

ANTI-N3pGlu AMYLOID BETA PEPTIDE ANTIBODIES AND USES THEREOF

The present invention relates to treatment of a disease with anti-N3pGlu A β antibodies, wherein the disease is characterized by deposition of Amyloid Beta (A β) in a patient. More specifically, the present invention relates to a short term induction treatment with N3pGlu A β antibodies of a disease characterized by deposition of A β in the brain, including Alzheimer's disease (AD), Down's syndrome, and cerebral amyloid angiopathy (CAA).

The deposits found in plaques of human patients are comprised of a heterogeneous mixture of A β peptides. N3pGlu A β , also referred to as N3pE A β , A β pE3-42, or A β _{p3-42}, is a truncated form of A β peptide and is found only in plaques. N3pGlu A β lacks the first two amino acid residues at the N-terminus of human A β and has a pyroglutamate which was derived from the glutamic acid at the third amino acid position. Although N3pGlu A β peptide is a minor component of the deposited A β in the brain, studies have demonstrated that N3pGlu A β peptide has aggressive aggregation properties and accumulates early in the deposition cascade.

Antibodies to N3pGlu A β are known in the art. For example, U.S. Patent Number 8,679,498 discloses anti-N3pGlu A β antibodies and methods of treating diseases such as Alzheimer's disease, with the antibodies. Passive immunization by long term chronic administration of antibodies against the A β , including N3pGlu A β , found in deposits has been shown to disrupt the A β aggregates and promote the clearance of plaques in the brain in various animal models. However, in humans long term chronic administration of A β antibodies has led to adverse events that include amyloid-related imaging abnormalities (ARIA), suggestive of vasogenic edema and sulcal effusions (ARIA-E), as well as microhaemorrhages and haemosiderin deposits (ARIA-H) as well as infusion site reactions and risk of immunogenicity. See Piazza and Winblad, "Amyloid-Related Imaging Abnormalities (ARIA) in Immunotherapy Trials for Alzheimer's Disease: Need for Prognostic Biomarkers?" Journal of Alzheimer's Disease, 52 (2016) 417-420.

Summary

In one aspect of the present disclosure, there is provided a use of an anti-N3pGlu A β antibody in the manufacture of a medicament for reducing amyloid beta (A β) deposits in the brain of a patient in need thereof, wherein the medicament comprises an intravenous dose of 10 to 60 mg/kg of the anti-N3pGlu A β antibody, wherein the medicament is to be administered more than one time to the patient at a frequency of once every month for a period of 6 months or less, and wherein the anti-N3pGlu A β antibody

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comprises a light chain variable region (LCVR) of SEQ ID NO: 25 and a heavy chain variable region (HCVR) of SEQ ID NO:26.

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Description

5 The present invention overcomes the problems associated with long term chronic
administration. Applicants found that short term induction treatment with relatively high doses of
anti-N3pGlu A β antibodies promotes significant clearance of plaques in the brain of patients with
A β deposits, and this clearance is surprisingly maintained for an extended period of time. The
short term induction treatment can include a one-time dose of an anti-N3pGlu antibody, a
biweekly dose of an anti-N3pGlu A β antibody for a period of 6 months, or a monthly dose of an
10 anti-N3pGlu A β antibody for a period of 6 months or less. In addition to reducing the adverse

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events caused by long term chronic dosing of antibodies against A β , additional benefits of the short term induction treatment include improved patient compliance, reduced infusion site reactions and risk of immunogenicity, significant cost savings for treatment as well as reduced disruption to the patient and caregiver's lives.

5 As such, the present invention provides a method of treating a disease characterized by deposition of A β , comprising administering to a patient positive for amyloid deposits an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 month or less. Particularly, the present invention provides a method of treating a disease characterized by deposition of A β , comprising administering to a patient positive for amyloid deposits an induction
10 dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 month or less. More particularly, the present invention provides a method to treat a disease characterized by A β deposits in the brain of a human patient comprising administering to the patient positive for amyloid deposits a one-time induction dose of 10 to 60 mg/kg of an anti-N3pGlu antibody. In another more particular embodiment, the present invention provides a method to treat a disease
15 characterized by A β deposits in the brain of a patient positive for amyloid deposits comprising administering to the patient an induction dose of 10 to 60 mg/kg every two weeks of an anti-N3pGlu A β antibody for a period of 6 months or less. In another more particular embodiment, the present invention provides a method to treat a disease characterized by A β deposits in the brain of a patient positive for amyloid deposits comprising administering to the patient a monthly
20 induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 months or less. In a preferred embodiment of the present invention, the one-time induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg. In a alternative preferred embodiment of the present invention, the biweekly and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg for a period of 6 months. In another more preferred embodiment,
25 the anti-N3pGlu A β antibody is selected from Table A.

Alternatively, the present invention provides a method of treating a disease characterized by deposition of A β , comprising administering to a patient positive for amyloid deposits a dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody followed optionally by one or more dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 month or less. Particularly, the present
30 invention provides a method to treat a disease characterized by A β deposits in the brain of a patient positive for amyloid deposits comprising administering to the patient 1-12 separate doses of 10 to 60 mg/kg of an anti-N3pGlu A β antibody in a period of 6 months or less. In another more particular embodiment, the present invention provides a method to treat a disease characterized by A β deposits in the brain of a patient positive for amyloid deposits comprising administering to the

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patient 6 separate doses of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 months or less. Alternatively, the present invention provides a method to treat a disease characterized by A β deposits in the brain of a patient positive for amyloid deposits comprising administering to the patient 12 separate doses of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 months or less. In a preferred embodiment of the present invention, the 6 or 12 separate doses administered to a patient are 20 to 40 mg/kg or 15 to 30 mg/kg (e.g., 6 separate doses of 20 mg/kg administered to a patient over 6 months). In another preferred embodiment, the one-time, 6 or 12 separate doses administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg, or 40mg/kg per dose. In another preferred embodiment the 6 separate doses are separated by monthly interval and the 12 separate doses are separated by intervals of 2 weeks. In a preferred embodiment, the anti-N3pGlu A β antibody is selected from Table A.

In an embodiment, the present invention provides a method of treating or preventing clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical CAA in a patient positive for amyloid deposits, comprising administering to a patient induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 month or less. Particularly, the present invention provides a method of treating or preventing clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical CAA in a patient positive for amyloid deposits, comprising administering to the patient a one-time induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody. In another particular embodiment, the present invention provides a method of treating or preventing clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical CAA in a patient positive for amyloid deposits, administering to the an induction dose of 10 to 60 mg/kg every two weeks of an anti-N3pGlu A β antibody for a period of 6 months or less. In another particular embodiment, the present invention provides a method of treating or preventing clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical CAA in a patient positive for amyloid deposits, administering to the patient a monthly induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 months or less. In a preferred embodiment of the invention for treating or preventing clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical CAA, the one-time, biweekly (every two weeks) and monthly induction dose administered to a patient is 20 to 40 mg/kg or 15 to 30 mg/kg. In a preferred embodiment of the present invention, the one-time induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg. In a alternative preferred embodiment of the present invention, the biweekly and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg for a period of 6

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months In another more preferred embodiment, the anti-N3pGlu A β antibody is selected from Table A.. The anti-N3pGlu A β antibody is preferably selected from Table A.

In another embodiment, the present invention provides a method of treating or preventing preclinical AD, prodromal AD (sometimes also referred to as A β -related mild cognitive impairment, MCI or MCI due to AD), mild AD, moderate AD and severe AD in a patient positive for amyloid deposits, comprising administering to a patient an induction dose of an anti-N3pGlu A β antibody for a period of 6 months or less. Particularly, the present invention provides a method of treating or preventing preclinical AD, prodromal AD, mild AD, moderate AD and severe AD in a patient positive for amyloid deposits, comprising administering to a patient an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 month or less. More particularly, the present invention provides a method of treating or preventing preclinical AD, prodromal AD, mild AD, moderate AD and severe AD in a patient positive for amyloid deposits, comprising administering to the patient a one-time induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody. In another more particular embodiment, the present invention provides a method of treating or preventing preclinical AD, prodromal AD, mild AD, moderate AD and severe AD in a patient positive for amyloid deposits, administering to the an induction dose of 10 to 60 mg/kg every two weeks of an anti-N3pGlu A β antibody for a period of 6 months or less. In another more particular embodiment, the present invention provides a method of treating or preventing preclinical AD, prodromal AD, mild AD, moderate AD and severe AD in a patient positive for amyloid deposits, administering to the patient a monthly induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 months or less. In a preferred embodiment of the invention for treating or preventing preclinical AD, prodromal AD, mild AD, moderate AD and severe AD, the one-time, biweekly (every two weeks) and monthly induction dose administered to a patient is 20 to 40 mg/kg or 15 to 30 mg/kg. In a preferred embodiment of the present invention, the one-time induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg. In an alternative preferred embodiment of the present invention, the biweekly and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg for a period of 6 months In another more preferred embodiment, the anti-N3pGlu A β antibody is selected from Table A.. The anti-N3pGlu A β antibody is preferably selected from Table A.

In another embodiment, the present invention provides a method of slowing cognitive decline in a patient diagnosed with pre-clinical Alzheimer's disease or clinical Alzheimer's disease, comprising administering to a patient an induction dose of an anti-N3pGlu A β antibody for a period of 6 months or less. Particularly, the present invention a method of slowing cognitive

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decline in a patient diagnosed with pre-clinical Alzheimer's disease or clinical Alzheimer's disease,, comprising administering to a patient an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 month or less. More particularly, the present invention provides a method of slowing cognitive decline in a patient diagnosed with pre-clinical

- 5 Alzheimer's disease or clinical Alzheimer's disease,, comprising administering to the patient a one-time induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody. In another more particular embodiment, the present invention provides a method of slowing cognitive decline in a patient diagnosed with pre-clinical Alzheimer's disease or clinical Alzheimer's disease,, administering to the patient an induction dose of 10 to 60 mg/kg every two weeks of an anti-
- 10 N3pGlu A β antibody for a period of 6 months or less. In another more particular embodiment, the present invention provides a method of slowing cognitive decline in a patient diagnosed with pre-clinical Alzheimer's disease or clinical Alzheimer's disease,, administering to the patient a monthly induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 months or less. In a preferred embodiment of the invention for slowing cognitive decline in a
- 15 patient diagnosed with pre-clinical Alzheimer's disease or clinical Alzheimer's disease, the one-time, biweekly and monthly induction dose administered to a patient is 20 to 40 mg/kg or 15 to 30 mg/kg. In a preferred embodiment of the present invention, the one-time induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg. In an alternative preferred embodiment of the present invention, the biweekly and monthly induction dose administered to a
- 20 patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg for a period of 6 months In another more preferred embodiment, the anti-N3pGlu A β antibody is selected from Table A. The anti-N3pGlu A β antibody is preferably selected from Table A.

In another embodiment, the present invention provides a method of slowing functional decline in a patient diagnosed with pre-clinical Alzheimer's disease or clinical Alzheimer's

25 disease, comprising administering to a patient an induction dose of an anti-N3pGlu A β antibody for a period of 6 months or less. Particularly, the present invention a method of slowing functional decline in a patient diagnosed with pre-clinical Alzheimer's disease or clinical Alzheimer's disease, comprising administering to a patient an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 month or less. More particularly, the present invention

30 provides a method of slowing functional decline in a patient diagnosed with pre-clinical Alzheimer's disease or clinical Alzheimer's disease, comprising administering to the patient a one-time induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody. In another more particular embodiment, the present invention provides a method of slowing functional decline in a patient diagnosed with pre-clinical Alzheimer's disease or clinical Alzheimer's disease,

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administering to the patient an induction dose of 10 to 60 mg/kg every two weeks of an anti-N3pGlu A β antibody for a period of 6 months or less. In another more particular embodiment, the present invention provides a method of slowing functional decline in a patient diagnosed with pre-clinical Alzheimer's disease or clinical Alzheimer's disease, administering to the patient a

5 monthly induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 months or less. In a preferred embodiment of the invention for slowing functional decline in a patient diagnosed with pre-clinical Alzheimer's disease or clinical Alzheimer's disease, the one-time, biweekly and monthly induction dose administered to a patient is 20 to 40 mg/kg or 15 to 30 mg/kg. In a preferred embodiment of the present invention, the one-time induction dose

10 administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg. In an alternative preferred embodiment of the present invention, the biweekly and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg for a period of 6 months. The anti-N3pGlu A β antibody is preferably selected from Table A.

In another embodiment the present invention provides a method of reducing brain A β amyloid plaque load in a patient diagnosed with pre-clinical or clinical Alzheimer's disease, comprising

15 administering to a patient an induction dose of an anti-N3pGlu A β antibody for a period of 6 months or less. Particularly, the present invention provides a method of reducing brain A β amyloid plaque load in a patient diagnosed with pre-clinical or clinical Alzheimer's disease, comprising administering to a patient an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β

20 antibody for a period of 6 month or less. More particularly, the present invention provides a method of reducing brain A β amyloid plaque load in a patient diagnosed with pre-clinical or clinical Alzheimer's disease, comprising administering to the patient a one-time induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody. In another more particular embodiment, the present invention provides a method of reducing brain A β amyloid plaque load in a patient

25 diagnosed with pre-clinical or clinical Alzheimer's disease, administering to the patient an induction dose of 10 to 60 mg/kg every two weeks of an anti-N3pGlu A β antibody for a period of 6 months or less. In another more particular embodiment, the present invention provides a method of reducing brain A β amyloid plaque load in a patient diagnosed with pre-clinical or clinical Alzheimer's disease, administering to the patient a monthly induction dose of 10 to 60 mg/kg of

30 an anti-N3pGlu A β antibody for a period of 6 months or less. In a preferred embodiment of the invention for a method of reducing brain A β amyloid plaque load in a patient diagnosed with pre-clinical or clinical Alzheimer's disease, the one-time, biweekly and monthly induction dose administered to a patient is 20 to 40 mg/kg or 15 to 30 mg/kg. In a preferred embodiment of the present invention, the one-time induction dose administered to a patient is 10mg/kg, 15 mg/kg,

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20mg/kg or 40mg/kg. In an alternative preferred embodiment of the present invention, the biweekly and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg for a period of 6 months. The anti-N3pGlu A β antibody is preferably selected from Table A.

- 5 In another embodiment the present invention provides a method of preventing memory loss or cognitive decline in clinically asymptomatic patients with low levels of A β 1-42 in the cerebrospinal fluid (CSF) and/or A β deposits in the brain, comprising administering to a patient an induction dose of an anti-N3pGlu A β antibody for a period of 6 months or less. Particularly, the present invention provides a method of preventing memory loss or cognitive decline in
- 10 clinically asymptomatic patients with low levels of A β 1-42 in the cerebrospinal fluid (CSF) and/or A β deposits in the brain, comprising administering to a patient an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 month or less. More particularly, the invention provides a method of preventing memory loss or cognitive decline in clinically
- 15 asymptomatic patients with low levels of A β 1-42 in the cerebrospinal fluid (CSF) and/or A β deposits in the brain, comprising administering to the patient a one-time induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody. In another more particular embodiment, the present invention provides a method of preventing memory loss or cognitive decline in clinically
- 20 asymptomatic patients with low levels of A β 1-42 in the cerebrospinal fluid (CSF) and/or A β deposits in the brain, comprising administering to the patient an induction dose of 10 to 60 mg/kg every two weeks of an anti-N3pGlu A β antibody for a period of 6 months or less. In another more particular embodiment, the present invention provides a method of preventing memory loss or cognitive decline in clinically asymptomatic patients with low levels of A β 1-42 in the cerebrospinal fluid (CSF) and/or A β deposits in the brain, administering to the patient a monthly induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 months or less.
- 25 In a preferred embodiment of the invention for a method of preventing memory loss or cognitive decline in clinically asymptomatic patients with low levels of A β 1-42 in the cerebrospinal fluid (CSF) and/or A β deposits in the brain, the one-time, biweekly and monthly induction dose administered to a patient is 20 to 40 mg/kg or 15 to 30 mg/kg. In another preferred embodiment of the present invention, the one-time induction dose administered to a patient is 10mg/kg, 15
- 30 mg/kg, 20mg/kg or 40mg/kg. In an alternative preferred embodiment of the present invention, the biweekly and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg for a period of 6 months. The anti-N3pGlu A β antibody is preferably selected from Table A.

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In another embodiment the present invention provides a method of treating clinically asymptomatic patients known to have an Alzheimer's disease-causing genetic mutation, comprising administering to a patient an induction dose of an anti-N3pGlu A β antibody for a period of 6 months or less. Particularly, the present provides a method of treating clinically asymptomatic patients known to have an Alzheimer's disease-causing genetic mutation, comprising administering to a patient an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 month or less. More particularly, the invention provides a method of treating clinically asymptomatic patients known to have an Alzheimer's disease-causing genetic mutation, comprising administering to the patient a one-time induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody. In another more particular embodiment, the present invention provides a method of treating clinically asymptomatic patients known to have an Alzheimer's disease-causing genetic mutation, comprising administering to the patient an induction dose of 10 to 60 mg/kg every two weeks of an anti-N3pGlu A β antibody for a period of 6 months or less. In another more particular embodiment, the present invention provides a method of treating clinically asymptomatic patients known to have an Alzheimer's disease-causing genetic mutation, administering to the patient a monthly induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 months or less. In the present invention "clinically asymptomatic patients known to have an Alzheimer's disease-causing genetic mutation", include patients known to have a PSEN1 E280A Alzheimer's disease-causing genetic mutation (Paisa mutation), a genetic mutation that causes autosomal-dominant Alzheimer's disease or are at higher risk for developing AD by virtue of carrying one or two APOE e4 alleles comprising administering to the said patient a pharmaceutical composition of the present invention. In a preferred embodiment of the invention for a method of treating clinically asymptomatic patients known to have an Alzheimer's disease-causing genetic mutation,, the one-time, biweekly and monthly induction dose administered to a patient is 20 to 40 mg/kg or 15 to 30 mg/kg. In another preferred embodiment of the present invention, the one-time induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg. In an alternative preferred embodiment of the present invention, the biweekly and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg for a period of 6 months. The anti-N3pGlu A β antibody is preferably selected from Table A.

In a further embodiment, the present invention provides a method of treating a disease characterized by deposition of A β in the brain, comprising administering to a patient an induction dose of an anti-N3pGlu A β antibody for a period of 6 months or less, wherein the A β deposit in the brain of a human patient is reduced by 35-100% within 6 months post induction dose

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treatment. Particularly, the present invention provides a method of treating a disease characterized by deposition of A β , comprising administering to a patient an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 month or less, wherein the A β deposit in the brain of a human patient is reduced by 35-100% within 6 months post induction dose treatment. More particularly, the present invention provides a method to treat a disease characterized by A β deposits in the brain of a human patient comprising administering to the patient a one-time induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody, wherein the A β deposit in the brain of a human patient is reduced by 35-100% within 6 months post induction dose treatment. In another more particular embodiment, the present invention provides a method to treat a disease characterized by A β deposits in the brain of a patient comprising administering to the patient an induction dose of 10 to 60 mg/kg every two weeks of an anti-N3pGlu A β antibody for a period of 6 months or less, wherein the A β deposit in the brain of a human patient is reduced by 35-100% within 6 months post induction dose treatment. In another more particular embodiment, the present invention provides a method to treat a disease characterized by A β deposits in the brain of a patient comprising administering to the patient a monthly induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 months or less, wherein the A β deposit in the brain of a human patient is reduced by 35-100% within 6 months post induction dose treatment. In a preferred embodiment of the present invention, the one-time induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg. In an alternative preferred embodiment of the present invention, the biweekly and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg for a period of 6 months. The anti-N3pGlu A β antibody is preferably selected from Table A.

In an embodiment, the present invention provides a method of treating clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, comprising administering to a patient an induction dose of an anti-N3pGlu A β antibody for a period of 6 months or less, wherein the A β deposit in the brain of a human patient is reduced by 35-100% within 6 months post induction dose treatment. Particularly, the present invention a method of treating clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, comprising administering to a patient an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 month or less, wherein the A β deposit in the brain of a human patient is reduced by 35-100% within 6 months post induction treatment. More particularly, the present invention provides a method of treating clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, comprising administering to the patient a one-time induction dose of 10 to 60 mg/kg

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of an anti-N3pGlu A β antibody, wherein the A β deposit in the brain of a human patient is reduced by 35-100% within 6 months post induction treatment. In another more particular embodiment, the present invention provides a method of treating clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, comprising
5 administering to the patient an induction dose of 10 to 60 mg/kg every two weeks of an anti-N3pGlu A β antibody for a period of 6 months or less, wherein the A β deposit in the brain of a human patient is reduced by 35-100% within 6 months post induction treatment. In another more particular embodiment, the present invention provides a method of treating clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy,
10 comprising administering to the patient a monthly induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 months or less, wherein the A β deposit in the brain of a human patient is reduced by 35-100% within 6 months post induction treatment. In an embodiment of the preferred invention, the anti-N3pGlu A β antibody is selected from Table A.

In an embodiment, the present invention provides a method of slowing cognitive and/or
15 functional decline in a patient diagnosed with pre-clinical Alzheimer's disease or clinical Alzheimer's disease, comprising administering to a patient an induction dose of an anti-N3pGlu A β antibody for a period of 6 months or less, wherein the A β deposit in the brain of a human patient is reduced by 35-100% within 6 months post induction dose treatment. Particularly, the present invention a method of slowing cognitive and/or functional decline in a patient diagnosed
20 with pre-clinical Alzheimer's disease or clinical Alzheimer's disease, comprising administering to a patient an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 month or less, wherein the A β deposit in the brain of a human patient is reduced by 35-100% within 6 months post induction treatment. More particularly, the present invention provides a method of slowing cognitive and/or functional decline in a patient diagnosed with pre-clinical
25 Alzheimer's disease or clinical Alzheimer's disease, comprising administering to the patient a one-time induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody, wherein the A β deposit in the brain of a human patient is reduced by 35-100% within 6 months post induction treatment. In another more particular embodiment, the present invention provides slowing cognitive and/or functional decline in a patient diagnosed with pre-clinical Alzheimer's disease or
30 clinical Alzheimer's disease, comprising administering to the patient an induction dose of 10 to 60 mg/kg every two weeks of an anti-N3pGlu A β antibody for a period of 6 months or less, wherein the A β deposit in the brain of a human patient is reduced by 35-100% within 6 months post induction treatment. In another more particular embodiment, the present invention provides a method of slowing cognitive and/or functional decline in a patient diagnosed with pre-clinical

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Alzheimer's disease or clinical Alzheimer's disease, comprising administering to the patient a monthly induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 months or less, wherein the A β deposit in the brain of a human patient is reduced by 35-100% within 6 months post induction treatment. In a preferred embodiment of the present invention, the one-time induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg. In an alternative preferred embodiment of the present invention, the biweekly and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg for a period of 6 months. The anti-N3pGlu A β antibody is preferably selected from Table A

In an embodiment, the present invention provides a method of treating clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical CAA with an anti-N3pGlu A β antibody for a period of 6 months or less, wherein the A β deposit in the brain of a human patient is reduced by 35-100% within 6 months post induction treatment and maintained in a reduced state for a period of 2-10 years post treatment. More preferably, for 2-5 years. Even more preferably, for 5-10 years. Particularly, the present invention provides a method of treating clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, comprising administering to a patient an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 month or less, wherein the A β deposit in the brain of a human patient is reduced by 35-100% within 6 months post induction treatment and maintained in a reduced state for a period of 2-10 years post treatment. More preferably, for 2-5 years. Even more preferably, for 5-10 years. More particularly, the present invention provides a method of treating clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, comprising administering to the patient a one-time induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody, wherein the A β deposit in the brain of a human patient is reduced by 35-100% within 6 months post induction treatment and maintained in a reduced state for a period of 1-10 years post treatment. More preferably, for 2-5 years. Even more preferably, for 5-10 years. In another more particular embodiment, the present invention provides a method of treating clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, comprising administering to the patient an induction dose of 10 to 60 mg/kg every two weeks of an anti-N3pGlu A β antibody for a period of 6 months or less, wherein the A β deposit in the brain of a human patient is reduced by 35-100% within 6 months post induction treatment and maintained in a reduced state for a period of 2-10 years post treatment. More preferably, for 2-5 years. Even more preferably, for 5-10 years. In another more particular embodiment, the present invention provides a method of treating clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical

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cerebral amyloid angiopathy, comprising administering to the patient a monthly induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 months or less, wherein the A β deposit in the brain of a human patient is reduced by 35-100% within 6 months post induction treatment and maintained in a reduced state for a period of 2-10 years post treatment. More preferably, for 2-5 years. Even more preferably, for 5-10 years. In a preferred embodiment of the present invention, the one-time induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg. In an alternative preferred embodiment of the present invention, the biweekly and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg for a period of 6 months. The anti-N3pGlu A β antibody is preferably selected from Table A.

The present invention also provides a method of treating a disease characterized by deposition of A β in the brain, comprising administering to a patient an induction dose of an anti-N3pGlu A β antibody for a period of 6 months or less followed by a maintenance dose of an anti-N3pGlu A β antibody every 12, 3, 5 or 10 years post completion of the induction treatment. Particularly, the present invention provides a method to treat a disease characterized by A β deposits in the brain of a human patient comprising administering to the patient positive for amyloid deposits a one-time induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody followed by a maintenance dose of an anti-N3pGlu A β antibody every 1, 2, 3, 5 or 10 years post completion of the induction treatment. In another more particular embodiment, the present invention provides a method to treat a disease characterized by A β deposits in the brain of a patient positive for amyloid deposits comprising administering to the patient an induction dose of 10 to 60 mg/kg every two weeks of an anti-N3pGlu A β antibody for a period of 6 months or less followed by a maintenance dose of an anti-N3pGlu A β antibody every 1, 2, 3, 5 or 10 years post completion of the induction treatment. In another more particular embodiment, the present invention provides a method to treat a disease characterized by A β deposits in the brain of a patient positive for amyloid deposits comprising administering to the patient a monthly induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 months or less followed by a maintenance dose of an anti-N3pGlu A β antibody every 1, 2, 3, 5 or 10 years post completion of the induction treatment. In one particular embodiment the maintenance dose of an A β antibody is given every year. In another particular embodiment the maintenance dose of an A β antibody is given every 2 years. In another particular embodiment the maintenance dose of an A β antibody is given every 3 years. In another particular embodiment the maintenance dose of an A β antibody is given every 5 years. In another particular embodiment the maintenance dose of an A β antibody is given every 10 years. In another particular embodiment the maintenance dose of an A β antibody is given every 2 to 5

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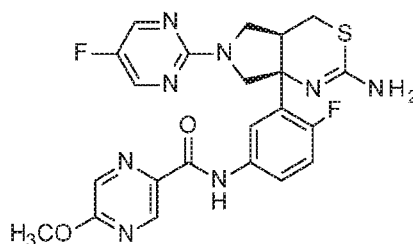
years. In another particular embodiment the maintenance dose of an A β antibody is given every 5 to 10 years. In an embodiment of the present invention the same anti-N3pGlu A β antibody is used for the induction and maintenance dose. In another embodiment of the present invention different anti-N3pGlu antibodies are used for the induction and maintenance doses. In an embodiment of the more particular invention, the anti-N3pGlu A β antibody administered in the induction and maintenance dose is selected from Table A.

In an embodiment, the present invention also provides a method of treating a disease characterized by deposition of A β in the brain, comprising administering to a patient an induction dose of an anti-N3pGlu A β antibody for a period of 6 months or less in simultaneous, separate, or sequential combination with an effective amount of a BACE inhibitor. In a particular embodiment, the present invention provides a method of treating a disease characterized by deposition of A β in the brain comprising administering to the patient a one-time induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody in simultaneous, separate, or sequential combination with an effective amount of a BACE inhibitor. In another particular embodiment, the present invention provides a method of treating a disease characterized by deposition of A β in the brain comprising administering to the patient an induction dose of 10 to 60 mg/kg every two weeks of an anti-N3pGlu A β antibody for a period of 6 months or less in simultaneous, separate, or sequential combination with an effective amount of a BACE inhibitor. In another particular embodiment, the present invention provides a method of treating a disease characterized by deposition of A β in the brain, comprising administering to the patient a monthly induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 months or less in simultaneous, separate, or sequential combination with an effective amount of a BACE inhibitor. In another preferred embodiment of the present invention, the one-time induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg. In an alternative preferred embodiment of the present invention, the biweekly and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg for a period of 6 months.

In a more particular embodiment of the present invention, the anti-N3pGlu A β antibody is preferably selected from Table A and the BACE inhibitor is selected from the group consisting of

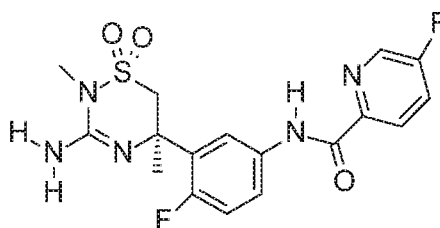
a) a compound of formula

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also referred to by the compound name N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide, or a pharmaceutically acceptable salt thereof ;

- b) tosylate salt of N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide;
- c) crystalline form of 2 N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4a,5,6,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a(4H)-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide; and
- d) a compound of the formula

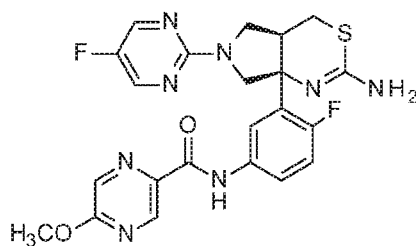


also referred to by the compound name N-[3-[(5R)-3-Amino-5,6-dihydro-2,5-dimethyl-1,1-dioxido-2H-1,2,4-thiadiazin-5-yl]-4-fluorophenyl]-5-fluoro-2-pyridinecarboxamide or the generic name, verubecestat, or a pharmaceutically acceptable salt thereof.

In another more particular embodiment of the present invention, the anti-N3pGlu A β antibody is preferably B12L and the BACE inhibitor is selected from the group consisting of

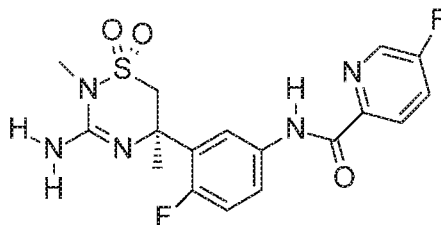
- a) a compound of formula

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also referred to by the compound name N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide, or a pharmaceutically acceptable salt thereof;

- b) tosylate salt of N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide;
- c) crystalline form of 2 N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4a,5,6,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a(4H)-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide; and
- d) a compound of the formula



also referred to by the compound name N-[3-[(5R)-3-Amino-5,6-dihydro-2,5-dimethyl-1,1-dioxido-2H-1,2,4-thiadiazin-5-yl]-4-fluorophenyl]-5-fluoro-2-pyridinecarboxamide or the generic name, verubecestat, or a pharmaceutically acceptable salt thereof.

In an embodiment, the present invention also provides a method of treating a disease characterized by deposition of A β in the brain, comprising administering to a patient a one-time induction dose of an anti-N3pGlu A β antibody for a period of 6 months or less in simultaneous, separate, or sequential combination with an effective amount of an A β antibody. In a particular embodiment, the present invention also provides a method of treating a disease characterized by deposition of A β in the brain, comprising administering to a patient a one-time, biweekly or monthly induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6

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months or less in simultaneous, separate, or sequential combination with an effective amount of an A β antibody, wherein the A β antibody comprises an amino acid light chain (LC) and an amino acid heavy chain (HC) selected from the group consisting of;

- A) LC of SEQ ID NO: 65 and HC of SEQ ID NO:66 (solanezumab);
- 5 B) LC of SEQ ID NO: 61 and HC of SEQ ID NO: 62 (crenezumab);
- C) LC of SEQ ID NO: 57 and HC of SEQ ID NO: 58 (aducunumab);
- D) LC of SEQ ID NO: 63 and HC of SEQ ID NO: 64 (BAN2401) and;
- E) LC of SEQ ID NO: 59 and HC of SEQ ID NO: 60 (gantenerumab).

10 In a preferred embodiment of the present invention, the one-time biweekly and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg. The anti-N3pGlu A β antibody is preferably selected from Table A.

In an embodiment, the present invention also provides a method of treating a disease characterized by deposition of A β in the brain, comprising administering to a patient a one-time, biweekly or monthly induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a
 15 period of 6 months or less in simultaneous, separate, or sequential combination with an effective amount of a 20 kD pegylated anti-A β Fab antibody, wherein the anti-A β Fab comprises an amino acid light chain variable region of SEQ ID NO: 55 and an amino acid heavy chain variable region of SEQ ID NO:56. In a preferred embodiment of the present invention, the one-time biweekly and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg.
 20 The anti-N3pGlu A β antibody is preferably selected from Table A.

In another embodiment of the present invention also provides a method of treating a disease characterized by deposition of A β in the brain, comprising administering to a patient a one-time, biweekly or monthly induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a
 25 period of 6 months or less in simultaneous, separate, or sequential combination with an effective amount of a symptomatic agent to treat Alzheimer's disease. Symptomatic agents can be selected from cholinesterase inhibitors (ChEIs) and/or a partial *N*-methyl-D-aspartate (NMDA) antagonists. In a preferred embodiment the agent is a ChEI. In another preferred embodiment the agent is a NMDA antagonist or a combination agent comprising a ChEI and NMDA antagonist. In a more preferred embodiment of the present invention, the one-time induction dose administered
 30 to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg. In an alternative more preferred embodiment of the present invention, the biweekly and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg for a period of 6 months. The anti-N3pGlu A β antibody is preferably selected from Table A.

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In another embodiment the present invention provides an anti-N3pGlu A β antibody for use in the treatment of clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, wherein the anti-N3pGlu A β antibody is administered to a patient at a dose of 10 to 60 mg/kg for a period of 6 months or less. Particularly, the present invention provides an anti-N3pGlu A β antibody for use in treatment of clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, wherein the anti-N3pGlu A β antibody is administered to a patient as a one-time induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody. In another more particular embodiment, the present invention provides an anti-N3pGlu A β antibody for use in the treatment of clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, wherein the anti-N3pGlu A β antibody is administered to a patient as an induction dose of 10 to 60 mg/kg every two weeks of an anti-N3pGlu A β antibody for a period of 6 months or less. In another more particular embodiment, the present invention provides an anti-N3pGlu A β antibody for use in the treatment of clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, wherein the anti-N3pGlu A β antibody is administered to a patient as an induction dose of 10 to 60 mg/kg monthly for a period of 6 months or less. In a preferred embodiment of the invention for use in the treatment or preventing of clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical CAA, the one-time, biweekly and monthly induction dose administered to a patient is 20 to 40 mg/kg or 15 to 30 mg/kg. In a preferred embodiment of the present invention, the one-time induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg. In an alternative preferred embodiment of the present invention, the biweekly and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg for a period of 6 months. Even more preferably, the anti-N3pGlu A β antibody is selected from Table A.

In another embodiment the present invention provides an anti-N3pGlu A β antibody for use in the treatment of prodromal AD, mild AD, moderate AD or severe AD, wherein the anti-N3pGlu A β antibody is administered to a patient at a dose of 10 to 60 mg/kg for a period of 6 months or less. Particularly, the present invention provides an anti-N3pGlu A β antibody for use in the treatment of prodromal AD, mild AD, moderate AD or severe AD, wherein the anti-N3pGlu A β antibody is administered to a patient as a one-time induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody. In another more particular embodiment, the present invention provides an anti-N3pGlu A β antibody for use in the treatment of prodromal AD, mild AD, moderate AD or severe AD, wherein the anti-N3pGlu A β antibody is administered to a patient as an induction dose of 10 to 60 mg/kg every two weeks of an anti-N3pGlu A β antibody for a period of 6 months or

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less. In another more particular embodiment, the present invention an anti-N3pGlu A β antibody for use in the treatment of prodromal AD, mild AD, moderate AD or severe AD, wherein the anti-N3pGlu A β antibody is administered to a patient as an induction dose of 10 to 60 mg/kg monthly for a period of 6 months or less. In a preferred embodiment of the invention for use in the in the treatment of prodromal AD, mild AD, moderate AD or severe AD, the one-time, biweekly and monthly induction dose administered to a patient is 20 to 40 mg/kg or 15 to 30 mg/kg. In a preferred embodiment of the present invention, the one-time induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg. In an alternative preferred embodiment of the present invention, the biweekly and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg for a period of 6 months. Even more preferably, the anti-N3pGlu A β antibody is selected from Table A.

In another embodiment the present invention provides an anti-N3pGlu A β antibody for use in preventing or slowing cognitive or functional decline in a patient diagnosed with a condition selected from clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, wherein the anti-N3pGlu A β antibody is administered to a patient at a dose of 10 to 60 mg/kg for a period of 6 months or less. Particularly, the present invention provides an anti-N3pGlu A β antibody for use in preventing or slowing cognitive decline in a patient diagnosed with a condition selected from clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, wherein the anti-N3pGlu A β antibody is administered to a patient as a one-time induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody. In another more particular embodiment, the present invention provides an anti-N3pGlu A β antibody for use in preventing or slowing cognitive decline in a patient diagnosed with a condition selected from clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, moderate AD or severe AD, wherein the anti-N3pGlu A β antibody is administered to a patient as an induction dose of 10 to 60 mg/kg every two weeks of an anti-N3pGlu A β antibody for a period of 6 months or less. In another more particular embodiment, the present invention an anti-N3pGlu A β antibody for use in preventing or slowing cognitive decline in a patient diagnosed with a condition selected from clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, wherein the anti-N3pGlu A β antibody is administered to a patient as an induction dose of 10 to 60 mg/kg monthly for a period of 6 months or less. In a preferred embodiment of the invention for use in preventing or slowing cognitive decline in a patient diagnosed with a condition selected from clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, the one-time,

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biweekly and monthly induction dose administered to a patient is 20 to 40 mg/kg or 15 to 30 mg/kg. In a preferred embodiment of the present invention, the one-time induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg. In an alternative preferred embodiment of the present invention, the biweekly and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg for a period of 6 months. Even more preferably, the anti-N3pGlu A β antibody is selected from Table A.

In another embodiment the present invention provides an anti-N3pGlu A β antibody for use in reducing A β amyloid plaque load in the brain of a patient diagnosed with pre-clinical or clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, wherein the anti-N3pGlu A β antibody is administered to a patient at a dose of 10 to 60 mg/kg for a period of 6 months or less. Particularly, the present invention provides an anti-N3pGlu A β antibody for use in reducing A β amyloid plaque load in the brain of a patient diagnosed with pre-clinical or clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, wherein the anti-N3pGlu A β antibody is administered to a patient as a one-time induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody. In another more particular embodiment, the present invention provides an anti-N3pGlu A β antibody for use in reducing A β amyloid plaque load in the brain of a patient diagnosed with pre-clinical or clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, wherein the anti-N3pGlu A β antibody is administered to a patient as an induction dose of 10 to 60 mg/kg every two weeks of an anti-N3pGlu A β antibody for a period of 6 months or less. In another more particular embodiment, the present invention provides an anti-N3pGlu A β antibody for use in reducing A β amyloid plaque load in the brain of a patient diagnosed with pre-clinical or clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, wherein the anti-N3pGlu A β antibody is administered to a patient as an induction dose of 10 to 60 mg/kg monthly for a period of 6 months or less. In a preferred embodiment of the invention for use in reducing A β amyloid plaque load in the brain of a patient diagnosed with pre-clinical or clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, the one-time, biweekly and monthly induction dose administered to a patient is 20 to 40 mg/kg or 15 to 30 mg/kg. In another preferred embodiment of the present invention, the one-time induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg. In an alternative preferred embodiment of the present invention, the biweekly and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg for a period of 6 months. Even more preferably, the anti-N3pGlu A β antibody is selected from Table A.

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In another embodiment the present invention provides an anti-N3pGlu A β antibody for use in treating clinically asymptomatic patients known to have Alzheimer's disease causing genetic mutation, wherein the anti-N3pGlu A β antibody is administered to a patient at a dose of 10 to 60 mg/kg for a period of 6 months or less. Particularly, the present invention provides an anti-N3pGlu A β antibody for use in treating asymptomatic patients known to have Alzheimer's disease causing genetic mutation, wherein the anti-N3pGlu A β antibody is administered to a patient as a one-time induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody. In another more particular embodiment, the present invention provides an anti-N3pGlu A β antibody for use in treating asymptomatic patients known to have Alzheimer's disease causing genetic mutation, wherein the anti-N3pGlu A β antibody is administered to a patient as an induction dose of 10 to 60 mg/kg every two weeks of an anti-N3pGlu A β antibody for a period of 6 months or less. In another more particular embodiment, the present invention provides an anti-N3pGlu A β antibody for use in treating asymptomatic patients known to have Alzheimer's disease causing genetic mutation, wherein the anti-N3pGlu A β antibody is administered to a patient as an induction dose of 10 to 60 mg/kg monthly for a period of 6 months or less. In a preferred embodiment of the invention for use in treating asymptomatic patients known to have Alzheimer's disease causing genetic mutation, the one-time, biweekly and monthly induction dose administered to a patient is 20 to 40 mg/kg or 15 to 30 mg/kg. In a preferred embodiment of the present invention, the one-time induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg. In an alternative preferred embodiment of the present invention, the biweekly and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg for a period of 6 months. The anti-N3pGlu A β antibody is selected from Table A.

In another embodiment the present invention provides for a use of an anti-N3pGlu A β antibody for the manufacture of a medicament for the treatment of clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, wherein the medicament comprises an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody administered to a patient for a period of 6 months or less. Particularly, the present invention provides for a use of an anti-N3pGlu A β antibody for the manufacture of a medicament for the treatment of clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, wherein the medicament comprises a one-time induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody administered to a patient.. In another more particular embodiment, the present invention provides for a use of an anti-N3pGlu A β antibody for the manufacture of a medicament for the treatment of clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, wherein the

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medicament comprises an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody administered to a patient every two weeks for a period of 6 months or less. In another more particular embodiment, the present invention provides for a use of an anti-N3pGlu A β antibody for the manufacture of a medicament for the treatment of clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, wherein the
5 medicament comprises an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody administered to a patient every month for a period of 6 months or less. In a preferred embodiment of the invention the one-time, biweekly and monthly induction dose administered to a patient is 20 to 40 mg/kg or 15 to 30 mg/kg. In another preferred embodiment of the present invention, the
10 one-time induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg. In an alternative preferred embodiment of the present invention, the biweekly and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg for a period of 6 months. Even more preferably, the anti-N3pGlu A β antibody is selected from Table A.

In another embodiment the present invention provides for a use of an anti-N3pGlu A β antibody for the manufacture of a medicament for the treatment of prodromal AD, mild AD,
15 moderate AD or severe AD, wherein the medicament comprises an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody administered to a patient for a period of 6 months or less. Particularly, the present invention provides for a use of an anti-N3pGlu A β antibody for the manufacture of a medicament for the treatment of prodromal AD, mild AD, moderate AD or
20 severe AD, wherein the medicament comprises a one-time induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody administered to a patient for a period of 6 months or less. In another more particular embodiment, the present invention provides for a use of an anti-N3pGlu A β antibody for the manufacture of a medicament for the treatment of prodromal AD, mild AD, moderate AD or severe AD, wherein the medicament comprises an induction dose of 10 to 60
25 mg/kg of an anti-N3pGlu A β antibody administered to a patient every two weeks for a period of 6 months or less. In another more particular embodiment, the present invention provides for a use of an anti-N3pGlu A β antibody for the manufacture of a medicament for the treatment of prodromal AD, mild AD, moderate AD or severe AD, wherein the medicament comprises an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody administered to a patient monthly for a period
30 of 6 months or less. In a preferred embodiment of the invention the one-time, biweekly and monthly induction dose administered to a patient is 20 to 40 mg/kg or 15 to 30 mg/kg. In another preferred embodiment of the present invention, the one-time induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg. In an alternative preferred embodiment of the present invention, the biweekly and monthly induction dose administered to a patient is

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10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg for a period of 6 months. Even more preferably, the anti-N3pGlu A β antibody is selected from Table A.

In another embodiment the present invention provides for a use of an anti-N3pGlu A β antibody for the manufacture of a medicament for preventing or slowing cognitive or functional decline in a patient diagnosed with a condition selected from clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, wherein the medicament comprises an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody administered to a patient for a period of 6 months or less. Particularly, the present invention provides for a use of an anti-N3pGlu A β antibody for the manufacture of a medicament for preventing or slowing cognitive decline in a patient diagnosed with a condition selected from clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, wherein the medicament comprises a one-time induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody administered to a patient for a period of 6 months or less. In another more particular embodiment, the present invention provides for a use of an anti-N3pGlu A β antibody for preventing or slowing cognitive decline in a patient diagnosed with a condition selected from clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, wherein the medicament comprises an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody administered every two weeks to a patient for a period of 6 months or less. In another more particular embodiment, the present invention provides for a use of an anti-N3pGlu A β antibody for preventing or slowing cognitive decline in a patient diagnosed with a condition selected from clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, wherein the medicament comprises a one-time induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody administered to a patient monthly for a period of 6 months or less. In a preferred embodiment of the invention the one-time, biweekly and monthly induction dose administered to a patient is 20 to 40 mg/kg or 15 to 30 mg/kg. In another preferred embodiment of the present invention, the one-time induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg. In an alternative preferred embodiment of the present invention, the biweekly and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg for a period of 6 months. Even more preferably, the anti-N3pGlu A β antibody is selected from Table A.

In another embodiment the present invention provides for a use of an anti-N3pGlu A β antibody for the manufacture of a medicament for treating asymptomatic patients known to have an Alzheimer's disease causing genetic mutation, wherein the medicament is administered to a

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patient at a dosage of 10 to 60 mg/kg of the anti-N3pGlu A β antibody for a period of 6 months or less. Particularly, the present invention provides for a use of an anti-N3pGlu A β antibody for the manufacture of a medicament for treating asymptomatic patients known to have an Alzheimer's disease causing genetic mutation, wherein the medicament comprises a one-time induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody administered to a patient for a period of 6 months or less. In another more particular embodiment, the present invention provides for a use of an anti-N3pGlu A β antibody treating asymptomatic patients known to have an Alzheimer's disease causing genetic mutation, wherein the medicament comprises an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody administered to a patient every two weeks for a period of 6 months or less. In another more particular embodiment, the present invention provides for a use of an anti-N3pGlu A β antibody treating asymptomatic patients known to have an Alzheimer's disease causing genetic mutation, wherein the medicament comprises an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody administered to a patient monthly for a period of 6 months or less. In a preferred embodiment of the invention the one-time, biweekly and monthly induction dose administered to a patient is 20 to 40 mg/kg or 15 to 30 mg/kg. In another preferred embodiment of the present invention, the one-time induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg. In an alternative preferred embodiment of the present invention, the biweekly and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg for a period of 6 months. Even more preferably, the anti-N3pGlu A β antibody is selected from Table A.

In another embodiment the present invention provides for a use of an anti-N3pGlu A β antibody for the manufacture of a medicament for reducing A β deposits in the brain of a patient, wherein the medicament comprises an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody administered to a patient for a period of 6 months or less, and wherein the A β deposit in the brain of a patient is reduced by 35-100% within 6 months post induction dose treatment. Particularly the present invention provides for a use of an anti-N3pGlu A β antibody for the manufacture of a medicament for reducing A β deposits in the brain of a patient, wherein the medicament comprises a one-time induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody administered to a patient for a period of 6 months or less, and wherein the A β deposit in the brain of a patient is reduced by 35-100% within 6 months post induction dose treatment. In another more particular embodiment, the present invention provides for a use of an anti-N3pGlu A β antibody for the manufacture of a medicament for reducing A β deposits in the brain of a patient, wherein the medicament comprises an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody administered to a patient every two weeks for a period of 6 months or less.

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and wherein the A β deposit in the brain of a patient is reduced by 35-100% within 6 months post induction dose treatment.. In another more particular embodiment, the present invention provides for a use of an anti-N3pGlu A β antibody for the manufacture of a medicament for reducing A β deposits in the brain of a patient, wherein the medicament comprises an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody administered to a patient monthly for a period of 6 months or less, and wherein the A β deposit in the brain of a patient is reduced by 35-100% within 6 months post induction dose treatment.. In a preferred embodiment of the invention the one-time, biweekly and monthly induction dose administered to a patient is 20 to 40 mg/kg or 15 to 30 mg/kg. In another preferred embodiment of the present invention, the one-time induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg. In an alternative preferred embodiment of the present invention, the biweekly and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg or 40mg/kg for a period of 6 months. Even more preferably, the anti-N3pGlu A β antibody is selected from Table A.

As used herein, "anti-N3pGlu A β antibody" refers to an antibody that binds preferentially to N3pGlu A β over A β ₁₋₄₀ or A β ₁₋₄₂. The sequence of N3pGlu A β is the amino acid sequence of SEQ ID NO: 31. In particular embodiments, the anti-N3pGlu A β antibodies comprise amino acid sequences listed in Table A. More specifically, the anti-N3pGlu A β antibodies of the present invention comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein said LCVR comprises LCDR1, LCDR2 and LCDR3 and HCVR comprises HCDR1, HCDR2 and HCDR3 which are selected from the group consisting of:

- a) LCDR1 is SEQ ID. NO: 17, LCDR2 is SEQ ID. NO: 18, LCDR3 is SEQ ID. NO: 19, HCDR1 is SEQ ID. NO: 20, HCDR2 is SEQ ID. NO: 22, and HCDR3 is SEQ ID. NO: 23; and
- b) LCDR1 is SEQ ID. NO: 17, LCDR2 is SEQ ID. NO: 18, LCDR3 is SEQ ID. NO: 19, HCDR1 is SEQ ID. NO: 21, HCDR2 is SEQ ID. NO: 22, and HCDR3 is SEQ ID. NO: 24;
- c) LCDR1 is SEQ ID. NO: 17, LCDR2 is SEQ ID. NO: 18, LCDR3 is SEQ ID. NO: 19, HCDR1 is SEQ ID. NO: 36, HCDR2 is SEQ ID. NO: 22, and HCDR3 is SEQ ID. NO: 37;
- d) LCDR1 is SEQ ID. NO: 4, LCDR2 is SEQ ID. NO: 6, LCDR3 is SEQ ID. NO: 7, HCDR1 is SEQ ID. NO: 1, HCDR2 is SEQ ID. NO: 2, and HCDR3 is SEQ ID. NO: 3; and

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- e) LCDR1 is SEQ ID. NO: 4, LCDR2 is SEQ ID. NO: 5, LCDR3 is SEQ ID. NO: 7, HCDR1 is SEQ ID. NO: 1, HCDR2 is SEQ ID. NO: 2, and HCDR3 is SEQ ID. NO: 3.

In other embodiments, the anti-N3pGlu A β antibodies of the present invention comprise a
5 light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein said
LCVR and HCVR are selected from the group consisting of:

- a) LCVR of SEQ ID NO: 25 and HCVR of SEQ ID NO: 26;
b) LCVR of SEQ ID NO: 25 and HCVR of SEQ ID NO: 27;
c) LCVR of SEQ ID NO: 32 and HCVR of SEQ ID NO: 34;
10 d) LCVR of SEQ ID NO: 9 and HCVR of SEQ ID NO: 8; and
e) LCVR of SEQ ID NO: 10 and HCVR of SEQ ID NO: 8.

In further embodiments, the anti-N3pGlu A β antibody comprises a light chain (LC) and a
heavy chain (HC), wherein said LC and HC are selected from the group consisting of :

- a) LC of SEQ ID NO: 28 and HC of SEQ ID NO: 29;
15 b) LC of SEQ ID NO: 28 and HC of SEQ ID NO: 30;
c) LC of SEQ ID NO: 33 and HC of SEQ ID NO: 35;
d) LC of SEQ ID NO: 12 and HC of SEQ ID NO: 11; and
e) LC of SEQ ID NO: 13 and HC of SEQ ID NO: 11.

In other embodiments, the anti-N3pGlu A β antibody comprises two light chains (LC) and
20 two heavy chains (HC), wherein each LC and each HC are selected from the group consisting of

- a) LC of SEQ ID NO: 28 and HC of SEQ ID NO: 29;
b) LC of SEQ ID NO: 28 and HC of SEQ ID NO: 30;
c) LC of SEQ ID NO: 33 and HC of SEQ ID NO: 35;
d) LC of SEQ ID NO: 12 and HC of SEQ ID NO: 11; and
25 e) LC of SEQ ID NO: 13 and HC of SEQ ID NO: 11.

In some embodiments, the anti-N3pGlu A β antibody comprises Antibody I, which has a
light chain (LC) and a heavy chain (HC) of SEQ ID NOs: 12 and 11 respectively. Antibody I
further has a light chain variable region (LCVR) and a heavy chain variable region (HCVR) of
SEQ ID NOs: 9 and 8 respectively. The HCVR of Antibody I further comprises HCDR1 of SEQ
30 ID NO: 1, HCDR2 of SEQ ID NO: 2, and HCDR3 of SEQ ID NO: 3. The LCVR of Antibody I
further comprises LCDR1 of SEQ ID NO: 4, LCDR2 of SEQ ID NO: 6 and LCDR3 of SEQ ID
NO: 7 respectively.

In some embodiments, the anti-N3pGlu A β antibody comprises Antibody II, which has a
light chain (LC) and a heavy chain (HC) of SEQ ID NOs: 13 and 11 respectively. Antibody II

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further has a light chain variable region (LCVR) and a heavy chain variable region (HCVR) of SEQ ID NOs: 10 and 8 respectively. The HCVR of Antibody II further comprises HCDR1 of SEQ ID NO: 1, HCDR2 of SEQ ID NO: 2, and HCDR3 of SEQ ID NO: 3. The LCVR of Antibody II further comprises LCDR1 of SEQ ID NO: 4, LCDR2 of SEQ ID NO: 5, and LCDR3 of SEQ ID NO: 7 respectively.

In some embodiments, the anti-N3pGlu A β antibody comprises B12L, which has a light chain (LC) and a heavy chain (HC) of SEQ ID NOs: 28 and 29 respectively. B12L further has a light chain variable region (LCVR) and a heavy chain variable region (HCVR) of SEQ ID NOs: 25 and 26 respectively. The HCVR of B12L further comprises HCDR1 of SEQ ID NO: 20, HCDR2 of SEQ ID NO: 22 and HCDR3 of SEQ ID NO: 23. The LCVR of B12L further comprises LCDR1 of SEQ ID NO: 17, LCDR2 of SEQ ID NO: 18 and LCDR3 of SEQ ID NO: 19 respectively.

In some embodiments, the anti-N3pGlu A β antibody comprises R17L which has a light chain (LC) and a heavy chain (HC) of SEQ ID NOs: 28 and 30 respectively. R17L further has a light chain variable region (LCVR) and a heavy chain variable region (HCVR) of SEQ ID NOs: 25 and 27 respectively. The HCVR of R17L further comprises HCDR1 of SEQ ID NO: 21, HCDR2 of SEQ ID NO: 22 and HCDR3 of SEQ ID NO: 24. The LCVR of R17L further comprises LCDR1 of SEQ ID NO: 17, LCDR2 of SEQ ID NO: 18 and LCDR3 of SEQ ID NO: 19 respectively.

In some embodiments, the anti-N3pGlu A β antibody comprises hE8L which has a light chain (LC) and a heavy chain (HC) of SEQ ID NOs: 33 and 35 respectively. hE8L further has a light chain variable region (LCVR) and a heavy chain variable region (HCVR) of in SEQ ID NOs: 32 and 34 respectively. The HCVR of hE8L further comprises HCDR1 of SEQ ID NO: 36, HCDR2 of SEQ ID NO: 22 and HCDR3 of SEQ ID NO: 37. The LCVR of hE8L further comprises LCDR1 of SEQ ID NO: 17, LCDR2 of SEQ ID NO: 18 and LCDR3 of SEQ ID NO: 19 respectively.

In some embodiments, the anti-N3pGlu A β antibody comprises Antibody VI which has a light chain variable region (LCVR) and a heavy chain variable region (HCVR) of SEQ ID NOs: 39 and 40 respectively.

In some embodiments, the anti-N3pGlu A β antibody comprises Antibody VII which has a light chain variable region (LCVR) and a heavy chain variable region (HCVR) of SEQ ID NOs: 41 and 42 respectively.

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In some embodiments, the anti-N3pGlu A β antibody comprises Antibody VIII which has a light chain variable region (LCVR) and a heavy chain variable region (HCVR) of SEQ ID NOs: 43 and 44 respectively.

5 In some embodiments, the anti-N3pGlu A β antibody comprises Antibody IX which has a light chain variable region (LCVR) and a heavy chain variable region (HCVR) of SEQ ID NOs: 45 and 46 respectively.

In some embodiments, the anti-N3pGlu A β antibody comprises Antibody X which has a light chain variable region (LCVR) and a heavy chain variable region (HCVR) of SEQ ID NOs: 47 and 48 respectively.

10 In some embodiments, the anti-N3pGlu A β antibody comprises Antibody XI which has a light chain variable region (LCVR) and a heavy chain variable region (HCVR) of SEQ ID NOs: 49 and 50 respectively.

In some embodiments, the anti-N3pGlu A β antibody comprises Antibody XII which has a light chain variable region (LCVR) and a heavy chain variable region (HCVR) of SEQ ID NOs: 51 and 52 respectively.

In some embodiments, the anti-N3pGlu A β antibody comprises Antibody XIII which has a light chain variable region (LCVR) and a heavy chain variable region (HCVR) of SEQ ID NOs: 53 and 54 respectively.

A person of skill in the art would recognize that an embodiment of the present invention provides a method of treating or preventing clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical CAA in a patient positive for amyloid deposits, comprising administering to a patient a one-time, biweekly or monthly induction dose of an anti-N3pGlu A β antibody for a period of 6 months or less, wherein the anti-N3pGlu A β antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein said LCVR and HCVR are selected from the group consisting of:

- 25 a) LCVR of SEQ ID NO: 25 and HCVR of SEQ ID NO: 26;
b) LCVR of SEQ ID NO: 25 and HCVR of SEQ ID NO: 27;
c) LCVR of SEQ ID NO: 32 and HCVR of SEQ ID NO: 34;
d) LCVR of SEQ ID NO: 9 and HCVR of SEQ ID NO: 8; and
30 e) LCVR of SEQ ID NO: 10 and HCVR of SEQ ID NO: 8.

Preferably the anti-N3pGlu A β antibody comprises a LCVR of SEQ ID NO: 25 and HCVR of SEQ ID NO: 26. More preferably the anti-N3pGlu A β antibody is administered one-time or biweekly. Even more preferably, the one-time or biweekly dose results in 35-100%

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reduction in A β deposit in the brain of the patient within 6 months of administration of the induction dose.

In another particular embodiments, the present invention provides a method of treating or preventing clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical CAA in a patient positive for amyloid deposits, comprising administering to a patient a one-time, biweekly or monthly induction dose of an anti-N3pGlu A β antibody for a period of 6 months or less, wherein the anti- N3pGlu A β antibody comprises a light chain (LC) and a heavy chain (HC), wherein said LC and HC are selected from the group consisting of :

- a) LC of SEQ ID NO: 28 and HC of SEQ ID NO: 29;
- b) LC of SEQ ID NO: 28 and HC of SEQ ID NO: 30;
- c) LC of SEQ ID NO: 33 and HC of SEQ ID NO: 35;
- d) LC of SEQ ID NO: 12 and HC of SEQ ID NO: 11; and
- e) LC of SEQ ID NO: 13 and HC of SEQ ID NO: 11.

Preferably the anti-N3pGlu A β antibody comprises a LC of SEQ ID NO: 28 and HC of SEQ ID NO: 29. More preferably the anti-N3pGlu A β antibody is administered one-time or biweekly. Even more preferably, the one-time or biweekly dose results in 35-100% reduction in A β deposit in the brain of the patient within 6 months of administration of the induction dose.

A further embodiment provides a method of treating or preventing clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical CAA in a patient positive for amyloid deposits, comprising administering to a patient a one-time, biweekly or monthly induction dose of an anti-N3pGlu A β antibody for a period of 6 months or less, wherein the anti-N3pGlu A β antibody comprises two light chains (LC's) and two heavy chains (HC's), wherein each LC and HC is selected from the group consisting of:

- a) LC of SEQ ID NO: 28 and HC of SEQ ID NO: 29;
- b) LC of SEQ ID NO: 28 and HC of SEQ ID NO: 30;
- c) LC of SEQ ID NO: 33 and HC of SEQ ID NO: 35;
- d) LC of SEQ ID NO: 12 and HC of SEQ ID NO: 11; and
- e) LC of SEQ ID NO: 13 and HC of SEQ ID NO: 11.

Preferably the anti-N3pGlu A β antibody comprises a two LC's of SEQ ID NO: 28 and HC's of SEQ ID NO: 29. More preferably the anti-N3pGlu A β antibody is administered one-time or biweekly. Even more preferably, the one-time or biweekly dose results in 35-100% reduction in A β deposit in the brain of the patient within 6 months of administration of the induction dose.

The present invention also provides a method of treating or preventing clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical CAA in a patient

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positive for amyloid deposits, comprising administering to a patient a one-time, biweekly or monthly induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 month or less, wherein the anti-N3pGlu A β antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein said LCVR and HCVR are selected

5 from the group consisting of:

- a) LCVR of SEQ ID NO: 25 and HCVR of SEQ ID NO: 26;
- b) LCVR of SEQ ID NO: 25 and HCVR of SEQ ID NO: 27;
- c) LCVR of SEQ ID NO: 32 and HCVR of SEQ ID NO: 34;
- d) LCVR of SEQ ID NO: 9 and HCVR of SEQ ID NO: 8; and
- 10 e) LCVR of SEQ ID NO: 10 and HCVR of SEQ ID NO: 8.

Preferably the anti-N3pGlu A β antibody comprises a LCVR of SEQ ID NO: 25 and HCVR of SEQ ID NO: 26. More preferably, the one-time, biweekly (every two weeks) and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg, 40mg/kg, 20 to 40 mg/kg or 15 to 30 mg/kg. Even more preferably the induction dose of the anti-N3pGlu A β

15 antibody is administered one-time or biweekly. Even more preferably, the one-time or biweekly dose results in 35-100% reduction in A β deposit in the brain of the patient within 6 months of administration of the induction dose.

In an embodiment, the present invention provides a method of treating or preventing clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical CAA in a

20 patient positive for amyloid deposits, comprising administering to a patient a one-time, biweekly or monthly induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 month or less, wherein the anti- N3pGlu A β antibody comprises a light chain (LC) and a heavy chain (HC), wherein said LC and HC are selected from the group consisting of :

- a) LC of SEQ ID NO: 28 and HC of SEQ ID NO: 29;
- 25 b) LC of SEQ ID NO: 28 and HC of SEQ ID NO: 30;
- c) LC of SEQ ID NO: 33 and HC of SEQ ID NO: 35;
- d) LC of SEQ ID NO: 12 and HC of SEQ ID NO: 11; and
- e) LC of SEQ ID NO: 13 and HC of SEQ ID NO: 11.

Preferably the anti-N3pGlu A β antibody comprises a LC of SEQ ID NO: 28 and a HC of

30 SEQ ID NO: 29. More preferably, the one-time, biweekly (every two weeks) and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg, 40mg/kg, 20 to 40 mg/kg or 15 to 30 mg/kg. Even more preferably the induction dose of the anti-N3pGlu A β antibody is administered one-time or biweekly. Even more preferably, the one-time or biweekly

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dose results in 35-100% reduction in A β deposit in the brain of the patient within 6 months of administration of the induction dose.

The present invention also provides a method of treating or preventing clinical or pre-clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical CAA in a patient positive for amyloid deposits, comprising administering to a patient a one-time, biweekly or monthly induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody for a period of 6 months or less, wherein the anti-N3pGlu A β antibody comprises two light chains (LC) and two heavy chains (HC), wherein each LC and HC is selected from the group consisting of:

- a) LC of SEQ ID NO: 28 and HC of SEQ ID NO: 29;
- b) LC of SEQ ID NO: 28 and HC of SEQ ID NO: 30;
- c) LC of SEQ ID NO: 33 and HC of SEQ ID NO: 35;
- d) LC of SEQ ID NO: 12 and HC of SEQ ID NO: 11; and
- e) LC of SEQ ID NO: 13 and HC of SEQ ID NO: 11.

Preferably the anti-N3pGlu A β antibody comprises two LC's of SEQ ID NO: 28 and two HC's of SEQ ID NO: 29. More preferably, the one-time, biweekly (every two weeks) and monthly induction dose administered to a patient is 10mg/kg, 15 mg/kg, 20mg/kg, 40mg/kg, 20 to 40 mg/kg or 15 to 30 mg/kg. Even more preferably the induction dose of the anti-N3pGlu A β antibody is administered one-time or biweekly. Even more preferably, the one-time or biweekly dose results in 35-100% reduction in A β deposit in the brain of the patient within 6 months of administration of the induction dose.

One of ordinary skill in the art will appreciate and recognize that "anti-N3pGlu A β antibody", and the specific antibodies, "hE8L", "B12L" and "R17L" are identified and disclosed along with methods for making and using said antibodies by one of ordinary skill in the art as set forth in U.S. Patent No. 8,679,498 B2, entitled "Anti-N3pGlu Amyloid Beta Peptide Antibodies and Uses Thereof", issued March 25, 2014 (U.S. Serial No. 13/810,895). See for example Table 1 of U.S. Patent No. 8,679,498 B2. Each of these three antibodies (e.g., "hE8L", "B12L" and "R17L") may be used as the anti-N3pGlu A β antibody of the present invention. One of ordinary skill in the art will appreciate and recognize that "anti-N3pGlu A β antibody", and the specific antibodies, "Antibody VI", "Antibody VII", "Antibody VIII", and "Antibody IX" are identified and disclosed along with methods for making and using said antibodies by one of ordinary skill in the art as set forth in WO2010/009987A2, entitled "Diagnosed Antibody Assay". Each of these four antibodies (e.g., "Antibody VI", "Antibody VII", "Antibody VIII", and "Antibody IX") may be used as the anti-N3pGlu A β antibody of the present invention.

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One of ordinary skill in the art will appreciate and recognize that “anti-N3pGlu A β antibody”, and the specific antibodies, “Antibody X” and “Antibody XI” are identified and disclosed along with methods for making and using said antibodies by one of ordinary skill in the art as set forth in WO 2011/151076 A2, entitled “Monoclonal Antibodies Targeting A β Monoclonal Antibodies”. Each of these two antibodies (e.g., “Antibody X” and “Antibody XI”) may be used as the anti-N3pGlu A β antibody of the present invention.

One of ordinary skill in the art will appreciate and recognize that “anti-N3pGlu A β antibody”, and the specific antibodies, “Antibody XII” and “Antibody XIII” are identified and disclosed along with methods for making and using said antibodies by one of ordinary skill in the art as set forth in WO 2012/136552A1, entitled “Antibodies Specific to Pyroglutamated A β ”. Each of these two antibodies (e.g., “Antibody XII” and “Antibody XIII”) may be used as the anti-N3pGlu A β antibody of the present invention.

One of ordinary skill in the art will appreciate and recognize that “A β antibody”, and the specific antibody, “aducanumab” is identified and disclosed along with methods for making and using said antibody by one of ordinary skill in the art as set forth in WO14089500A1, entitled “A Method of Reducing Brain Amyloid Plaques Using Anti-A β Antibodies”, published June 12, 2014. This may be used as the A β antibody of the present invention.

One of ordinary skill in the art will appreciate and recognize that “A β antibody”, and the specific antibody, “gantenerumab” is identified and disclosed along with methods for making and using said antibody by one of ordinary skill in the art as set forth in WO2007068429, entitled “Antibodies Against Amyloid Beta 4 with Glycosylated in the Variable Region”, published June 21, 2007. This may be used as the A β antibody of the present invention.

One of ordinary skill in the art will appreciate and recognize that “A β antibody”, and the specific antibody, “crenezumab” is identified and disclosed along with methods for making and using said antibody by one of ordinary skill in the art as set forth in 2015120280A1, entitled “Methods of treating alzheimer's disease”, published August 13, 2015. This may be used as the A β antibody of the present invention.

One of ordinary skill in the art will appreciate and recognize that “A β antibody”, and the specific antibody, “BAN 2401” is identified and disclosed along with methods for making and using said antibody by one of ordinary skill in the art as set forth in US 8025878 B2, entitled “Protofibril selective antibodies and the use thereof”, issued September 27, 2011. This may be used as the A β antibody of the present invention.

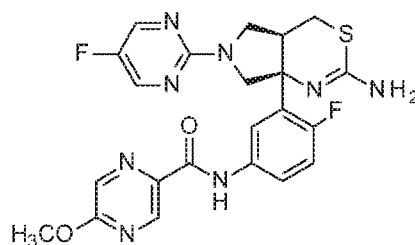
One of ordinary skill in the art will appreciate and recognize that “A β antibody”, and the specific antibody, “solanezumab” is identified and disclosed along with methods for making and

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using said antibody by one of ordinary skill in the art as set forth in US Patent No. 7,195,761 B2, entitled "Humanized Antibodies that Sequester ABeta Peptide", issued March 27, 2007. This may be used as the A β antibody of the present invention.

One of ordinary skill in the art will appreciate and recognize that "A β antibody", and the specific antibody, "Antibody XIV" is identified and disclosed along with methods for making and using said antibody by one of ordinary skill in the art as set forth in U.S. Patent No. 8,066,999 B1, entitled "Pegylated A β FAB", issued November 29, 2011 (U.S. Application No. 12/521,309). This may be used as the A β antibody of the present invention.

The compound of formula:

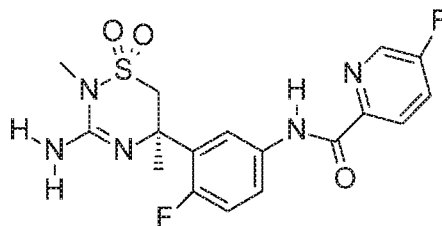


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or a pharmaceutically acceptable salt thereof, is disclosed as a BACE inhibitor and can be prepared by one of ordinary skill in the art as set forth in U.S. Patent No. 8,841,293 B1, entitled "Tetrahydropyrrolothiazine Compounds", issued September 23, 2014 (U.S. Application No. 14/195,897); see in particular, Example 4, N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide. The tosylate salt of N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide can be prepared by one of ordinary skill in the art as set forth in PCT/US2016/014423. The crystalline form of N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide can be prepared by one of ordinary skill in the art as set forth in WO 2016/043996, entitled "A Tetrahydropyrrolo[3,4-D][1,3] Thiazine-Derivative as BACE Inhibitor".

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The compound of the formula:



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or a pharmaceutically acceptable salt thereof, is disclosed as a BACE inhibitor and can be prepared by one of ordinary skill in the art as set forth in U.S. Patent No. 8,729,071 B1, entitled “Iminothiadiazine Dioxide Compounds As BACE Inhibitors, Compositions and Their Use” issued May 20, 2014. Crystalline forms and crystalline forms of the tosylate salt of N-[3-[(5R)-3-
 5 Amino-5,6-dihydro-2,5-dimethyl-1,1-dioxido-2H-1,2,4-thiadiazin-5-yl]-4-fluorophenyl]-5-fluoro-2-pyridinecarboxamide, verubecestat, are disclosed and can be prepared by one of ordinary skill in the art as set forth in WO2016/053767, entitled “Novel Crystalline forms of a BACE Inhibitor, Compositions, and their Use”.

In addition, amino acid sequences for certain anti-N3pGlu A β antibodies used in the
 10 present invention are provided below in Table A:

Table A-Antibody Amino Acid Sequences

Anti-N3pGlu Antibody	LCVR	HCVR	LC	HC
Antibody I	9	8	12	11
Antibody II	10	8	13	11
Antibody III (B12L)	25	26	28	29
Antibody IV (R17L)	25	27	28	30
Antibody V(hE8L)	32	34	33	35
Antibody VI (5-5-6)	39	40		
Antibody VII (6-1-6)	41	42		
Antibody VIII(17-4-3)	43	44		
Antibody IX (24-2-3)	45	46		
Antibody X (9D5H6)	47	48		
Antibody XI (8C4)	49	50		
Antibody XII (5C9 (LuAb1h)	51	52		
Antibody XIII (2E83 (LuAb2h)	53	54		

With respect to “Antibody I”, “Antibody II”, “Antibody III”, “Antibody IV”, and
 15 “Antibody V”, additional amino acid sequences for such antibodies are provided in Table B:

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Table B-Antibody CDR Amino Acid Sequences

Antibody SEQ ID NOs						
Antibody	LCDR1	LCDR2	LCDR3	HCDR1	HCDR2	HCDR3
I	4	6	7	1	2	3
II	4	5	7	1	2	3
III (B12L)	17	18	19	20	22	23
IV (R17L)	17	18	19	21	22	24
V (hE8L)	17	18	19	36	22	37

As used herein, an “antibody” is an immunoglobulin molecule comprising two Heavy Chain (HC) and two Light Chain (LC) interconnected by disulfide bonds. The amino terminal portion of each LC and HC includes a variable region responsible for antigen recognition via the complementarity determining regions (CDRs) contained therein. The CDRs are interspersed with regions that are more conserved, termed framework regions. Assignment of amino acids to CDR domains within the LCVR and HCVR regions of the antibodies of the present invention is based on the following: Kabat numbering convention (Kabat, et al., Ann. NY Acad. Sci. 190:382-93 (1971); Kabat et al., Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242 (1991)), and North numbering convention (North et al., A New Clustering of Antibody CDR Loop Conformations, Journal of Molecular Biology, 406:228-256 (2011)). Following the above method, the CDRs of the present invention were determined (Table B).

The anti-N3pGlu A β antibodies of the present invention include kappa LC and IgG HC. In a particular embodiment, the anti-N3pglu A β antibodies of the present invention are of the human IgG1 isotype.

The antibodies of the present invention are monoclonal antibodies (“mAbs”). Monoclonal antibodies can be produced, for example, by hybridoma technologies, recombinant technologies, phage display technologies, synthetic technologies, e.g., CDR-grafting, or combinations of such or other technologies known in the art. The monoclonal antibodies of the present invention are human or humanized. Humanized antibodies can be engineered to contain one or more human framework regions (or substantially human framework regions) surrounding CDRs derived from a non-human antibody. Human framework germline sequences can be obtained from ImunoGeneTics (INGT) via their website, <http://imgt.cines.fr>, or from *The Immunoglobulin FactsBook* by Marie-Paule Lefranc and Gerard Lefranc, Academic 25 Press, 2001, ISBN

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012441351. Techniques for generating human or humanized antibodies are well known in the art. In another embodiment of the present invention, the antibody, or the nucleic acid encoding the same, is provided in isolated form. As used herein, the term "isolated" refers to a protein, peptide or nucleic acid that is not found in nature and is free or substantially free from other

5 macromolecular species found in a cellular environment. "Substantially free", as used herein, means the protein, peptide or nucleic acid of interest comprises more than 80% (on a molar basis) of the macromolecular species present, preferably more than 90% and more preferably more than 95%.

The anti-N3pGlu A β antibody of the present invention is administered as a pharmaceutical
10 composition. The pharmaceutical composition comprising an antibody of the present invention can be administered to a patient at risk for, or exhibiting, diseases or disorders as described herein by parental routes (e.g., subcutaneous, intravenous, intraperitoneal, intramuscular). Subcutaneous and intravenous routes are preferred.

The terms "treatment," "treating" or "to treat" and the like include restraining, slowing or
15 stopping the progression or severity of an existing symptom, condition, disease, or disorder in a patient. The term "patient" refers to a human.

The term "prevention" means prophylactic administration of the antibody of the present invention to an asymptomatic patient or a patient with pre-clinical Alzheimer's disease to prevent onset or progression of the disease.

20 The terms "disease characterized by deposition of A β " or a disease characterized by A β deposits" are used interchangeably and refer to a disease that is pathologically characterized by A β deposits in the brain or in brain vasculature. This includes diseases such as Alzheimer's disease, Down's syndrome, and cerebral amyloid angiopathy. A clinical diagnosis, staging or progression of Alzheimer's disease can be readily determined by the attending diagnostician or
25 health care professional, as one skilled in the art, by using known techniques and by observing results. This generally includes some form of brain plaque imaging, mental or cognitive assessment (e.g. Clinical Dementia Rating – summary of boxes (CDR-SB), Mini-Mental State Exam (MMSE) or Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog)) or functional assessment (e.g. Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-
30 ADL). The cognitive and functional assessment can be used to determine changes in a patients cognition (e.g. cognitive decline) and function (e.g. functional decline). "Clinical Alzheimer's disease" as used herein is a diagnosed stage of Alzheimer's disease. It includes conditions diagnosed as prodromal Alzheimer's disease, mild Alzheimer's disease, moderate Alzheimer's disease and severe Alzheimer's disease. The term "pre-clinical Alzheimer's disease" is a stage

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that precedes clinical Alzheimer's disease, where measurable changes in biomarkers (such as CSF A β 42 levels or deposited brain plaque by amyloid PET) indicate the earliest signs of a patient with Alzheimer's pathology, progressing to clinical Alzheimer's disease. This is usually before symptoms such as memory loss and confusion are noticeable. Pre-clinical Alzheimer's disease

5 also includes pre-symptomatic autosomal dominant carriers, as well as patients with higher risk for developing AD by virtue of carrying one or two APOE e4 alleles.

For patients undergoing brain plaque imaging, a patient is positive for amyloid deposits when amyloid is detected in the brain by methods such as amyloid imaging with radiolabeled PET compounds. An example of one such amyloid PET imaging compound is florbetapir F 18, which

10 bind with high specificity to amyloid plaques. The chemical formula of florbetapir F 18 is $C_{20}H_{25}^{18}FN_2O_3$. Amyloid imaging with radiolabeled PET compounds can be used to determine if A β deposit in the brain of a human patient is reduced by 35-100% within 6 months post induction treatment. A person of skill in the art can correlate the standardized uptake value ratio (SUVR) values obtained from amyloid imaging (with radiolabeled PET compounds) to calculate the %

15 reduction in A β deposit in the brain of the patient before and after treatment. The SUVR values can be converted to standardized centiloid units, where 100 is average for AD and 0 is average for young controls, allowing comparability amongst amyloid PET tracers, and calculation of reduction according to centiloid units (Klunk et al., *Alzheimers Dement*, 2015;11:1-15). As used herein, "a period of 6 months or less" refers to a period of time that is 6 months or less than 6 full

20 consecutive calendar months, and wherein each month has 28-31 days. At the least this period includes a one-time induction dose given in a single administration.

A reduction or slowing of cognitive decline can be measured by cognitive assessments such as Clinical Dementia Rating – summary of boxes (CDR-SB), Mini-Mental State Exam (MMSE) or Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog). A reduction or slowing of

25 functional decline can be measured by functional assessments such as Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL).

An "induction dose" is a dose of an anti-N3pGlu A β antibody that causes a sharp reduction in A β deposit in the brain of a human patient within 6 months of treatment. A "one-time" dose is an induction dose that is administered once to a patient. A "one-time" dose can also be a dose that is

30 administered to a patient once with a prolonged period of time, such as 2-10 years, between doses if such a dose is needed. Whether a patients needs more than one "one-time" induction dose can be determined by a diagnostician or health care professional by using known techniques and by observing results. A "biweekly" dose is a dose of that is administered to a patient every two weeks.

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A "maintenance dose" is a dose administered to a patient after the induction dose treatment. A maintenance dose is an amount of antibody or drug administered to maintain the desired therapeutic response including reduced A β deposit in the brain of a human patient. A maintenance dose can be dose that is the same or lower in amount of antibody or drug compared to the induction dose.

As used herein, "mg/kg" means an amount, in milligrams, of antibody or drug administered to a patient based on his or her bodyweight in kilograms. A dose is given at one time. For example, a 10mg/kg dose of antibody for a patient weighing 70 kg would be a single 700 mg dose of antibody given in a single administration. Similarly, a 40mg/kg dose of antibody for a patient weighing 80 kg would be a 3200 mg dose of antibody given at a single administration.

As used herein, the phrase "in combination with" refers to the administration of an anti-N3pGlu A β antibody of the present invention, with another molecule (a "combination molecule," such as a BACE inhibitor, symptomatic agent or A β antibody), simultaneously, or sequentially in any order, or any combination thereof. The two molecules may be administered either as part of the same pharmaceutical composition or in separate pharmaceutical compositions. The anti-N3pGlu A β antibody can be administered prior to, at the same time as, or subsequent to administration of the combination molecule, or in some combination thereof. Where the combination molecule is administered at repeated intervals (e.g. during a standard course of treatment), the anti-N3pGlu A β antibody can be administered prior to, at the same time as, or subsequent to, each administration of the combination molecule, or some combination thereof, or at different intervals in relation to therapy with the combination molecule, or in a single or series of dose(s) prior to, at any time during, or subsequent to the course of treatment with the combination molecule. One of ordinary skill in the art would recognize that a BACE inhibitor refers to a therapeutic agent, preferably a small molecule that inhibits the beta-secretase 1 enzyme, and can prevent the formation of amyloid plaque. Examples of BACE inhibitors are herein disclosed.

"Symptomatic agents," as used herein refer to therapeutic agents used to treat the cognitive manifestations of Alzheimer's symptomatically and have not shown to have any effect on Alzheimer disease progression. These include acetyl cholinesterase inhibitors and NMDA receptor antagonists. The cholinesterase inhibitors approved for the management of AD symptoms include: donepezil (brand name AriceptTM), galantamine (RazadyneTM), and rivastigmine (branded as Exelon and ExelonTM Patch). Memantine (also known as NAMEDA®) is an approved NMDA receptor antagonist. NAMZARIC® is a combination agent comprising both an acetyl cholinesterase inhibitor and NMDA receptor antagonist.

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The following Examples and assays demonstrate that the antibodies of the present invention are useful for treating a disease characterized by deposition of A β , such as of Alzheimer's disease, Down's syndrome, and CAA. It should be understood however, that the following Examples are set forth by way of illustration and not limitation, and that various
 5 modifications may be made by one of ordinary skill in the art.

Examples

Example 1: Single dose efficacy in aged transgenic mice

10 Single dose longitudinal effects of the murine surrogate mE8c anti-N3pGlu antibody (IgG2a) (U.S. Patent No. 8,679,498 B1) observed in aged PDAPP transgenic mice (18.5 to 20-months old). To mimic A β deposition rates and conditions in humans with Alzheimer's disease, mice are placed on a chow diet containing a BACE inhibitor LY2811376 (0.015%) four days prior to receiving a single intraperitoneal injection of biotinylated mE8c antibody or biotinylated
 15 control antibody of the same isotype, and remain on this diet for the duration of the study. A prior 4-month study demonstrated in aged PDAPP mice treated with the BACE inhibitor in feed resulted in a level of BACE inhibition that led to no change in the deposited A β over the 4-month interval (i.e. no further deposition and no clearance of deposited A β occurred). Animals are sacrificed 4, 8, 12, or 16 weeks after the single injection of biotinylated mE8c antibody (20 mg/kg
 20 or 100 mg/kg) or biotinylated control antibody (100mg/kg). An additional control group of transgenic mice is sacrificed at study initiation (time zero cohort) and at 4, 8, 12, or 16 weeks (age matched control cohort). Hippocampus tissue is analyzed by acid urea gels to measure the A β 1-42 via denaturing conditions.

Following the procedure essentially as described above, there was no significant
 25 difference in the levels of A β 1-42 between the isotype control injected at 4, 8, 12, or 16-weeks (age matched control cohort) as compared to the time zero cohort. As such, the control animals were combined into one control group for comparison with animals injected with biotinylated mE8c antibody. Mice that received a single injection of 20mg/kg biotinylated mE8c antibody had reduced levels of hippocampal A β 1-42 as compared to control animals at 4-weeks (-6%), 8-weeks
 30 (-32%; Dunnett's multiple comparison, $p = 0.0091$), 12-weeks (-17%), and 16-weeks (-19%). The aged PDAPP mice that received a single injection of 100mg/kg biotinylated mE8c antibody had reduced levels of hippocampal A β 1-42 as compared to control animals at 4-weeks (-23%), 8-weeks (-28%; Dunnett's multiple comparison, $p = 0.0252$), 12-weeks (-14%), and 16-weeks (-17%).

Example 2: Single dose target engagement in aged transgenic mice

5 To determine in-vivo target engagement of deposited plaque after a single dose of N3pGlu antibody, frozen hemi-brains from the single dose antibody study described in Example 1 are analyzed histologically to determine the percent area of hippocampus demonstrating antibody bound to plaque at 0, 4, 8, 12, and 16 weeks after a single dose of antibody.

10 Brains are sectioned and immunohistochemistry is performed on sister sections with an anti-human antibody (to detect the bound N3pGlu antibody) and 3D6 (to detect the total amount of deposited target in the section). Percent area bound by the N3pGlu antibody is normalized against the total amount of deposited target in the section.

Following procedures essentially as described above, the total area covered by deposited A β was not significantly different across all groups and the average hippocampal area covered by the stain varied from 27 to 39%. Little to no target engagement was observed for control animals. Significant target engagement was observed 4, 8, 12, and 16-weeks after the single dose of 20 mg/kg (2.8% (p < 0.0001), 1.9% (p < 0.0001), 1.1% (p = 0.003), 0.6% (p = 0.0323), respectively) or 100mg/kg (5.5% (p < 0.0001), 4.0% (p < 0.0001), 2.6% (p < 0.0001), 1.5% (p = 0.0002), respectively) of biotinylated mE8c antibody (as compared to controls). Dunn non-parametric analysis was used to determine p-values. The average area of target engagement in mE8c-injected animals was highest after 4-weeks of treatment and the average target engagement decreased longitudinally at the subsequent 8, 12, and 16-week time points (1.9%, 1.1%, 0.6% respectively for the 20 mg/kg mE8c group, and 4.0%, 2.6%, and 1.5% respectively for the 100 mg/kg mE8c group). Due to the high level of variability, significant differences were not observed between the 20 and 100mg/kg mE8c single dose injected animals for the matched time points except for week 12 and 16 (p-value = 0.0465, 0.0432 unadjusted Wilcoxon).

Example 3: Single-Dose and Multiple-Dose, Dose-Escalation Clinical Trial for Alzheimer's Disease

30 A phase I, double-blind, randomized, placebo-controlled, parallel-group, single-dose followed by multiple-dose, dose-escalation study in patients with MCI due to AD or mild-to-moderate AD was conducted to assess the safety, tolerability, and PK of single and multiple IV doses of LY3002813 (Antibody III). AD patients were enrolled into the single-ascending dose (SAD) phase and were each administered a single intravenous (IV) dose of Antibody III (5 dosing

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cohorts from 0.1 mg/kg IV to 10 mg/kg IV) or placebo followed by a 12-week follow-up period for each dose level. After the follow-up period, the same patients proceeded into the multiple-ascending dose (MAD) phase (5 cohorts) and were administered IV doses of Antibody III (0.3 mg/kg IV to 10 mg/kg IV) or placebo approximately once per month for up to 4 doses depending on the initial doses. This phase concluded with a 12-week follow-up period.

The results of the single-dose study, wherein the PK of Antibody III was assessed up to 84 days after a single dose, showed the mean terminal elimination half-life was approximately 4 days after single-dose administration from 0.1 mg/kg to 3.0 mg/kg, and was increased to approximately 10 days (243 hours) at the 10-mg/kg dose level. The mean clearance values at each dose level ranged from 26.3 mL/hour (10 mg/kg) to 35.6 mL/hour (1.0 mg/kg).

The results of the multiple-dose study, wherein patients entered the multiple-dose phase 12 weeks after receiving a single dose in the SAD phase, showed Antibody III concentrations were significantly lower following multiple doses of Antibody III than following the first single dose. In contrast to the other dose levels, at the 10-mg/kg dose level, Antibody III concentrations were generally similar to those observed after single-dose administration. Most patients at dose levels ≤ 3 mg/kg had serum Antibody III concentrations below the limits of detection 28 days after dosing. Patients receiving 10 mg/kg had sustained quantifiable concentrations 28 days after dosing.

Greater than 90% of the patients with AD had treatment-emergent antidrug antibodies (ADAs) 3 months after the first dose at all dose groups; titers tended to increase by the end of the MAD phase and persist 3 months after the last dose. The rapid decline of Antibody III concentrations after multiple-dose administration may be at least partly associated with the presence of ADAs. Treatment group also experienced increased infusion related reactions upon multiple dosing.

Florbetapir scans were performed at baseline and after the last MAD dose, separated by approximately 7 months. The change in whole grey matter standardized uptake value ratio (SUVr) with cerebellum as a reference region was compared across dose cohorts, and the SUVr values were converted to standardized centiloid (CL) units. There was a significant reduction in cerebral amyloid (as assessed by florbetapir PET imaging) in the 6 patients who received 3 to 5 doses of 10 mg/kg of Antibody III intravenously over 6 months, without cerebral vasogenic edema or microhemorrhage complications in this dose group. The mean reduction of 44 CL units corresponds to a mean 40-50% reduction in brain amyloid.

Florbetapir scans in extended follow up from three subjects treated with 3-5 doses of 10 mg/kg IV of Antibody III (vs 2 placebo) demonstrated sustained amyloid removal 18 months after

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last dose. The data indicate that short term (and possibly single) dose of anti-N3pGlu A β antibodies (such as Antibody III) is sufficient to result in a sustained removal of amyloid. Chronic dosing with anti-N3pGlu A β antibodies is not required to maintain clearance of cerebral amyloid.

5

Example 4: Single-Dose and Multiple-Dose Clinical Trial for Alzheimer's Disease

As a result of the significant target engagement (amyloid reduction by florbetapir PET) that was identified after 3 to 5 doses of LY3002813 (Antibody III) 10 mg/kg intravenously over 6 months, a Phase Ib study is in progress to confirm that different dosing regimens (single-dose, short-term "induction" dosing with higher, more frequent dosing; and chronic dosing for maximal PD effect) can mitigate immunogenicity and immune safety issues, and produce sustained amyloid reduction. A phase Ib, double-blind, randomized within cohort, placebo-controlled, parallel-group, single-and multiple-dose study in patients with MCI due to AD or mild-to-moderate AD is being conducted to assess the safety, tolerability, and PK of single and multiple IV doses of Antibody III. The study will be conducted in at least seven cohorts, including single IV doses at 10 mg/kg, 20 mg/kg, or 40 mg/kg (cohorts 1, 2, and 3, respectively), IV doses every two weeks for 24 weeks at 10 mg/kg or 20 mg/kg (cohorts 4 and 5, respectively), and IV doses every four weeks for up to 72 weeks at 10 mg/kg or 20 mg/kg (cohorts 6 and 7, respectively).

The primary target engagement outcome is the reduction of cerebral amyloid as measured by quantitative amyloid PET imaging (florbetapir CL) assessed at baseline and at 12 weeks, 24 weeks, 36 weeks, 48 weeks, and 72 weeks after starting treatment.

The results demonstrate that 10mg/kg, 20mg/kg and 40mg/kg single doses and 10mg/kg multiple doses of Antibody III can reduce amyloid at 12 weeks (mean reductions in cohorts to date ranging from -12 to -39 CL by florbetapir PET). For the patients who have had additional scans beyond 12 weeks, the amyloid clearance is sustained in the single dose cohorts, and further amyloid clearance is observed with dosing in the multiple dose cohort.

Example 5: Expression and Purification of Engineered N3pGlu A β Antibodies

Anti-N3pGlu A β antibodies of the present invention can be expressed and purified essentially as follows. An appropriate host cell, such as HEK 293 EBNA or CHO, is either transiently or stably transfected with an expression system for secreting antibodies using an optimal predetermined HC:LC vector ratio or a single vector system encoding both HC and LC. Clarified media, into which the antibody has been secreted, is purified using any of many commonly-used techniques. For example, the medium may be conveniently applied to a Protein A

30

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or G Sepharose FF column that has been equilibrated with a compatible buffer, such as phosphate buffered saline (pH 7.4). The column is washed to remove nonspecific binding components. The bound antibody is eluted, for example, by pH gradient (such as 0.1 M sodium phosphate buffer pH 6.8 to 0.1 M sodium Citrate buffer (pH 2.5). Antibody fractions are detected, such as by SDS-PAGE, and then are pooled. Further purification is optional, depending on the intended use. The antibody may be concentrated and/or sterile filtered using common techniques. Soluble aggregate and multimers may be effectively removed by common techniques, including size exclusion, hydrophobic interaction, ion exchange, or hydroxyapatite chromatography. The purity of the antibody after these chromatography steps is greater than 99%. The product may be immediately frozen at -70°C. or may be lyophilized. The amino acid sequences for the anti- N3pGlu A β antibodies are provided in Table A.

Example 6: Binding Affinity and Kinetics

The binding affinity and kinetics of anti-N3pGlu A β antibody of the present invention (Antibody I or Antibody II) to pE3-42 A β peptide or to A β 1-40 peptide is measured by surface plasmon resonance using BIACORE® 3000 (GE Healthcare). The binding affinity is measured by capturing the anti-N3pGlu A β antibody via immobilized protein A on a BIACORE® CMS chip, and flowing pE3-42 A β peptide or A β 1-40 peptide, starting from 100 nM in 2-fold serial dilution down to 3.125 nM. The experiments are carried out at 25 °C in HBS-EP buffer (GE Healthcare BR100669; 10 mM HEPES, 150 mM NaCl, 3 mM EDTA, 0.05% surfactant P20, pH 7.4).

For each cycle, the antibody is captured with 5 μ L injection of antibody solution at a 10 μ g/mL concentration with 10 μ L/min. flow rate. The peptide is bound with 250 μ L injection at 50 μ L/min, and then dissociated for 10 minutes. The chip surface is regenerated with 5 μ L injection of glycine buffer at pH 1.5 at 10 μ L/min flow rate. The data is fit to a 1: 1 Langmuir binding model to derive k_{on} , k_{off} , and to calculate K_D . Following procedures essentially as described above, the following parameters (shown in Table C) were observed.

Table C. Binding affinity and kinetics.

Antibody	k_{on} ($\times 10^5$ 1/MS)	k_{off} ($\times 10^{-4}$ 1/s)	K_D (nM)
I	1.39	1.31	0.71
II	3.63	1.28	0.35
III	3.62	2.7	0.75
IV	4.03	3.72	0.92

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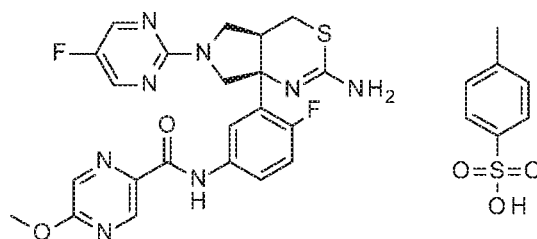
V	5.78	3.21	0.55
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No appreciable binding to A β 1-40 was detected, indicating that Antibodies I-V bound preferentially to pE3-42 A β peptide as compared to A β 1-40.

5 Example 7: *Ex Vivo* Target Engagement

To determine *ex vivo* target engagement on brain sections from a fixed PDAPP brain, immunohistochemical analysis is performed with an exogenously added anti-N3pGlu A β antibodies of the present invention (hE8L, B12L, R17L, Antibody I or Antibody II). Cryostat serial coronal sections from aged PDAPP mice (25-month old) are incubated with 20 μ g/mL of an
 10 exemplified N3pGlu A β antibody of the present invention. Secondary HRP reagents specific for human IgG are employed and the deposited plaques are visualized with DAB-Plus (DAKO). Biotinylated murine 3D6 antibody followed by Step-HRP secondary is used as a positive control. The positive control antibody (biotinylated 3D6) labeled significant quantities of deposited A β in the PDAPP hippocampus, and the anti – N3pGlu A β antibodies (hE8L, B12L, R17L, Antibody I
 15 or Antibody II) labeled a subset of deposits. These histological studies demonstrated that the anti – N3pGlu A β antibodies of the present invention engaged deposited A β target *ex vivo*.

Example 8: Synthesis of N-[3-[(4aR,7aS)-2-Amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide; toluenesulfonic acid
 20



Crystalline Form 2 N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide hydrated (149.15 mg) is added to ethyl acetate (2 mL). The sample is stirred at 1000 rpm at a
 25 temperature of 80°C. *p*-Toluenesulfonic acid (70 mg dissolved in ethyl acetate (1 mL)) is added to the stirring solution, and it is stirred overnight at 80°C to produce a slurry of a white solid which is isolated by vacuum filtration to provide the title compound.

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Alternative Preparation A of N-[3-[(4aR,7aS)-2-Amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide; toluenesulfonic acid

5 N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide (9.5 g, 19 mmol) and *p*-toluenesulfonic acid (3.80 g, 19.8 mmol) are added to tetrahydrofuran (31 mL), water (7.9 mL), and 2-propanol (8.6 mL). The solution is heated to 40 °C. To the warm solution is added 2-propanol (200.0 mL) over approximately 3 hours. The mixture is seeded shortly after the start of the 2-propanol addition with a portion of the title compound (500 mg, 0.75 mmol). After the
10 solvent addition is complete, the mixture is cooled to approximately 20 °C over 1-3 hours. The mixture is heated from approximately 20 °C to approximately 55 °C over a target time of 2 hours. The temperature is held at 55 °C for 1 hour and then cooled to about 20 °C over approximately 4 hours. The slurry is stirred for at least 10 hours at approximately 20 °C. The slurry is filtered and the wet cake is washed with water (57 mL). The product is dried *in vacuo* at 45 °C for at least 10
15 hours to give the title compound (10.4 g, 81%). ES/MS (*m/z*): 500 (M+H).

Alternative Preparation B of N-[3-[(4aR,7aS)-2-Amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide; toluenesulfonic acid

20 N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide hydrated (20.7 g) is slurried at 170 rpm in 60:40 THF:H₂O (85 mL) in a 500 mL 3-necked round bottomed flask equipped with a nitrogen bubbler, IKA® mechanical motor/agitator attached to a glass shaft having a TEFLON® banana blade, and a thermocouple connected to a programmable J-KEM®
25 temperature controller. *p*-Toluenesulfonic acid monohydrate (7.6 g, 1.03 eq) is dissolved in a mixture of 60:40 THF:H₂O (20 mL) and the solution added all at once to the stirring N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide slurry at 23 °C, leading almost immediately to a clear reddish tan solution. The agitation rate is then increased to 200 rpm as
30 over 15 minutes, water (22 mL) is added to the solution, which is then seeded with N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide toluenesulfonic acid (750 mg, 3 wt % seed load) and is then stirred at 23 °C for a further 15 minutes. Over 6 hours, water (226 mL, total solvent of 353 mL; or 13.6 vol., final solvent ratio of 17.5:82.5 THF:H₂O) is added to the

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slurry, which is then stirred overnight (22 hours) at 23 °C. The slurry is filtered via vacuum, rinsed with 15:85 THF:H₂O (2×20 mL), then left on vacuum for 20 minutes while cracks which form in the product wet cake are manually pressed closed. The wet solids are dried at 40 °C under vacuum for about 72 hours to give the title compound as a white crystalline solid (24.07 g, 90.0 wt %).

The crystalline N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide; toluenesulfonic acid is characterized by an XRD pattern using CuKα radiation as having diffraction peaks (2-theta values) as described in Table D below, and in particular having peaks at diffraction angle 2-theta of 5.0° in combination with one or more of the peaks selected from the group consisting of 19.6°, 13.8°, and 18.5°; with a tolerance for the diffraction angles of 0.2 degrees.

Table D: X-ray powder diffraction peaks of crystalline Example 8

Peak	Angle (2-Theta°) +/- 0.2°	Relative Intensity (% of most intense peak)
1	5.0	100.0
2	13.4	22.9
3	13.8	37.3
4	14.4	20.2
5	15.3	28.8
6	17.5	25.9
7	18.5	30.7
8	19.6	45.8
9	20.4	17.7
10	25.6	30.1

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Sequences

<SEQ ID NO: 1; PRT1; Artificial> (HCDR1 - Antibody I and Antibody II)
 KASGYTFTDYYIN
 5

<SEQ ID NO: 2; PRT1; Artificial> (HCDR2 - Antibody I and Antibody II)
 WINPGSGNTKYNEKFKG

<SEQ ID NO: 3; PRT1; Artificial> (HCDR3 - Antibody I and Antibody II)
 10 TREGETVY

<SEQ ID NO: 4; PRT1; Artificial> (LCDR1 - Antibody I and Antibody II)
 KSSQSLLYSRGKTYLN

15 <SEQ ID NO: 5; PRT1; Artificial> (LCDR2 - Antibody II)
 YAVSKLDS

<SEQ ID NO: 6; PRT1; Artificial> (LCDR2 - Antibody I)
 YDVSKLDS
 20

<SEQ ID NO: 7; PRT1; Artificial> (LCDR3 - Antibody I and Antibody II)
 VQGTHYPFT

<SEQ ID NO: 8; PRT1; Artificial> (HCVR - Antibody I and Antibody II)
 25 QVQLVQSGAEVKKPGSSVKVSCKASGYTFTDYYINWVRQAPGQGLEWMGWINPGSGNT
 KYNEKFKGRVTITADESTSTAYMELSSLRSEDTAVYYCTREGETVYWGQGTLLVTVSS

<SEQ ID NO: 9; PRT1; Artificial> (LCVR - Antibody I)
 DVVMTQSPLSLPVTLGQPASISCKSSQSLLYSRGKTYLNWFQQRPGQSPRRLIYDVSKLDS
 30 GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCVQGTHYPFTFGQGTKLEIK

<SEQ ID NO: 10; PRT1; Artificial> (LCVR - Antibody II)
 DIQMTQSPSTLSASVGDRVTITCKSSQSLLYSRGKTYLNWLQQKPGKAPKLLIYAVSKLD
 SGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCVQGTHYPFTFGQGTKLEIK

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<SEQ ID NO: 11; PRT1; Artificial>

(HC - Antibody I and Antibody II)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFTDYYINWVRQAPGQGLEWMGWINPGSGNT
 KYNEKFKGRVTITADESTSTAYMELSSLRSEDTAVYYCTREGETVYWGQGTLLTVSSAS
 5 TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
 YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSV
 FLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST
 YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL
 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQ
 10 QGNVFSCSVMHEALHNHYTQKSLSLSPG

<SEQ ID NO: 12; PRT1; Artificial>

(LC - Antibody I)

DVVMTQSPSLPVTLGQPASISCKSSQSLLYSRGKTYLNWFQQRPGQSPRRLIYDVSKLDS
 GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCVQGTHYPFTFGQGTKLEIKRTVAAPSVFI
 15 FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSL
 STLTLKADYEEKHKVYACEVTHQGLSPVTKSFNRGEC

<SEQ ID NO: 13; PRT1; Artificial>

(LC - Antibody II)

DIQMTQSPSTLSASVGDRVTITCKSSQSLLYSRGKTYLNWLQKPGKAPKLLIYAVSKLD
 20 SGVPSRFSGSGSGTEFTLTISSLQPDFFATYYCVQGTHYPFTFGQGTKLEIKRTVAAPSVFI
 FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSL
 STLTLKADYEEKHKVYACEVTHQGLSPVTKSFNRGEC

<SEQ ID NO: 14; DNA; Artificial> Exemplified DNA for Expressing Antibody Heavy Chain of

25 SEQ ID NO: 11
 CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCTCGGTGAAG
 GTCTCCTGCAAGGCTTCTGGATACACCTTCACCGACTATTATATCAACTGGGTGCGAC
 AGGCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAACCCTGGCAGTGGTAATA
 CAAAGTACAATGAGAAGTTCAAGGGCAGAGTCACGATTACCGCGGACGAATCCACG
 30 AGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTAC
 TGTACAAGAGAAGGCGAGACGGTCTACTGGGGCCAGGGAACCCTGGTCACCGTCTCC
 TCAGCCTCCACCAAGGGCCCATCGGTCTTCCCGCTAGCACCTCCTCCAAGAGCACCT
 CTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGA
 CGGTGTCGTGGAACCTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCTGTCC

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TACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTT
GGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGG
ACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACCTCACACATGCCCACCGTGCCCAG
CACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCC AAAACCCAAGGACA
5 CCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACG
AAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCA
AGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTC
ACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAAC
AAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGA
10 GAACCACAGGTGTACACCCTGCCCCCATCCCGGGACGAGCTGACCAAGAACCAGGTC
AGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAG
AGCAATGGGCAGCCGGAGAACAAC TACAAGACCACGCCCCCGTGCTGGACTCCGA
CGGCTCCTTCTTCCTCTATAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGG
GAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAA
15 GAGCCTCTCCCTGTCTCCGGGT

<SEQ ID NO: 15; DNA; Artificial> Exemplified DNA for Expressing Antibody Light Chain of
SEQ ID NO: 12

GATGTTGTGATGACTCAGTCTCCACTCTCCCTGCCCCGTACCCCTTGGACAGCCGGCCT
20 CCATCTCCTGCAAGTCTAGTCAAAGCCTCCTGTACAGTCGCGGAAAAACCTACTTGA
ATTGGTTTCAGCAGAGGCCAGGCCAATCTCCAAGGCGCCTAATTTATGATGTTTCTAA
ACTGGACTCTGGGGTCCCAGACAGATT CAGCGGCAGTGGGTCAGGCACTGATTTTCA
ACTGAAAATCAGCAGGGTGGAGGCTGAGGATGTTGGGGTTTATTACTGCGTGCAAGG
TACACACTACCCTTTCACTTTTGGCCAAGGGACCAAGCTGGAGATCAAACGGACCGT
25 GGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAAC
GCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGG
AAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGA
CAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGCAAAGCAGACT
ACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCC
30 TCACAAAGAGCTTCAACAGGGGAGAGTGC

<SEQ ID NO: 16; DNA; Artificial> Exemplified DNA for Expressing Antibody Light Chain of
SEQ ID NO: 13

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GACATCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAGAGTCA
 CCATCACTTGCAAGTCCAGTCAGAGTCTCCTGTACAGTCGCGGAAAAACCTATTTGA
 ACTGGCTCCAGCAGAAACCAGGGAAAGCCCCCTAAGCTCCTGATCTATGCTGTCTCCA
 AACTGGACAGTGGGGTCCCATCAAGGTTTCAGCGGCAGTGGATCTGGGACAGAATTCA
 5 CTCTCACCATCAGCAGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCGTGCAGGG
 TACACATTATCCTTTCACTTTTGGCCAGGGGACCAAGCTGGAGATCAAACGGACCGT
 GGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
 GCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGG
 AAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGA
 10 CAGCAAGGACAGCACCTACAGCCTCAGCAGCACCTGACGCTGAGCAAAGCAGACT
 ACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCCG
 TCACAAAGAGCTTCAACAGGGGAGAGTGC

<SEQ ID NO: 17; PRT1; Artificial> (LCDR1- B12L/R17L/hE8L)
 15 KSSQSLLYSRGKTYLN

<SEQ ID NO: 18; PRT1; Artificial> (LCDR2 - B12L/R17L/hE8L)
 AVSKLDS

20 <SEQ ID NO: 19; PRT1; Artificial> (LCDR3 - B12L/R17L/hE8L)
 VQGTHYPFT

<SEQ ID NO: 20; PRT1; Artificial> (HCDR1 - B12L)
 25 GYDFTRYIN

<SEQ ID NO: 21; PRT1; Artificial> (HCDR1 - R17L)
 GYTFTRYIN

<SEQ ID NO: 22; PRT1; Artificial> (HCDR2 - B12L/R17L/hE8L)
 30 WINPGSGNTKYNEKFKG

<SEQ ID NO: 23; PRT1; Artificial> (HCDR3 - B12L)
 EGITVY

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<SEQ ID NO: 24; PRT1; Artificial>

(HCDR3 - R17L)

EGTTVY

<SEQ ID NO: 25; PRT1; Artificial>

(LCVR - B12L/R17L)

5 DIVMTQTPLSLSVTPGQPASISCKSSQSLLYSRGKTYLNWLLQKPGQSPQLLIYAVSKLDS
GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCVQGTHYPFTFGQGTKLEIK

<SEQ ID NO: 26; PRT1; Artificial>

(HCVR - B12L)

10 QVQLVQSGAEVKKPGSSVKVSCKASGYDFTRY~~YIN~~WVRQAPGQGLEWMGWINPGSGN
TKYNEKFKGRVTITADESTSTAYMELSSLRSEDTAVYYCAREGITVYWGQGTTVTVSS

<SEQ ID NO: 27; PRT1; Artificial>

(HCVR - R17L)

15 QVQLVQSGAEVKKPGSSVKVSCKASGYTFTRY~~YIN~~WVRQAPGQGLEWMGWINPGSGNT
KYNEKFKGRVTITADESTSTAYMELSSLRSEDTAVYYCAREGTTVYWGQGTTVTVSS

<SEQ ID NO: 28; PRT1; Artificial>

(LC - B12L/R17L)

20 DIVMTQTPLSLSVTPGQPASISCKSSQSLLYSRGKTYLNWLLQKPGQSPQLLIYAVSKLDS
GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCVQGTHYPFTFGQGTKLEIKRTVAAPSVFI
FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSLS
STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

<SEQ ID NO: 29; PRT1; Artificial>

(HC - B12L)

25 QVQLVQSGAEVKKPGSSVKVSCKASGYDFTRY~~YIN~~WVRQAPGQGLEWMGWINPGSGN
TKYNEKFKGRVTITADESTSTAYMELSSLRSEDTAVYYCAREGITVYWGQGTTVTVSSAS
TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSV
FLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST
YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
30 QGNVFSCSVMHEALHNHYTQKSLSLSPG

<SEQ ID NO: 30; PRT1; Artificial>

(HC - R17L)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFTRY~~YIN~~WVRQAPGQGLEWMGWINPGSGNT
KYNEKFKGRVTITADESTSTAYMELSSLRSEDTAVYYCAREGTTVYWGQGTTVTVSSAS

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TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
 YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSV
 FLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST
 YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL
 5 KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
 QGNVFSCSVMHEALHNHYTQKSLSLSPG

N3pGlu Aβ (SEQ ID NO: 31)

[pE]FRHDSGYEVHHQKL VFFAEDVGSNKGAIIGLMVGGGVIA
 10

<SEQ ID NO, 32; PRTI; Artificial> (LCVR-hE8L)
 DIVMTQTPLSLSVTPGQPASISCKSSQSLLYSRGKTYLNWLLQKPGQSPQLLIYAVSKLDS
 GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCYQGTHYPFTFGQGTKLEIK

15 <SEQ ID NO, 33; PRTI; Artificial> (LC-hE8L)
 DIVMTQTPLSLSVTPGQPASISCKSSQSLLYSRGKTYLNWLLQKPGQSPQLLIYAVSKLDS
 GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCYQGTHYPFTFGQGTKLEIKRTVAAPSVFI
 FPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS
 STLTLISKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC

20 <SEQ ID NO, 34; PRTI; Artificial> (HCVR-hE8L)
 QVQLVQSGAEVKKPGSSVKVSCKASGYTFDYYINWVRQAPGQGLEWMGWINPGSGNT
KYNEKFKGRVTITADESTSTAYMELSSLRSEDTAVYYCAREGETVYWGQGTTTVVSS

25 <SEQ ID NO, 35; PRTI; Artificial> (HC-hE8L)
 QVQLVQSGAEVKKPGSSVKVSCKASGYTFDYYINWVRQAPGQGLEWMGWINPGSGNT
KYNEKFKGRVTITADESTSTAYMELSSLRSEDTAVYYCAREGETVYWGQGTTTVVSSAS
 TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
 YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSV
 30 FLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST
 YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL
 T KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQ
 QGNVFSCSVMHEALHNHYTQKSLSLSPG

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<SEQ ID NO: 36; PRT1; Artificial> (HCDR1-hE8L)
GYTFTDYYIN

5 <SEQ ID NO: 37; PRT1; Artificial> (HCDR3-hE8L)
EGETVY

<SEQ ID NO: 38; PRT1; Artificial> (Aβ 1-42)
DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGGVIA

10 <SEQ ID NO: 39; PRT1; Artificial> (LCVR -- Antibody VI)
MVSSAQFLFLLVLWIQETNGDVVMTQTPLTSLVTIGQPASISCKSSQSLL
YSDGKTYLNWLLQRPQGSPMRLIYLVSKLDSGVPDRFTGSGSGTDFTLK
ISRVEAEDLGVYYCVQGTHTFPFTFGSGTKLEIKRADAAPTVSIFPP

15 <SEQ ID NO: 40; PRT1; Artificial> (HCVR -- Antibody VI)
MGWSGVFLFLLSGTAGVHSEVQLQQSGPELVKPGASMKISCKASGYSFTG
YTMNWVKQSHGKNLEWIGLINPYSGVTRYNQKFKGKATLIVDKSSSTAYM
ELLSLTSEDSAVYYCTREAKREWDETYWGQGTLLTVSAAKTTPPSV

20 <SEQ ID NO: 41; PRT1; Artificial> (LCVR -- Antibody VII)
MVSTAQFLFLLVLWIQETNGDVVMTQTPLTSLVTIGQPASISCKSSQSLL
YSDGKTYLNWLLQRPQGSPMRLIYLVSKLDSGVPDRFTGSGSGTDFTLK
ISRVEAEDLGVYYCVQGTHTFPFTFGSGTKLEIKRADAAPTVSIFPPS

25 <SEQ ID NO: 42; PRT1; Artificial> (HCVR -- Antibody VII)
MGWSGVFIFLLSGTAGVHSEVQLQQSGPELVKPGASMKISCKASGYSFTG
YTMNWVKQSHGKNLEWIGLINPYNGVTRYNQKFKGKATLIVDKSSSTAY
MELLSLTSEDSAVYYCTREAKREWDETYWGQGTLLTVSAAKTTPPSVYPL

30 <SEQ ID NO: 43; PRT1; Artificial> (LCVR -- Antibody VIII)
MKLPVRLLVLVFWIPVSSSDVVMQTPLSLPVSLGDQASISCRSSQSLVH
SDGNTYLHWYLVKPGQSPKLLIYKVSNRFSGVPDRFSGSGSGTDFTLKIS
RVEAEDLGVYFCSQSTHVPPTFGGGTKLEIKRADAAPTVSIFPPSS

35 <SEQ ID NO: 44; PRT1; Artificial> (HCVR -- Antibody VIII)
MDFGLSLLIFVLILKGVQCEVKLVESGGGLVQPGGSRKLSAASGFTFSDY

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GMAWVRQAPGKGPEWVAFISNLAYSIIYADTVTGRFTISRENAKNTLYLEM
SSLRSEDAMYYCARYDYDNILDYVMDYWGQGTSTVTVSSAKTTPPSVYPL

<SEQ ID NO: 45; PRT1; Artificial> (LCVR -- Antibody IX)

5 MKLPVRLVLWIQETKGDVVLQTPLTSLVTIGQPASISCKSSQSLLYSN
GKTYLNWLLQRPQGQSPKRLIYVVSKLDSGVPDRFTGSGSGTDFTLKISRV
EAEDLGYYCVQGTHFPFTFGSGTKLEIKRADAAPTVSIFPPSS

<SEQ ID NO: 46; PRT1; Artificial> (HCVR -- Antibody IX)

10 MGWSGVFLFLLSVTEGVHSQVQLQQSGAELVRPGSSVKISCKASGYIFNN
YWINWVKQRPQGQGLEWIGQIYPGDGDTNYNGKFKGKATLTADKSSSTAY
MQLSSLTSEDSAVYFCAREGYIVYWGGQTLVTVSAAKTTPPSVYPL

<SEQ ID NO: 47; PRT1; Artificial> (LCVR -- Antibody X)

15 DVVMTQTPLSLPVSLGDQASISCRSSQSLLHSNGNTYLHWYLQKPGQSPKLLI
YKVSNRFSGVDPDRFSGSGSGTDFTLKISRVEAEDLGVYFCSQSTHVPLTFGAGT

<SEQ ID NO: 48; PRT1; Artificial> (HCVR -- Antibody X)

20 QLQQSGAELMKPGASVKISCKATGYTFSSYWIEWVKQRPBGHGLEWIGEILPGR
GSTHYNEKFKGKATFTADTSSNTAYMQLSSLTSEDSAVYYCARSPITTSYDWG
QGTTLTVSS

<SEQ ID NO: 49; PRT1; Artificial> (LCVR -- Antibody XI)

25 SCRSSQSLVHSNGNTYLHWYLQKPGQSPKLLIYKVSNRFSGVDPDRFSGSGSGT
DFTLKISRVEAEDLGVYFCSQSTHVPLTFGAGT

<SEQ ID NO: 50; PRT1; Artificial> (HCVR -- Antibody XI)

AELKKPGASVKISCKATGYTFRSYWIEWVKQRPBGHGLEWIGEILPGRGSTKY
NEKFKGKATFTADTSSNTANMQLSSLTSEDSAVYYCARSPITTSY

30

<SEQ ID NO: 51; PRT1; Artificial> (LCVR -- Antibody XII)

DVVLQTPTPLSVTIGQPASISCKSSQSLLHSNGESYLNWLFQRPQGQSPKRLIY
AVSKLDSGVPDRFTGSGSGTDFTLKISRVEAEDLGVYYCVQGTHFPFTFGGG
TKLEIK

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<SEQ ID NO: 52; PRT1; Artificial> (HCVR – Antibody XII)

QIQQQSGPELVKPGAAVKISCKASGYTFTDYYLNWVKQKPGQGLEWIGWIY
PGSGNVKYNEKFKGKATLTADTSSNTAHMQLSSLTSEDNAVYFCTREGLIVY
5 WGQGTLLTVSA

<SEQ ID NO: 53; PRT1; Artificial> (LCVR – Antibody XIII)

DVVLTTQTPLTSLVTIGQPASISCKSSQSLLYSNGKTYLNWLLQRPGQSPKRLIY
VVSKLDSGVDPDRFTGSGSGTDFTLKISRVEAEDLGVYYCVQGTHYPFTFGGGT
10 KLEIK

<SEQ ID NO: 54; PRT1; Artificial> (HCVR – Antibody XIII)

QIQQQSGPDLVKPGASVKISCKASGYTFTDYYINWVKQKPGQGLEWIGWLN
GSGNTKYNEKFKGKATMTVDTTSSVTVMQLSSLTSEDSAVYFCTREGPIDYWG
15 RGTSTTVSS

<SEQ ID NO: 55; PRT1; Artificial> (LCVR – Antibody XIV)

DIVMTQTPLSLSVTPGQPASISCSQSLIYSDGNAYLHWYLQKP
GQSPQLLIYKVSNRFSGVDPDRFSGSGTDFTLKISRVEAEDVG
20 VYYCTQSTHSPWTFGGGTKVEIK

<SEQ ID NO: 56; PRT1; Artificial> (HCVR – Antibody XIV)

EVQLVESGGGLVKPGGSLRLSCAASGYTFSRYSMWVRQAPG
KGLEWVGQINIRGCNTYYPDTVKGRFTISRDDSKNTLYLQMNS
LKTEDTAVYYCTTGDFWGQGTLLTVSS
25

<SEQ ID NO: 57; PRT1; Artificial> (LC – Antibody XV)

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQKPGKAPKLLIYA
ASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQSYSTPLTFGG
GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV
30 DNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

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<SEQ ID NO: 58; PRT1; Artificial>

(HC -- Antibody XV)

QVQLVESGGGVVQPGRSLRLSCAASGFAFSSYGMHWVRQAPGKGLEWVAV
 IWFDGTTKKYYTDSVKGRFTISRDN SKNTLYLQMNTLRAEDTAVYYCARDR
 GIGARRGPYYMDVWGKGTTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALG
 5 CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSL
 GTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLF
 PPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
 EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
 REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 10 TPPVLDSGDSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSL
 SPG

<SEQ ID NO: 59; PRT1; Artificial>

(LC -- Antibody XVI)

DIVLTQSPATLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGVPA
 15 RFSGSGSGTDFTLTISLLEPEDFATYYCLQIYNMPITFGQGTKVEIKRTVAAPSVFIFPPSDE
 QLKSGTASVVCLLNMFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLS
 KADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC

<SEQ ID NO: 60; PRT1; Artificial>

(HC -- Antibody XVI)

QVELVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAINAS
 20 GTRTYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGKGNTHKPYGYVRY
 FDVWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL
 TSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT
 HTCPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVE
 25 VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ
 PREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDG
 SFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK

<SEQ ID NO: 61; PRT1; Artificial>

(LC -- Antibody XVII)

DIVMTQSPLSLPVTPGEPASISCRSSQSLVYSNGDTYLHWYLQKPGQSPQLLIY
 30 KVSNRFSGVPPDRFSGSGSGTDFTLKISRVEAEDVGVYYCSQSTHVPWTFGQGT
 KVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNMFYPREAKVQWKVDNALQ
 SGNSQESVTEQDSKDYSLSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSF
 NRGEC

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<SEQ ID NO: 62; PRT1; Artificial>

(HC – Antibody XVII)

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYGMSWVRQAPGKGLELVASIN
 SNGGSTYYPD SVKGRFTISRDN AKNSLYLQMNSLRAEDTAVYYCASGDYWG
 5 QGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG
 ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKYTCNV D HKPSNTKVDKR
 VESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVVSQEDP
 EVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKC
 KVS NKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS
 10 DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSV M
 HEALHNHYTQKSLSLSLG

<SEQ ID NO: 63; PRT1; Artificial>

(LC – Antibody XVIII)

DVVMTQSPLSLPVT PGAPASISCRSSQSIVHSNGNTYLEWYLQKPGQSPK
 15 LLIYKVS NRFS GVPDRFSGSGSGTDFTLRISRVEAEDVGIYYCFQGSHVP
 PTFGPGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK
 VQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACE
 VTHQGLSSPVTKSFNRGEC

<SEQ ID NO: 64; PRT1; Artificial>

(HC – Antibody XVIII)

EVQLVESGGGLVQPGGSLRLSCSASGFTFSSFGMHWVRQAPGKGLEWVAY
 20 ISSGSSTIYYGDTVKGRTISRDN AKNSLFLQMSSLRAEDTAVYYCAREG
 GYYYGRSYTMDYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAAALG
 CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
 GTQFYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLF
 25 PPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
 EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
 REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
 TPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSL
 SPGK

30

<SEQ ID NO: 65; PRT1; Artificial>

(LC – Antibody XIX)

DVVMTQSPLSLPVT LGQPASISCRSSQSLIYSDGNAYLHWFLQKPGQSPRLLIY
 KVS NRFS GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCSQSTHVPWTFGQGT
 KVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ

-57-

SGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF
NRGEC

<SEQ ID NO: 66; PRT1; Artificial>

(HC -- Antibody XIX)

5 EVQLVESGGGLVQPGGSLRLSCAASGFTFSRYSMSWVRQAPGKGLELVAQINS
VGNSTYYPDITVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCASGDYWGQG
TLVTVSSASTKGPSVFPLAPSSKSTSGGTAAAGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN
10 WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL
PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL
SPGK

15

WE CLAIM:

1. Use of an anti-N3pGlu A β antibody in the manufacture of a medicament for reducing amyloid beta (A β) deposits in the brain of a patient in need thereof, wherein the medicament comprises an intravenous dose of 10 to 60 mg/kg of the anti-N3pGlu A β antibody, wherein the medicament is to be administered more than one time to the patient at a frequency of once every month for a period of 6 months or less, and wherein the anti-N3pGlu A β antibody comprises a light chain variable region (LCVR) of SEQ ID NO: 25 and a heavy chain variable region (HCVR) of SEQ ID NO:26.
2. The use according to claim 1, wherein the anti-N3pGlu A β antibody comprises a light chain (LC) of SEQ ID NO: 28 and a heavy chain (HC) of SEQ ID NO:29.
3. The use according to claim 1, wherein the medicament is to be administered at a frequency of once every month for a total of 2-6 separate doses.
4. The use according to claim 1, wherein 6 separate doses of the medicament are to be administered to the patient at a frequency of once every month.
5. The use according to claim 1, wherein the patient has preclinical Alzheimer's disease (AD), clinical Alzheimer's disease, Down's syndrome, clinical cerebral amyloid angiopathy, or pre-clinical cerebral amyloid angiopathy.
6. The use according to claim 1, wherein the patient has preclinical AD, prodromal AD, mild AD, moderate AD, or severe AD.
7. The use according to claim 1, wherein the intravenous dose of the anti-N3pGlu A β antibody to be administered to the patient is from 10 to 40 mg/kg.
8. The use according to claim 1, wherein the intravenous dose of the anti-N3pGlu A β antibody to be administered to the patient is from 10 to 20 mg/kg.
9. The use according to claim 1, wherein the intravenous dose of the anti-N3pGlu A β antibody to be administered to the patient is from 15 to 30 mg/kg.
10. The use according to claim 1, wherein the intravenous dose of the anti-N3pGlu A β antibody to be administered to the patient is selected from 10 mg/kg, 15 mg/kg, 20 mg/kg and 40 mg/kg.
11. The use according to claim 1, wherein the intravenous dose of the anti-N3pGlu A β antibody to be administered to the patient is 10 mg/kg.
12. The use according to claim 1, wherein the intravenous dose of the anti-N3pGlu A β antibody to be administered to the patient is 20 mg/kg.

13. The use according to claim 1, wherein the intravenous dose of the anti-N3pGlu A β antibody to be administered to the patient is 40 mg/kg.
- 5 14. The use according to claim 1, wherein the A β deposits in the brain of the patient are reduced by 35-100% within 6 months post treatment.
15. The use according to claim 1, wherein the A β deposits in the brain of the patient are reduced by 50% within 6 months post treatment.
- 10 16. The use according to claim 1, wherein the reduction of A β deposit in the brain of the patient is maintained for a period of 2 to 10 years post treatment.
- 15 17. The use according to claim 1, wherein the reduction of A β deposit in the brain of the patient is maintained for a period of 3 to 5 years post treatment.
18. The use according to claim 1, wherein the intravenous dose of the N3pGlu A β antibody to be administered to the patient is 700 mg per dose for a patient weighing 70 kg.
- 20 19. The use according to claim 1, wherein amyloid PET imaging scans are used to determine whether the patient is positive for amyloid deposits in the brain.
- 25 20. The use according to claim 1, wherein the patient carries one or two APOE e4 alleles.
21. The use according to claim 1, wherein the anti-N3pGlu A β antibody is a humanized antibody.