to the ADAS-COG score of the subject before treatment.

EXAMPLES:

Example 1: Clinical Efficacy of CT1812

[0065] *Methods*: A Phase 2 clinical trial (NCT03522129) was conducted enrolling patients with mild-to-moderate Alzheimer's disease (MMSE 18-26) into the

Randomized, double-blind, placebo-controlled, single dose administration of CT1812 followed by hourly sampling of lumbar CSF via indwelling catheter for 24 hours. The primary objective of the study was to evaluate target engagement of CT1812 treatment by measuring the displacement of Aβ oligomers into cerebrospinal fluid (CSF). The was quantified by a measuring change from the baseline CSF Aβ oligomer concentration after dosing with CT1812 versus placebo. Microimmunoelectrodes (Yuede et al 2016) coated with oligomer-specific antibody, A11 were placed in CSF samples of Alzheimer's disease patient samples to detect soluble Aβ after a single dose of CT1812 (560mg) or placebo.

[0066] *Results:* Microimmunoelectrode (MIE) measurements of Aβ oligomers in CSF show a drug-dependent rise in Aβ oligomers over time. After a pre-dose baseline was established, MIE measurements of oligomer levels showed an apparent increase with time in the CSF of patients receiving a single dose of CT1812 (vertical dashed line) but not in patient receiving placebo (Figure 1). The slopes for Patients 1 and 3 were significantly non-zero [$p<0.001$ for each patient, $R^2= 0.7720$ ($F = 91.45$) and $R^2 = 0.7898$ ($F = 101.5$), respectively while the linear slope for the placebo -treated patient (Patient 2) was not different from zero ($p = 0.6849$, $R2 = 0.06891$ $F = 1.998$.

[0067] MIE measurements were confirmed using Western Blot to measure protein levels. Alzheimer's disease patient CSF samples (N=3 patients) were run on native Western Blot probed with AB specific antibody, 82E1. Following the single dose of CT1812 (vertical dashed line), Oligomer levels showed an apparent increase with time in the CSF of patients receiving a single dose of CT1812 (vertical dashed line) but not in patient receiving placebo (Figure 2). The slopes for Patients 1 and 3 were significantly non-zero [$p<0.001$ for each patient, $R^2= 0.9808$ ($F = 41.91$) and $R2 = 0.3997$ ($F = 17.31$), respectively] while the linear slope for the placebo -treated patient (Patient 2) was not different from zero ($p = 0.0.6849$, $R^2 = 0.006437$ $F = 0.1684$). Spearman correlation analysis shows significant correlation between MIE and western blot oligomer measurements (Figure 3, $r – 0.74$, $p = 3x\ 10^{-13}$).

[0068] Interestingly, this robust drug-related increase in Ab oligomers over time is specific to oligomers. Percent change from baseline in Aβ 40 and 42 monomers were similar in all three patients (<50% increase). Aβ oligomer increased more than 200% in the two treated patients but did not increase in the placebo-treated patient. CSF Aβ oligomer

levels were fit to a linear regression and the significance of the slope difference from zero was determined for each patient (Figure 4 (measured by microimmunoelectrodes); Figure 5 (measured by Western Blot)). A summary of plasma and CSF data are presented in Table 1 and Figure 6.

Matrix	Subject	C_{max} (ng/mL)	t_{max} (hr)	$AUC_{0\text{-last}}$ (hr*ng/mL)	CSF/Plasma Ratio	
					C_{max}[a]	$AUC_{0\text{-last}}$[b]
Plasma	90001	695	1.00	3160	0.0358	0.0381
	90003	250	2.00	1210	0.0291	0.0384
CSF	90001	24.9	2.00	120	-	-
	90003	7.27	3.00	46.4	-	-

[a] based on C_{max}; [b] based on $AUC_{0\text{-last}}$
$AUC_{0\text{-last}}$: area under the curve from time 0 to the last measurable concentration; C_{max}: maximum observed concentration; t_{max}: time of maximum concentration

Table 1: Summary of plasma and CSF data from NCT03522129

[0069] *Summary:* The results of this study provide early proof of principle that we may be able to measure target engagement in Alzheimer's disease patients. The pharmacokinetics of this study suggest that there is an exposure dependent relationship with the rise in oligomers.

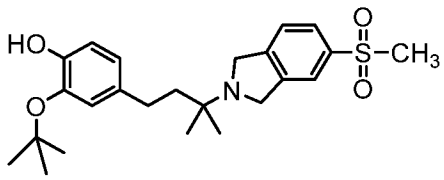
Example 2: CT1812 treatment reduces cognitive decline

[0070] Patients treated for at least 6 months (185 days) with CT1812 were compared with patients who received placebo. Patients receiving CT1812 demonstrated a three-point difference Alzheimer's Disease Assessment Score (ADAS-COG) between treated and untreated patients at day 185, representing a clinically meaningful magnitude of change suggesting a trend for improved cognitive outcomes (Figure 7). Patients treated for at least 6 months (185 days) with CT1812 had lower Aβ protein (p=0.017) in treated versus placebo patients (Figure 8).

CLAIMS

We claim:

1. A method of reducing amyloid β monomer levels in a subject comprising administering to the subject a therapeutically effective amount of a compound of formula:



or a pharmaceutically acceptable salt thereof.

2. The method of claim 1, wherein the subject is a human.

3. The method of claim 1, wherein the subject is a subject with cognitive decline.

4. The method of claim 3, wherein the cognitive decline is Alzheimer's disease.

5. The method of claim 1, wherein the subject is a subject with Alzheimer's disease.

6. The method of claim 1, wherein the compound is administered for at least 6 months.

7. The method of claim 1, wherein the therapeutically effective amount is a total daily dose of about 10 mg to about 2000 mg administered for at least 6 months.

8. The method of claim 1, wherein the therapeutically effective amount is a total daily dose of about 300 mg administered for at least 6 months.

9. The method of claim 1, wherein the therapeutically effective amount is a total daily dose of 100 mg administered for at least 6 months.

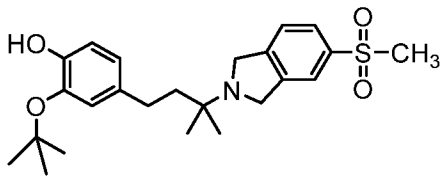
10. The method of claim 1, wherein the amyloid β monomer is selected from Aβ 1-40 and Aβ 1-42.

11. The method of claim 1, wherein the method of reducing amyloid β monomer levels is relative to amyloid β monomer levels prior to administration of the compound.

12. The method of claim 1, wherein the amyloid β levels are measured from cerebral spinal fluid, hippocampal interstitial fluid, plasma or a combination thereof.

13. The method of claim 1, wherein administering a therapeutically effective amount of the compound results in a reduction in the Alzheimer's Disease Assessment Score (ADAS-COG) score of a subject as compared to the ADAS-COG score of the subject before treatment.

14. A method of reducing amyloid β monomer levels in a subject comprising administering to the subject a therapeutically effective amount of a pharmaceutical composition comprising a compound of formula:



or a pharmaceutically acceptable salt thereof,

wherein the pharmaceutical composition comprises at least one pharmaceutically acceptable excipient.

15. The method of claim 14, wherein the subject is a human.

16. The method of claim 14, wherein the subject is a subject with cognitive decline.

17. The method of claim 16, wherein the cognitive decline is Alzheimer's disease.

18. The method of claim 14, wherein the subject is a subject with Alzheimer's disease.

19. The method of claim 14, wherein the pharmaceutical composition is administered for at least 6 months.

20. The method of claim 14, wherein the therapeutically effective amount is a total daily dose of about 10 mg to about 2000 mg administered for at least 6 months.

21. The method of claim 14, wherein the therapeutically effective amount is a total daily dose of about 300 mg administered for at least 6 months.

22. The method of claim 14, wherein the therapeutically effective amount is a total daily dose of 100 mg administered for at least 6 months.

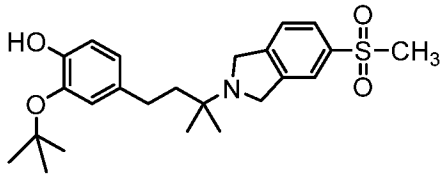
23. The method of claim 14, wherein the amyloid β monomer is selected from Aβ 1-40 and Aβ 1-42.

24. The method of claim 14, wherein the method of reducing amyloid β monomer levels is relative to amyloid β monomer levels prior to administration of the compound.

25. The method of claim 14, wherein the amyloid β levels are measured from cerebral spinal fluid, hippocampal interstitial fluid, plasma or a combination thereof.

26. The method of claim 14, wherein administering a therapeutically effective amount of the pharmaceutical composition results in a reduction in the Alzheimer's Disease Assessment Score (ADAS-COG) score of a subject as compared to the ADAS-COG score of the subject before treatment.

27. A method of elevating amyloid β oligomer levels in a subject comprising administering to the subject a therapeutically effective amount of a compound of formula:



or a pharmaceutically acceptable salt thereof.

28. The method of claim 27, wherein the subject is a human.

29. The method of claim 27, wherein the subject is a subject with cognitive decline.

30. The method of claim 29, wherein the cognitive decline is Alzheimer's disease.

31. The method of claim 27, wherein the subject is a subject with Alzheimer's disease.

32. The method of claim 27, wherein the compound is administered orally.

33. The method of claim 27, wherein the therapeutically effective amount is a total daily dose of about 10 mg to about 2000 mg.

34. The method of claim 27, wherein the therapeutically effective amount is a total daily dose of about 560 mg.

35. The method of claim 27, wherein the therapeutically effective amount is a total daily dose of about 300 mg.

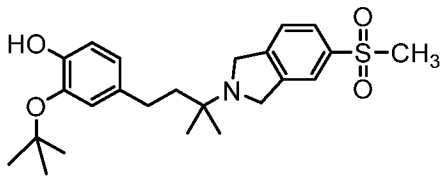
36. The method of claim 27, wherein the therapeutically effective amount is a total daily dose of 100 mg.

37. The method of claim 27, wherein the method of elevating amyloid β oligomer levels is relative to amyloid β oligomer levels prior to administration of the compound.

38. The method of claim 27, wherein the amyloid β levels are measured from cerebral spinal fluid, hippocampal interstitial fluid, plasma or a combination thereof.

39. The method of claim 27, wherein the amyloid β levels are measured within 24 hours of CT1812 administration.

40. A method of treating cognitive decline in a subject comprising administering to the subject a therapeutically effective amount of a compound of formula:



or a pharmaceutically acceptable salt thereof.

41. The method of claim 40, wherein the subject is a human.

42. The method of claim 40, wherein the cognitive decline is Alzheimer's disease.

43. The method of claim 40, wherein the compound is administered for at least 6 months.

44. The method of claim 40, wherein the therapeutically effective amount is a total daily dose of about 10 mg to about 2000 mg administered for at least 6 months.

45. The method of claim 40, wherein the therapeutically effective amount is a total daily dose of about 300 mg administered for at least 6 months.

46. The method of claim 40, wherein the therapeutically effective amount is a total daily dose of 100 mg administered for at least 6 months.

47. The method of claim 40, wherein administering a therapeutically effective amount of the compound results in a change in levels of amyloid β in a subject.

48. The method of claim 47, wherein the levels of amyloid β are relative to amyloid β monomer levels prior to administration of the compound.

49. The method of claim 47, wherein the change in the levels of amyloid β is selected from a reduction in amyloid β monomers, an increase in amyloid β oligomers, or both.

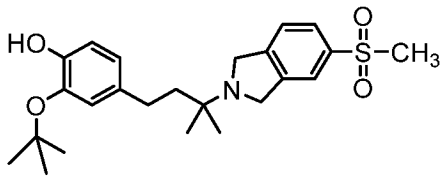
50. The method of claim 47, wherein the amyloid β monomers is selected from Aβ 1-40 and Aβ 1-42.

51. The method of claim 47, wherein the amyloid β levels are measured from cerebral spinal fluid, hippocampal interstitial fluid, plasma or a combination thereof.

52. The method of claim 40, wherein administering a therapeutically effective amount of the compound results in a reduction in the Alzheimer's Disease Assessment Score (ADAS-COG) score of a subject as compared to the ADAS-COG score of the subject before treatment.

53. The method of claim 40, wherein administering a therapeutically effective amount of the compound results in at a least 3 point reduction in the Alzheimer's Disease Assessment Score (ADAS-COG) score of a subject.

54. A method of treating Alzheimer's disease in a subject comprising administering to the subject a therapeutically effective amount of a compound of formula:



or a pharmaceutically acceptable salt thereof.

55. The method of claim 54, wherein the subject is a human.

56. The method of claim 54, wherein the compound is administered for at least 6 months.

57. The method of claim 54, wherein the therapeutically effective amount is a total daily dose of about 10 mg to about 2000 mg administered for at least 6 months.

58. The method of claim 54, wherein the therapeutically effective amount is a total daily dose of about 300 mg administered for at least 6 months.

59. The method of claim 54, wherein the therapeutically effective amount is a total daily dose of 100 mg administered for at least 6 months.

60. The method of claim 54, wherein administering a therapeutically effective amount of the compound results in a change in levels of amyloid β in a subject.

61. The method of claim 60, wherein the levels of amyloid β are relative to amyloid β monomer levels prior to administration of the compound.

62. The method of claim 60, wherein the change in the levels of amyloid β is selected from a reduction in amyloid β monomers, an increase in amyloid β oligomers, or both.

63. The method of claim 60, wherein the amyloid β monomers is selected from Aβ 1-40 and Aβ 1-42.

64. The method of claim 60, wherein the amyloid β levels are measured from cerebral spinal fluid, hippocampal interstitial fluid, plasma or a combination thereof.

65. The method of claim 54, wherein administering a therapeutically effective amount of the compound results in a reduction in the Alzheimer's Disease Assessment Score (ADAS-COG) score of a subject as compared to the ADAS-COG score of the subject before treatment.

66. The method of claim 54, wherein administering a therapeutically effective amount of the compound results in an at least 3 point reduction in the Alzheimer's Disease Assessment Score (ADAS-COG) score of a subject as compared to the ADAS-COG score of the subject before treatment.

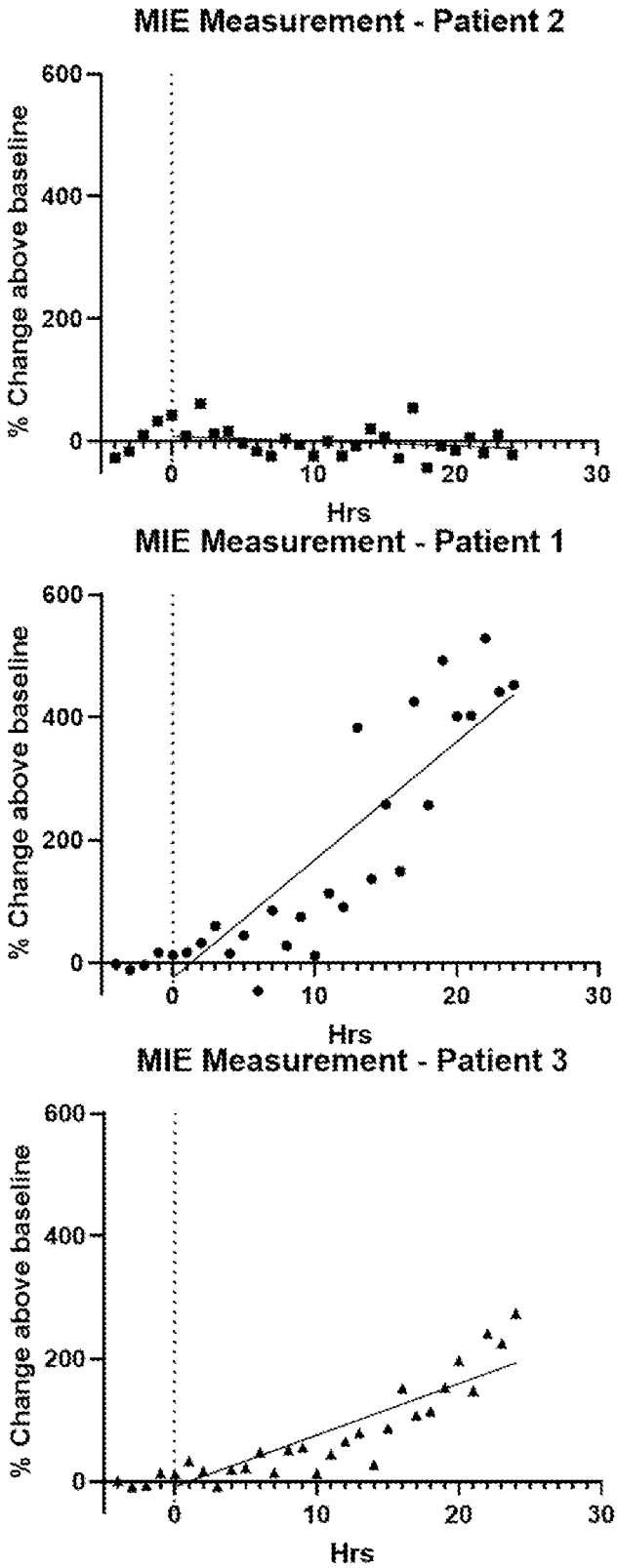

MIE Measurement - Patient 2
% Change above baseline
600
400
200
0
0
10
20
30
Hrs
MIE Measurement - Patient 1
% Change above baseline
600
400
200
0
0
10
20
30
Hrs
MIE Measurement - Patient 3
% Change above baseline
600
400
200
0
0
10
20
30
Hrs

Figure 1

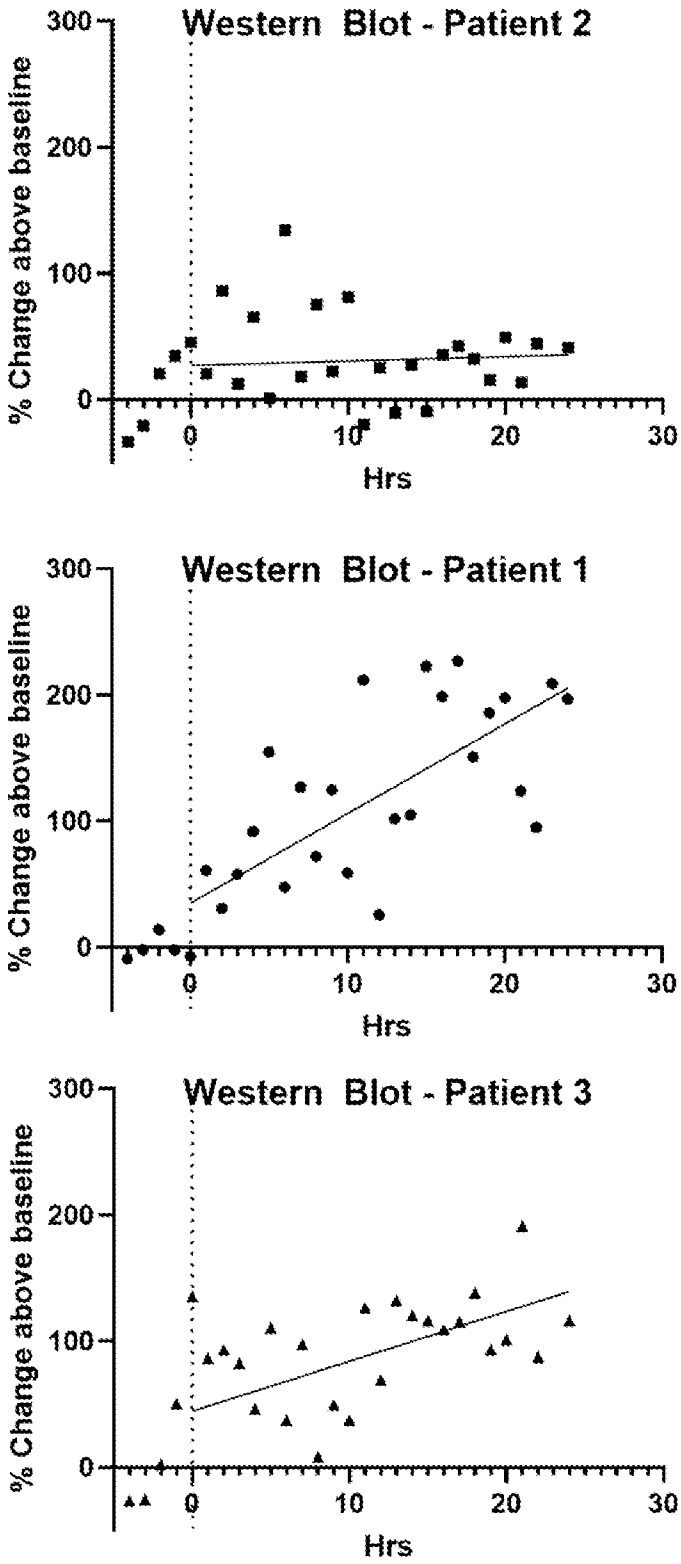

Western Blot - Patient 2
% Change above baseline
300
200
100
0
0
10
20
30
Hrs
Western Blot - Patient 1
% Change above baseline
300
200
100
0
0
10
20
30
Hrs
Western Blot - Patient 3
% Change above baseline
300
200
100
0
0
10
20
30
Hrs

Figure 2

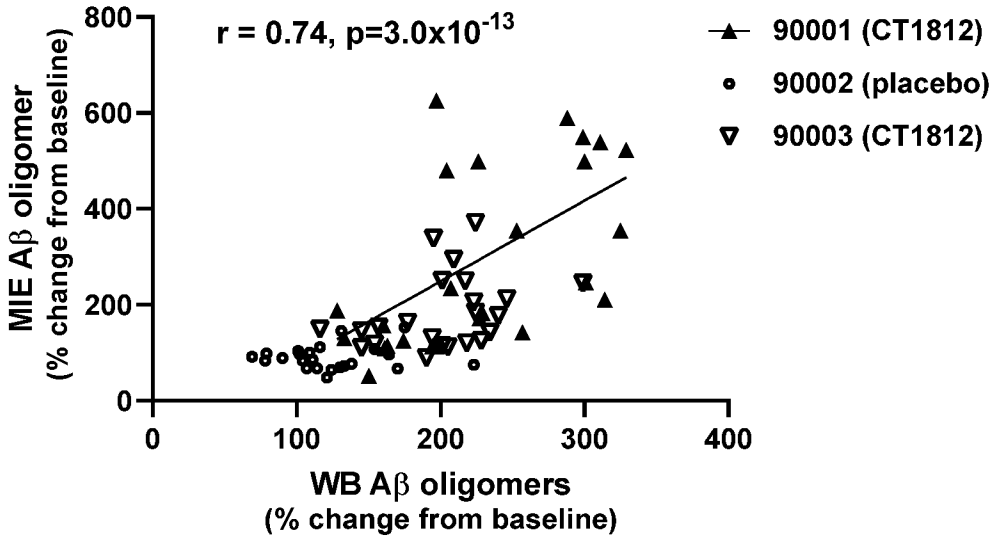

r = 0.74, p=3.0x10-13
MIE Aβ oligomer
(% change from baseline)
800
600
400
200
0
0
100
200
300
400
WB Aβ oligomers
(% change from baseline)
90001 (CT1812)
90002 (placebo)
90003 (CT1812)

Figure 3

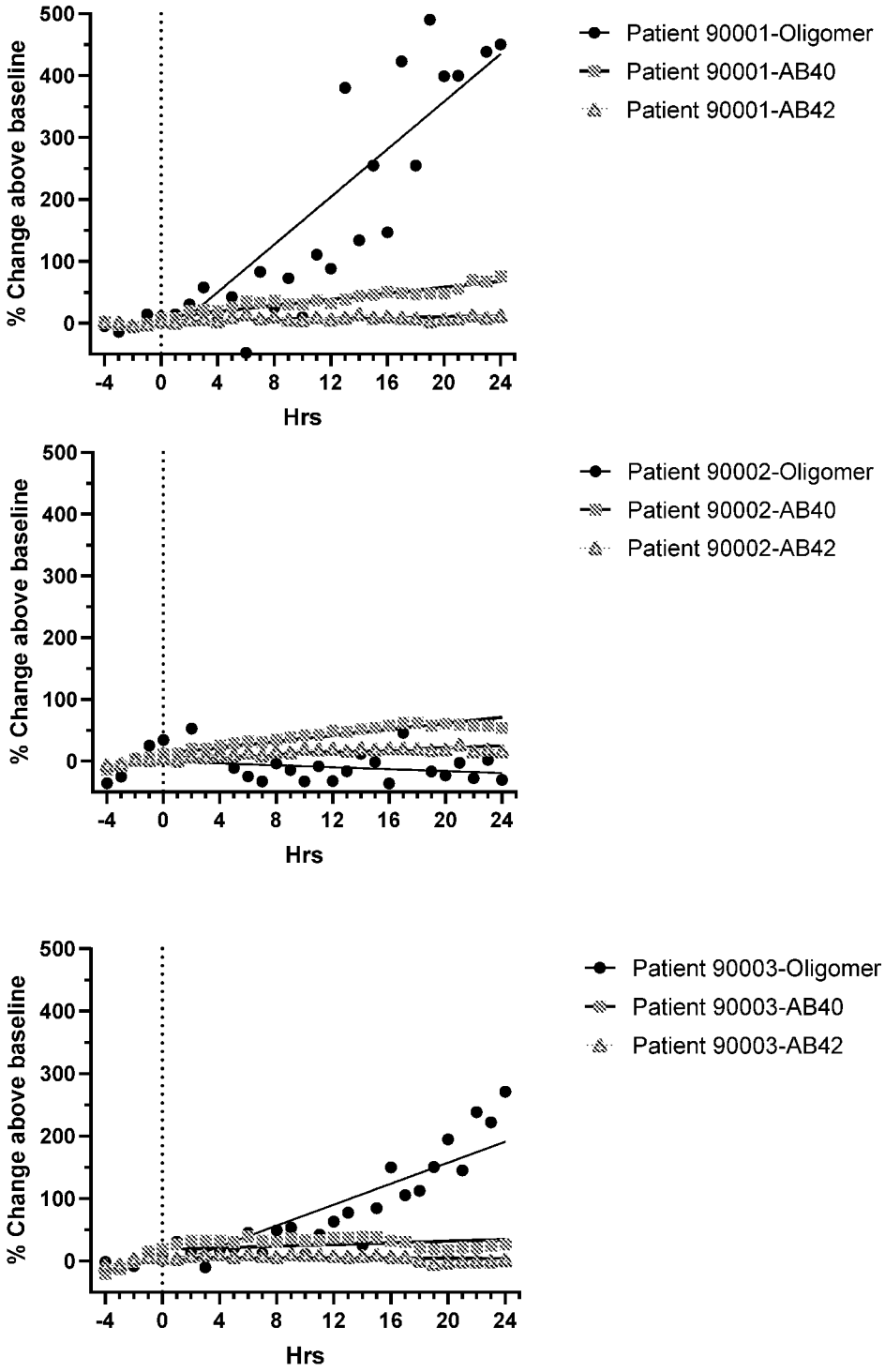

% Change above baseline
500
400
300
200
100
0
-4
0
4
8
12
16
20
24
Hrs
Patient 90001-Oligomer
Patient 90001-AB40
Patient 90001-AB42
Patient 90002-Oligomer
Patient 90002-AB40
Patient 90002-AB42
Patient 90003-Oligomer
Patient 90003-AB40
Patient 90003-AB42

Figure 4

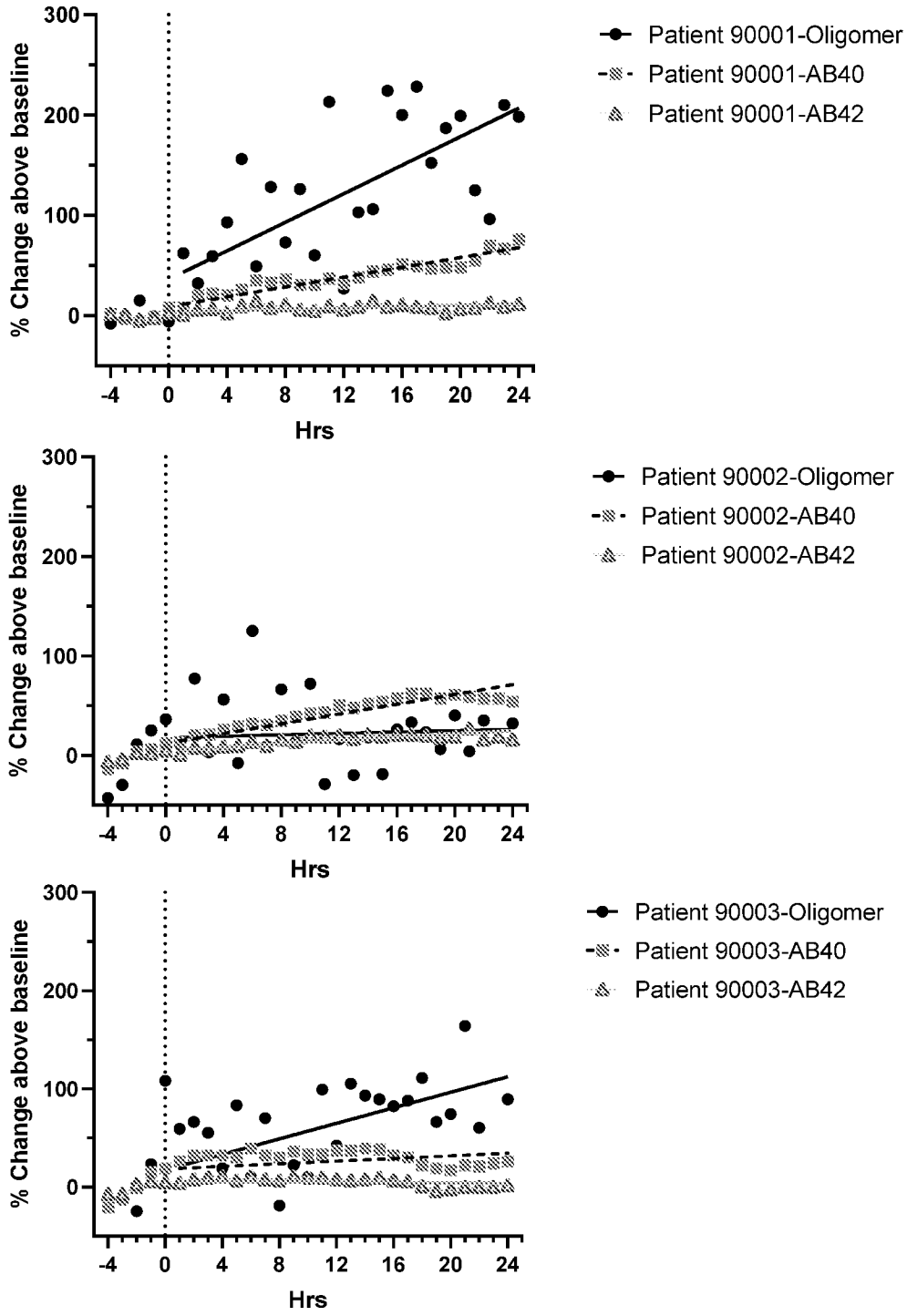

% Change above baseline
300
200
100
0
-4
0
4
8
12
16
20
24
Hrs
Patient 90001-Oligomer
Patient 90001-AB40
Patient 90001-AB42
Patient 90002-Oligomer
Patient 90002-AB40
Patient 90002-AB42
Patient 90003-Oligomer
Patient 90003-AB40
Patient 90003-AB42

Figure 5

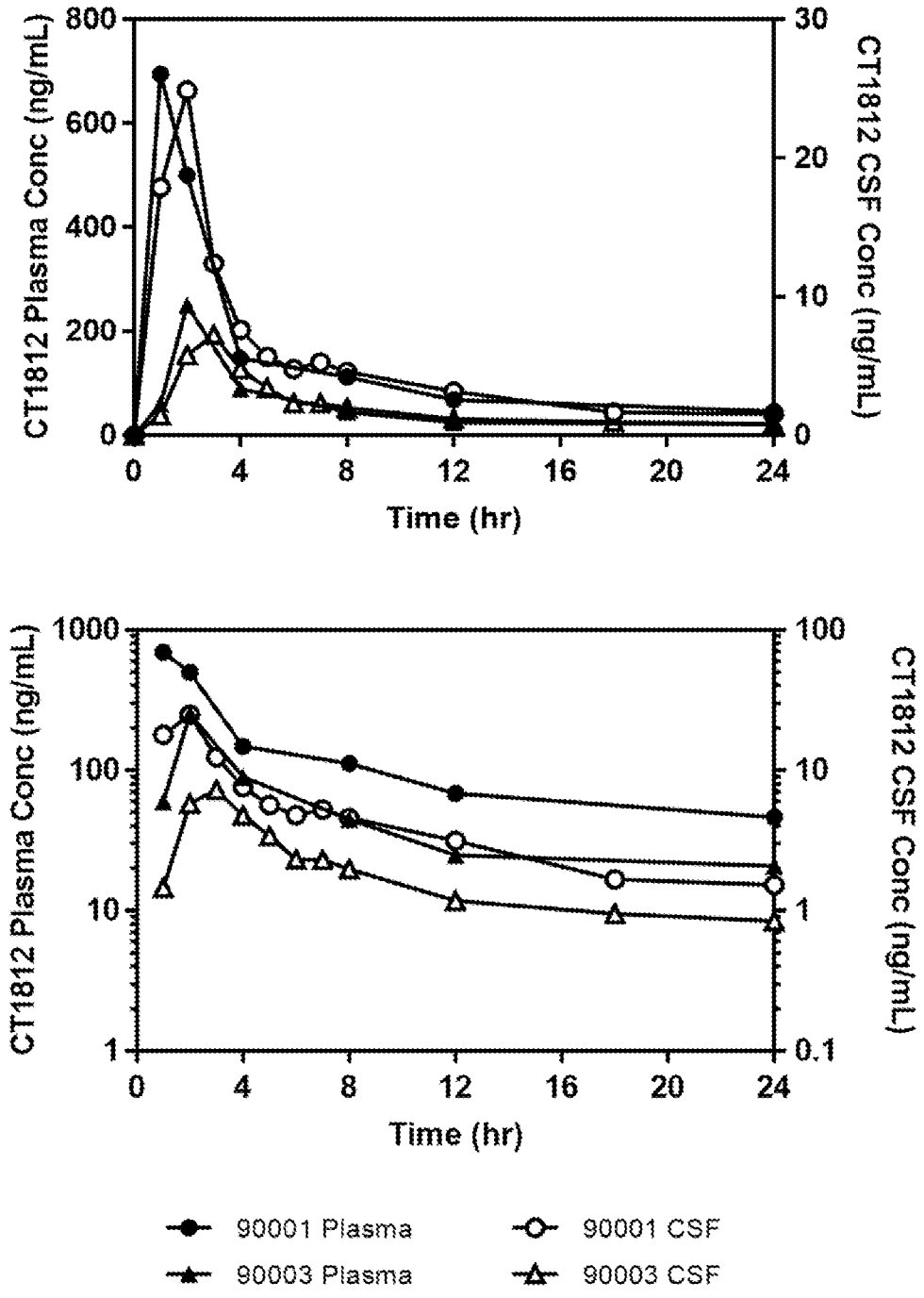

CT1812 Plasma Conc (ng/mL)
CT1812 CSF Conc (ng/mL)
Time (hr)
800
600
400
200
0
30
20
10
0
0
4
8
12
16
20
24
1000
100
10
1
100
10
1
0.1
90001 Plasma
90001 CSF
90003 Plasma
90003 CSF

Figure 6

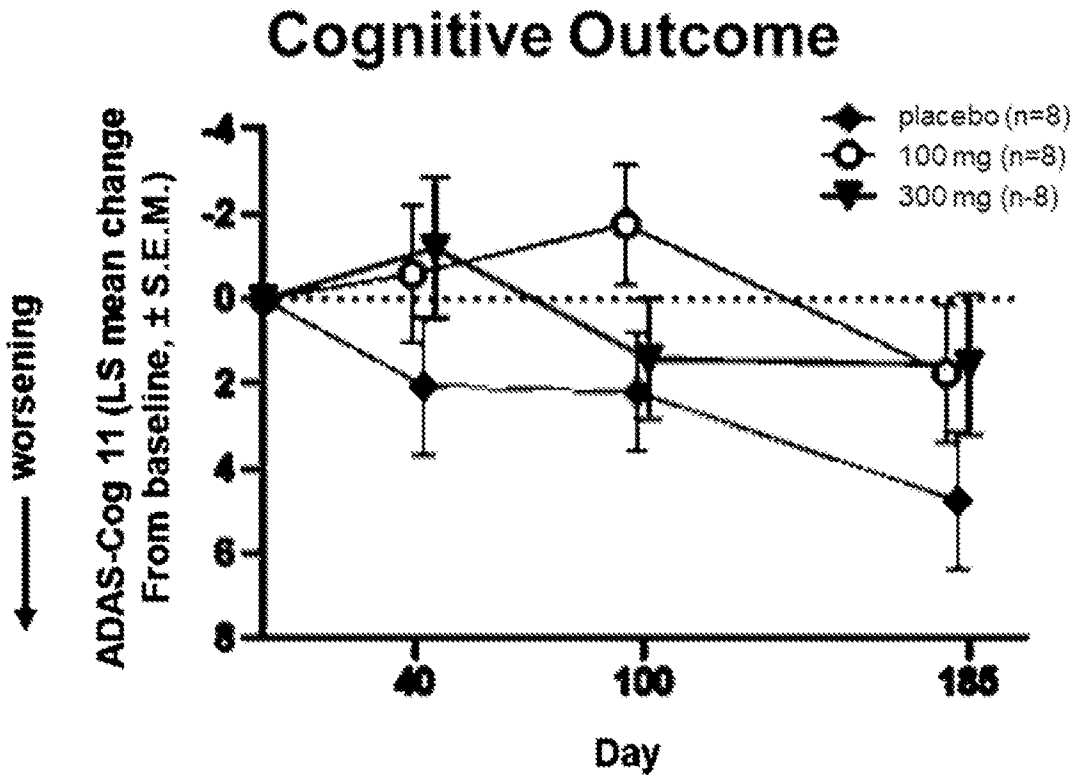

Cognitive Outcome
placebo (n=8)
100 mg (n=8)
300 mg (n-8)
worsening
ADAS-Cog 11 (LS mean change
From baseline, ± S.E.M.)
4
2
0
2
4
6
8
40
100
185
Day

Figure 7

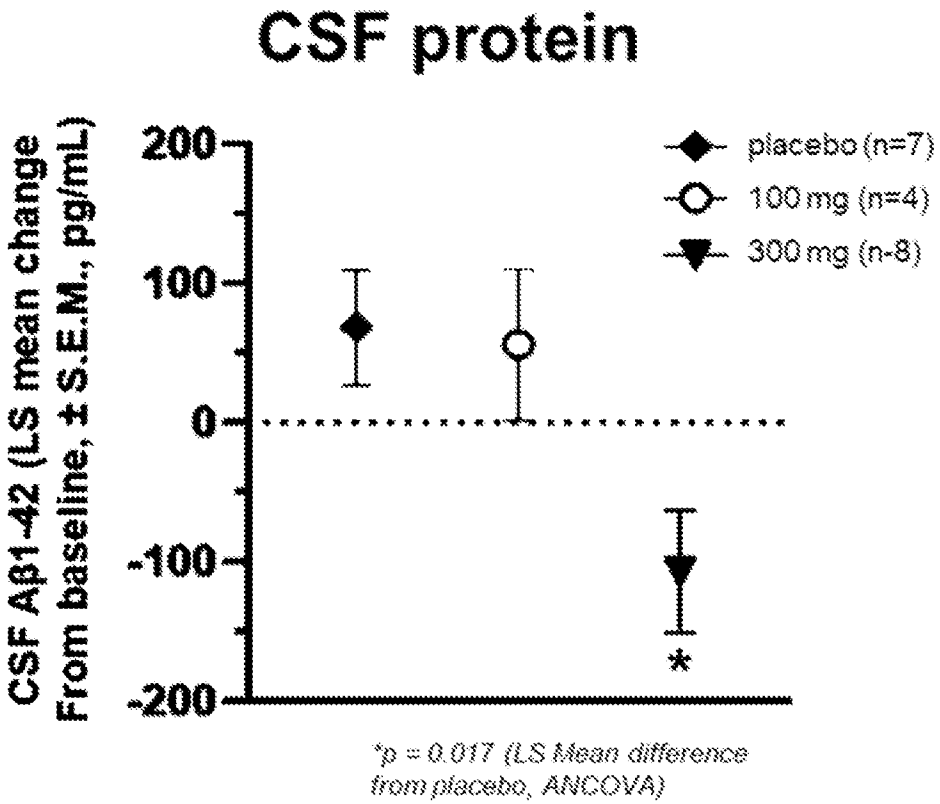

CSF protein
CSF Aβ1-42 (LS mean change From baseline, ± S.E.M., pg/mL)
200
100
0
-100
-200
placebo (n=7)
100 mg (n=4)
300 mg (n-8)
*
*p = 0.017 (LS Mean difference from placebo, ANCOVA)

Figure 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/18023

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
(see extra sheet)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-26

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/18023

A. CLASSIFICATION OF SUBJECT MATTER

IPC - C07K 16/18; C12P 21/08; G01N 33/68 (2021.01)

CPC - A61P 25/00; A61P 25/28; C07K 16/18; G01N 33/6896

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)
See Search History document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2017/0144970 A1 (COGNITION THERAPEUTICS INC) 25 May 2017 (25.05.2017), especially: pg 6, col 2, first formula; para [0007]; para [0059]; para [0062]; para [0089]; para [0116]; para [0117]; para [0122]; para [0125]; para [0270]; para [0279]; para [0326]; para [0355].	1-26
A	CANO et al."The ADAS-cog in Alzheimer's Disease clinical trials: Psychometric evaluation of the sum and its parts" by Cano et al.; see pg 3, para 2.	1-26
A	GEERTS et al. "Impact of amyloid-beta changes on cognitive outcomes in Alzheimer's disease: analysis of clinical trials using a quantitative systems pharmacology model", Alzheimer's Research & Therapy. 2018. 10:14, 14 pages.	1-26

☐ Further documents are listed in the continuation of Box C. ☐ 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
"D" document cited by the applicant in the international application
"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
2 June 2021	JUN 25 2021
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Lee Young Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 21/18023

--BOX III - LACK OF UNITY--

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I: Claims 1-26, drawn to a method of reducing amyloid beta monomer levels in a subject comprising administering to the subject a therapeutically effective amount of a compound or a pharmaceutical composition comprising a compound of formula indicated in claim 1.

Group II: Claims 27-39, drawn to a method of elevating amyloid beta oligomer levels in a subject comprising administering to the subject a therapeutically effective amount of a compound of formula indicated in claim 27.

Group III: Claims 40-53, drawn to a method of treating cognitive decline in a subject comprising administering to the subject a therapeutically effective amount of a compound of formula indicated in claim 40.

Group IV: Claims 54-66, drawn to a method of treating Alzheimer' s disease in a subject comprising administering to the subject a therapeutically effective amount of a compound of formula indicated in claim 54.

The inventions listed as Groups I, II, III and IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features

Group I requires a method of reducing amyloid beta monomer levels in a subject, which is not required by Groups II-IV.

Group II requires a method of elevating amyloid beta oligomer levels in a subject, which is not required by Groups I or III-IV.

Group III requires a method of treating cognitive decline in a subject, which is not required by Groups I-II or IV.

Group IV requires a method of treating Alzheimer' s disease in a subject, which is not required by Groups I-III,

Shared Common Features

The only feature shared by Groups I, II, III and IV that would otherwise unify the groups is a compound of formula indicated in claim 1. However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is anticipated by US 2017/0144970 A1 to Cognition Therapeutics Inc (hereinafter 'COGNITION'). Cognition teaches a compound of formula indicated in claim 1 (pg 6, col 2, first formula).

As the technical features were known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups. Groups I, II, III and IV therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.