

METHODS OF TREATING NEUROLOGICAL DISORDERS WITH ANTI-ABETA ANTIBODIES

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application claims priority to U.S. Provisional Application No. 63/618,054, filed January 5, 2024, which is incorporated by reference in its entirety.

SEQUENCE LISTING

[002] A computer readable form of the Sequence Listing is filed with this application by electronic submission and is incorporated into this application by reference in its entirety. The Sequence Listing is contained in the file created on December 27, 2024, having the file name "20-1030-WO3_SEQLIST.xml" and is 21 kb in size.

FIELD

[003] The present disclosure relates to anti-Amyloid beta (A β) antibodies as well as compositions and methods of their use.

BACKGROUND

[004] Alzheimer's disease (AD) is a progressive disease resulting in senile dementia. The disease is generally categorized as late onset, which occurs in old age (65+years) and early onset, which develops well before the senile period, i.e., between 35 and 60 years. Disease pathology appears to be the same for both types of disease, but abnormalities tend to be more severe and widespread in cases beginning at an earlier age. The disease is characterized by at least two types of lesions in the brain, neurofibrillary tangles and senile plaques. Neurofibrillary tangles are intracellular deposits of microtubule associated tau protein consisting of two filaments twisted about each other in pairs. Senile plaques (i.e., amyloid plaques) are areas of disorganized neuropil up to 150 μ m across with extracellular amyloid deposits at the center which are visible by microscopic analysis of sections of brain tissue.

[005] The principal constituent of the plaques is a peptide termed amyloid beta (A β or Abeta) or β -amyloid peptide. A β peptide is a 4-kDa internal fragment of 39-43 amino acids of a larger transmembrane glycoprotein termed amyloid precursor protein (APP). As a result of proteolytic processing of APP by different secretase enzymes, A β is primarily found in

both a short form, 40 amino acids in length, and a long form, ranging from 42-43 amino acids in length. Part of the hydrophobic transmembrane domain of APP is found at the carboxy end of A β and may account for the ability of A β to aggregate into plaques, particularly in the case of the long form. Accumulation of amyloid plaques in the brain eventually leads to neuronal cell death. The physical symptoms associated with this type of neural deterioration characterize Alzheimer's disease.

[006] Monoclonal antibodies (mAbs) targeting amyloid beta have been demonstrated clinically to reduce amyloid plaque burden in patients. The FDA has granted accelerated approval for the anti-amyloid β antibodies aducanumab and lecanemab. The FDA approvals of these antibodies were based on the antibodies demonstrating a reduction of amyloid beta on PET imaging, a surrogate endpoint that was determined to be reasonably likely to predict clinical benefit. Indeed, clinical trials of anti-amyloid β antibodies, including aducanumab and lecanemab, showed that reduction in plaque burden was associated with slowing of cognitive decline in Alzheimer's disease. However, these treatments suffer from limited efficacy and/or treatment-related side effects. Further, these antibodies require intravenous administration and/or frequent high-dose subcutaneous administration, leading to a burden on patients and caregivers. Therefore, there remains a need for efficacious and safe anti-amyloid β antibodies for the treatment of Alzheimer's disease, particularly those that are efficacious when subcutaneously administered as part of a relatively infrequent dosing regimen.

SUMMARY

[007] The present disclosure relates to antibodies (and antibody fragments) that specifically bind to A β , methods of producing such antibodies and antibody fragments and associated nucleic acids, methods of treatment of patients with A β -related neurological disorders, pharmaceutical formulations and compositions of antibodies that show high affinity binding to A β for prophylactic and/or therapeutic use to, for example, treat, reduce the risk of or delay the outset of amyloidogenic disease, prevent, reduce or inhibit markers of amyloidogenic disease, e.g., amyloid plaques, and improve cognition. The present disclosure further relates to methods of detecting amyloid plaques and measuring the efficacy of treatment in patients being treated for amyloidogenic disease. The disclosure is based, at least in part, on the identification and characterization of monoclonal antibodies that specifically bind to A β peptide and are effective at reducing plaque burden and neutralizing soluble A β species associated with amyloidogenic disorders.

[008] In one aspect, the present disclosure provides a method of treating Alzheimer's disease in a subject, comprising administering to the subject about 205 mg to about 400 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks. In another aspect, the present disclosure provides a method of reducing brain amyloid beta plaque in a subject, comprising administering to the subject about 205 mg to about 400 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks. In another aspect, the present disclosure provides a method of converting a subject from amyloid positive to amyloid negative, comprising administering to the subject about 205 mg to about 400 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks.

[009] In some embodiments, the method comprises administering about 300 mg to about 400 mg of the anti-amyloid β antibody or antigen-binding fragment thereof. In some embodiments, the method comprises administering about 350 mg to about 400 mg of the anti-amyloid β antibody or antigen-binding fragment thereof. In some embodiments, the method comprises administering about 250 mg of the anti-amyloid β antibody or antigen-binding fragment thereof. In some embodiments, the method comprises administering about 300 mg of the anti-amyloid β antibody or antigen-binding fragment thereof. In some embodiments, the method comprises administering 350 mg of the anti-amyloid β antibody or antigen-binding fragment thereof. In some embodiments, the method comprises administering about 400 mg of the anti-amyloid β antibody or antigen-binding fragment thereof. In some embodiments, the anti-amyloid β antibody is administered once about every 4 weeks.

[0010] In another aspect, the present disclosure provides a method of treating Alzheimer's disease in a subject, comprising administering to the subject about 45 mg to about 200 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof twice every 3-5 weeks. In another aspect, the present disclosure provides a method of treating Alzheimer's disease in a subject, comprising administering to the subject about 100 mg to about 200 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks. In another aspect, the present disclosure provides a method of reducing brain amyloid beta plaque in a subject, comprising administering to the subject about 100 mg to about 200 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks. In another aspect, the present disclosure provides a method of converting a subject from amyloid positive to amyloid negative, comprising

administering to the subject about 100 mg to about 200 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks.

[0011] In another aspect, the present disclosure provides a method of treating Alzheimer's disease in a subject, comprising administering to the subject about 45 mg to about 200 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof once about every 2 weeks. In another aspect, the present disclosure provides a method of treating Alzheimer's disease in a subject, comprising administering to the subject about 100 mg to about 200 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof once about every 2 weeks. In another aspect, the present disclosure provides a method of reducing brain amyloid beta plaque in a subject, comprising administering to the subject about 100 mg to about 200 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof once about every 2 weeks. In another aspect, the present disclosure provides a method of converting a subject from amyloid positive to amyloid negative, comprising administering to the subject about 100 mg to about 200 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof once about every 2 weeks.

[0012] In some embodiments, the method comprises administering about 45 mg to about 100 mg of the anti-amyloid β antibody or antigen-binding fragment thereof once about every 2 weeks. In some embodiments, the method comprises administering about 150 mg to about 200 mg of the anti-amyloid β antibody or antigen-binding fragment thereof once about every 2 weeks. In some embodiments, the method comprises administering about 200 mg of the anti-amyloid β antibody or antigen-binding fragment thereof once about every 2 weeks.

[0013] In some embodiments, the anti-amyloid β antibody or antigen-binding fragment thereof is administered in a composition comprising a pharmaceutically acceptable diluent. In some embodiments, the administration is intravenous or subcutaneous. In some embodiments, the administration is subcutaneous.

[0014] In some embodiments, the anti-amyloid β antibody or an antigen-binding fragment thereof binds to an epitope located within the N-terminus of an A β peptide, and the epitope includes at least one amino acid selected from amino acids 1-10 of the A β peptide. In some embodiments, the anti-amyloid β antibody or an antigen-binding fragment thereof binds to an epitope comprising at least one amino acid selected from amino acids 1-7 of the A β peptide. In some embodiments, the anti-amyloid β antibody or an antigen-binding fragment

thereof binds to amyloid β_{1-42} protofibrils with an apparent KD of about 5 nM or less. In some embodiments, the anti-amyloid β antibody or an antigen-binding fragment thereof binds to amyloid β_{1-42} protofibrils with an apparent KD of about 1 nM or less. In some embodiments, the anti-amyloid β antibody or an antigen-binding fragment thereof binds to amyloid β_{1-28} monomers with an apparent KD of about 10 nM or less.

[0015] In some embodiments, the anti-amyloid β antibody or antigen-binding fragment thereof is administered as a pharmaceutical composition comprising the anti-amyloid β antibody or antigen-binding fragment thereof and a pharmaceutically acceptable diluent. In some embodiments, the administration is intravenous or subcutaneous. In some embodiments, the administration is subcutaneous.

[0016] In some embodiments, the anti-amyloid β antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising heavy chain CDR1, CDR2, and CDR3 and a light chain variable region comprising light chain CDR1, CDR2, and CDR3, wherein.

heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 3,
heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 4,
heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 5,
light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 6,
light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 7, and
light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 8.

[0017] In some embodiments, the heavy chain variable region, excluding the CDRs, is at least 95% identical to the amino acid sequence of SEQ ID NO: 1, and the light chain variable region, excluding the CDRs, is at least 95% identical to the amino acid sequence of SEQ ID NO: 2. In some embodiments, the heavy chain variable region, excluding the CDRs, is at least 98% identical to the amino acid sequence of SEQ ID NO: 1, and the light chain variable region, excluding the CDRs, is at least 98% identical to the amino acid sequence of SEQ ID NO: 2. In some embodiments, the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 1, and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 2. In some embodiments, the heavy chain variable region consists of SEQ ID NO: 1, and wherein the light chain variable region consists of the amino acid sequence of SEQ ID NO: 2.

[0018] In some embodiments, the anti-amyloid β antibody is a humanized IgG1. In some embodiments, the anti-amyloid β antibody is a full antibody, a chimeric antibody, a CDR-grafted antibody, or a recombinant antibody.

[0019] In some embodiments, the anti-amyloid β antibody or antigen-binding fragment thereof further comprises a heavy chain constant region comprising an amino acid sequence at least 95% identical to SEQ ID NO: 9 and/or a light chain constant region comprising an amino acid sequence at least 95% identical to SEQ ID NO: 10. In some embodiments, the anti-amyloid β antibody or antigen-binding fragment thereof further comprises a heavy chain constant region comprising an amino acid sequence at least 98% identical to SEQ ID NO: 9 and/or a light chain constant region comprising an amino acid sequence at least 98% identical to SEQ ID NO: 10. In some embodiments, the anti-amyloid β antibody comprises a heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 9, with or without the C-terminal lysine, and a light chain constant region comprising an amino acid sequence of SEQ ID NO: 10. In some embodiments, the anti-amyloid β antibody comprises a heavy chain constant region consisting essentially of an amino acid sequence of SEQ ID NO: 9, with or without the C-terminal lysine, and a light chain constant region consisting essentially of an amino acid sequence of SEQ ID NO: 10.

[0020] In some embodiments, the anti-amyloid β antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain comprising an amino acid sequence of SEQ ID NO: 12. In some embodiments, the anti-amyloid β antibody comprises a heavy chain consisting essentially of an amino acid sequence of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain consisting essentially of an amino acid sequence of SEQ ID NO: 12. In some embodiments, the anti-amyloid β antibody comprises a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12. In some embodiments, the anti-amyloid β antibody is h2731.

[0021] In another aspect, the present disclosure provides a method of treating Alzheimer's disease in a subject, the method comprising subcutaneously administering to the subject about 250 mg of an anti-amyloid β antibody once about every 4 weeks; the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

[0022] In another aspect, the present disclosure provides a method of treating Alzheimer's disease in a subject, the method comprising subcutaneously administering to the subject about 300 mg of an anti-amyloid β antibody once about every 4 weeks; the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

[0023] In another aspect, the present disclosure provides a method of treating Alzheimer's disease in a subject, the method comprising subcutaneously administering to the subject about 350 mg of an anti-amyloid β antibody once about every 4 weeks; the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

[0024] In another aspect, the present disclosure provides a method of treating Alzheimer's disease in a subject, the method comprising subcutaneously administering to the subject about 400 mg of an anti-amyloid β antibody once about every 4 weeks; the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12. In another aspect, the present disclosure provides a method of treating Alzheimer's disease in a subject, the method comprising subcutaneously administering to the subject about 200 mg of an anti-amyloid β antibody once about every 2 weeks; the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12. In another aspect, the present disclosure provides a method of reducing amyloid plaque in a subject, the method comprising subcutaneously administering to the subject about 300 mg of an anti-amyloid β antibody once about every 4 weeks; the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

[0025] In another aspect, the present disclosure provides a method of reducing amyloid plaque in a subject, the method comprising subcutaneously administering to the subject about 250 mg of an anti-amyloid β antibody once about every 4 weeks; the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12. In another aspect, the present disclosure provides a method of reducing amyloid plaque in a subject, the method comprising subcutaneously administering to the subject about 300 mg of an anti-amyloid β antibody once about every 4 weeks; the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-

terminal lysine, and a light chain of SEQ ID NO: 12. In another aspect, the present disclosure provides a method of reducing amyloid plaque in a subject, the method comprising subcutaneously administering to the subject about 400 mg of an anti-amyloid β antibody once about every 4 weeks; the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12. In another aspect, the present disclosure provides a method of reducing amyloid plaque in a subject, the method comprising subcutaneously administering to the subject about 200 mg of an anti-amyloid β antibody once about every 2 weeks; the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

[0026] In another aspect, the present disclosure provides a method of treating Alzheimer's disease in a subject, comprising subcutaneously administering to the subject a dose of an anti-A β antibody sufficient to achieve a C_{ave} value of about 20 $\mu\text{g/mL}$ to about 40 $\mu\text{g/mL}$, the anti-A β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12. In another aspect, the present disclosure provides a method of treating Alzheimer's disease in a subject, comprising subcutaneously administering to the subject a dose of an anti-A β antibody sufficient to achieve an $AUC_{0-\text{tau}}$ value of about 15,000 $\text{hr} \cdot \mu\text{g/mL}$ to about 30,000 $\text{hr} \cdot \mu\text{g/mL}$, the anti-A β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

[0027] In some embodiments, a maximum concentration over a dosing interval (C_{max}) of the anti-amyloid β antibody or antigen binding fragment thereof in the subject is about 30 $\mu\text{g/mL}$ to about 60 $\mu\text{g/mL}$. In some embodiments, a C_{max} value of the anti-amyloid β antibody or antigen binding fragment thereof in the subject is about 50 $\mu\text{g/mL}$ to about 60 $\mu\text{g/mL}$. In some embodiments, a C_{max} value of the anti-amyloid β antibody or antigen binding fragment thereof in the subject does not exceed about 60 $\mu\text{g/mL}$. In some embodiments, the C_{max} value is a serum C_{max} value. In some embodiments, the C_{max} value is a plasma C_{max} value.

[0028] In some embodiments, an average concentration over the dosing interval (C_{ave} value) of the anti-amyloid β antibody or antigen binding fragment thereof in the subject is about 20 $\mu\text{g/mL}$ to about 40 $\mu\text{g/mL}$. In some embodiments, a C_{ave} value of the anti-amyloid β antibody or antigen binding fragment thereof in the subject is about 30 $\mu\text{g/mL}$ to about 40

$\mu\text{g/mL}$. In some embodiments, a C_{ave} value of the anti-amyloid β antibody or antigen binding fragment thereof in the subject does not exceed about $40 \mu\text{g/mL}$. In some embodiments, the C_{ave} value is a serum C_{ave} value. In some embodiments, the C_{ave} value is a plasma C_{ave} value.

[0029] In some embodiments, the area under the concentration-time curve for dosing interval ($\text{AUC}_{0-\text{tau}}$ value) of the anti-amyloid β antibody or antigen binding fragment thereof in the subject is about $15,000 \text{ hr} \cdot \mu\text{g/mL}$ to about $30,000 \text{ hr} \cdot \mu\text{g/mL}$. In some embodiments, the $\text{AUC}_{0-\text{tau}}$ value of the anti-amyloid β antibody or antigen binding fragment thereof in the subject is about $20,000 \text{ hr} \cdot \mu\text{g/mL}$ to about $30,000 \text{ hr} \cdot \mu\text{g/mL}$. In some embodiments, the $\text{AUC}_{0-\text{tau}}$ value of the anti-amyloid β antibody or antigen binding fragment thereof in the subject does not exceed about $30,000 \text{ hr} \cdot \mu\text{g/mL}$. In some embodiments, the $\text{AUC}_{0-\text{tau}}$ value is a serum $\text{AUC}_{0-\text{tau}}$ value. In some embodiments, the $\text{AUC}_{0-\text{tau}}$ value is a plasma $\text{AUC}_{0-\text{tau}}$ value.

[0030] In some embodiments, brain amyloid beta plaque in the subject is reduced. In some embodiments, the reduction of brain amyloid beta plaque comprises a reduction of at least about 30 centiloids to about 70 centiloids. In some embodiments, the reduction of brain amyloid beta plaque comprises a reduction of from about 45 centiloids to about 80 centiloids. In some embodiments, the reduction of brain amyloid beta plaque comprises a reduction of about 50 centiloids to about 85 centiloids. In some embodiments, the reduction of brain amyloid beta plaque comprises a reduction of at least about 40% to about 90%. In some embodiments, the reduction of brain amyloid beta plaque comprises a reduction of from about 60% to about 100%.

[0031] In some embodiments, the reduction of brain amyloid beta plaque is a reduction compared to baseline (the value prior to beginning treatment using a method of the present disclosure). In some embodiments, the reduction of brain amyloid beta plaque is a reduction compared to the subject prior to the administration of the anti-amyloid β antibody.

[0032] In some embodiments, the reduction of brain amyloid beta plaque is achieved after 6 months of treatment. In some embodiments, the reduction of brain amyloid beta plaque is achieved after about 12 months of treatment. In some embodiments, the reduction of brain amyloid beta plaque is achieved after about 18 months of treatment. In some embodiments, the reduction of brain amyloid beta plaque is assessed by Positron Emission Tomography (PET).

[0033] In some embodiments, the subject is converted from amyloid positive to amyloid negative.

[0034] In some embodiments, treating comprises increasing a probability of converting the subject from amyloid positive to amyloid negative. In some embodiments, treating comprises a probability of converting the subject from amyloid positive to amyloid negative by about 10% to about 40%. In some embodiments, treating comprises a probability of converting the subject from amyloid positive to amyloid negative by about 30% to about 60%. In some embodiments, treating comprises a probability of converting the subject from amyloid positive to amyloid negative by about 40% to about 80%. In some embodiments, the probability of converting the subject from amyloid positive to amyloid negative is a probability after about 6 months of treatment. In some embodiments, the probability of converting the subject from amyloid positive to amyloid negative is a probability after about 12 months of treatment. In some embodiments, the probability of converting the subject from amyloid positive to amyloid negative is a probability after about 18 months of treatment.

[0035] In some embodiments, treating comprises slowing, halting, or reversing decline in cognitive function. In some embodiments, treating comprises slowing decline in cognitive function. In some embodiments, cognitive function is measured by at least one of the following CRD-SB, ADAS-Cog14, ADCOMS, and ADCS MCI-ADL. In some embodiments, cognitive function is measured by ADCOMS.

[0036] In another aspect, the present disclosure provides a method of modulating a biomarker in a subject, comprising administering to the subject from about 205 mg to about 400 mg of an anti-amyloid β antibody once about every 3-5 weeks, the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12. In another aspect, the present disclosure provides a method of modulating a biomarker in a subject, comprising administering to the subject from about 100 mg to about 200 mg of an anti-amyloid β antibody twice about every 3-5 weeks, the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

[0037] In another aspect, the present disclosure provides a method of increasing a ratio of A β 42/40 in a subject, comprising administering to the subject about 205 mg to about 400 mg of an anti-amyloid β antibody once about every 3-5 weeks, the anti-amyloid β antibody

comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12. In another aspect, the present disclosure provides a method of increasing a ratio of A β 42/40 in a subject, comprising administering to the subject about 100 mg to about 200 mg of an anti-amyloid β antibody twice about every 3-5 weeks, the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

[0038] In another aspect, the present disclosure provides a method of decreasing an amount of phospho-tau in a subject, comprising administering to the subject about 205 mg to about 400 mg of an anti-amyloid β antibody thereof once about every 3-5 weeks, the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12. In another aspect, the present disclosure provides a method of decreasing an amount of phospho-tau in a subject, comprising administering to the subject about 100 mg to about 200 mg of an anti-amyloid β antibody thereof twice about every 3-5 weeks, the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

[0039] In some embodiments, the administration comprises a single subcutaneous injection. In some embodiments, a biomarker in the subject is modulated. In some embodiments, the biomarker in the subject is modulated compared to baseline. In some embodiments, the method further comprises detecting a biomarker in a sample collected from the subject. In some embodiments, the method further comprises quantifying a biomarker in a sample collected from the subject.

[0040] In some embodiments, the biomarker comprises the ratio of A β 42/40 in the subject. In some embodiments, the ratio of A β 42/40 in the subject increases at least 25%. In some embodiments, the ratio of A β 42/40 in the subject increases at least 50%. In some embodiments, the ratio of A β 42/40 in the subject increases about 25% to about 100%. In some embodiments, the ratio of A β 42/40 in the subject increases about 50% to about 100%.

[0041] In some embodiments, the biomarker comprises a phospho-tau value. In some embodiments, the phospho-tau value comprises at least one of the following: a p181-tau value, a p212-tau value, p217-tau value, a p231-tau value, and a p235-tau value. In some embodiments, the phospho-tau value comprises a p181-tau value. In some embodiments, the

phospho-tau value comprises a p212-tau value. In some embodiments, the phospho-tau value comprises a p217-tau value. In some embodiments, the phospho-tau value comprises a p231-tau value. In some embodiments, the phospho-tau value comprises a p235-tau value. In some embodiments, the phospho-tau value decreases. the phospho-tau value decreases at least about 10%. In some embodiments, the phospho-tau value decreases about 10% to about 30%. In some embodiments, the phospho-tau value decreases about 20% to about 30%.

[0042] In some embodiments, the sample comprises blood or a portion thereof collected from the subject. In some embodiments, the sample comprises plasma collected from the subject. In some embodiments, the sample comprises serum collected from the subject. In some embodiments, the sample comprises cerebral spinal fluid ("CSF") collected from the subject.

[0043] In some embodiments, the method comprises a risk of ARIA-E that is less than about 45%. In some embodiments, the method comprises a risk of ARIA-E from about 25% to about 45%. In some embodiments, the method comprises a risk of ARIA-E of less than about 75%. In some embodiments, the method comprises a risk of ARIA-E of about 50% to about 75%. In some embodiments, the method comprises a risk of symptomatic ARIA-E that is less than about 15%. In some embodiments, the method comprises a risk of symptomatic ARIA-E that is less than about 30%. In some embodiments, the risk of ARIA-E is a risk of severe ARIA-E.

[0044] In some embodiments, the risk of ARIA-E is the risk after about 6 months of treatment. In some embodiments, the risk of ARIA-E is the risk after about 12 months of treatment. In some embodiments, the risk of ARIA-E is the risk after about 18 months of treatment. In some embodiments, the subject does not experience symptomatic ARIA-E during treatment.

[0045] In some embodiments, the method comprises a risk of ARIA-H that is less than about 35%, or the method comprises a risk of ARIA-H from about 10% to about 35%, or the risk of ARIA-H is a risk of severe ARIA-H. In some embodiments, the risk of ARIA-H is the risk after about 6 months of treatment. In some embodiments, the risk of ARIA-H is the risk after about 12 months of treatment. In some embodiments, the risk of ARIA-H is the risk after about 18 months of treatment. In some embodiments, the subject does not experience symptomatic ARIA-H during treatment.

[0046] In some embodiments, ARIA-E and/or ARIA-H is assessed by Magnetic Resonance Imaging ("MRI").

[0047] In some embodiments, the subject is an APOE4 homozygous subject. In some embodiments, the subject is an APOE4 heterozygous subject or an APOE4 noncarrier. In some embodiments, the method further comprises determining the APOE4 status of the subject prior to administration.

[0048] In some embodiments, the duration of the treatment is at least 6 months. In some embodiments, the duration of the treatment is at least 12 months. In some embodiments, the duration of the treatment is at least 18 months.

[0049] In some embodiments, the administration is performed using a syringe. In some embodiments, the administration is performed using an autoinjector.

[0050] In some embodiments, the subject is a mammal. In some embodiments, the subject is a human.

BRIEF DESCRIPTION OF THE DRAWINGS

[0051] **FIG. 1** is a schematic representation of a clinical trial plan for a single ascending dose study of h2731 in healthy volunteers and Alzheimer's disease subjects. Certain inclusion criteria, dosages, and a schedule of certain assessments are shown.

[0052] **FIG. 2** is a schematic representation of a clinical trial plan for a multiple ascending dose study of h2731 in Alzheimer's disease subjects. Certain inclusion criteria, dosages, and a schedule of certain assessments are shown.

[0053] **FIG. 3** shows details of an open label extension study of h2731 in some Alzheimer's disease subjects who were enrolled in either the single ascending dose study of Example 2 or the multiple ascending dose study of Example 3. Certain dosages and a schedule of certain assessments are shown.

DESCRIPTION

[0054] Monoclonal antibodies (mAbs) targeting the N-terminus of amyloid beta (A β) have been demonstrated clinically to reduce amyloid plaque burden and at least two such antibodies, aducanumab and lecanemab, showed that significant reduction in plaque burden

was associated with slowing of cognitive decline in Alzheimer's disease (AD). Preclinical studies have also indicated that monoclonal antibodies (mAbs) targeting N-terminal epitopes of A β elicit an antibody-dependent microglial-mediated A β -plaque clearance and neutralization of soluble toxic A β oligomers both *in vitro* and *in vivo*. It is hypothesized that administration of N-terminal A β targeting mAbs slows disease progression via clearance of A β plaques and neutralization of soluble A β aggregates in patients with AD. The present disclosure provides methods of treating Alzheimer's disease and/or reducing amyloid plaque by intravenous or subcutaneous administration of N-terminal A β targeting mAbs.

[0055] Before describing particular aspects of the disclosure in more detail, a number of terms are defined.

Definitions

[0056] The term "antibody" includes intact antibodies and binding fragments thereof. Typically, fragments compete with the intact antibody from which they were derived for specific binding to the target. Fragments include separate heavy chains, light chains Fab, Fab', F(ab')₂, F(ab)c, Fv and single domain antibodies. Single (variable) domain antibodies include VH regions separated from their VL partners (or vice versa) in conventional antibodies (Ward et al., 1989, Nature 341: 544-546) as well as VH regions (sometimes known as VHH) from species such as Camelidae or cartilaginous fish (e.g., a nurse shark) in which VH regions are not associated with VL regions (see, e.g., WO 9404678). Single domain antibodies in which one chain is separated from its natural partners are sometimes known as Dabs and single domain antibodies from Camelidae or cartilaginous fish are sometimes known as nanobodies. Constant regions or parts of constant regions may or may not be present in single domain antibodies. For example, natural single variable region antibodies from Camelidae include a VHH variable region, and CH2 and CH3 constant regions. Single domain antibodies can be subject of humanization by analogous approaches to conventional antibodies. The Dabs type of antibodies is usually obtained from antibodies of human origin. NANOBODY types of antibodies are of Camelidae or shark origin and can be subject to humanization. Fragments can be produced by recombinant DNA techniques, or by enzymatic or chemical separation of intact immunoglobulins. The term "antibody" also includes a bispecific antibody. A bispecific or bifunctional antibody is an artificial hybrid antibody having two different heavy/light chain pairs and two different

binding sites (see, e.g., Songsivilai and Lachmann, *Clin. Exp. Immunol.*, 79:315-321 (1990); Kostelny et al., *J. Immunol.*, 148:1547-53 (1992)).

[0057] An immunoglobulin light or heavy chain variable region (also sometimes referred to herein as a “light chain variable domain” (“VL domain”) or “heavy chain variable domain” (“VH domain”), respectively) consists of a “framework” region interrupted by three “complementarity determining regions” or “CDRs.” The framework regions serve to align the CDRs for specific binding to an epitope of an antigen. The CDRs include the amino acid residues of an antibody that are primarily responsible for antigen binding. From amino-terminus to carboxyl-terminus, both VL and VH domains comprise the following framework (FR) and CDR regions: FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. CDRs 1, 2, and 3 of a VL domain are also sometimes referred to herein, respectively, as CDR-L1, CDR-L2, and CDR-L3; CDRs 1, 2, and 3 of a VH domain are also sometimes referred to herein, respectively, as CDR-H1, CDR-H2, and CDR-H3. When the application discloses a VL sequence with R as the C-terminal residue, the R can alternatively be considered as being the N-terminal residue of the light chain constant region. Thus, the application should also be understood as disclosing the VL sequence without the C-terminal R.

[0058] The assignment of amino acids to each VL and VH domain is in accordance with any conventional definition of CDRs. Conventional definitions include, the Kabat definition (Kabat, *Sequences of Proteins of Immunological Interest* (National Institutes of Health, Bethesda, MD, 1987 and 1991), the Chothia definition (Chothia & Lesk, *J. Mol. Biol.* 196:901-917, 1987; Chothia et al., *Nature* 342:878-883, 1989); a composite of Chothia Kabat CDR in which CDR-H1 is a composite of Chothia and Kabat CDRs; the AbM definition used by Oxford Molecular’s antibody modelling software; and, the contact definition of Martin et al (bioinfo.org.uk/abs) (see Table A). Kabat provides a widely used numbering convention (Kabat numbering) in which corresponding residues between different heavy chains or between different light chains are assigned the same number. When an antibody is said to comprise CDRs by a certain definition of CDRs (e.g., Kabat) that definition specifies the minimum number of CDR residues present in the antibody (i.e., the Kabat CDRs). It does not exclude that other residues falling within another conventional CDR definition but outside the specified definition are also present. For example, an antibody comprising CDRs defined by Kabat includes among other possibilities, an antibody in which the CDRs contain Kabat CDR residues and no other CDR residues, and an antibody in which CDR H1 is a

composite Chothia-Kabat CDR H1 and other CDRs contain Kabat CDR residues and no additional CDR residues based on other definitions.

Table A

Conventional Definitions of CDRs Using Kabat Numbering

Loop	Kabat	Chothia	Composite of Chothia & Kabat	AbM	Contact
L1	L24--L34	L24--L34	L24--L34	L24--L34	L30--L36
L2	L50--L56	L50--L56	L50--L56	L50--L56	L46--L55
L3	L89--L97	L89--L97	L89--L97	L89--L97	L89--L96
H1	H31--H35B	H26--H32..H34*	H26--H35B*	H26--H35B	H30--H35B
H2	H50--H65	H52--H56	H50--H65	H50--H58	H47--H58
H3	H95--H102	H95--H102	H95--H102	H95--H102	H93--H101

*CDR-H1 by Chothia can end at H32, H33, or H34 (depending on the length of the loop). This is because the Kabat numbering scheme places insertions of extra residues at 35A and 35B, whereas Chothia numbering places them at 31A and 31B. If neither H35A nor H35B (Kabat numbering) is present, the Chothia CDR-H1 loop ends at H32. If only H35A is present, it ends at H33. If both H35A and H35B are present, it ends at H34.

[0059] In some embodiments, the CDRs of the humanized antibodies of the present invention are of a definition selected from the group of Kabat, Chothia, Kabat/Chothia Composite, AbM and Contact.

[0060] One or several amino acids at the amino or carboxy terminus of the light and/or heavy chain, such as a C-terminal lysine of the heavy chain, may be missing or derivatized in a portion or all of the molecules. Substitutions can be made in the constant regions to reduce or increase effector function such as complement-mediated cytotoxicity or ADCC (see, e.g., Winter et al., US Patent No. 5,624,821; Tso et al., US Patent No. 5,834,597; and Lazar et al., Proc. Natl. Acad. Sci. USA 103:4005, 2006), or to prolong half-life in humans (see, e.g., Hinton et al., J. Biol. Chem. 279:6213, 2004). Exemplary substitutions include a Gln at position 250 and/or a Leu at position 428 (EU numbering is used in this paragraph for the

constant region) for increasing the half-life of an antibody. Substitution at any or all of positions 234, 235, 236 and/or 237 reduce affinity for Fcγ receptors, particularly FcγRI receptor (see, e.g., US 6,624,821). An alanine substitution at positions 234, 235, and 237 of human IgG1 can be used for reducing effector functions. Some antibodies have alanine substitution at positions 234, 235 and 237 of human IgG1 for reducing effector functions. Optionally, positions 234, 236 and/or 237 in human IgG2 are substituted with alanine and position 235 with glutamine (see, e.g., US 5,624,821). In some antibodies, a mutation at one or more of positions 241, 264, 265, 270, 296, 297, 322, 329, and 331 by EU numbering of human IgG1 is used. In some antibodies, a mutation at one or more of positions 318, 320, and 322 by EU numbering of human IgG1 is used. In some antibodies, positions 234 and/or 235 are substituted with alanine and/or position 329 is substituted with glycine. In some antibodies, positions 234 and 235 are substituted with alanine. In some antibodies, the isotype is human IgG2 or IgG4. As an example, the C-terminal lysine on SEQ ID NO: 11 (heavy chain) or SEQ ID NO: 9 (heavy chain constant region) is optional such that SEQ ID NO: 11 and SEQ ID NO: 9 may be considered with or without the C-terminal lysine.

[0061] The term "humanized immunoglobulin" or "humanized antibody" refers to an immunoglobulin or antibody that includes at least one humanized immunoglobulin or antibody chain (i.e., at least one humanized light or heavy chain). The term "humanized immunoglobulin chain" or "humanized antibody chain" (i.e., a "humanized immunoglobulin light chain" or "humanized immunoglobulin heavy chain") refers to an immunoglobulin or antibody chain (i.e., a light or heavy chain, respectively) having a variable region that includes a variable framework region substantially from a human immunoglobulin or antibody and complementarity determining regions (CDRs) (e.g., at least one CDR, preferably two CDRs, more preferably three CDRs) substantially from a non-human immunoglobulin or antibody, and further includes constant regions (e.g., at least one constant region or portion thereof, in the case of a light chain, and preferably three constant regions in the case of a heavy chain). The term "humanized variable region" (e.g., "humanized light chain variable region" or "humanized heavy chain variable region") refers to a variable region that includes a variable framework region substantially from a human immunoglobulin or antibody and complementarity determining regions (CDRs) substantially from a non-human immunoglobulin or antibody. "Excluding the CDRs" as used herein means the portions of the antibody that do not include the amino acids of the CDRS, for example the framework regions and antibody constant regions.

[0062] Accordingly, regions or residues of a humanized immunoglobulin or antibody, or of a humanized immunoglobulin or antibody chain, except possibly the CDRs, are substantially identical to the corresponding regions or residues of one or more native human immunoglobulin sequences. The term "corresponding region" or "corresponding residue" refers to a region or residue on a second amino acid or nucleotide sequence which occupies the same (i.e., equivalent) position as a region or residue on a first amino acid or nucleotide sequence, when the first and second sequences are optimally aligned for comparison purposes.

[0063] The term "epitope" or "antigenic determinant" refers to a site on an antigen to which an antibody binds. An epitope can be formed from contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of one or more proteins. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, and more usually, at least 5 or 8-10 amino acids in a unique spatial conformation. When an epitope is said to be within a range of amino acid residues in a protein (e.g., within residues 1 to 6 of A β), the range is inclusive of the residues defining its borders. Certain residues within the range contribute to the epitope, whereas others may not. The residues that form the epitope may or may not be contiguous with one another. Similarly, when an antibody binds to an epitope found within a particular range of amino acids, the antibody need not contact all the amino acids residues within the range, and the residues of the epitope that are contacted by the antibody may or may not be contiguous with one another. Methods of determining spatial conformation of epitopes include, for example, x-ray crystallography and 2-dimensional nuclear magnetic resonance. See, e.g., Epitope Mapping Protocols, in *Methods in Molecular Biology*, Vol. 66, Glenn E. Morris, Ed. (1996).

[0064] Antibodies that recognize the same epitope can be identified in a simple immunoassay showing the ability of one antibody to block or compete with the binding of another antibody to a target antigen, i.e., a competitive binding assay. Competitive binding is determined in an assay in which the immunoglobulin under test inhibits specific binding of a reference antibody to a common antigen, such as A β . Numerous types of competitive binding assays are known, for example: solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (see Stahl

et al., *Methods in Enzymology* 9:242 (1983)); solid phase direct biotin-avidin EIA (see Kirkland et al., *J. Immunol.* 137:3614 (1986)); solid phase direct labeled assay, solid phase direct labeled sandwich assay (see Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Press (1988)); solid phase direct label RIA using I-125 label (see Morel et al., *Mol. Immunol.* 25(1):7 (1988)); solid phase direct biotin-avidin EIA (Cheung et al., *Virology* 176:546 (1990)); and direct labeled RIA. (Moldenhauer et al., *Scand. J. Immunol.* 32:77 (1990)). Typically, such an assay involves the use of purified antigen bound to a solid surface or cells bearing either of these, an unlabeled test immunoglobulin and a labeled reference immunoglobulin. Competitive inhibition is measured by determining the amount of label bound to the solid surface or cells in the presence of the test immunoglobulin. Usually the test immunoglobulin is present in excess. Usually, when a competing antibody is present in excess, it will inhibit specific binding of a reference antibody to a common antigen by at least 50-55%, 55-60%, 60-65%, 65-70%, 70-75%, or more.

[0065] Competition between antibodies is determined by an assay in which an antibody under test inhibits specific binding of a reference antibody (e.g. 3D6, aducanumab, bapineuzumab) to a common antigen (see, e.g., Junghans et al., *Cancer Res.* 50:1495, 1990). A test antibody competes with a reference antibody if an excess of a test antibody (e.g., at least 2×, 5×, 10×, 20× or 100×) inhibits binding of the reference antibody by at least 50% but preferably 75%, 90% or 99% as measured in a competitive binding assay. Antibodies identified by competition assay (competing antibodies) include antibodies binding to the same epitope as the reference antibody and antibodies binding to an adjacent epitope sufficiently proximal to the epitope bound by the reference antibody for steric hindrance to occur.

[0066] The epitope of an antibody can also be defined by X-ray crystallography of the antibody bound to its antigen to identify contact residues. Alternatively, two antibodies have the same epitope if all amino acid mutations in the antigen that reduce or eliminate binding of one antibody reduce or eliminate binding of the other. Two antibodies have overlapping epitopes if some amino acid mutations that reduce or eliminate binding of one antibody reduce or eliminate binding of the other.

[0067] An epitope is also recognized by immunologic cells, for example, B cells and/or T cells. Cellular recognition of an epitope can be determined by in vitro assays that measure antigen-dependent proliferation, as determined by ³H-thymidine incorporation, by cytokine

secretion, by antibody secretion, or by antigen-dependent killing (cytotoxic T lymphocyte assay).

[0068] Exemplary epitopes or antigenic determinants can be found within the human amyloid precursor protein (APP) but are preferably found within the A β peptide of APP. Multiple isoforms of APP exist, for example APP⁶⁹⁵, APP⁷⁵¹, and APP⁷⁷⁰. Amino acids within APP are assigned numbers according to the sequence of the APP⁷⁷⁰ isoform (see e.g., GenBank Accession No. P05067).

[0069] A β (also referred to herein as beta amyloid peptide and A-beta) peptide is a about 4-kDa internal fragment of 39-43 amino acids of APP (A β 39, A β 40, A β 41, A β 42, and A β 43). A β 40, for example, consists of residues 672-711 of APP and A β 42 consists of residues 673-713 of APP. As a result of proteolytic processing of APP by different secretase enzymes *in vivo* or *in situ*, A β is found in both a "short form", 40 amino acids in length, and a "long form", ranging from 42-43 amino acids in length. Preferred epitopes or antigenic determinants, as described herein, are located within the N-terminus of the A β peptide and include residues within amino acids 1-10 of A β , preferably from residues 1-3, 1-4, 1-5, 1-6, 1-7, or 3-7 of A β 42. Additional referred epitopes or antigenic determinants include residues 2-4, 5, 6, 7, or 8 of A β , residues 3-5, 6, 7, 8, or 9 of A β , or residues 4-7, 8, 9, or 10 of A β 42.

[0070] "Soluble" or "dissociated" A β refers to A β species that are either monomeric, aggregated, oligomeric, associated or not with other proteins and lipids, which remain in solution (supernatant) after centrifugation at 100,000 $\times$ g. "Insoluble" A β refers to aggregated A β species, amyloid (beta-sheet) or not, that do not remain in solution after 100,000 $\times$ g centrifugation, for example, A β held together by noncovalent bonds. A β (e.g., A β 42) is believed to aggregate, at least in part, due to the presence of hydrophobic residues at the C-terminus of the peptide (part of the transmembrane domain of APP). One method to prepare soluble A β is to dissolve lyophilized peptide in neat DMSO with sonication. The resulting solution is centrifuged to remove any insoluble particulates.

[0071] "Specific binding" of an antibody means that the antibody exhibits appreciable affinity for antigen or a preferred epitope and, preferably, does not exhibit significant cross reactivity. "Appreciable" or preferred binding includes binding with an affinity of at least 10^6 , 10^7 , 10^8 , 10^9 M⁻¹, or 10^{10} M⁻¹. Affinities greater 10^7 M⁻¹, preferably greater than 10^8 M⁻¹ are more preferred. Values intermediate of those set forth herein are also intended to be within

the scope of the present disclosure and a preferred binding affinity can be indicated as a range of affinities, for example, 10^6 to 10^{10} M^{-1} , preferably 10^7 to 10^{10} M^{-1} , more preferably 10^8 to 10^{10} M^{-1} . An antibody that "does not exhibit significant cross reactivity" is one that will not appreciably bind to an undesirable entity (e.g., an undesirable proteinaceous entity). For example, an antibody that specifically binds to A β will appreciably bind A β but will not significantly react with non-A β proteins or peptides (e.g., non-A β proteins or peptides included in plaques). An antibody specific for a preferred epitope will, for example, not significantly cross-react with remote epitopes on the same protein or peptide. Specific binding can be determined according to any art-recognized means for determining such binding. Preferably, specific binding is determined according to Scatchard analysis and/or competitive binding assays.

[0072] Binding fragments are produced by recombinant DNA techniques, or by enzymatic or chemical cleavage of intact immunoglobulins. Binding fragments include Fab, Fab', F(ab')₂, Fabc, Fv, single chains, and single-chain antibodies.

[0073] The term "peripheral administration" as used herein includes, e.g., intravenous, intraarterial, intraperitoneal, intramuscular, subcutaneous, intranasal, intra-ocular/vitreous, rectal, or vaginal administration. While all these forms of administration are clearly contemplated as being within the scope of the disclosure, an example of a form for administration would be a solution for injection, in particular for subcutaneous, intravenous or intraarterial injection or drip. A suitable pharmaceutical composition for injection can comprise a buffer, a surfactant, optionally a stabilizer agent, etc. Preparations for peripheral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Preservatives and other additives can also be present such as, for example, antimicrobials, antioxidants, chelating agents, and inert gases and the like.

[0074] The term "patient" includes human and other mammalian subjects that receive either prophylactic or therapeutic treatment. In some embodiments, the term "individual" is used interchangeably with "patient."

[0075] The term "subject" includes human and other subjects that receive either prophylactic or therapeutic treatment, and includes, but is not limited to "patients" described herein.

[0076] The term "effective dose" or "effective dosage" is defined as an amount sufficient to achieve or at least partially achieve the desired effect. The term "therapeutically effective dose" is defined as an amount sufficient to cure or at least partially arrest the disease and its complications in a patient already suffering from the disease. Amounts effective for this use will depend upon the severity of the infection and the general state of the patient's own immune system.

[0077] The term "treatment" as used herein, is defined as the application or administration of a therapeutic agent to a patient, or application or administration of a therapeutic agent to an isolated tissue or cell line from a patient, who has a disease, a symptom of disease or a predisposition toward a disease, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect the disease, the symptoms of disease or the predisposition toward disease.

[0078] The term "amyloidogenic disease" includes any disease associated with (or caused by) the formation or deposition of insoluble amyloid fibrils or amyloid plaques. Exemplary amyloidogenic diseases include, but are not limited to systemic amyloidosis, Alzheimer's disease, mature onset diabetes, Parkinson's disease, Huntington's disease, fronto-temporal dementia, Down's syndrome, mild cognitive impairment, prion-related transmissible spongiform encephalopathies (kuru and Creutzfeldt-Jacob disease in humans and scrapie and BSE in sheep and cattle, respectively), and the like. Different amyloidogenic diseases are defined or characterized by the nature of the polypeptide component of the fibrils deposited. For example, in subjects or patients having Alzheimer's disease, β -amyloid protein (e.g., wild-type, variant, or truncated β -amyloid protein) is the characterizing polypeptide component of the amyloid deposit. Accordingly, Alzheimer's disease is an example of a "disease characterized by deposits of $A\beta$ " or a "disease associated with deposits of $A\beta$ ", e.g., in the brain of a subject or patient. The terms " β -amyloid protein", " β -amyloid peptide", " β -amyloid", " $A\beta$ " and " $A\beta$ peptide" are used interchangeably herein.

[0079] An individual is at increased risk of a disease if the subject has at least one known risk-factor (e.g., genetic, biochemical, family history, situational exposure) placing individuals with that risk factor at a statistically significant greater risk of developing the disease than individuals without the risk factor.

[0080] The term “symptom” refers to subjective evidence of a disease, such as altered gait, as perceived by the patient. A “sign” refers to objective evidence of a disease as observed by a physician.

[0081] Statistical significance means $p < 0.05$.

[0082] “Half-life ($t_{1/2}$)” refers to the time required for the concentration of the antigen binding polypeptide to reach half of its original value. The serum half-life of proteins can be measured by pharmacokinetic studies according to the method described by Kim et al. (Eur. J. of Immuno. 24: 542, 1994). According to this method, radiolabeled protein is injected intravenously into mice and its plasma concentration is periodically measured as a function of time, for example, at about 3 minutes to about 72 hours after the injection. Other methods for pharmacokinetic analysis and determination of the half-life of a molecule will be familiar to those skilled in the art. Details may be found in Kenneth, A et al: Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists and in Peters et al, Pharmacokinetic analysis: A Practical Approach (1996).

[0083] “Clearance (CL)” refers to the volume of plasma irreversibly cleared of a protein per unit time. Clearance is calculated as the Dose/AUC (AUC: is the Area Under Curve or Area under the plasma drug concentration time curve). Clearance can also be calculated by the rate of drug elimination divided by the plasma concentration of the drug (rate of elimination = $CL \times \text{concentration}$)

[0084] “Mean Residence Time (MRT)” is the average time that the antigen binding polypeptides reside in the body before being irreversibly eliminated. Calculated as $MRT = AUMC/AUC$.

[0085] “Steady state concentration” (C_{ss}) is the concentration reached when the drug elimination rate becomes equal to drug administration rate as a result of continued drug administration. C_{ss} fluctuates between peak and trough levels and is measured in microgram/ml.

[0086] “Baseline” as used herein is the value of a parameter before or at the time of administration of the pharmaceutical composition of the present invention, including, for example, the value of a given biomarker or a subject’s status prior to the first administration of an antibody of the present disclosure.

[0087] “Amyloid negative” means the subject does not possess brain amyloid beta plaque that is observable using positron emission tomography (“PET”) and includes, but is not limited to, subjects having a centiloid value of zero.

[0088] “Amyloid positive” means the subject possesses brain amyloid beta plaque that is observable using PET.

[0089] “ARIA risk” or “risk of ARIA” as used herein, refers to the probability that a subject will develop an Amyloid Related Imaging Abnormality that is observable on by MRI. A total ARIA risk includes the risk of developing observable ARIA-E and/or observable ARIA-H. In contrast, “a risk of ARIA-E” refers only to the probability that a subject will develop ARIA-E observable by MRI, irrespective of whether the subject develops observable ARIA-H, and “a risk of ARIA-H” refers only to the probability that a subject will develop ARIA-H observable by MRI, irrespective of whether the subject develops observable ARIA-E. ARIA risk may be assessed at baseline (prior to the administration of an anti-amyloid β antibody of the present disclosure) or, alternatively, during or after treatment.

Treatment Regimes

[0090] Prophylactic applications: pharmaceutical compositions or medicaments are administered to a patient susceptible to, or otherwise at risk of, Alzheimer's disease or other amyloidogenic disease in an amount sufficient to eliminate or reduce the risk, lessen the severity, or delay the outset of the disease, including biochemical, histologic and/or behavioral symptoms of the disease, its complications and intermediate pathological phenotypes presenting during development of the disease. Patient susceptibility or risk for developing an amyloidogenic disease can be determined, for example, from a genetic marker, a biochemical marker, unspecified hereditary risk or other means. In therapeutic applications, compositions or medicaments are administered to a patient suspected of, or already suffering from such a disease in an amount sufficient to cure, or at least partially arrest, the symptoms of the disease (biochemical, histologic and/or behavioral), including its complications and intermediate pathological phenotypes in development of the disease.

[0091] In some embodiments, administration of agent reduces or eliminates cognitive impairment in patients that have not yet developed characteristic Alzheimer's, or other amyloidogenic disease cognitive pathology. An amount adequate to accomplish therapeutic or prophylactic treatment is defined as a therapeutically- or prophylactically-effective dose.

In both prophylactic and therapeutic regimes, agents are usually administered in several dosages until a sufficient immune response has been achieved, where "immune response" or "immunological response" includes the development of a humoral (antibody mediated) and/or a cellular (mediated by antigen-specific T cells or their secretion products) response directed against an antigen in a recipient subject. Such a response can be an active response, i.e., induced by administration of immunogen, or a passive response, i.e., induced by administration of immunoglobulin or antibody or primed T-cells.

[0092] In some embodiments, antibody is administered on multiple occasions. Intervals between single dosages can be weekly, monthly or yearly. In some embodiments, a single dosage may be administered about once or twice every week, about once or twice every two weeks, about once or twice every three weeks, about once or twice every four weeks, about once or twice every five weeks, or about once or twice every six weeks. In one particular embodiment, antibody is administered once about every four weeks intravenously or subcutaneously. In another embodiment, antibody is administered once about every two weeks intravenously or subcutaneously.

[0093] Intervals can also be irregular as indicated by measuring blood levels of antibody to A β in the patient. In some methods, dosage is adjusted to achieve a plasma antibody concentration of 1-1000 μ g/ml and in some methods 25-300 μ g/ml. Alternatively, antibody can be administered as a sustained release formulation, in which case less frequent administration is required. Dosage and frequency vary depending on the half-life of the antibody in the patient. In general, human antibodies show the longest half-life, followed by humanized antibodies, chimeric antibodies, and nonhuman antibodies.

[0094] In some embodiments, a patient with Alzheimer's disease administered a pharmaceutically effective amount of an anti-A β antibody (or antigen-binding fragment thereof) as described herein is treated by reduction in amyloid plaque burden, measured by PET imaging.

[0095] In another embodiment, antibody can be administered in a fixed amount at each administration. For example, a fixed amount of about 200 mg, about 250, about 300 mg, about 350 mg, or about 400 mg can be administered at one time to an individual. In one particular embodiment, about 250 mg of antibody is administered once about every four weeks subcutaneously. In one particular embodiment, about 300 mg of antibody is

administered once about every four weeks subcutaneously. In one particular embodiment, about 350 mg of antibody is administered once about every four weeks subcutaneously. In one particular embodiment, about 400 mg of antibody is administered once about every four weeks subcutaneously. In one particular embodiment, about 200 mg of antibody is administered twice about every four weeks subcutaneously. In one particular embodiment, about 200 mg of antibody is administered once about every two weeks subcutaneously.

[0096] In another particular embodiment, about 250 mg of h2731 is administered once about every four weeks subcutaneously. In another particular embodiment, about 300 mg of h2731 is administered once about every four weeks subcutaneously. In another particular embodiment, about 350 mg of h2731 is administered once about every four weeks subcutaneously. In another particular embodiment, about 400 mg of h2731 is administered once about every four weeks subcutaneously. In another particular embodiment, about 200 mg of h2731 is administered twice about every four weeks subcutaneously. In another particular embodiment, about 200 mg of h2731 is administered once about every two weeks subcutaneously.

[0097] The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic. In prophylactic applications, compositions containing the present antibodies or a cocktail thereof are administered to a patient not already in the disease state to enhance the patient's resistance. Such an amount is defined as a "prophylactic effective dose." In this use, the precise amounts again depend upon the patient's state of health and general immunity. A relatively low dosage is administered at relatively infrequent intervals over a long period of time. Some patients continue to receive treatment for the rest of their lives.

[0098] In therapeutic applications, a relatively high dosage at relatively short intervals is sometimes required until progression of the disease is reduced or terminated, and in some aspects, until the patient shows partial or complete amelioration of symptoms of disease. Thereafter, the patent can be administered a prophylactic regime.

[0099] Administration: therapeutic agents can be administered by parenteral, topical, intravenous, oral, subcutaneous, intraarterial, intracranial, intraperitoneal, intranasal, intraocular or intramuscular means for prophylactic and/or therapeutic treatment. Intramuscular injection is most typically performed in the arm or leg muscles. In some

methods, agents are injected directly into a particular tissue where deposits have accumulated, for example intracranial injection. Intramuscular injection or intravenous infusion are preferred for administration of antibody. In some methods, particular therapeutic antibodies are injected directly into the cranium. In some methods, antibodies are administered as a sustained release composition or device. In some embodiments, antibodies are administered subcutaneously using an autoinjector device.

Dosing Regimens

[00100] The present disclosure provides methods of treating neurological disorders (e.g., Alzheimer's Disease), the method comprising administering a composition comprising an anti-amyloid β antibody. For example, in some embodiments, the present disclosure provides a method of treating Alzheimer's disease in a subject, comprising administering to the subject about 205 mg to about 400 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks.

[00101] The present disclosure also provides methods of reducing amyloid plaque in a subject. For example, in some embodiments, the present disclosure provides a method of reducing amyloid plaque in a subject, comprising administering to the subject about 205 mg to about 400 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks.

[00102] The present disclosure further provides methods of converting a subject from amyloid positive to amyloid negative. For example, in some embodiments, the present disclosure provides a method of converting a subject from amyloid positive to amyloid negative, comprising administering to the subject about 205 mg to about 400 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks.

[00103] In some embodiments, the method comprises administering to the subject about 205 mg to about 400 mg (e.g., about 250 mg to about 400 mg, about 300 mg to about 400 mg, or about 350 mg to about 400 mg) of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks. In some embodiments, the method comprises administering to the subject about 205 mg to about 400 mg (e.g., about 250 mg to about 400 mg, about 300 mg to about 400 mg, or about 350 mg to about 400 mg) of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 4 weeks.

[00104] In example embodiments, the method comprises administering to the subject about 295 mg to about 305 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks. In example embodiments, the method comprises administering to the subject about 345 mg to about 355 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks. In example embodiments, the method comprises administering to the subject about 395 mg to about 405 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks.

[00105] In some embodiments, the method comprises administering to the subject about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, or about 400 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks. In some embodiments, the method comprises administering to the subject about 300 mg, about 350 mg, or about 400 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks (e.g., once about every 4 weeks).

[00106] In example embodiments, the method comprises administering to the subject about 250 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks. In example embodiments, the method comprises administering to the subject about 300 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks. In example embodiments, the method comprises administering to the subject about 350 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks. In example embodiments, the method comprises administering to the subject about 400 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks.

[00107] In example embodiments, the method comprises administering to the subject about 250 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 4 weeks. In example embodiments, the method comprises administering to the subject about 300 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof

once about every 4 weeks. In example embodiments, the method comprises administering to the subject about 350 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 4 weeks. In example embodiments, the method comprises administering to the subject about 400 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 4 weeks.

[00108] In some embodiments, the method comprises administering the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 4 weeks. In some embodiments, the method comprises administering the anti-amyloid β antibody or an antigen-binding fragment thereof once about a month. In some embodiments, the method comprises administering the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 28 days.

[00109] In some embodiments, the method comprises administering the anti-amyloid β antibody or an antigen-binding fragment thereof as a single administration (e.g., a single subcutaneous injection) once about every 3-5 weeks. In some embodiments, the method comprises administering the anti-amyloid β antibody or an antigen-binding fragment thereof as a single administration once about every 4 weeks. In some embodiments, the method comprises administering the anti-amyloid β antibody or an antigen-binding fragment thereof as a single administration once every 4 weeks. In some embodiments, the method comprises administering the anti-amyloid β antibody or an antigen-binding fragment thereof as a single administration once about a month. In some embodiments, the method comprises administering the anti-amyloid β antibody or an antigen-binding fragment thereof as a single administration once about every 28 days.

[00110] In some embodiments, the present disclosure provides a method of treating Alzheimer's disease in a subject, comprising administering to the subject about 45 mg to about 200 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks (e.g., once about every 2 weeks). In some embodiments, the present disclosure provides a method of treating Alzheimer's disease in a subject, comprising administering to the subject about 100 mg to about 200 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks (e.g., once about every 2 weeks).

[00111] In some embodiments, the present disclosure provides a method of reducing amyloid plaque in a subject, comprising administering to the subject about 45 mg to about 200 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks (e.g., once about every 2 weeks). In some embodiments, the present disclosure provides a method of reducing amyloid plaque in a subject, comprising administering to the subject about 100 mg to about 200 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks (e.g., once about every 2 weeks).

[00112] In some embodiments, the present disclosure provides a method of converting a subject from amyloid positive to amyloid negative, comprising administering to the subject about 45 mg to about 200 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks (e.g., once about every 2 weeks). In some embodiments, the present disclosure provides a method of converting a subject from amyloid positive to amyloid negative, comprising administering to the subject about 100 mg to about 200 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks (e.g., once about every 2 weeks).

[00113] In some embodiments, the method comprises administering to the subject about 70 mg, about 100 mg to about 200 mg (e.g., about 125 mg to about 200 mg, about 150 mg to about 200 mg, or about 175 mg to about 200 mg) of the anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks (e.g., once about every 2 weeks).

[00114] In example embodiments, the method comprises administering to the subject about 65 mg to about 75 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof. In example embodiments, the method comprises administering to the subject about 145 mg to about 155 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof. In example embodiments, the method comprises administering to the subject about 195 mg to about 205 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks (e.g., once about every 2 weeks).

[00115] In some embodiments, the method comprises administering to the subject about 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg,

about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, or about 200 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks (e.g., once every 2 weeks). In some embodiments, the method comprises administering to the subject about 150 mg, or about 200 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks (e.g., once about every 2 weeks).

[00116] In example embodiments, the method comprises administering to the subject about 70 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks. In example embodiments, the method comprises administering to the subject about 70 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 2 weeks.

[00117] In example embodiments, the method comprises administering to the subject about 100 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks. In example embodiments, the method comprises administering to the subject about 100 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 2 weeks.

[00118] In example embodiments, the method comprises administering to the subject about 200 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks. In example embodiments, the method comprises administering to the subject about 200 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 2 weeks.

[00119] In some embodiments, the method comprises administering the anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 4 weeks. In some embodiments, the method comprises administering the anti-amyloid β antibody or an antigen-binding fragment thereof twice about a month. In some embodiments, the method comprises administering the anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 28 days.

[00120] In some embodiments, the method comprises administering the anti-amyloid β antibody or an antigen-binding fragment thereof as a single administration (e.g., a single subcutaneous injection) once about every 1-3 weeks. In some embodiments, the method

comprises administering the anti-amyloid β antibody or an antigen-binding fragment thereof as a single administration once about every 2 weeks. In some embodiments, the method comprises administering the anti-amyloid β antibody or an antigen-binding fragment thereof as a single administration once every 2 weeks. In some embodiments, the method comprises administering the anti-amyloid β antibody or an antigen-binding fragment thereof as a single administration once about every 14 days.

[00121] In some embodiments, the method comprises administering the anti-amyloid β antibody or an antigen-binding fragment thereof as an injection. In some embodiments, the method comprises administering the anti-amyloid β antibody or an antigen-binding fragment thereof as a parenteral injection. In some embodiments, the method comprises administering the anti-amyloid β antibody or an antigen-binding fragment thereof via intravenous injection or subcutaneous injection. In example embodiments, the method comprises administering the anti-amyloid β antibody or an antigen-binding fragment thereof as a subcutaneous injection. In some embodiments, the method comprises administering the anti-amyloid β antibody or an antigen-binding fragment thereof via an autoinjector.

Anti-A β Antibodies

[00122] The present disclosure provides methods of using an antibody or fragment thereof that specifically binds to A β peptide. In some aspects, the present disclosure utilizes anti-amyloid β antibodies or fragments thereof that achieve therapeutic efficacy using monthly subcutaneous dosing. The present disclosure further describes selecting and designing anti-amyloid β antibodies or fragments thereof suitable for monthly subcutaneous dosing.

[00123] In some embodiments, monoclonal antibodies for use in the disclosure bind to an epitope within residues 1-6 of A β (with the first N terminal residue of natural A β designated 1). Some monoclonal antibodies bind to an epitope within amino acids 1-6, some to an epitope within 1-5, and some to an epitope within 1-4. Some antibodies bind to epitopes within amino acids 1-3, 2-5, 3-5, 2-4, 2-5, 2-6, 3-5, or 3-6. When an antibody is said to bind to an epitope within specified residues, such as A β 1-6 for example, what is meant is that the antibody specifically binds to a polypeptide containing at least one of the specified residues (i.e., at least one amino acid from A β 1-6 in this an example); such antibody does not necessarily contact every residue within A β 1-6. In some embodiments, the antibody binds to

an epitope including at least one amino acid from acid selected from amino acids 1-10 of the A β peptide. In another aspect, the antibody binds to an epitope including at least one amino acid from acid selected from amino acids 1-7 of the A β peptide. Additional amino acids of the epitope may be outside the region of amino acids 1-10 or amino acids 1-7.

[00124] The antibodies used in such methods can be humanized, human or fragments thereof (e.g., antigen binding fragments) and can be monoclonal or polyclonal, as described herein. In yet another aspect, the disclosure features administering antibodies prepared from a human immunized with A β peptide, which human can be the patient to be treated with antibody.

[00125] In some embodiments, the anti-amyloid β antibody or fragment includes a heavy chain variable region having a heavy chain CDR1, CDR2 and CDR3 and a light chain variable region comprising a light chain CDR1, CDR2 and CDR3 from the constructs show in Table 1.

Table 1

Construct ID	VH/VL Sequences		SEQ ID	CDR Sequences		SEQ ID
h2731	VH	EVQLLESGGGLVQPGGS	1	1 GFTFS NYGMS		3
		LRLSCAASGFTFSNYGM		2 SIRSG SGRTY YSDNV KG		4
		SWVRQAPGKGLEWVASI		3 YDHYS GSSDY		5
	VL	RSGSGRTYYSDNVKGRF	2			
		TISRDN SKNTLYLQMNS				
		LRAEDTAVYYCVRYDHY				
		SGSSDYWGQGTILVTVSS				
		DVVMTQSPFLSLPVTLGE		1 KSSQS LLDYD GKTYL N		6
		PASISCKSSQSLLDYDG		2 RVTNR DT		7
		KTYLNWLLQKPGQSPQR		3 WQGT H FPRS		8
		LIYRV TNRDTGVPDRFS				
		GSGSGTDFTLKISRVEA				
		EDVGVYYCWQGT H FPRS				
		FGQGTKVEIK				

[00126] In some embodiments, the anti-amyloid β antibody or fragment of the disclosure includes a heavy chain variable region (VH) as shown for one of the constructs in Table 1. In some embodiments, the anti-amyloid β antibody or fragment also includes light chain variable region (VL) as shown for one of the constructs in Table 1.

[00127] In some embodiments, the anti-amyloid β antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising heavy chain CDR1, CDR2, and

CDR3 and a light chain variable region comprising light chain CDR1, CDR2, and CDR3, wherein

heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 3,
heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 4,
heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 5,
light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 6,
light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 7, and
light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 8.

[00128] In some embodiments, for example, the anti-amyloid β antibody or fragment thereof for use in methods of the present disclosure include a heavy chain variable region that is at least 90% (e.g., at least 95%, at least 98%, or 100%) identical to SEQ ID NO: 1 and the light chain variable region, excluding the CDRs, that is at least 90% (e.g., at least 95%, at least 98%, or 100%) identical to SEQ ID NO: 2.

[00129] In some embodiments, the heavy chain variable region, excluding the CDRs, is at least 95% identical to the amino acid sequence of SEQ ID NO: 1, and the light chain variable region, excluding the CDRs, is at least 95% identical to the amino acid sequence of SEQ ID NO: 2. In some embodiments, the heavy chain variable region, excluding the CDRs, is at least 98% identical to the amino acid sequence of SEQ ID NO: 1, and the light chain variable region, excluding the CDRs, is at least 98% identical to the amino acid sequence of SEQ ID NO: 2. In some embodiments, the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 1, and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 2. In some embodiments, the heavy chain variable region consists of SEQ ID NO: 1, and wherein the light chain variable region consists of the amino acid sequence of SEQ ID NO: 2.

[00130] In some embodiments, the anti-amyloid β antibody is a full antibody, a chimeric antibody, a CDR-grafted antibody, or a recombinant antibody. In some embodiments, the anti-amyloid β antibody is a humanized IgG. In some embodiments, the anti-amyloid β antibody is a humanized IgG1.

[00131] In some embodiments, the anti-amyloid β antibody or fragment thereof for use in methods of the present disclosure also include a heavy chain constant region that is at least 75% identical to SEQ ID NO: 9. For example, the heavy chain constant region may be 75%

identical, 80%, identical, 85% identical, 90% identical, 95% identical, 96% identical, 97% identical, 98% identical, 99% identical, of 100% identical to SEQ ID NO: 9.

[00132] In some embodiments, the anti-amyloid β antibody or fragment thereof for use in methods of the present disclosure also include a light chain constant region that is at least 75% identical to SEQ ID NO: 10. For example, the light chain constant region may be 75% identical, 80%, identical, 85% identical, 90% identical, 95% identical, 96% identical, 97% identical, 98% identical, 99% identical, of 100% identical to SEQ ID NO: 10.

[00133] In some embodiments, the anti-amyloid β antibody or antigen-binding fragment thereof further comprises a heavy chain constant region comprising an amino acid sequence at least 95% identical to SEQ ID NO: 9 and/or a light chain constant region comprising an amino acid sequence at least 95% identical to SEQ ID NO: 10. In some embodiments, the anti-amyloid β antibody or antigen-binding fragment thereof further comprises a heavy chain constant region comprising an amino acid sequence at least 98% identical to SEQ ID NO: 9 and/or a light chain constant region comprising an amino acid sequence at least 98% identical to SEQ ID NO: 10. In some embodiments, the anti-amyloid β antibody comprises a heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 9, with or without the C-terminal lysine, and a light chain constant region comprising an amino acid sequence of SEQ ID NO: 10. In some embodiments, the anti-amyloid β antibody comprises a heavy chain constant region consisting essentially of an amino acid sequence of SEQ ID NO: 9, with or without the C-terminal lysine, and a light chain constant region consisting essentially of an amino acid sequence of SEQ ID NO: 10.

[00134] In some embodiments, the anti-amyloid β antibody or antigen-binding fragment thereof further comprises a heavy chain comprising an amino acid sequence at least 95% identical to SEQ ID NO: 11 and/or a light chain comprising an amino acid sequence at least 95% identical to SEQ ID NO: 12. In some embodiments, the anti-amyloid β antibody or antigen-binding fragment thereof further comprises a heavy chain comprising an amino acid sequence at least 98% identical to SEQ ID NO: 11 and/or a light chain comprising an amino acid sequence at least 98% identical to SEQ ID NO: 12. In example embodiments, the anti-amyloid β antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain comprising an amino acid sequence of SEQ ID NO: 12. In example embodiments, the anti-amyloid β antibody comprises a heavy chain constant region consisting essentially of an amino acid sequence of

SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain constant region consisting essentially of an amino acid sequence of SEQ ID NO: 12. In example embodiments, the anti-amyloid β antibody comprises a heavy chain constant region consisting of an amino acid sequence of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain constant region consisting of an amino acid sequence of SEQ ID NO: 12. In example embodiments, the anti-amyloid β antibody is h2731.

[00135] A variant antibodies or fragments that are less than 100% identical to the sequences described in Table 1A (plus any constant region) can differ from an anti-A β antibody of Table 1 by as few as 1 to 15 amino acid residues, as few as 1 to 10 amino acid residues, such as 6-10, as few as 5, as few as 4, 3, 2, or even 1 amino acid residue. A “conservative amino acid substitution” is one in which the amino acid residue is replaced with an amino acid residue having a side chain with a similar charge. Families of amino acid residues having side chains with similar charges have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity (e.g., the ability to bind an A β polypeptide).

[00136] For example, it is possible to introduce mutations only in a framework region(s) of the antibody molecules (i.e., in a region(s) excluding the CDRs). Introduced mutations can be silent or neutral missense mutations, i.e., have no, or little, effect on an antibody's ability to bind antigen. These types of mutations can be useful to optimize codon usage or improve a hybridoma's antibody production. Alternatively, non-neutral missense mutations can alter an antibody's ability to bind antigen. One of skill in the art would be able to design and test mutant molecules with desired properties such as no alteration in antigen binding activity or alteration in binding activity (e.g., improvements in antigen binding activity or change in antibody specificity). Following mutagenesis, the encoded protein can routinely be expressed and the functional and/or biological activity of the encoded protein, (e.g., ability to

immunospecifically bind at least one epitope of an A β polypeptide) can be determined using techniques described herein or by routinely modifying techniques known in the art.

[00137] In each of the foregoing embodiments, the antibody or fragment of the disclosure may be a humanized antibody as described herein. For example, the antibody may be a human IgG1 antibody. In addition, the antibody may be a full antibody, a chimeric antibody, a CDR-grafted antibody, or a recombinant antibody. Fragments of the antibody may be a Fab, Fab', F(ab')₂, Fabc, or Fv. Fragments are produced by recombinant DNA techniques, or by enzymatic or chemical separation of intact immunoglobulins.

[00138] The antibody h2731 possesses several physicochemical properties that make it suitable for use in methods of the present disclosure, including, for example, properties described in Tables 2 and 3. Additional properties, including pharmacokinetic parameters, are discussed herein.

Table 2

IC ₅₀ Ratio (h2731:hBP) A β ₁₋₄₂ fibrils	IC ₅₀ (μ g/mL h2731) A β aggregates	EC ₅₀ (ng/mL h2731) A β ₁₋₄₂ fibrils	EC ₅₀ (h2731 ng/mL) A β _{pE3-42} fibrils
0.61	5.024	36.71	> 100

[00139] Table 2 provides IC₅₀ and/or EC₅₀ values data for h2731 binding various amyloid β species, including A β ₁₋₄₂ fibrils, A β ₁₋₄₂ aggregates and A β _{pE3-42} fibrils. *See, e.g.*, US Patent No. 11,440,953.

[00140] An assay based on the competition (inhibition) of binding of a labeled antibody to an antigen-coated plate was used to determine IC₅₀ for h2731. The IC₅₀ was then divided by the IC₅₀ for bapineuzumab (hBP) to yield a half maximal inhibitory concentration (IC₅₀) ratio, shown in Column 1 of Table 2. The ratio of 0.61 demonstrates that h2731 exhibits better performance than hBP in binding A β ₁₋₄₂ fibrils. Using a similar competition assay, it was demonstrated that h2731 exhibits an IC₅₀ value of 5.024 μ g/mL (Column 2 of Table 2), which several fold lower than the IC₅₀ value observed for hBP.

[00141] The direct binding of h2731 to A β ₁₋₄₂ and A β _{pE3-42} fibrils was also assessed by ELISA (Columns 3 and 4 of Table 2), providing an EC₅₀ value of 36.71 ng/mL for h2731

against A β ₁₋₄₂ fibrils, h2731 demonstrated strong affinity to fibrils and significantly greater avidity than aducanumab. Further, a 3-fold increase in assay signal (OD490) and a 15 to 20-fold lower estimated EC₅₀ indicated increased overall binding and relative avidity of h2731 to fibrillar A β relative to aducanumab.

[00142] However, while h2731 binds with high apparent affinity to the N-terminus of full length A β , it does not specifically bind to pyroglutamate-modified A β (A β _{pE3-42}). h2731 bound with a half-maximal effective concentration (EC₅₀) of 8.1 ng/mL (54 pM) to fibrillar A β species with an unmodified N-terminus (A β ₁₋₄₂). h2731 demonstrated no detectable binding to A β _{pE3-42} up to 100ng/ml.

Table 3

	1:1 binding ka (1/Ms)	kd (1/s)	Apparent KD (M)	Rmax (RU)
A β ₁₋₄₂ fibrils	3.72e+5	2.62e-5	7.04e-11	50.7
A β ₁₋₂₈	1.19e+5	5.95e-4	5.01e-9	78.3

Abeta: amyloid beta, A β ; ka: association rate constant; kd: dissociation rate constant; KD: apparent equilibrium dissociation constant; mAb: monoclonal antibody; R_{max}: maximum response; SPR: surface plasmon resonance.

[00143] Table 3 provides additional amyloid β binding data for h2731, including data on binding dynamics of h2731 to recombinant A β ₁₋₄₂ fibrils and A β ₁₋₂₈ monomer. As shown in Column 2 of Table 3, h2731 binds A β ₁₋₄₂ fibrils and A β ₁₋₂₈ monomer with association constants of $3.72 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ and $1.19 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ respectively. Although aducanumab binds A β fibrils at a faster association rate (ka), the much slower dissociation rate (kd) of h2731 of the disclosure resulted in greater measured avidity (i.e., lower KD*) than aducanumab.

[00144] Off-rate data (kd) are for h2731 shown in Column 3 of Table 3, providing kd values of $2.62 \times 10^{-5} \text{ s}^{-1}$ and $5.95 \times 10^{-4} \text{ s}^{-1}$ for h2731 against A β ₁₋₄₂ fibrils and A β ₁₋₂₈ monomer, respectively. The enhanced relative avidity of h2731 of the disclosure for fibrillar

A β observed by ELISA was confirmed by SPR equilibrium binding kinetics (Column 4 of Table 3), which indicated a 5- to 11-fold greater avidity (apparent K_D) than aducanumab, including 4-7 nM binding affinity for A β ₁₋₂₈ monomer.

[00145] In additional embodiments, the methods of the present disclosure may utilize one or more of several different anti-amyloid β antibodies or fragments thereof. In particular, antibodies suitable for use in methods of the present disclosure possess physiochemical and pharmacological properties, discussed herein, that allow for therapeutically effective dosing using once monthly subcutaneous administration and/or twice monthly subcutaneous administration. Additional exemplary anti-amyloid β antibodies suitable for use in methods of the present disclosure include those in US Patent No. 11,440,953, which is herein incorporated by reference in its entirety.

[00146] In some embodiments, the anti-amyloid β antibody or binding fragments, variant, or derivative binds to A β (or a fragment or variant thereof) with an off rate ($k(\text{off})$) of less than or equal to $5 \times 10^{-2} \text{ sec}^{-1}$, 10^{-2} sec^{-1} , $5 \times 10^{-3} \text{ sec}^{-1}$ or 10^{-3} sec^{-1} . In certain embodiments, the anti-amyloid β antibody or binding fragments, variant, or derivative binds to A β (or a fragment or variant thereof) with an off rate ($k(\text{off})$) of less than or equal to $5 \times 10^{-4} \text{ sec}^{-1}$, 10^{-4} sec^{-1} , $5 \times 10^{-5} \text{ sec}^{-1}$, or 10^{-5} sec^{-1} , $5 \times 10^{-6} \text{ sec}^{-1}$, 10^{-6} sec^{-1} , $5 \times 10^{-7} \text{ sec}^{-1}$ or 10^{-7} sec^{-1} .

[00147] In some embodiments, the anti-amyloid β antibody or binding fragments, variant, or derivative binds to A β (or a fragment or variant thereof) with an on rate ($k(\text{on})$) of greater than or equal to $10^3 \text{ M}^{-1} \text{ sec}^{-1}$, $5 \times 10^3 \text{ M}^{-1} \text{ sec}^{-1}$, $10^4 \text{ M}^{-1} \text{ sec}^{-1}$ or $5 \times 10^4 \text{ M}^{-1} \text{ sec}^{-1}$. In certain embodiments, the anti-amyloid β antibody or binding fragments, variant, or derivative binds to A β (or a fragment or variant thereof) with an on rate ($k(\text{on})$) greater than or equal to $10^5 \text{ M}^{-1} \text{ sec}^{-1}$, $5 \times 10^5 \text{ M}^{-1} \text{ sec}^{-1}$, $10^6 \text{ M}^{-1} \text{ sec}^{-1}$, or $5 \times 10^6 \text{ M}^{-1} \text{ sec}^{-1}$ or $10^7 \text{ M}^{-1} \text{ sec}^{-1}$.

[00148] Anti-A β antibodies or antigen-binding fragments, variants or derivatives thereof, as described herein can also be described or specified in terms of their binding affinity A β . Binding affinities can include those with a dissociation constant or K_d less than $5 \times 10^{-2} \text{ M}$, 10^{-2} M , $5 \times 10^{-3} \text{ M}$, 10^{-3} M , $5 \times 10^{-4} \text{ M}$, 10^{-4} M , $5 \times 10^{-5} \text{ M}$, 10^{-5} M , $5 \times 10^{-6} \text{ M}$, 10^{-6} M , $5 \times 10^{-7} \text{ M}$, 10^{-7} M , $5 \times 10^{-8} \text{ M}$, 10^{-8} M , $5 \times 10^{-9} \text{ M}$, 10^{-9} M , $5 \times 10^{-10} \text{ M}$, 10^{-10} M , $5 \times 10^{-11} \text{ M}$, 10^{-11} M , $5 \times 10^{-12} \text{ M}$, 10^{-12} M , $5 \times 10^{-13} \text{ M}$, 10^{-13} M , $5 \times 10^{-14} \text{ M}$, 10^{-14} M , $5 \times 10^{-15} \text{ M}$, or 10^{-15} M .

[00149] The present disclosure will be more fully described by the following non-limiting examples.

[00150] SEQ ID NO: 1 h2731_VH (Variable Heavy) Amino Acid Sequence

EVQLLES^{GGGLVQ}PGGSLRLSCAASGFTFSNYGMSWVRQAPGKGLEWVASIRSGSGRTYYSDNVKGRF
TISRDN^{SKNTLYLQ}MNSLRAEDTAVYYCVRYDHYSGSSDYWGQGTFLVTVSS

[00151] SEQ ID NO: 2 h2731_VL (Variable Light) Amino Acid Sequence

DVVM^{TQSPLSLPVT}LGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRV^{TNRDT}GVPDRFS
GSGSGTDFTLKISRVEAEDVGVYYCWQGT^HFP^{RS}FGQGTKEIK

[00152] SEQ ID NO: 3: VH CDR1 GFTFSNYGMS

[00153] SEQ ID NO: 4: VH CDR2 SIRSGSGRTYYSDNVKG

[00154] SEQ ID NO: 5: VH CDR3 YDHYSGSSDY

[00155] SEQ ID NO: 6: VL CDR1 KSSQSLLDYDGKTYLN

[00156] SEQ ID NO: 7: VL CDR2 RVTNRDT

[00157] SEQ ID NO: 8: VL CDR3 WQGT^HFP^{RS}

[00158] SEQ ID NO: 9: huIgG1 Constant Amino Acid Sequence

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT^{SV}WNSGALTSGVHTFPAVLQSSGL
YSLSSV^{TV}FPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVF
LFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
SVLTVLHQDWLNGKEYKCKVSNKALPAPIEK^TISKAKGQPREPQVY^{TL}PPSREEMTKNQVSL
TCLVKGFIYPSDIAVEWESNGQPENNYK^{TT}PPVLDSDGSFFLYSKLTVDKSRWQQGNV^FSCSV
MHEALHNHYTQKSLSLSPGK

[00159] SEQ ID NO: 10: huKappa Constant Amino Acid Sequence

RTVAAPS^{VFI}FPSPDEQLKSGTASV^VCLLN^{FY}PREAKVQWKVDNALQSGNSQESVTEQDSK
DSTYSLSS^{TL}TLTSKADYEKHKVYACEVTHQGLSSPVT^KSFNRGEC

[00160] SEQ ID NO: 11: h2731 Complete Heavy Chain Amino Acid Sequence

EVQLLES^{GGGLVQ}PGGSLRLSCAASGFTFSNYGMSWVRQAPGKGLEWVASIRSGSGRTYY
SDNVKGRFTISRDN^{SKNTLYLQ}MNSLRAEDTAVYYCVRYDHYSGSSDYWGQGTFLVTVSSA
STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT^{SV}WNSGALTSGVHTFPAVLQSSG

LYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP
SVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEM
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSDGSFFLYSKLTVDKSRWQ
QGNVFSCSVMHEALHNHYTQKSLSLSPGK

[00161] SEQ ID NO: 12: h2731 Complete Light Chain Amino Acid Sequence

DVVMTQSPLSLPVTLLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLLYRVNTRD
TGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSGQGTQKVEIKRTVAAPSV
FIAPPSSDEQLKSGTASVVCLLNNFYPRQAKVQWKVDNALQSGNSQESVTEQDSKDYSL
SSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC

[00162] SEQ ID NO: 13: h2731_VH (Variable Heavy) Nucleotide Sequence

GAAAGTGCAGCTTCTGGAGAGCGGGGCGGCCTGGTGCAGCCGGGCGGATCCCTGAGACTGTC
CTGTGCCGCGTCCGGTTTTACCTTCTCCAACCTACGGAATGTCATGGGTCCGCCAAGCACCCG
GAAAGGGATTGGAATGGGTGGCTTCGATCCGGTCCGGCTCGGGACGGACCTACTACTCCGAT
AACGTCAAGGGCAGATTCACCTATTAGCCGGGACAAACAGCAAGAATACCCTGTACCTCCAAAT
GAACTCCCTGAGGGCCGAGGACACCGCCGTGTATTACTGCGTGCGCTACGACCACTACTCGG
GTTCTCTGATTACTGGGGACAGGGGACCCTCGTGACTGTGTCAAGC

[00163] SEQ ID NO: 14: h2731_VL (Variable Light) Nucleotide Sequence

GATGTCGTGATGACTCAGTCACCTCTGTCCCTGCCTGTGACCCTTGGGGAACCCGCCTCGAT
CTCGTGCAAGAGCTCCCAGAGCCTGCTCGACTATGATGGAAAGACCTACCTGAACTGGTTGC
TCCAAAAGCCGGGCCAGAGCCCCAGAGGCTGATCTACCGCGTGACCAACCGCGACACCGGG
GTGCCGGACCGGTTCTCCGGATCCGGCAGCGGCACTGACTTCACCCCTGAAAATTTCCAGAGT
GGAAGCCGAGGACGTGGGAGTGTACTACTGTTGGCAGGGTACTCACTTTCCACGGTCCTTCG
GTCAAGGAACCAAGGTCGAGATCAAG

[00164] SEQ ID NO: 15: hulg1 Constant Nucleotide Sequence

GCCAGCACTAAGGGGCCTAGCGTCTTTCCGCTGGCCCCGTCTCCAAGTCCACTTCGGGTGG
AACCGCGGCACTGGGGTGCCTCGTGAAGGACTACTTCCCCGAGCCGGTCACCGTGTCTGGA
ACTCGGGAGCCCTGACCTCCGGAGTGCATACTTTCCCTGCGGTGCTGCAGTCCTCCGGGCTC
TACTCGCTGTCAAGCGTGGTCACCGTCCCGAGCTCATCCCTGGGTACTCAGACCTACATTTG

CAACGTGAACCACAAACCTTCCAACACCAAGGTCGACAAGAAAGTGGAGCCTAAGAGCTGCG
ACAAGACCCACACCTGTCCCCCGTGTCCCGCCCCCTGAGCTGCTGGGCGGCCCCAGCGTGTT
CTCTTCCCGCCTAAGCCGAAGGACACTCTGATGATCTCGAGAACCCCTGAAGTGACCTGTGT
GGTGGTGGATGTGTCCACGAGGATCCGGAAGTGAAGTTCAATTGGTACGTGGACGGAGTGG
AAGTCCATAACGCCAAGACCAAGCCCCGCGAGGAACAGTACAACCTCAACTTACCGGGTGGTG
TCAGTGCTGACCGTGCTGCACCAAGATTGGCTGAACGGGAAGGAGTACAAGTGCAAAGTCTC
CAACAAGGCGCTGCCGGCCCCCATTTGAAAAGACCATCAGCAAGGCTAAGGGCCAGCCCCGGG
AACCACAGGTCTACACCTTGCCCCCTTCCCGGGAGGAAATGACCAAGAACCAAGTGTGCTG
ACGTGCCTGGTCAAGGGCTTTTATCCATCTGACATCGCCGTGGAGTGGGAAAGCAACGGCCA
GCCGGAAAACAACCTACAAGACTACCCCGCCTGTGCTGGACTCCGACGGCTCGTTCTTCCTGT
ATTCCAAGCTCACCGTGGATAAGTCCAGATGGCAGCAGGGCAATGTGTTTCACTGTCAGCGTG
ATGCATGAGGCCCTGCACAACCACTACACTCAGAAATCACTGTCCCTTTCCCCCGGAAAGTA
A

[00165] SEQ ID NO: 16: huKappa Constant Nucleotide Sequence

CGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGG
AACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGA
AGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTACAGAGCAGGACAGCAAG
GACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAA
AGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACA
GGGGAGAGTGTTAA

[00166] SEQ ID NO: 17: h2731 Complete Heavy Chain Nucleotide Sequence

GAGGTGCAGCTCTTGGAGTCTGGGGGAGGCTTGGTGCAGCCAGGGGGGTCCCTAAGACTCTC
CTGTGCAGCCTCTGGATTACCTTCTCCAACCTATGGCATGTCTTGGGTCCGCCAGGCTCCAG
GGAAGGGACTGGAGTGGGTGCTTCTATTGCTCCGGTAGTGGTAGGACATACTACTCAGAT
AACGTGAAGGGCCGGTTCACAATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAAT
GAACAGCCTGAGAGCCGAGGATACGGCCGTTTATTACTGTGTGCGCTACGACCATTAATCTG
GATCCTCTGACTACTGGGGCCAAGGCACCCCTTGTACAGTCTCCTCAGCCTCCACCAAGGGC
CCATCGGTCTTCCCCCTGGCACCCCTCTTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGG
CTGCCTTGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTGCTGGAACCTCAGGCGCCCTGA
CCAGCGGCGTGACACCTTCCCGGCTGTCTACAGTCTCAGGACTCTACTCCCTCAGCAGC
GTGGTGAAGTGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAA
GCCCAGCAACACCAAGGTGGATAAGAAGGTTGAGCCCAAATCTTGTGACAAAACCTCACACAT

GCCCACCGTGCCACAGCACCTGAACTCCTGGGGGACCGTCAGTCTTCCTGTTCCCCCAAAA
 CCCAAGGACACCCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAG
 CCACGAAGACCCAGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCA
 AGACAAAGCCGAGAGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCCTC
 CTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCC
 AGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAAACCACAGGTGTACA
 CCCTGCCCTCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAA
 GGCTTCTATCCCAGCGACATCGCCGTCGAGTGGGAGAGCAATGGGCAGCCGGAGAACAATA
 CAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTATTTCCAAGCTCACCG
 TGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTG
 CACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCCGGGAAA

[00167] SEQ ID NO: 18: h2731 Complete Light Chain Nucleotide Sequence

GATGTTGTGATGACCCAGTCCCCACTCTCTTTGCCCCGTACCCTTGGAGAACCTGCCTCCAT
 CTCTTGCAAGTCAAGTCAGAGCCTCTTAGATTACGATGGAAAGACATATTTGAATTGGTTGC
 TGCAGAAGCCAGGCCAGTCTCCACAGCGCCTAATCTATCGGGTGACCAACCGGGACACTGGA
 GTCCCTGACAGGTTCAAGTGGCAGTGGATCAGGGACAGATTTACACTGAAAATCAGCAGAGT
 GGAGGCTGAGGATGTGGGAGTTTATTATTGCTGGCAAGGCACACATTTTCCGCGCTCTTTTCG
 GACAGGGGACCAAGGTGGAAATAAAACGAAGTGTGGCTGCACCATCTGTCTTCATCTTCCCG
 CCATCTGATGAGCAGCTTAAGTCCGGAAGTGTAGCGTTGTGTGCCTGCTGAATAAATTCTA
 TCCCAGAGAGGCCAAAGTACAGTGAAGGTGGATAACGCCCTCCAATCGGGAAACTCCCAGG
 AGAGCGTCACAGAGCAGGACAGCAAAGACAGCACCTACAGCCTCAGCAGCACCCCTGACGCTG
 AGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAG
 CTCGCCCCGTACAAAGAGCTTCAACAGGGGAGAGTGT

Pharmaceutical Compositions

[00168] In some embodiments, the anti-A β antibody or fragment thereof is administered as part of a pharmaceutical composition. Several methods of preparing pharmaceutical compositions comprising anti-A β antibodies, or antigen-binding fragments, variants, or derivatives thereof to a subject in need thereof are known. In some embodiments, the anti-A β antibodies or antigen-binding fragments thereof are formulated for parenteral administration. In example embodiments, the anti-A β antibodies or antigen-binding fragments thereof are formulated for subcutaneous injection.

[00169] For the purposes of the disclosure, a pharmaceutically effective amount of an anti-A β antibody, or antigen-binding fragment, variant, or derivative thereof, means an amount sufficient to achieve effective binding to a target and to achieve a benefit, e.g., reduce brain amyloid plaques without affecting vascular amyloid, or minimizes the occurrence of microhemorrhage during chronic dosing of the anti-A β antibody or antigen-binding fragment thereof. In some embodiments, an anti-A β antibody or antigen-binding fragment, variant, or derivative thereof crosses the blood-brain barrier in an effective amount to reduce brain amyloid plaques.

[00170] The amount of an anti-A β antibody, or fragment, variant, or derivative thereof, to be combined with the carrier materials to produce a single dosage form will vary depending upon the subject treated and the particular mode of administration. Dosage regimens also can be adjusted to provide the optimum desired response (e.g., a therapeutic or prophylactic response).

[00171] The present disclosure provides several pharmaceutically effective amounts of anti-A β antibodies or antigen-binding fragment thereof (e.g., about 205 mg to about 400 mg and additional amounts and/or ranges disclosed herein). The present disclosure therefore provides the use of pharmaceutical compositions comprising these amounts in the methods disclosed herein. Such pharmaceutically effective amounts can be administered as a single dose, multiple doses or over an established period of time in an infusion. In example embodiments, these pharmaceutical compositions are administered as a single dose. In example embodiments, these pharmaceutical compositions are administered as a single subcutaneous injection.

[00172] For example, in some aspects, the present disclosure provides a method of treating Alzheimer's disease in a subject, comprising administering to the subject a pharmaceutical composition comprising from about 205 mg to about 400 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks.

[00173] In some aspects, the present disclosure provides a method of reducing amyloid plaque in a subject, comprising administering to the subject a pharmaceutical composition comprising from about 205 mg to about 400 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks.

[00174] In some aspects, the present disclosure provides a method of converting a subject from amyloid positive to amyloid negative, comprising administering to the subject a pharmaceutical composition comprising from about 205 mg to about 400 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks (e.g., once about every 4 weeks).

[00175] For example, in some aspects, the present disclosure provides a method of treating Alzheimer's disease in a subject, comprising administering to the subject a pharmaceutical composition comprising from about 45 mg to about 200 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks. (In some aspects, the present disclosure provides a method of treating Alzheimer's disease in a subject, comprising administering to the subject a pharmaceutical composition comprising from about 100 mg to about 200 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks.

[00176] For example, in some aspects, the present disclosure provides a method of treating Alzheimer's disease in a subject, comprising administering to the subject a pharmaceutical composition comprising from about 45 mg to about 200 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof once about every 2 weeks. (In some aspects, the present disclosure provides a method of treating Alzheimer's disease in a subject, comprising administering to the subject a pharmaceutical composition comprising from about 100 mg to about 200 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof once about every 2 weeks.

[00177] In some aspects, the present disclosure provides a method of reducing amyloid plaque in a subject, comprising administering to the subject a pharmaceutical composition comprising from about 45 mg to about 200 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks. In some aspects, the present disclosure provides a method of reducing amyloid plaque in a subject, comprising administering to the subject a pharmaceutical composition comprising from about 100 mg to about 200 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks.

[00178] In some aspects, the present disclosure provides a method of converting a subject from amyloid positive to amyloid negative, comprising administering to the subject a

pharmaceutical composition comprising from about 45 mg to about 200 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks. In some aspects, the present disclosure provides a method of converting a subject from amyloid positive to amyloid negative, comprising administering to the subject a pharmaceutical composition comprising from about 100 mg to about 200 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks.

[00179] In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 295 mg to about 305 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks. In some embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 345 mg to about 355 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks. In example embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 395 mg to about 405 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks. In example embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 195 mg to about 205 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks.

[00180] In example embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 250 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks. In example embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 300 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks. In example embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 350 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks. In example embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 400 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks. In example embodiments, these pharmaceutical compositions are administered as a single subcutaneous injection once about every 3-5 weeks (e.g., once about every 4 weeks).

[00181] In example embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 250 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 4 weeks. In example embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 300 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 4 weeks. In example embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 350 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 4 weeks. In example embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 400 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 4 weeks. In example embodiments, these pharmaceutical compositions are administered as a single subcutaneous injection once about every 4 weeks.

[00182] In example embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 70 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks (e.g., once about every 2 weeks). In example embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 70 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 2 weeks.

[00183] In example embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 200 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks (e.g., once about every 2 weeks). In example embodiments, the method comprises administering to the subject a pharmaceutical composition comprising about 200 mg of the anti-amyloid β antibody or an antigen-binding fragment thereof once about every 2 weeks.

[00184] In another aspect, the present disclosure features administering an antibody with a pharmaceutical carrier as a pharmaceutical composition. Alternatively, the antibody can be administered to a patient by administering a polynucleotide encoding at least one antibody chain. The polynucleotide is expressed to produce the antibody chain in the patient. Optionally, the polynucleotide encodes heavy and light chains of the antibody. The polynucleotide is expressed to produce the heavy and light chains in the patient. In exemplary embodiments, the patient is monitored for level of administered antibody in the blood of the patient.

[00185] In some embodiments, the pharmaceutical composition comprises a pharmaceutically effective amount of an anti-A β antibody or fragment thereof and a pharmaceutically acceptable diluent. As discussed herein, anti-A β antibodies, or antigen-binding fragments, variants, or derivatives thereof can be formulated so as to facilitate administration and promote stability of the active agent. In certain embodiments, pharmaceutical compositions in accordance with the present disclosure comprise a pharmaceutically acceptable, non-toxic, sterile carrier such as physiological saline, non-toxic buffers, preservatives and the like.

[00186] The pharmaceutical compositions used in this disclosure comprise pharmaceutically acceptable carriers, including, e.g., ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol, and wool fat.

[00187] Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal and the like. In many cases, isotonic agents can be included, for example, sugars, polyalcohols or salts in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[00188] Preparations for parenteral administration (e.g., intravenous or subcutaneous injection) include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives can also be present such as, for example,

antimicrobials, antioxidants, chelating agents, and inert gases and the like. Furthermore, the pharmaceutical composition of the disclosure can comprise further agents such as dopamine or psychopharmacologic drugs, depending on the intended use of the pharmaceutical composition.

[00189] Therapeutic compositions for use in methods of the present disclosure are typically substantially pure from undesired contaminants. This means that the agent is typically at least 50% w/w pure of interfering proteins and other contaminants arising from its production or purification but does not exclude the possibility that the agent is combined with an excess of pharmaceutical acceptable carrier(s) or other vehicle intended to facilitate its use. Sometimes monoclonal antibodies (or other therapeutic agents) are at least 60%, 70%, 80%, 90%, 95% or 99% w/w pure of interfering proteins and contaminants from production or purification.

Pharmacokinetic Endpoints

[00190] The present disclosure provides dosing regimens for anti-amyloid β antibodies that are designed to achieve drug exposure profiles in subjects that are suitable for the clearance of amyloid plaque and/or treatment of neurodegenerative diseases (e.g., Alzheimer's disease). To this end, the present disclosure provides methods of administering anti-amyloid β antibodies to achieve particular pharmacokinetic endpoints in subjects, including, for example, values of the following parameters that are suitable for plaque clearance and/or treatment of the disease: average concentration over the dosing interval (C_{ave}), steady state concentration over the dosing interval (C_{ss}), maximum concentration over the dosing interval (C_{max}), area under the concentration-time curve from time zero to infinity $AUC_{0-\infty}$, and the area under the concentration-time curve for dosing interval (AUC_{0-tau}). In various embodiments, these pharmacokinetic endpoints can be assessed in a number of bodily fluids collected from the subject, including, for example, whole blood, blood serum, blood plasma, and/or CSF.

Maximum Drug Concentration (C_{max})

[00191] Thus, in another aspect, the present disclosure provides a method of treating Alzheimer's disease in a subject, comprising subcutaneously administering to the subject a dose of an anti-A β antibody sufficient to achieve a C_{max} value (steady state C_{max} value) of about 30 $\mu\text{g/mL}$ to about 60 $\mu\text{g/mL}$. In another aspect, the present disclosure provides a

method of reducing amyloid plaque in a subject, comprising subcutaneously administering to the subject a dose of an anti-A β antibody sufficient to achieve a C_{max} value of about 30 $\mu\text{g/mL}$ to about 60 $\mu\text{g/mL}$. In another aspect, the present disclosure provides a method of converting a subject from amyloid positive to amyloid negative, comprising subcutaneously administering to the subject a dose of an anti-A β antibody sufficient to achieve a C_{max} value of about 30 $\mu\text{g/mL}$ to about 60 $\mu\text{g/mL}$. In example embodiments, the anti-A β antibody comprises a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

[00192] In some embodiments, treating comprises achieving a C_{max} of the anti-amyloid β antibody or antigen binding fragment thereof in the subject of about 30 $\mu\text{g/mL}$ to about 60 $\mu\text{g/mL}$ (e.g., about 35 $\mu\text{g/mL}$ to about 60 $\mu\text{g/mL}$, about 40 $\mu\text{g/mL}$ to about 60 $\mu\text{g/mL}$, about 45 $\mu\text{g/mL}$ to about 60 $\mu\text{g/mL}$, about 30 $\mu\text{g/mL}$ to about 55 $\mu\text{g/mL}$, about 35 $\mu\text{g/mL}$ to about 55 $\mu\text{g/mL}$, about 30 $\mu\text{g/mL}$ to about 50 $\mu\text{g/mL}$, or about 35 $\mu\text{g/mL}$ to about 50 $\mu\text{g/mL}$). In some embodiments, the C_{max} value is a steady state serum C_{max} value. In some embodiments, the C_{max} value is a steady state plasma C_{max} value.

Average Drug Concentration (C_{ave})

[00193] In another aspect, the present disclosure provides a method of treating Alzheimer's disease in a subject, comprising subcutaneously administering to the subject a dose of an anti-A β antibody sufficient to achieve a serum C_{ave} value of about 20 $\mu\text{g/mL}$ to about 40 $\mu\text{g/mL}$. In another aspect, the present disclosure provides a method of reducing amyloid plaque in a subject, comprising subcutaneously administering to the subject a dose of an anti-A β antibody sufficient to achieve a serum C_{ave} value of about 20 $\mu\text{g/mL}$ to about 40 $\mu\text{g/mL}$. In another aspect, the present disclosure provides a method of converting a subject from amyloid positive to amyloid negative, comprising subcutaneously administering to the subject a dose of an anti-A β antibody sufficient to achieve a serum C_{ave} value of about 20 $\mu\text{g/mL}$ to about 40 $\mu\text{g/mL}$. In example embodiments, the anti-A β antibody comprises a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

In some embodiments, treating comprises achieving a C_{max} of the anti-amyloid β antibody or antigen binding fragment thereof in the subject of about 20 $\mu\text{g/mL}$ to about 40 $\mu\text{g/mL}$ (e.g., about 23 $\mu\text{g/mL}$ to about 40 $\mu\text{g/mL}$, about 25 $\mu\text{g/mL}$ to about 40 $\mu\text{g/mL}$, about 28 $\mu\text{g/mL}$ to

about 40 µg/mL, about 30 µg/mL to about 40 µg/mL, about 35 µg/mL to about 40 µg/mL, about 20 µg/mL to about 38 µg/mL, about 23 µg/mL to about 38 µg/mL, about 25 µg/mL to about 38 µg/mL, about 28 µg/mL to about 38 µg/mL, about 20 µg/mL to about 35 µg/mL, about 20 µg/mL to about 30 µg/mL, or about 25 µg/mL to about 30 µg/mL). In some embodiments, the C_{ave} value is a steady state serum C_{ave} value. In some embodiments, the C_{ave} value is a steady state plasma C_{ave} value.

Area Under the Concentration-Time Curve for the Dosing Interval ($AUC_{0-\tau}$)

[00194] In another aspect, the present disclosure provides a method of treating Alzheimer's disease in a subject, comprising subcutaneously administering to the subject a dose of an anti-A β antibody sufficient to achieve an area under the concentration-time curve for the dosing interval ($AUC_{0-\tau}$) value of about 15,000 hr*µg/mL to about 30,000 hr*µg/mL. In another aspect, the present disclosure provides a method of reducing amyloid plaque in a subject, comprising subcutaneously administering to the subject a dose of an anti-A β antibody sufficient to achieve a $AUC_{0-\tau}$ value of about 15,000 hr*µg/mL to about 30,000 hr*µg/mL. In another aspect, the present disclosure provides a method of converting a subject from amyloid positive to amyloid negative, comprising subcutaneously administering to the subject a dose of an anti-A β antibody sufficient to achieve a $AUC_{0-\tau}$ value of about 15,000 hr*µg/mL to about 30,000 hr*µg/mL. In example embodiments, the anti-A β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

[00195] In some embodiments, treating comprises achieving an $AUC_{0-\tau}$ value (steady state $AUC_{0-\tau}$ value) of the anti-amyloid β antibody or antigen binding fragment thereof in the subject is about 15,000 hr*µg/mL to about 30,000 hr*µg/mL (e.g., 16,000 hr*µg/mL to about 30,000 hr*µg/mL, 18,000 hr*µg/mL to about 30,000 hr*µg/mL, 20,000 hr*µg/mL to about 30,000 hr*µg/mL, 22,000 hr*µg/mL to about 30,000 hr*µg/mL, or 25,000 hr*µg/mL to about 30,000 hr*µg/mL). In some embodiments, treating comprises achieving an $AUC_{0-\tau}$ value (steady state $AUC_{0-\tau}$ value) of the anti-amyloid β antibody or antigen binding fragment thereof in the subject is about 15,000 hr*µg/mL to about 25,000 hr*µg/mL (e.g., 16,000 hr*µg/mL to about 25,000 hr*µg/mL, 18,000 hr*µg/mL to about 25,000 hr*µg/mL, 20,000 hr*µg/mL to about 25,000 hr*µg/mL, or 22,000 hr*µg/mL to about 25,000 hr*µg/mL). In some embodiments, the $AUC_{0-\tau}$ value is a steady state serum $AUC_{0-\tau}$ value. In some embodiments, the $AUC_{0-\tau}$ value is a steady state plasma $AUC_{0-\tau}$ value.

Amyloid Plaque Clearance

[00196] The present disclosure further provides the use of anti-amyloid β antibodies to reduce amyloid plaque in a subject. Amyloid plaque reduction has been shown to correlate with slowing of cognitive decline during treatment with anti-amyloid β antibodies. *See, e.g.,* M. Shi, et al., *Impact of Anti-amyloid- β Monoclonal Antibodies on the Pathology and Clinical Profile of Alzheimer's Disease: A Focus on Aducanumab and Lecanemab*, 14 FRONT. AGING NEUROSCI. 1 (2022); C.H. van Dyck, et al., *Lecanemab in Early Alzheimer's Disease* 388 N. ENGL. J. MED. 9 (2023). Indeed, the FDA granted accelerated approval to both aducanumab and lecanemab based on plaque reduction data from clinical trials.

[00197] Thus, in another aspect, the present disclosure provides a method of treating Alzheimer's disease in a subject having amyloid plaque, the method comprising:

- (a) administering to the subject a composition comprising from about 205 mg to about 400 mg (e.g., 250 mg, 300 mg, 350 mg, or 400 mg) of an anti-amyloid β antibody once about every 4 weeks, the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12; and
- (b) reducing the amyloid plaque in the subject.

[00198] Thus, in another aspect, the present disclosure provides a method of treating Alzheimer's disease in a subject having amyloid plaque, the method comprising:

- (a) administering to the subject a composition comprising from about 45 mg to about 400 mg (e.g., 70 mg, 100 mg, 150 mg, or 200 mg) of an anti-amyloid β antibody once about every 2 weeks, the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12; and
- (b) reducing the amyloid plaque in the subject.

[00199] Detection of brain amyloid plaques is conducted by methods known to one of skill in the art. In some embodiments, the method further comprises assessing the amyloid by Positron Emission Tomography (PET) imaging. In some embodiments, the amyloid reduction is determined by PET. PET imaging agents are known to one of skill in the art and include ¹⁸F-florbetapir, florbetaben F18, and flutemetamol F18. In some embodiments, amyloid plaque, as measured by PET, is quantified by a composite standard uptake value ratio

(SUVR). In some embodiments, amyloid plaque, as measured by PET, is calculated using the Centiloid scale. In some embodiments, change in amyloid plaque burden is measured by change in SUVR over time. In some embodiments, change in amyloid plaque burden is measured by change in Centiloid over time. See, Navitsky M, Joshi AD, Kennedy I, et al., Standardization of amyloid quantitation with florbetapir standardized uptake value ratios to the Centiloid scale, *Alzheimers Dement* 2018 14:1565-71 and Oishi AD, Pontecorvo MJ, Lu M, et al., A Semiautomated Method for Quantification of F 18 Florbetapir PET Images, *J Nucl Med.* 2015; 56(11):1736-41.

[00200] Thus, in another aspect, the present disclosure provides a method of reducing amyloid plaque in a subject, the method comprising:

- (a) administering to the subject a composition comprising from about 205 mg to about 400 mg of an anti-amyloid β antibody once about every 4 weeks, the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12; and
- (b) reducing the amyloid plaque in the subject, as determined by PET.

[00201] In another aspect, the present disclosure provides a method of treating Alzheimer's disease in a subject, comprising:

- (a) observing a first amyloid plaque value obtained from a first PET scan of the subject;
- (b) subcutaneously administering to the subject a composition comprising from about 205 mg to about 400 mg of an anti-amyloid β antibody once about every 3-5 weeks, the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12; or
- (c) observing a second amyloid plaque value obtained from a second PET scan of the subject; and
- (d) comparing the first amyloid plaque value to the second amyloid plaque value, thereby observing a reduction in amyloid plaque in the subject.

[00202] In another aspect, the present disclosure provides a method of treating Alzheimer's disease in a subject having amyloid plaque, the method comprising:

- (a) performing a first PET scan on the subject, thereby observing a first amyloid plaque value;
- (b) administering to the subject a composition comprising from about 205 mg to about 400 mg of an anti-amyloid β antibody once about every 3-5 weeks; the anti-amyloid β

antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12;

- (c) performing a second PET scan on the subject, thereby observing a second amyloid plaque value; and
- (d) comparing the first amyloid plaque value to the second amyloid plaque value, thereby observing a reduction in amyloid plaque in the subject.

[00203] In another aspect, the present disclosure provides a method of reducing amyloid plaque in a subject, comprising:

- (a) observing a first amyloid plaque value obtained from a first PET scan of the subject;
- (b) subcutaneously administering to the subject a composition comprising from about 205 mg to about 400 mg of an anti-amyloid β antibody once about every 3-5 weeks, the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12; or
- (c) observing a second amyloid plaque value obtained from a second PET scan of the subject; and
- (d) comparing the first amyloid plaque value to the second amyloid plaque value, thereby observing a reduction in amyloid plaque in the subject.

[00204] In another aspect, the present disclosure provides a method of reducing amyloid plaque in a subject having amyloid plaque, the method comprising:

- (a) performing a first PET scan on the subject, thereby observing a first amyloid plaque value;
- (b) administering to the subject a composition comprising from about 205 mg to about 400 mg of an anti-amyloid β antibody once about every 3-5 weeks; the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12;
- (c) performing a second PET scan on the subject, thereby observing a second amyloid plaque value; and
- (d) comparing the first amyloid plaque value to the second amyloid plaque value, thereby observing a reduction in amyloid plaque in the subject.

[00205] In another aspect, the present disclosure provides a method of reducing amyloid plaque in a subject having amyloid plaque, the method comprising:

- (a) performing a first PET scan on the subject, thereby observing a first amyloid plaque value;
- (b) administering to the subject a composition comprising from about 45 mg to about 200 mg of an anti-amyloid β antibody once about every 2 weeks; the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12;
- (c) performing a second PET scan on the subject, thereby observing a second amyloid plaque value; and
- (d) comparing the first amyloid plaque value to the second amyloid plaque value, thereby observing a reduction in amyloid plaque in the subject.

[00206] In some embodiments, treating comprises a reduction in amyloid beta plaque (i.e., brain amyloid beta plaque) in the subject. In some embodiments, the treatment results in the subject achieving a reduction of amyloid beta plaque. In some embodiments, the subject achieves a reduction of amyloid beta plaque as assessed by PET.

[00207] In some embodiments, the reduction of amyloid beta plaque comprises a reduction by at least about 10 centiloids (e.g., at least about 15 centiloids, at least about 20 centiloids, at least about 25 centiloids, or at least about 30 centiloids). In some embodiments, the reduction of amyloid beta plaque comprises a reduction by at least about 30 centiloids after 6 months of treatment (e.g., at least about 35 centiloids, at least about 40 centiloids, at least about 45 centiloids, at least about 50 centiloids, at least about 55 centiloids, or at least about 60 centiloids). In some embodiments, the reduction of amyloid beta plaque is achieved after about 6 months of treatment. In some embodiments, the reduction of amyloid beta plaque is achieved after about 12 months of treatment. In some embodiments, the reduction of amyloid beta plaque is achieved after about 18 months of treatment.

[00208] In some embodiments, the reduction of amyloid beta plaque comprises a reduction by about 10 centiloids to about 90 centiloids (e.g., about 20 centiloids to about 90 centiloids, about 30 centiloids to about 90 centiloids, about 40 centiloids to about 90 centiloids, or about 50 centiloids to about 90 centiloids). In some embodiments, the reduction of amyloid beta plaque comprises a reduction by about 10 centiloids to about 80 centiloids (e.g., about 20 centiloids to about 80 centiloids, about 30 centiloids to about 80 centiloids, about 40 centiloids to about 80 centiloids, or about 50 centiloids to about 80 centiloids). In some embodiments, the reduction of amyloid beta plaque comprises a reduction by about 10

centiloids to about 70 centiloids (e.g., about 20 centiloids to about 70 centiloids, about 30 centiloids to about 70 centiloids, about 40 centiloids to about 70 centiloids, or about 50 centiloids to about 70 centiloids). In some embodiments, the reduction of amyloid beta plaque comprises a reduction by about 10 centiloids to about 60 centiloids (e.g., about 20 centiloids to about 60 centiloids, about 30 centiloids to about 60 centiloids, about 40 centiloids to about 60 centiloids, or about 50 centiloids to about 60 centiloids). In some embodiments, the reduction of amyloid beta plaque is achieved after about 6 months of treatment. In some embodiments, the reduction of amyloid beta plaque is achieved after about 12 months of treatment. In some embodiments, the reduction of amyloid beta plaque is achieved after about 18 months of treatment.

[00209] In some embodiments, the reduction of amyloid beta plaque comprises a reduction by at least about 10 centiloids after about 6 months of treatment (e.g., at least about 15 centiloids, at least about 20 centiloids, at least about 25 centiloids, or at least about 30 centiloids). In some embodiments, the reduction of amyloid beta plaque comprises a reduction by at least about 30 centiloids after about 6 months of treatment (e.g., at least about 35 centiloids, at least about 40 centiloids, at least about 45 centiloids, or at least about 50 centiloids). In some embodiments, the reduction of amyloid beta plaque comprises a reduction by about 10 centiloids, about 15 centiloids, about 20 centiloids, about 25 centiloids, about 30 centiloids, about 35 centiloids, about 40 centiloids, about 45 centiloids, about 50 centiloids, about 55 centiloids, about 60 centiloids, about 65 centiloids, about 70 centiloids, about 75 centiloids, about 80 centiloids, about 85 centiloids, about 90 centiloids or about 95 centiloids. In some embodiments, the reduction of amyloid beta plaque is achieved after about 6 months of treatment. In some embodiments, the reduction of amyloid beta plaque is achieved after about 12 months of treatment. In some embodiments, the reduction of amyloid beta plaque is achieved after about 18 months of treatment.

[00210] In some embodiments, the reduction of amyloid beta plaque comprises a reduction by about 10 centiloids to about 80 centiloids after about 6 months of treatment (e.g., about 20 centiloids to about 80 centiloids, about 30 centiloids to about 80 centiloids, about 10 centiloids to about 60 centiloids, or about 10 centiloids to about 50 centiloids). In some embodiments, the reduction of amyloid beta plaque comprises a reduction by about 30 centiloids to about 70 centiloids after about 6 months of treatment (e.g., about 40 centiloids to

about 70 centiloids, about 50 centiloids to about 70 centiloids, about 30 centiloids to about 60 centiloids, or about 30 centiloids to about 50 centiloids).

[00211] In some embodiments, the reduction of amyloid beta plaque comprises a reduction by at least about 25 centiloids after about 12 months of treatment (e.g., at least about 35 centiloids, at least about 40 centiloids, at least about 45 centiloids, or at least about 50 centiloids). In some embodiments, the reduction of amyloid beta plaque comprises a reduction by at least about 40 centiloids after about 12 months of treatment (e.g., at least about 45 centiloids, at least about 50 centiloids, at least about 55 centiloids, or at least about 60 centiloids).

[00212] In some embodiments, the reduction of amyloid beta plaque comprises a reduction by about 20 centiloids to about 90 centiloids after about 12 months of treatment (e.g., about 30 centiloids to about 90 centiloids, about 40 centiloids to about 90 centiloids, about 20 centiloids to about 80 centiloids, or about 20 centiloids to about 70 centiloids). In some embodiments, the reduction of amyloid beta plaque comprises a reduction by about 45 centiloids to about 80 centiloids after about 12 months of treatment (e.g., about 50 centiloids to about 80 centiloids, about 55 centiloids to about 80 centiloids, about 45 centiloids to about 75 centiloids, or about 45 centiloids to about 70 centiloids).

[00213] In some embodiments, the reduction of amyloid beta plaque comprises a reduction by at least about 35 centiloids after about 18 months of treatment (e.g., at least about 40 centiloids, at least about 45 centiloids, at least about 50 centiloids, or at least about 55 centiloids). In some embodiments, the reduction of amyloid beta plaque comprises a reduction of at least about 50 centiloids after about 18 months of treatment (e.g., at least about 55 centiloids, at least about 60 centiloids, at least about 65 centiloids, or at least about 70 centiloids).

[00214] In some embodiments, the reduction of amyloid beta plaque comprises a reduction by about 30 centiloids to about 100 centiloids after about 18 months of treatment (e.g., about 40 centiloids to about 100 centiloids, about 50 centiloids to about 100 centiloids, about 30 centiloids to about 95 centiloids, or about 30 centiloids to about 90 centiloids). In some embodiments, the reduction of amyloid beta plaque comprises a reduction by about 50 centiloids to about 85 centiloids after about 18 months of treatment (e.g., about 65 centiloids

to about 85 centiloids, about 70 centiloids to about 85 centiloids, about 50 centiloids to about 80 centiloids, or about 50 centiloids to about 75 centiloids).

[00215] In some embodiments, the reduction in amyloid beta plaque comprises a reduction of at least about 30% (e.g., at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, or at least about 70%). In some embodiments, the reduction of amyloid beta plaque comprises a reduction of about 30% to about 100% (e.g., about 40% to about 100%, about 50% to about 100%, about 60% to about 100%, or about 70% to about 100%). In some embodiments, reduction of amyloid beta plaque in the subject comprises a reduction of about 30% to about 90% (e.g., about 40% to about 90%, about 50% to about 90%, about 60% to about 90%, or about 70% to about 90%). In some embodiments, the reduction of amyloid beta plaque comprises a reduction of about 30% to about 80% (e.g., about 40% to about 80%, about 50% to about 80%, or about 60% to about 80%). In some embodiments, the reduction of amyloid beta plaque comprises a reduction of about 30% to about 70% (e.g., about 40% to about 70%, or about 50% to about 70%). In some embodiments, the reduction of amyloid beta plaque comprises a reduction of about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%. In some embodiments, the reduction of amyloid beta plaque is achieved after about 6 months of treatment. In some embodiments, the reduction of amyloid beta plaque is achieved after about 12 months of treatment. In some embodiments, the reduction of amyloid beta plaque is achieved after about 18 months of treatment.

[00216] In some embodiments, the reduction in amyloid beta plaque comprises a reduction of at least about 20% after about 6 months of treatment (e.g., at least 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, or at least about 50%). In some embodiments, the reduction of amyloid beta plaque comprises a reduction of about 20% to about 90% after about 6 months of treatment (e.g., about 30% to about 90%, about 40% to about 90%, or about 50% to about 90%). In some embodiments, reduction of amyloid beta plaque in the subject comprises a reduction of about 30% to about 70% after about 6 months of treatment (e.g., about 35% to about 70%, about 40% to about 70%, about 30% to about 65%, or about 30% to about 60%).

[00217] In some embodiments, the reduction in amyloid beta plaque comprises a reduction of at least about 30% after about 12 months of treatment (e.g., at least 35%, at least about

40%, at least about 45%, at least about 50%, at least about 55%, or at least about 60%). In some embodiments, the reduction of amyloid beta plaque comprises a reduction of about 30% to about 100% after about 12 months of treatment (e.g., about 40% to about 100%, about 50% to about 100%, or about 50% to about 90%). In some embodiments, reduction of amyloid beta plaque in the subject comprises a reduction of about 60% to about 100% after about 12 months of treatment (e.g., about 65% to about 100%, about 70% to about 100%, about 65% to about 95%, or about 65% to about 90%).

[00218] In some embodiments, the reduction in amyloid beta plaque comprises a reduction of at least about 40% after about 18 months of treatment (e.g., at least 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, or at least about 70%). In some embodiments, the reduction of amyloid beta plaque comprises a reduction of about 40% to about 100% after about 18 months of treatment (e.g., about 50% to about 100%, about 60% to about 100%, or about 50% to about 90%). In some embodiments, reduction of amyloid beta plaque in the subject comprises a reduction of about 65% to about 100% after about 18 months of treatment (e.g., about 70% to about 100%, about 75% to about 100%, about 65% to about 95%, or about 65% to about 90%).

[00219] In some embodiments, the reduction in amyloid beta plaque comprises a reduction of amyloid beta plaque in the subject comprises a reduction by at least 0.05 PET Standard Update Value Ratio ("SUVr") units (e.g., at least 0.10 PET SUVr units, at least 0.15 PET SUVr units, at least 0.20 PET SUVr units, or at least 0.25 PET SUVr unit). In some embodiments, the reduction of amyloid beta plaque comprises a reduction by at least 0.25 PET SUVr units (e.g., at least 0.30 PET SUVr units, at least 0.35 PET SUVr units, or at least 0.40 PET SUVr units, or at least 0.45 PET SUVr). In some embodiments, the reduction of amyloid beta plaque comprises a reduction by at least 0.50 PET SUVr units (e.g., at least 0.55 PET SUVr units, at least 0.60 PET SUVr units, or at least 0.65 PET SUVr units, or at least 0.70 PET SUVr units).

[00220] In some embodiments, the reduction of amyloid beta plaque occurs after about 6 months (e.g., after about 24 weeks) of treatment. In some embodiments, the reduction of amyloid beta plaque occurs after about 12 months (e.g., after about 48 weeks) of treatment. In some embodiments, the reduction of amyloid beta plaque occurs after about 18 months (e.g., after about 72 weeks) of treatment. In some embodiments, the reduction of amyloid beta plaque is compared to baseline (amyloid plaque values prior to beginning treatment).

[00221] In some embodiments, the treatment results in the subject achieving amyloid negative status. In some embodiments, the subject is converted from amyloid positive status to amyloid negative status.

[00222] In another aspect, the present disclosure provides a method of converting a subject from amyloid positive to amyloid negative, the method comprising:

- (a) administering to the subject a composition comprising from about 205 mg to about 400 mg of an anti-amyloid β antibody once about every 4 weeks, the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12; and
- (b) reducing the amyloid plaque in the subject, such that the subject is amyloid negative, as determined by PET.

[00223] In another aspect, the present disclosure provides a method of converting a subject from amyloid positive to amyloid negative, the method comprising:

- (a) administering to the subject a composition comprising from about 45 mg to about 200 mg of an anti-amyloid β antibody once about every 2 weeks, the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12; and
- (b) reducing the amyloid plaque in the subject, such that the subject is amyloid negative, as determined by PET.

[00224] In some embodiments, treating comprises at least about 10% (e.g., at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 45%, or at least about 50%) of subjects being converted from amyloid positive status to amyloid negative status. In some embodiments, treating comprises about 10% to about 90% (e.g., about 20% to about 90%, about 30% to about 90%, about 40% to about 90%, about 10% to about 80%, about 10% to about 70%, or about 10% to about 60%) of subjects being converted from amyloid positive status to amyloid negative status. In some embodiments, treating comprises about 30% to about 80% (e.g., about 40% to about 80%, about 50% to about 80%, about 30% to about 70%, or about 30% to about 60%) of subjects being converted from amyloid positive status to amyloid negative status. In some embodiments, the achievement of amyloid negative status occurs after about 6 months of treatment. In some embodiments, the achievement of amyloid negative status occurs after about 12 months of

treatment. In some embodiments, the achievement of amyloid negative status occurs after about 18 months of treatment.

[00225] In some embodiments, treating comprises at least about 5% (e.g., at least about 10%, at least about 15%, at least about 20%, or at least about 25%) of subjects being converted from amyloid positive status to amyloid negative status after about 6 months. In some embodiments, treating comprises about 5% to about 50% (e.g., about 10% to about 50%, about 20% to about 50%, about 10% to about 45%, or about 10% to about 40%) of subjects being converted from amyloid positive status to amyloid negative status after about 6 months. In some embodiments, treating comprises about 10% to about 40% (e.g., about 15% to about 40%, about 20% to about 40%, about 10% to about 35%, or about 10% to about 30%) of subjects being converted from amyloid positive status to amyloid negative status after about 6 months.

[00226] In some embodiments, treating comprises at least about 15% (e.g., at least about 20%, at least about 25%, at least about 30%, or at least about 35%) of subjects being converted from amyloid positive status to amyloid negative status after about 12 months. In some embodiments, treating comprises about 15% to about 80% (e.g., about 20% to about 80%, about 30% to about 80%, about 15% to about 75%, or about 15% to about 70%) of subjects being converted from amyloid positive status to amyloid negative status after about 12 months. In some embodiments, treating comprises about 30% to about 60% (e.g., about 35% to about 60%, about 40% to about 60%, about 30% to about 55%, or about 30% to about 50%) of subjects being converted from amyloid positive status to amyloid negative status after about 12 months.

[00227] In some embodiments, treating comprises at least about 25% (e.g., at least about 30%, at least about 35%, at least about 40%, or at least about 45%) of subjects being converted from amyloid positive status to amyloid negative status after about 18 months. In some embodiments, treating comprises about 25% to about 100% (e.g., about 30% to about 100%, about 40% to about 100%, about 25% to about 95%, or about 25% to about 90%) of subjects being converted from amyloid positive status to amyloid negative status after about 18 months. In some embodiments, treating comprises about 40% to about 80% (e.g., about 45% to about 80%, about 50% to about 80%, about 40% to about 75%, or about 40% to about 70%) of subjects being converted from amyloid positive status to amyloid negative status after about 18 months.

[00228] In some embodiments, amyloid beta plaque in a subject is measured about 3 months, 6 months, 12 months, and/or 18 months after treatment is initiated. In some embodiments, amyloid beta plaque in a subject is measured, about once a month, about once every 3 months, about once every 6 months, or about once every year after treatment is initiated.

Cognitive Decline

[00229] Cognitive decline is a feature of neurodegenerative diseases, including Alzheimer's disease. Initial stages of cognitive decline in Alzheimer's disease may manifest as forgetfulness. However, as the disease progresses, the effects of cognitive decline more broadly affect the patient's life and behavior, affecting executive function, language skills, and visuospatial processing. This, in turn, may lead to issues with decision-making, problem-solving, and independent living. Finally, Alzheimer's disease culminates in significant cognitive decline and dementia, leading to impairments in basic memory retention affected and simple daily activities.

[00230] Recent evidence has demonstrated a link between reduction in brain amyloid load and slowing of cognitive decline in Alzheimer's patients. See, e.g., Y. Zhang, et al., *Amyloid β -based therapy for Alzheimer's disease: challenges, successes and future*, 8 SIGNAL TRANSDUCTION AND TARGETED THERAPY 248 (2023). For example, a phase 2 clinical trial of donanemab showed both a reduction in brain amyloid load and a slowing of cognitive decline. More recently, a phase 3 clinical trial of lecanemab also reported both a reduction in brain amyloid plaque and a slowing of cognitive decline. In light of this recent clinical evidence, a causal link is emerging between clearing amyloid plaque and slowing cognitive decline in patients.

[00231] In some embodiments, treating Alzheimer's disease may include the slowing, halting, and/or reversing of cognitive decline in subjects. In some embodiments, treating comprises slowing, halting, and/or reversing a decline in cognitive function. In another embodiment, treating comprises a reduction (e.g., slowing or halting) in a decline in cognitive function. In another embodiment, treating comprises slowing a decline in cognitive function. In another embodiment, treating comprises halting a decline in cognitive function. In another embodiment, treating comprises reversing a decline in cognitive function.

[00232] Various cognitive assessment tools are available and can be used in conjunction with methods of the present disclosure, including, for example, Mini-Mental State Exam (MMSE), Alzheimer's Disease Composite Score (ADCOMS), Alzheimer's Disease Assessment Scale - Cognitive (ADAS-COG) (including, for example a 14-item Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog14)), Activities of Daily Living for Mild Cognitive Impairment (ADCS-ADL-MCI), Clinician Interview-Based Impression (CIBI), Neurological Test Battery (NTB), Disability Assessment for Dementia (DAD), Clinical Dementia Rating-sum of boxes (CDR-SB), Neuropsychiatric Inventory (NPI). In some embodiments, treating comprises slowing, halting and/or reversing of cognitive decline as assessed using one of these cognitive assessment tools. In another embodiment, methods of the present disclose further comprise monitoring the subject by at least one of these cognitive assessment tools.

[00233] In some embodiments, cognitive function is measured by at least one of the following CRD-SB, ADAS-Cog14, ADCOMS, and ADCS MCI-ADL. In some embodiments, cognitive function is measured using CRD-SB. In some embodiments, cognitive function is measured using ADAS-Cog14. In some embodiments, cognitive function is measured using ADCOMS. In some embodiments, cognitive function is measured using ADCS MCI-ADL.

[00234] In some embodiments, cognitive function is measured on multiple occasions, such as before administering the dosage and at week 4, week 16, 6 months, and/or 1 year after administering the dosage. In some embodiments, cognitive function is measured about 3 months, 6 months, 12 months, and/or 18 months after treatment is initiated. In some embodiments, cognitive function is measured, about once a month, about once every 3 months, about once every 6 months, or about once every year after treatment is initiated.

Biomarker Modulation

[00235] In another aspect, the present disclosure provides a method of modulating a biomarker in a subject, comprising administering to the subject a composition comprising from about 205 mg to about 400 mg of an anti-amyloid β antibody once about every 3-5 weeks, the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12. In another embodiment, the present disclosure provides a method of modulating a biomarker in a subject, comprising

administering to the subject a composition comprising from about 100 mg to about 200 mg of an anti-amyloid β antibody twice about every 3-5 weeks (e.g., once about every 2 weeks), the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

Amyloid Beta Ratio

[00236] In some embodiments, the biomarker comprises the ratio of $A\beta_{42}/A\beta_{40}$ in the subject. The $A\beta_{42}/A\beta_{40}$ ratio (e.g., the ratio of amyloid β_{42} to amyloid β_{40} in CSF and/or blood) has been demonstrated to be associated with well-established indicators of AD, including amyloid PET and CSF biomarkers, with lower $A\beta_{42}/A\beta_{40}$ ratios (e.g., an $A\beta_{42}/A\beta_{40}$ ratio <0.150) corresponding to higher amyloid plaque burden. See, e.g., C. Delaby, et al., *The $A\beta_{1-42}/A\beta_{1-40}$ ratio in CSF is more strongly associated to tau markers and clinical progression than $A\beta_{1-42}$ alone*, 14 ALZHEIMER'S RESEARCH & THERAPY 20 (2022); X. Chang, et al., *A Review of Application of $A\beta_{42}/A\beta_{40}$ Ratio in Diagnosis and Prognosis of Alzheimer's Disease*, 90 J. ALZHEIMER'S DISEASE 495 (2002). For example, total plasma $A\beta_{42}/A\beta_{40}$ ratio has demonstrated value in the identification of individuals suffering from mild cognitive impairment (MCI), in the prediction of progression to dementia, and in the detection of underlying AD pathology revealed by FDG-PET, Amyloid-PET and CSF biomarkers. See, e.g., V. Perez-Grijalba, et al., *Plasma $A\beta_{42}/A\beta_{40}$ Ratio Detects Early Stages of Alzheimer's Disease and Correlates with CSF and Neuroimaging Biomarkers in the AB255 Study*, 6 J. PREVENTION OF ALZHEIMER'S DISEASE 34, (2019). Thus, changes in $A\beta_{42}/A\beta_{40}$ ratio may be useful in following individuals throughout the course of treatment, e.g., with an increase in the $A\beta_{42}/A\beta_{40}$ ratio signaling a reduction in amyloid plaque burden during treatment.

[00237] Further, an emerging trend in the treatment of Alzheimer disease (AD) is the shift of the therapeutic target population from people with dementia or MCI to cognitively healthy people at risk of AD. This population of at-risk people is difficult to identify if β -amyloid ($A\beta$) positivity is the primary criterion for eligibility in clinical trials. Using this metric, the screening rate of failure (SRF) rises to $>70\%$ in this population. See, e.g., J. D. Doecke, et al., *Total $A\beta_{42}/A\beta_{40}$ ratio in plasma predicts amyloid-PET status, independent of clinical AD diagnosis*, 94 NEUROLOGY 1580 (2020). $A\beta_{42}/A\beta_{40}$ ratio may be useful in identifying this population and following them throughout treatment (e.g., prophylactic treatment).

[00238] Thus, the present disclosure provides method of modulating a ratio of A β 42/40 in a subject, comprising administering to the subject a composition comprising from about 205 mg to about 400 mg of an anti-amyloid β antibody once every 3-5 weeks, the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12. In some embodiments, the modulating comprises increasing the ratio of A β 42/40 in the subject.

[00239] In another aspect, the present disclosure provides a method of increasing a ratio of A β 42/40 in a subject, comprising administering to the subject a composition comprising from about 205 mg to about 400 mg of an anti-amyloid β antibody once about every 3-5 weeks, the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

[00240] In another aspect, the present disclosure provides a method of increasing a ratio of A β 42/40 in a subject, comprising administering to the subject a composition comprising from about 100 mg to about 200 mg of an anti-amyloid β antibody twice about every 3-5 weeks (e.g., once about every 2 weeks), the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

[00241] A method of increasing a ratio of A β 42/40 in a subject, the method comprising:

- (a) administering to the subject a composition comprising from about 205 mg to about 400 mg of an anti-amyloid β antibody once about every 3-5 weeks, the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12; and
- (b) determining an A β 42/40 ratio value derived from a sample collected from the subject, wherein the A β 42/40 ratio value demonstrates an increase in the ratio of A β 42/40 in the subject.

[00242] A method of increasing a ratio of A β 42/40 in a subject, the method comprising:

- (a) administering to the subject a composition comprising from about 100 mg to about 200 mg of an anti-amyloid β antibody twice about every 3-5 weeks, the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12; and

- (b) determining an A β 42/40 ratio value derived from a sample collected from the subject, wherein the A β 42/40 ratio value demonstrates an increase in the ratio of A β 42/40 in the subject.

[00243] In some embodiments, the A β 42/40 ratio value increases at least about 10% (e.g., about 15%, about 20%, about 25%, about 30%, about 35%, or about 40%). In some embodiments, the A β 42/40 ratio value increases about 10% to about 150% (e.g., about 20% to about 150%, about 30% to about 150%, about 10% to about 120%, about 20% to about 120%, about 30% to about 120%, about 10% to about 100%, or about 20% to about 100%). In some embodiments, the A β 42/40 ratio value increases about 25% to about 100% (e.g., about 30% to about 100%, about 35% to about 100%, about 40% to about 100%, about 25% to about 90%, about 25% to about 80%, about 35% to about 90%, or about 35% to about 80%). In some embodiments, the A β 42/40 ratio value increases compared to baseline.

Phospho-Tau

[00244] Phospho-tau (p-tau) species have emerged as the most promising biomarkers of Alzheimer's disease. *See, e.g., S. Janelidze, et al., Head-to-head comparison of 10 plasma phospho-tau assays in prodromal Alzheimer's disease.* 19 *BRAIN* 1591-1601 (2023). Hyperphosphorylation of tau is a hallmark of Alzheimer's disease pathology, leading to self-aggregation of p-tau bundles in diseased subjects. *See, e.g., C.-X. Gong, K. Iqbal, Hyperphosphorylation of Microtubule-Associated Protein Tau: A Promising Therapeutic Target for Alzheimer Disease,* 15 *CURRENT MED. CHEM.* 2331 (2009). Phospho-tau levels (e.g., in blood) correlate with amyloid beta (A β) pathology and disease severity, as well as with established cerebrospinal fluid (CSF) and neuroimaging biomarkers. *See, e.g., Kac, P.R., et al. Diagnostic value of serum versus plasma phospho-tau for Alzheimer's disease.* 14 *ALZ RES THERAPY* 65 (2022). Phospho-tau further differentiates biomarker-positive AD dementia from other dementias as well as A β -negative controls, thereby demonstrating specificity to AD versus non-AD neurodegenerative diseases. Thus, p-tau levels can inform clinical diagnosis and eligibility for therapies, including treatment with anti-amyloid β antibodies. Further, p-tau species have the capacity to help expand access to AD diagnostics worldwide, as p-tau species can be measured in blood samples, which, in contrast to cerebrospinal fluid, do not require lumbar puncture to acquire. *See, e.g., F. Gonzalez-Ortiz, et al., Plasma phospho-tau in Alzheimer's disease: towards diagnostic and therapeutic trial applications.* 18 *MOL. NEURODEGENERATION* 18 (2023).

[00245] Several phospho-tau species have been identified as biomarkers for Alzheimer's disease, including p181-tau, p212-tau, p217-tau, p231-tau, and p235-tau. For example, plasma values of p-tau181, p-tau217 and p-tau231 have demonstrated associations with in vivo pathological hallmarks and autopsy-verified diagnosis. Several of these p-tau species are highly accurate at detecting brain amyloidosis and predicting whether patients will progress to cognitive impairment and neurodegeneration. Further, p-tau levels have been shown to change in subjects undergoing anti-amyloid β therapy, correlating with amyloid clearance. *See, e.g., F. Gonzalez-Ortiz (2023).*

[00246] In some aspects, the present disclosure provides a method of modulating an amount of phospho-tau in a subject, comprising administering to the subject a composition comprising from about 205 mg to about 400 mg of an anti-amyloid β antibody thereof once about every 3-5 weeks, the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12. In some aspects, the present disclosure provides a method of modulating an amount of phospho-tau in a subject, comprising administering to the subject a composition comprising from about 100 mg to about 200 mg of an anti-amyloid β antibody thereof twice about every 3-5 weeks (e.g., once about every 2 weeks), the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12. In some embodiments, the modulating comprises increasing the amount of phospho-tau in the subject.

[00247] Thus, in some embodiments, the biomarker comprises a phospho-tau value. In some embodiments, the phospho-tau value comprises at least one of the following: a p181-tau value, a p212-tau value, p217-tau value, a p231-tau value, and a p235-tau value. In some embodiments, the phospho-tau value comprises a p181-tau value. In some embodiments, the phospho-tau value comprises a p212-tau value. In some embodiments, the phospho-tau value comprises a p217-tau value. In some embodiments, the phospho-tau value comprises a p231-tau value. In some embodiments, the phospho-tau value comprises a p235-tau value.

[00248] In some embodiments, the phospho-tau value decreases about 5% to about 50% (e.g., about 10% to about 50%, about 15% to about 50%, about 20% to about 50%, about 10% to about 45%, about 10% to about 40%, or about 10% to about 35%). In some embodiments, the phospho-tau value decreases about 10% to about 30% (e.g., about 15% to about 30%, about 20% to about 30%, about 10% to about 25%, about 15% to about 25%, or

about 20% to about 30%). In some embodiments, the phospho-tau value decreases compared to baseline.

[00249] In some embodiments, the p181-tau value decreases about 5% to about 50% (e.g., about 10% to about 50%, about 15% to about 50%, about 20% to about 50%, about 10% to about 45%, about 10% to about 40%, or about 10% to about 35%). In some embodiments, the p181-tau value decreases about 10% to about 30% (e.g., about 15% to about 30%, about 20% to about 30%, about 10% to about 25%, about 15% to about 25%, or about 20% to about 30%). In some embodiments, the p181-tau value decreases compared to baseline.

In some embodiments, the p217-tau value decreases about 5% to about 50% (e.g., about 10% to about 50%, about 15% to about 50%, about 20% to about 50%, about 10% to about 45%, about 10% to about 40%, or about 10% to about 35%). In some embodiments, the p217-tau value decreases about 10% to about 30% (e.g., about 15% to about 30%, about 20% to about 30%, about 10% to about 25%, about 15% to about 25%, or about 20% to about 30%). In some embodiments, the p217-tau value decreases compared to baseline.

Amyloid Related Imaging Abnormalities (ARIA)

[00250] Treatment with amyloid β -targeted passive immunotherapy with (including, for example, aducanumab (Aduhelm), lecanemab, donanemab, and gantenerumab) comes with a significant risk of amyloid-related imaging abnormality (ARIA). *See, e.g., M. Filippi, et al., Amyloid-Related Imaging Abnormalities and β -Amyloid-Targeting Antibodies A Systematic Review*. 79 JAMA NEUROL. 291 (2022). ARIA is the most common side effect of anti-amyloid β antibodies, and can be classified as ARIA-E (cerebral edema, involving the breakdown of the tight endothelial junctions of the blood-brain barrier and subsequent accumulation of fluid) and ARIA-H (cerebral microhemorrhages (mH), small haemorrhages on the brain that are often accompanied by hemosiderosis). ARIA-E can be associated with acute neuroinflammation and overwhelming of the perivascular clearance systems, and ARIA-H may be related to vascular amyloid clearance and subsequent weakening and/or rupture of small blood vessels. *See, e.g., H. Hampel, et al., Amyloid-related imaging abnormalities (ARIA): radiological, biological and clinical characteristics*, 146 BRAIN 4414 (2023).

[00251] While often asymptomatic and detected only via MRI, in some instances ARIA may be symptomatic. For example, ARIA has been shown to include a number of side

effects, such as headache, worsening confusion, dizziness, visual disturbances, nausea, and seizures. Further, at least one fatality related to ARIA-E during aducanumab treatment and at least one fatality due to ARIA-H during donanemab treatment has been reported to date. *See, e.g., C.G. Withington & R.S. Turner, Amyloid-Related Imaging Abnormalities With Anti-amyloid Antibodies for the Treatment of Dementia Due to Alzheimer's Disease*. 13 FRONTIERS IN NEUROLOGY 1 (2022). The risk of ARIA-H increases with age and cerebrovascular disease, and ARIA rates are generally higher in ApoE4 homozygous patients (ApoE4 carriers) compared to either ApoE4 non-carriers or ApoE4 heterozygous patients. Furthermore, increased risk of ARIA-E has been observed at treatment initiation and corresponds with higher dosage and with >4 of microhemorrhages on a baseline MRI.

[00252] In some embodiments, the treatment comprises a risk of ARIA-E that is less than about 70% (e.g., less than about 65%, less than about 60%, less than about 55%, or less than about 50%). In some embodiments, the treatment comprises a risk of ARIA-E that is less than about 45% (e.g., less than about 40%, less than about 35%, less than about 30%, less than about 25%, or less than about 20%). In some embodiments, the treatment comprises a risk of ARIA-E that is less than about 15% (e.g., less than about 14%, less than about 13%, less than about 12%, less than about 11%, or less than about 10%).

[00253] In some embodiments, the treatment results in less than about 45% (e.g., less than about 40%, less than about 35%, less than about 30%, less than about 25%, or less than about 20%) of subjects experiencing symptomatic ARIA-E. In some embodiments, the treatment results less than about 15% (e.g., less than about 14%, less than about 13%, less than about 12%, less than about 11%, or less than about 10%) of subjects experiencing symptomatic ARIA-E. In some embodiments, the treatment results in less than about 10% (e.g., less than about 9%, less than about 8%, less than about 7%, less than about 6%, or less than about 5%) of subjects experiencing symptomatic ARIA-E.

[00254] In some embodiments, the risk of ARIA-E is a risk of severe ARIA-E. In some embodiments, the risk of ARIA-E is a risk of moderate+ ARIA-E. In some embodiments, the risk of ARIA-E is a risk of moderate ARIA-E. In some embodiments, the risk of ARIA-E is a risk of mild+ ARIA-E. In some embodiments, the risk of ARIA-E is a risk of mild ARIA-E. In some embodiments, the risk of ARIA-E comprises a risk of FLAIR hyper-intensity at more than one location, wherein each FLAIR location has an extent of 5-10 cm. In some embodiments, the risk of ARIA-E comprises a risk of FLAIR hyper-intensity at one location,

wherein the FLAIR location has an extent of 5-10 cm. In some embodiments, the risk of ARIA-E comprises a risk of FLAIR hyper-intensity at more than one location, wherein each FLAIR location has an extent of less than 5 cm, and wherein each FLAIR location is confined to the sulcus, cortex, and/or subcortical white matter. In some embodiments, the risk of ARIA-E comprises a risk of FLAIR hyper-intensity at one location, wherein the FLAIR location has an extent of less than 5 cm, and wherein the FLAIR location is confined to the sulcus, cortex, and/or subcortical white matter.

[00255] In some embodiments, the subject is an APOE4 homozygous subject and the treatment comprises a risk of ARIA-E that is less than about 75% (e.g., less than about 70%, less than about 65%, less than about 60%, less than about 55%, or less than about 50%) in the APOE4 homozygous subject. In some embodiments, the subject is an APOE4 homozygous subject, and the treatment comprises a risk of symptomatic ARIA-E that is less than about 30% (e.g., less than about 25%, less than about 20%, or less than about 15%) in the APOE4 homozygous subject

[00256] In some embodiments, the subject is an APOE4 heterozygous subject or an APOE4 negative subject and the treatment comprises a risk of ARIA-E that is less than about 45% (e.g., less than about 40%, less than about 35%, less than about 30%, less than about 25%, or less than about 20%) in the APOE4 heterozygous subject or the APOE4 negative subject. In some embodiments, the subject is an APOE4 heterozygous subject or an APOE4 negative subject and the treatment comprises a risk of symptomatic ARIA-E that is less than about 15% (e.g., less than about 14%, less than about 13%, less than about 12%, less than about 11%, or less than about 10%) in the APOE4 heterozygous subject or the APOE4 negative subject. In some embodiments, the risk of ARIA-E is the risk after about 6 months (e.g., about 24 weeks) of treatment. In some embodiments, the risk of ARIA-E is the risk after about 12 months (e.g., about 48 weeks) of treatment. In some embodiments, the risk of ARIA-E is the risk after about 18 months (e.g., about 72 weeks) of treatment.

[00257] In some embodiments, the treatment comprises a risk of ARIA-H that is less than about 25% (e.g., less than about 22%, less than about 20%, less than about 18%, or less than about 16%). In some embodiments, the treatment comprises a risk of ARIA-H that is less than about 15% (e.g., less than about 14%, less than about 13%, less than about 12%, less than about 11%, or less than about 10%).

[00258] In some embodiments, the risk of ARIA-H is a risk of severe ARIA-H. In some embodiments, the risk of ARIA-H is a risk of moderate ARIA-H. In some embodiments, the risk of ARIA-H is a risk of mild ARIA-H. In some embodiments, the risk of ARIA-H comprises a risk of ≤ 4 new incidents of microhemorrhages and/or a risk of ≤ 1 focal area of superficial siderosis. In some embodiments, the risk of ARIA-H comprises a risk of ≤ 9 new incidents of microhemorrhages and/or a risk of ≤ 2 focal area of superficial siderosis.

[00259] In some embodiments, the risk of ARIA-H is the risk after about 6 months (e.g., about 24 weeks) of treatment. In some embodiments, the risk of ARIA-H is the risk after about 12 months (e.g., about 48 weeks) of treatment. In some embodiments, the risk of ARIA-H is the risk after about 18 months (e.g., about 72 weeks) of treatment.

[00260] In some embodiments, the treatment results in less than about 25% (e.g., less than about 22%, less than about 20%, less than about 18%, or less than about 16%) of subjects experiencing ARIA-H. In some embodiments, the treatment results in less than about 15% (e.g., less than about 14%, less than about 13%, less than about 12%, less than about 11%, or less than about 10%, less than about 9%, less than about 8%, less than about 7%, less than about 6%, or less than about 5%) of subjects experiencing ARIA-H.

[00261] In some embodiments, the ARIA-E and/or ARIA-H levels (e.g., % of subjects experiencing ARIA-E and/or ARIA-H) are the ARIA-E and/or ARIA-H levels after about 6 months (e.g., about 24 weeks) of treatment. In some embodiments the ARIA-E and/or ARIA-H levels are the ARIA-E and/or ARIA H levels after about 12 months (e.g., about 48 weeks) of treatment. In some embodiments, the ARIA-E and/or ARIA-H are the ARIA-E and/or ARIA H levels after about 18 months (e.g., about 72 weeks) of treatment.

[00262] In some embodiments, the subject does not experience symptomatic ARIA, as assessed by Magnetic Resonance Imaging (MRI). In some embodiments, the subject does not experience symptomatic ARIA-E, as assessed by MRI. In some embodiments, the subject does not experience symptomatic ARIA-H, as assessed by MRI.

Treatment Amenable Patients

[00263] The present disclosure includes the treatment and/or prevention of amyloidogenic diseases, including Alzheimer's disease, by administration of the antibodies, fragments and pharmaceutical compositions of the present disclosure. Further, the present disclosure

provides the use of the anti-amyloid β antibodies to generate a beneficial therapeutic response in a patient (e.g., induction of phagocytosis of A β , reduction of plaque burden, inhibition of plaque formation, reduction of neuritic dystrophy, neutralization of soluble, toxic A β species, improving cognitive function, and/or reversing, treating or preventing cognitive decline. The disclosure is also directed to the use of the disclosed antibodies and fragments in the manufacture of a medicament for the treatment or prevention of an amyloidogenic disease using, for example, dosing regimens of the present disclosure. For example, the use of the disclosed antibodies and fragments in the manufacture of a medicament for the treatment or prevention of an Alzheimer's by administering (e.g., subcutaneously administering) to a patient a therapeutically effective amount (e.g., from 200 mg to 400 mg about once every 4 weeks, 300 mg about once every 4 weeks, 350 mg about once every 4 weeks, 400 mg about once every 4 weeks, or 200 mg about once every 2 weeks) of the anti-amyloid β antibody or fragment thereof. Such methods are useful for preventing or treating Alzheimer's disease in human patients.

[00264] Patients amenable to treatment include individuals at risk of disease but not showing symptoms, as well as patients presently showing symptoms. In the case of Alzheimer's disease, potentially anyone who lives long enough is at risk of Alzheimer's disease. Thus, the present methods include administering prophylactically to the general population without the need for any assessment of the risk of the subject patient. The present methods are especially useful for individuals who have a known genetic risk of Alzheimer's disease. Such individuals include those having relatives who have experienced this disease, and those whose risk is determined by analysis of genetic or biochemical markers. Genetic markers of risk toward Alzheimer's disease include mutations in the APP gene, particularly mutations at position 717 and positions 670 and 671 referred to as the Hardy and Swedish mutations, respectively. Other markers of risk are mutations in the presenilin genes, PS1 and PS2, and ApoE4, family history of AD, hypercholesterolemia or atherosclerosis. Individuals presently suffering from Alzheimer's disease can be recognized from characteristic dementia, as well as the presence of risk factors described above. In addition, a number of diagnostic tests are available for identifying individuals who have AD. These include measurement of CSF tau and A β 42 levels. Elevated tau and decreased A β 42 levels signify the presence of AD. Individuals suffering from Alzheimer's disease can also be diagnosed by ADRDA criteria as discussed in the Examples section.

[00265] Treatment in asymptomatic patients can begin at any age (e.g., 10, 20, 30). Usually, however, it is not necessary to begin treatment until a patient reaches 40, 50, 60, or 70. Treatment typically entails multiple dosages over a period of time. Treatment can be monitored by assaying antibody levels over time. If the response falls, a booster dosage is indicated. In the case of potential Down's syndrome patients, treatment can begin antenatally by administering therapeutic agent to the mother or shortly after birth.

APOE4 Status

[00266] Subjects carrying the apolipoprotein E ϵ 4 allele (APOE4) are at increased risk of ARIA during treatment with anti-amyloid therapies. *See, e.g., C. Dagostin, et al., Efficacy of anti-amyloid- β monoclonal antibody therapy in early Alzheimer's disease: a systematic review and meta-analysis. NEUROLOGICAL SCIENCES (2023).* Subjects homozygous for APOE4 are at highest risk, due in part to their increased burden of aggregated β amyloid in cerebral microvessels. Furthermore, ongoing research suggests that, during treatment, APOE4 carriers exhibit a larger perivascular A β clearance, leading to greater vascular permeability and extravasation of fluid and erythrocytes, thereby resulting higher in ARIA-E and ARIA-H rates. *See, e.g., M. Roytman, et al., Amyloid-Related Imaging Abnormalities: An Update. 220 AM. J. ROENTGENOLOGY 562 (2023).*

[00267] In some embodiments, the subject is an APOE4 heterozygous subject or an APOE4 negative subject. In some embodiments, the subject is an APOE4 homozygous subject. In some embodiments, the subject is an APOE4 heterozygous subject. In some embodiments, the subject is an APOE4 negative subject (non-carrier).

In Vivo Detection

[00268] In another aspect, the disclosure provides methods for detecting amyloid plaques and deposits in a patient having or at risk of developing an amyloidogenic disease. Such methods are useful for diagnosing or confirming amyloidogenic disease or susceptibility to it. For example, the methods can be used in patients with dementia symptoms, wherein observation of abnormal amyloid deposits likely indicates Alzheimer's disease. The methods can also be used in asymptomatic patients. The presence of abnormal deposits of amyloid indicates susceptibility to future symptomatic disease.

[00269] In some embodiments, the method comprises administering to a subject/patient an antibody or fragment thereof of the disclosure and detecting the antibody or fragment thereof bound to A β .

[00270] Antibody and/or antibody fragments thereof can be administered by any suitable means that results in delivery to the tissue to be visualized, e.g., administered directly into the brain by intravenous injection into the patient's body or by intracranial injection. Dosage of the antibody and/or fragment thereof can comprise a therapeutic dose, subtherapeutic dose or a supratherapeutic dose. In some embodiments the antibody or fragment thereof is labeled, comprising a fluorescent label, a paramagnetic label, or a radioactive label. The choice of label depends on the means of detection. For example, fluorescent labels are suitable for visual detection. The use of paramagnetic labels is suitable for tomographic detection without surgical intervention. In some embodiments, the radioactive label is detected using positron emission tomography (PET) or single-photon emission computed tomography (SPECT).

[00271] In another aspect, the disclosure provides methods for measuring the efficacy of treatment in a subject being treated for an amyloidogenic disease. In some embodiments, a first level of amyloid plaque in a subject is measured prior to treatment by administering an antibody or fragment thereof of the disclosure and detecting a first amount of the antibody or fragment thereof bound to A β in the subject. A treatment can then be administered to the subject, followed by measuring a second level of amyloid plaque in the subject, and detecting the antibody or fragment thereof bound to A β in the subject. In some embodiments, a decrease in the level of amyloid plaque indicates a positive response to treatment, and in some embodiments, no change in the level of amyloid plaque or a small increase in amyloid plaque indicates a positive response to treatment. In some embodiments, levels of amyloid plaque can be measured utilizing the methods of detecting amyloid plaques described herein.

[00272] In some embodiments, diagnosis of an amyloidogenic disease can be performed, for example, by comparing the number, size, and/or intensity of labeled positions from a measured first level (i.e., baseline) to a subsequent second level of amyloid plaque in a subject. An increase over time indicates disease progression, no change indicates, and fewer or less intense amyloid plaques over time indicates remission.

[00273] Agents of the disclosure can optionally be administered in combination with other agents that are at least partly effective in treatment of amyloidogenic disease. In the case of

Alzheimer's and Down's syndrome, in which amyloid deposits occur in the brain, agents of the disclosure can also be administered in conjunction with other agents that increase passage of the agents of the disclosure across the blood-brain barrier.

EXAMPLES

[00274] The following examples have been included to illustrate modes disclosed herein. Certain aspects of the following examples are described in terms of techniques and procedures found or contemplated by the present co-inventors to work well in the practice disclosed herein. In light of the present disclosure and the general level of skill in the art, those of skill appreciate that the following examples are intended to be exemplary only and that numerous changes, modifications, and alterations may be employed without departing from the scope of the disclosure.

Example 1. Reducing amyloid plaques in patients

[00275] To reduce amyloid plaques, which has been associated with inhibiting, reducing, and/or reversing the symptoms of Alzheimer's disease, a pharmaceutically effective amount of an anti-A β antibody (or antigen-binding fragment thereof) is administered to the patients, such as one or more of the antibodies described herein.

[00276] Patients: Individuals that are suspected of having or have been diagnosed with an amyloid plaque-associated disease, such as Alzheimer's disease, are selected for treatment with an anti-A β antibody.

[00277] Treatment: Patients are administered 300 mg of anti-A β antibody h2731 subcutaneously once about every 4 weeks. Patients are administered 350 mg of anti-A β antibody h2731 subcutaneously once about every 4 weeks. Patients are administered 400 mg of anti-A β antibody h2731 subcutaneously once about every 4 weeks. Patients are administered 200 mg of anti-A β antibody h2731 subcutaneously once about every 2 weeks.

[00278] Plaque reduction and improvement in symptoms of Alzheimer's disease can be measured as described herein.

[00279] A patient with Alzheimer's disease administered 300 mg, 350 mg, or 400 mg of anti-A β antibody h2731 subcutaneously once about every 4 weeks is treated by reduction in amyloid plaque burden, measured by PET imaging. Alternatively, a patient with Alzheimer's

disease administered 200 mg of anti-A β antibody h2731 subcutaneously once about every 2 weeks is treated by reduction in amyloid plaque burden, measured by PET imaging. A patient is further treated by slowing of cognitive decline, measured using methods described herein.

Example 2. Phase 1 single ascending dose study to evaluate the safety, tolerability, immunogenicity, and pharmacokinetics of h2731

[00280] This example describes a phase 1, randomized, double-blind, placebo-controlled, single ascending dose (SAD) study to evaluate the safety, tolerability, and immunogenicity, of h2731 at doses of 200 mg and 400 mg. The purposes of this study is to characterize the plasma pharmacokinetics (PK) profile of h2731 in healthy volunteers (HV) and patients who have AD, and specifically AD patients who have parenchymal amyloid load confirmed by molecular imaging. AD subjects will be required to meet the National Institute on Aging and Alzheimer's Association (NIA-AA) research criteria and guidelines for AD (McKhann, 2011) or mild cognitive impairment (MCI) due to AD (Albert, 2011).

Study Rational

[00281] Preclinical studies in transgenic mice that generate a surplus of A β demonstrated that antibodies targeting A β N-terminus are able to enter the brain and decrease amyloid deposits in brain tissue and cerebral vasculature (Bard, 2000). Clinical evidence shows that monoclonal antibodies directed towards N-terminus amyloid are able to remove and reduce deposition of A β aggregates from the brain, and attenuate cognitive decline (Sevigny, 2016; Swanson, 2021; Aduhelm USPI, 2021).

[00282] Preclinical studies show that h2731 removed A β plaques rapidly and robustly by enhancing microglial-mediated clearance mechanisms. See, e.g., US Patent No. 11,440,953. These data suggest that h2731 has the potential to slow clinical decline in patients with AD. Doses of 200 mg and 400 mg for Phase 1 clinical testing is based on CNS fractional occupancy modeled from predictions of clinical exposure at these doses.

Study Objectives

[00283] The primary objective of the study is to evaluate the safety and tolerability of h2731 when administered as a single dose, including (1) general safety, tolerability, and

immunogenicity in all subjects and (2) target-related safety and tolerability in subjects with confirmed presence of parenchymal amyloid.

[00284] A secondary objective of the study is to characterize the PK profile of h2731 and cerebrospinal fluid (CSF) PK profile of h2731 after SC administration as a single dose.

Study Design

[00285] Figure 1 is a schematic representation of the study plan. The study will comprise at least three dose cohorts of subjects with biologically confirmed AD (AD Cohort 1, AD Cohort 2, and AD Cohort 3). The study will further comprise two healthy volunteer ("HV") cohorts (HV Cohort 1 and HV Cohort 2). These five cohorts include the following: AD Cohort 1 (70 mg), AD Cohort 2 (200 mg), AD Cohort 3 (400 mg), HV Cohort 1 (70 mg), and HV Cohort 2 (200 mg), each of which will be dosed subcutaneously ("SC") with their respective dose.

[00286] Following initial on-site observation, subjects will return for four follow-up visits over approximately 12 weeks during which safety assessments and PK collections will be completed. Selected cohorts (HV Cohort A and HV Cohort 2) may additionally undergo CSF collection by lumbar puncture at Days 3 and 29. MRI scans will be taken on day zero for all subjects, and additional MRI scans will be taken on days 29 and 85 for AD cohorts (AD Cohort 1, AD Cohort 2, and AD Cohort 3) to assess ARIA rates.

Endpoints

[00287] Primary endpoints will include:

- Safety and tolerability based on adverse event ("AE") reporting (incidence of AEs, SAEs, and h2731-related AEs), ECGs, clinical laboratory tests, vital signs, and physical examinations
- Immunogenicity measured by the confirmed presence of ADAs in plasma
- Amyloid-related imaging abnormalities (ARIA-H and ARIA-E) and other emergent radiological findings

[00288] Secondary endpoints may include

- Plasma PK of h2731
- CSF PK of h2731

- C_{obs} of h2731 at each sampling time

Inclusion Criteria

[00289] Each cohort will contain approximately eight subjects with body mass indices (BMI) between 18.0 and 32.0 kg/m².

[00290] AD subjects will be selected according to inclusion criteria that include the following:

- (a) have a confirmed or suspected diagnosis of AD based on either probable AD with evidence of the AD pathophysiological process according to National Institute on Aging and Alzheimer's Association (NIA-AA) criteria (McKhann et al., *Alzheimers Dement.*, 7(3):264-9, 2011) or high likelihood of AD according to NIA-AA criteria (Albert et al., *Alzheimers Dement.*, 7(3):270-79, 2011);
- (b) have gradual and progressive change in memory function for ≥ 6 months reported by subject or study partner;
- (c) a screening Mini-Mental State Examination (MMSE) score ≥ 18 ; and
- (d) evidence of AD pathological process, as confirmed on amyloid PET scan.

Exclusion Criteria

[00291] Subjects will be selected based on exclusion criteria that include the following. Subjects must not meet any of the exclusion criteria, including the following criteria:

- (a) Impaired coagulation (prothrombin time $1.2 \times \text{ULN}$) or other coagulopathy
- (b) History of severe, clinically significant (persistent neurologic deficit or structural brain damage) central nervous system (CNS) trauma (e.g., cerebral contusion), epilepsy
- (c) Have any contraindications for MRI studies, including claustrophobia, the presence of contraindicated metal (ferromagnetic) implants, or cardiac pacemaker
- (d) Anti-coagulation medications within 3 months of screening with no plans to initiate any prior to randomization or history of prolonged bleeding after minor trauma. Note: low dose aspirin is permitted (up to 162 mg/day).

- (e) History or presence of posterior reversible encephalopathy syndrome (PRES) (Fugate, et al, Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. Lancet Neurol. 2015;14(9):914-25.)

Clinical Laboratory Evaluations

[00292] Laboratory analysis of hematology, clinical chemistry, coagulation, urinalysis plasma, biomarkers, and CSF will be conducted. Central and local pregnancy testing will be conducted.

[00293] Brain MRI will be read locally and the scan will be submitted to the centralized MRI vendor for final determination of MRI eligibility, and to provide central assessment of baseline ARIA findings. MRIs should be performed using 1.5 or 3.0-T scanners, and the same scanner should be used for an individual subject for the duration of the study. The first MRI will occur during the screening period as a baseline measure to confirm structural brain imaging-based eligibility criteria. MRI scans will include, but are not limited to, the following sequences: T2-weighted FLAIR, 2-dimensional (2D) T2*-weighted gradient echo (GRE) or susceptibility weighted imaging (SWI). Diffusion weighted, 3-dimensional (3D) T1-weighted GRE. MRI scans will be evaluated and read by a MRI central reader, which will provide the diagnostic reads and assessments of MRI outcome measures. MRI data (Day 29 MRI data from all subjects and any other available MRI and safety data) will be made available for the DSMB for confirmation of h2731 dose.

[00294] CSF Analysis, if performed, in Cohorts will undergo 2 LPs: the first LP on Day 3 (48 hours after study drug administration) and the second LP on Day 29. The CSF will be analyzed to determine levels of h2731. CSF samples with clear evidence of blood contamination should not be used for PK assessment. CSF analyses will also include but are not limited to standard analyses including pressure, color, glucose, proteins, lactate, red blood cells, and white blood cells.

[00295] Amyloid PET Imaging will be used for biological confirmation of diagnosis of AD as evidence of presence of pathological hallmark findings of β -amyloid-composed neuritic plaques. Isotope-labelled compounds that show high affinity toward aggregated forms of β -amyloid (tracers) can provide evidence of β -amyloid in vivo. Three radioligand are being used for screening purposes: [18F]florbetapir /AV45 (Amyvid), [18F]flutemetamol

(Vizamyl), and [18F]florbetaben (Neuraceq). Subjects in Cohorts 1-4 will undergo amyloid PET acquisition to confirm biologically the diagnosis of AD. A positive PET scan using [18F]florbetapir /AV45, [18F]flutemetamol, or [18F]florbetaben acquired outside of this trial protocol within 18 months prior to the first screening visit may be permissible to confirm patient inclusion with confirmation by a central read.

[00296] APOE4 status (e.g., APOE4/APOE4, APOE4/APOE3, APOE3/APOE3, APOE4/APOE2, APOE3/APOE2) will be determined by central assessment for subjects enrolling into Cohorts 1 to 4.

Additional Assessments

[00297] The Cogstate CBB (Maruff, 2013) will be administered to subjects at the first screening visit (Day -72 to -8). The CBB is a brief (approximately 15 minutes), computer-based cognitive test battery designed to measure memory, working memory psychomotor function, and attention. The CBB has been shown to be a sensitive tool for detecting AD-related cognitive decline in healthy older adults and in adults with amnesic mild cognitive impairment (Darby, 2002; Lim, 2013) as well as for improvement in cognition arising from treatment with cognition enhancing drugs (Davison, 2011; Jaeger, 2011; Nathan, 2013).

[00298] The MMSE (Folstein, 1975) will be administered to subjects at the first screening visit (Day -72 to -8), prior to the Cogstate CBB assessment, to determine if the subject meets entry criteria for cognitive impairment.

[00299] Subjects will undergo plasma sampling for Biomarkers of AD pathology including, but not limited to A β 42/40, and biomarkers associated with tau pathology including, but not limited to, total tau, p181-tau, and p217-tau.

[00300] Subjects will undergo PK sampling for plasma and CSF h2731.

[00301] Plasma anti-h2731 antibody levels will be measured (antibodies detected with an electrochemiluminescent assay (ECLIA).

[00302] ARIA Assessment: a screening MRI scan will be used to exclude subjects with pre-existing vasogenic edema (ARIA-E), >4 microhemorrhages, or >1 area of superficial siderosis (ARIA H). In addition to scheduled MRIs, unscheduled MRIs may be obtained at the discretion of the Investigator upon suspicion of ARIA based on appearance of symptoms.

MRIs will be scheduled prior to study drug administration (baseline) for all subjects and at the Day 29 and Day 85 visits (28- and 84-days post dose, respectively) for subjects with AD, and will be assessed, classified, and documented for radiographic evidence of ARIA.

Example 3: Phase 1 multiple ascending dose study to evaluate the safety, tolerability, immunogenicity, pharmacokinetics, and pharmacodynamics of h2731 in subjects with Alzheimer's Disease

[00303] This example describes a phase 1, randomized, double-blind, placebo-controlled, multiple ascending dose (MAD) study to assess the safety, tolerability, and immunogenicity, PK, and pharmacodynamics (PD) effects of h2731 in patients with AD. Figure 2 is a schematic representation of the study plan.

Study Objectives

[00304] As discussed in further detail below, the primary objective of the study is to evaluate the safety, tolerability, and immunogenicity of h2731 after multiple SC doses. The secondary objectives of the study are to characterize the PK profile of h2731 after multiple SC doses, to characterize the plasma and CSF PK profile of h2731 after multiple SC doses, and to assess the PD effects of h2731 on brain amyloid plaque deposition after multiple SC doses. Exploratory objectives of the study are to assess PD effects of h2731 on blood and CSF biomarkers after multiple SC doses and to assess ARIA findings by apolipoprotein E4 (APOE4) status.

Study Population

[00305] The study consists of two parts, each studying a different group of subjects: Group A, subjects with AD who are heterozygous or non-carriers of apolipoprotein E4 (APOE4) alleles (referred to as the non-homozygote population) and Group B, subjects with AD who are homozygous for APOE4 (referred to as the homozygote population). The dose levels of h2731 to be assessed will be the same for the non-homozygote (Group A) and homozygote (Group B) populations.

[00306] Apolipoprotein E (APOE) genotype status has been demonstrated to impact the onset of AD (Corder, 1993; van Duijn, 1994) as well as rates of ARIA following treatment with anti-A β antibodies (Arrighi, 2016; Ketter, 2017; Muralidharan, 2022). Development of

ARIA is dose-dependent, and most events occur within the first few months after initiation of anti-A β treatment (Muralidharan, 2022). Patients with AD who possess 1 copy of the APOE4 allele may possess an elevated risk of anti-A β antibody-mediated ARIA compared to APOE4 non-carriers, although the risk demonstrated across clinical trials is somewhat inconsistent. However, patients who are APOE4 homozygous (possessing 2 alleles) consistently demonstrate higher incidents of ARIA compared to both APOE4 heterozygous and non-carrier patients.

Rationale for Dose Selection

[00307] The proposed doses of 300 mg, 350 mg, and 400 mg (each subcutaneously administered once a month) and 200 mg administered subcutaneously twice a month, are based on analysis of estimated target engagement (fractional occupancy [fOcc]) levels resulting from simulated clinical drug exposure levels at these doses, balancing predictions of efficacious exposure and the potential for inducing ARIA. These doses are further supported by results from the completed nonclinical toxicity studies with repeated dose administration for up to 3 months, and will be confirmed based on the certain information from the single ascending dose (SAD) study of Example 2, including:

- All safety and tolerability data through Day 15 from selected cohorts dosed at 200 mg and/or 400 mg;
- PK data through Day 29 from selected cohorts dosed at 70 mg, 200 mg, and/or 400 mg (approximately 8 subjects per cohort; 6 receiving h2731 and 2 receiving placebo); and
- Day 29 MRI results from selected cohorts dosed at 70 mg and/or 200 mg (approximately 12 subjects; 9 receiving h2731 and 3 receiving placebo).

Study Design

[00308] This Phase 1, randomized, double-blind, placebo-controlled, multiple ascending dose study will be conducted in two dose cohorts in subjects with biologically confirmed AD to assess the safety, tolerability, immunogenicity, PK, and PD of h2731.

[00309] The study consists of two parts, each evaluating a different group of subjects: Group A, subjects with AD who are heterozygous or non-carriers of APOE4 alleles and Group B, subjects with AD who are homozygous for APOE4. The two dose cohorts for each

group are described in Table 4. A cohort treating patients with 200 mg once every two weeks (twice a month) can be assessed as either a fourth cohort (e.g., Cohorts A-4 and/or B-4), or in the place of any of the cohorts described in Table 4.

Table 4

Group A: APOE4 heterozygous (e.g., E3/E4) or APOE4 non-carrier (eg, E2/E3, E2/E2)	Group B: APOE4 homozygous (i.e, E4/E4)
Cohort A-1: 300 mg	Cohort B-1: 300 mg
Cohort A-2: 350 mg	Cohort B-2: 350 mg
Cohort A-3: 400 mg	Cohort B-3: 400 mg

[00310] Subjects with AD who are APOE4 heterozygous or non-carriers of APOE4 alleles will be assigned to Group A; subjects who are homozygous for APOE4 will be assigned to Group B.

[00311] For each Group A cohort, subjects will be randomly assigned to h2731 or placebo in a 3:1 ratio. Randomization will be stratified by APOE4 carrier status (APOE4 heterozygous or APOE4 non-carrier).

[00312] For each Group B cohort, approximately 12 subjects will be randomly assigned to h2731 or placebo in a 3:1 ratio: 9 subjects will receive h2731, and 3 subjects will receive placebo.

Treatment Period

[00313] Study drug (300 mg, 350 mg, or 400 mg) will be administered every 4 weeks starting on Day 1 for a total of up to 6 doses (or 200 mg every 2 weeks). Subjects will receive the first dose of study drug (h2731 or placebo) administered subcutaneously on Day 1. Subjects will undergo safety assessments including adverse event (AE) monitoring, clinical laboratory tests, vital signs, physical examinations, and electrocardiograms (ECGs), as well as blood collections for PK, anti-drug antibody (ADA), and biomarker (BM) analysis. Subjects will be released from the study site 8 hours after dosing, after completing scheduled post-dose assessments.

[00314] Dosing will continue every 4 weeks. Safety assessments and blood collections for PK, ADA, and BM analysis will be completed. MRI findings, as assessed by the central reader, must be reviewed prior to dosing to evaluate for the presence of ARIA.

[00315] After the last administration of study drug, subjects will return to the study site for the Week 24 (Day 169) visit to complete an end of treatment (EOT) visit that includes safety assessments, blood collections for PK, ADA, and BM analysis, and amyloid PET imaging assessment.

[00316] Subjects who participate in the optional CSF collection will be scheduled for CSF collection to occur within 1 to 5 days after the Week 24 (Day 169) imaging visit (MRI and PET). Subjects may be released after 4 hours of observation.

Dose Escalation/Dose Determination

[00317] The dose levels of each cohort will be determined by a limited number of unblinded Sponsor representatives based on review and interpretation of all available safety, tolerability, PD, and PK information for h2731.

[00318] Safety and tolerability data will be evaluated in an ongoing and periodic manner throughout this study and SAD study of Example 2. Safety and tolerability data will be evaluated to provide a recommendation on the decision to enroll cohorts when the minimum data requirements have been met.

Suspension of Dosing on Subject Level

[00319] Dosing depends on the presence and severity of amyloid-related imaging findings related to underlying vasogenic edema (ARIA-E) or hemorrhage (ARIA-H) observed prior to each administration of h2731 or placebo based on MRI findings, as assessed by the MRI central reader, and potential symptoms of ARIA reported by the subject or observed by the Investigator.

[00320] An MRI visit will be scheduled up to 7 days before each dosing visit. ARIA severity classifications based on radiographic findings are summarized in Table 5. MRI results must be reviewed prior to dosing.

Table 5

ARIA Type	Mild	Mild+	Moderate	Moderate+	Severe
ARIA-E	FLAIR hyper-intensity confined to sulcus or cortex / subcortical white matter in 1 location; Extent of <5 cm	FLAIR hyper-intensity cortex/ subcortical white matter in >1 location; Extent of <5 cm	FLAIR hyper-intensity in 1 location; Extent of 5-10 cm	FLAIR hyper-intensity >1 location; Extent of 5-10 cm each	FLAIR hyperintensity measuring >10 cm, often with significant subcortical white matter and/or sulcal involvement. ≥ 1 separate site of involvement may be noted
	Mild	Moderate		Severe	
ARIA-H/ micro- hemorrhage	≤ 4 new incidents microhemorrhages ^a	5-9 new incidents microhemorrhages ^a		≥ 10 new incidents microhemorrhages ^a	
ARIA-H Superficial siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis		>2 focal areas of superficial siderosis	

ARIA-E = amyloid-related imaging findings related to underlying vasogenic edema; ARIA-H = amyloid-related imaging findings related to intracerebral hemorrhage; FLAIR = fluid-attenuated inversion recovery
a. New microhemorrhage counted cumulatively compared to screening visit.

Source: adapted from Aduhelm USPI, 2021 and Bracoud, 2017

[00321] All intracerebral hemorrhage greater than 1 cm are considered radiographically severe.

[00322] Dosing may be suspended based on a moderate and/or severe ARIA-E finding based on either ARIA-E Clinical Severity or ARIA-E Radiographic Severity. Any new ARIA-H (microhemorrhage or superficial siderosis) finding, except for asymptomatic mild ARIA-H, leads to suspension of dosing of h2731 for the subject.

[00323] If dosing is suspended, the scheduled dose should be completely omitted, and subsequent visits should be continued as scheduled. When the subject is able to re-initiate treatment (Section 7.11.3), administration of h2731 or placebo should resume at the same dose at the time of the next scheduled dose. Omitted doses will not be replaced.

Endpoints

[00324] Primary endpoints will include:

- Safety and tolerability based on AE reporting (incidence of AEs, SAEs, and h2731-related AEs), vital signs, physical and neurological examinations, 12-lead ECGs, clinical laboratory tests
- Injection site reactions based on Investigator assessment
- Nature, frequency, severity, and timing of MRI findings of ARIA, including incidence of symptomatic ARIA-E and/or ARIA-H; incidence of isolated ARIA-E (only ARIA-E, no ARIA-H), and isolated ARIA-H (only ARIA-H, no ARIA-E); and incidence of concurrent ARIA-E and ARIA-H
- Presence of ADAs in plasma

[00325] Secondary endpoints will include:

- Plasma PK of h2731
- Maximum observed concentration (C_{max})
- Time of the maximum measured concentration (T_{max})
- Last concentration time point before the next administration (C_{trough})
- Area under the concentration-time curve from time zero to infinity (AUC_{0-∞})
- Area under the plasma concentration-time curve for dosing interval (AUC_{0-tau})
- Area under the plasma concentration-time curve accumulation ratio over one dosing interval from the first to last dose (RAUC)
- Apparent volume of distribution (V_d)
- Average concentration over the dosing interval (C_{avg})
- Apparent total body clearance (CL/F)
- CSF PK of h2731 (optional CSF collection)
 - Observed concentration (C_{obs}) of h2731 in plasma and CSF at each sampling time of CSF collection
- Change from baseline in brain amyloid plaque deposition as measured by amyloid positron emission tomography (PET) scan at Week 24 (Day 169)

[00326] Exploratory endpoints will include:

- Change in blood-based biomarkers from baseline through Week 24 (Day 169) including but not limited to A β 42/40 ratio, p181-tau, and p217-tau
- Change in CSF biomarkers from baseline through Week 24 (Day 169) including but not limited to A β 42/40 ratio, p181-tau, and p217- tau (for subjects in optional CSF collection)
- Nature, frequency, severity, and timing of MRI findings by APOE4 status (APOE4 heterozygous or APOE4 non-carrier), including incidence of symptomatic ARIA-E and/or ARIA-H; incidence of isolated ARIA-E (only ARIA-E, no ARIA-H), and isolated ARIA-H (only ARIA-H, no ARIA-E); and incidence of concurrent ARIA-E and ARIA-H

Inclusion Criteria

[00327] AD subjects will be selected according to inclusion criteria that include the following:

- Subjects between 55 and 85 years having a body mass index between 18.0 and 32.0 kg/m², inclusive;
- Gradual and progressive change in memory function for ≥ 6 months reported by subjects or study partner;
- Alzheimer's pathologic change with either mild cognitive impairment or mild dementia (Stage 2, 3 or 4) according to National Institute on Aging and Alzheimer's Association (NIA-AA) criteria (Jack, 2018; Appendix 3); and
- Screening MMSE score ≥ 18 .

Exclusion Criteria

- Exclusion Criteria are similar to Example 2, with the additional exclusion of family history of dominantly inherited AD

[00328] Clinical laboratory evaluations, Cogstate assessment, MMSE assessment, PK sampling, biomarker analysis, and ARIA assessment will be performed using methods similar to those set forth in Example 2.

Results

[00329] The results of this MAD study will show a reduction in amyloid plaque in treated patients (e.g., amyloid reduction described in the present disclosure) with relatively low ARIA rates (e.g., ARIA rates and ARIA risks described in the present disclosure).

Example 4: Phase 1 open label extension study to evaluate the safety, tolerability, immunogenicity, pharmacokinetics, and pharmacodynamics of h2731 in subjects with Alzheimer's Disease

[00330] This example describes an open-label extension (OLE) study for subjects with Alzheimer's disease who participated in and completed the single ascending dose study (SAD) of Example 2 or participated in and completed the treatment period of the multiple ascending dose study (MAD) of Example 3, and meet eligibility criteria for this OLE as described further herein.

Study Design

[00331] All subjects will receive up to 12 doses of h2731 in this OLE as summarized in Figure 3. h2731 will be administered once every 4 weeks by subcutaneous injection for a total of up to 12 doses. All subjects from the SAD study will receive 400 mg h2731 and subjects from the MAD study will receive a dose of 300 mg, 350 mg, or 400 mg once a month or 200 mg twice a month of h2731 based on their cohort assignment (Cohorts A-1, A-2, A-3, B-1, B-2, or B-3) in the core study.

Study Objectives

[00332] The primary objective of the OLE is to evaluate long-term safety, tolerability, and immunogenicity of h2731. The secondary objective of the OLE is to characterize PK profile of h2731. Exploratory objectives include assessing the effect of h2731 on amyloid positron emission tomography (PET) and assessing the PD effects of h2731 on plasma biomarkers.

Eligibility Criteria

[00333] For subjects from the SAD study of Example 2, screening and enrollment into this OLE can occur after completion of a Day 85 visit.

[00334] For subjects from the MAD study of Example 3, screening and enrollment into this OLE must occur no more than 18 weeks (127 days) after Week 24/End of Treatment (EOT) and will be based on the following:

[00335] If there is no ARIA at the Week 24/EOT in the study SAD study of Example 1, subjects can enter this OLE if all eligibility criteria are met and no more than 18 weeks have elapsed since the Week 24/EOT visit and first dose for the OLE study. Eligible subjects will be encouraged to be dosed within 2 weeks of the Week 24/EOT visit for a more seamless transition.

[00336] If ARIA (either new or ongoing) that does not require dose suspension is detected at the Week 24/EOT visit from the MAD study of Example 2, subjects can enter the OLE study if all eligibility criteria are met and no more than 18 weeks have elapsed since the Week 24/EOT visit and first dose of the OLE.

[00337] If ARIA (either new or ongoing) that requires dose suspension is detected at the Week 24/EOT visit of MAD study, subjects can enter this OLE if (1) the ARIA finding has stabilized (for ARIA-H) or resolved (for ARIA-E) and (2) no more than 18 weeks have elapsed since the Week 24/EOT visit of the MAD study and first dose of the OLE and (3) it is acceptable to resume dosing with h2731 in the opinion of the Investigator as guided by clinical judgment, and (4) all eligibility criteria are met.

[00338] If ARIA has not stabilized or resolved after 18 weeks (127 days) have elapsed since the Week 24/EOT visit of the MAD study, the subject is not eligible to enroll in OLE and will complete follow-up in the MAD study.

Endpoints

[00339] Primary endpoints will include:

- Safety and tolerability based on AE reporting (incidence of adverse events [AEs], serious adverse events [SAEs], and h2731-related AEs), clinical laboratory tests, vital signs, and physical examinations;
- Nature, frequency, severity, and timing of magnetic resonance imaging (MRI) findings of ARIA, including amyloid-related imaging findings related to underlying vasogenic edema (ARIA E); amyloid-related imaging findings related to intracerebral

hemorrhage (ARIA-H); incidence of symptomatic ARIA-E and/or ARIA-H; and incidence of concurrent ARIA-E and ARIA-H

- Presence of anti-drug antibodies (ADAs) in plasma

[00340] Secondary Endpoints will include plasma concentration of h2731.

[00341] Exploratory Endpoints will include:

- brain amyloid levels as measured by PET imaging; and
- plasma-based biomarkers including but not limited to A β 42, A β 40, amyloid beta peptide ratio 42/40 (A β 42/40), p181-tau, p217-tau.

[00342] Additional analyses may be performed to evaluate brain amyloid centiloid change from the core study baseline after 24 and 48 weeks of treatment in the OKE. For this analysis, all time points are presented relative to start of h2731 exposure. Percentage (%) of subjects who reach amyloid negativity based on amyloid PET scan at Week 24 (Day 169) and Week 48 (Day 337) will also be presented.

[00343] The PK/PD relationship between centiloid reduction and cumulative dose of h2731 may be summarized. Additional analysis may be performed to examine the PK/PD relationship between centiloid reduction and h2731 plasma exposure.

[00344] Inclusion Criteria include completion of the SAD study of Example 2 (AD cohorts only) or completed the treatment period in the MAD study of Example 3, are those as in Example 3.

[00345] Exclusion criteria include those listed in Example 3, including ARIA that would prohibit dosing as shown in the Tables 4 and 5 from Example 3.

Results

[00346] The results of this OLE study will show a reduction in amyloid plaque in treated patients (e.g., amyloid reduction described in the present disclosure) with relatively low ARIA rates (e.g., ARIA rates and ARIA risks described in the present disclosure).

[00347] All publications (including GenBank Accession numbers, UniProtKB/Swiss-Prot accession numbers and the like), patents and patent applications cited are herein incorporated

by reference in their entirety for all purposes to the same extent as if each individual publication, patent and patent application was specifically and individually indicated to be incorporated by reference in its entirety for all purposes. Any feature, step, element, embodiment, or aspect of the disclosure can be used in combination with any other unless specifically indicated otherwise. Although the present disclosure has been described in some detail by way of illustration and example for purposes of clarity and understanding, it will be apparent that certain changes and modifications may be practiced within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A method of treating Alzheimer's disease in a subject, comprising administering to the subject about 205 mg to about 400 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks.
2. A method of reducing brain amyloid beta plaque in a subject, comprising administering to the subject about 205 mg to about 400 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks.
3. A method of converting a subject from amyloid positive to amyloid negative, comprising administering to the subject about 205 mg to about 400 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof once about every 3-5 weeks.
4. The method of any one of claims 1 to 3, wherein the method comprises administering about 300 mg to about 400 mg of the anti-amyloid β antibody or antigen-binding fragment thereof.
5. The method of any one of claims 1 to 3, wherein the method comprises administering about 350 mg to about 400 mg of the anti-amyloid β antibody or antigen-binding fragment thereof.
6. The method of any one of claims 1 to 3, wherein the method comprises administering about 300 mg of the anti-amyloid β antibody or antigen-binding fragment thereof.
7. The method of any one of claims 1 to 3, wherein the method comprises administering about 350 mg of the anti-amyloid β antibody or antigen-binding fragment thereof.
8. The method of any one of claims 1 to 3, wherein the method comprises administering about 400 mg of the anti-amyloid β antibody or antigen-binding fragment thereof.
9. The method of any one of claims 1 to 8, wherein the anti-amyloid β antibody is administered once about every 4 weeks.

10. A method of treating Alzheimer's disease in a subject, comprising administering to the subject about 100 mg to about 200 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks.
11. A method of reducing brain amyloid beta plaque in a subject, comprising administering to the subject about 100 mg to about 200 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks.
12. A method of converting a subject from amyloid positive to amyloid negative, comprising administering to the subject about 100 mg to about 200 mg of an anti-amyloid β antibody or an antigen-binding fragment thereof twice about every 3-5 weeks.
13. The method of any one of claims 10 to 12, wherein the method comprises administering about 150 mg to about 200 mg of the anti-amyloid β antibody or antigen-binding fragment thereof.
14. The method of any one of claims 10 to 12, wherein the method comprises administering about 200 mg of the anti-amyloid β antibody or antigen-binding fragment thereof.
15. The method of any one of claims 10 to 14, wherein the anti-amyloid β antibody or antigen-binding fragment thereof is administered once about every 2 weeks.
16. The method of any one of claims 1 to 15, wherein the anti-amyloid β antibody or an antigen-binding fragment thereof binds to an epitope located within the N-terminus of an A β peptide, and the epitope includes at least one amino acid selected from amino acids 1-10 of the A β peptide.
17. The method of claim 16, wherein the anti-amyloid β antibody or an antigen-binding fragment thereof binds to an epitope comprising at least one amino acid selected from amino acids 1-7 of the A β peptide.

18. The method of any one of claims 1 to 17, wherein the anti-amyloid β antibody or an antigen-binding fragment thereof binds to amyloid β_{1-42} protofibrils with an apparent KD of about 5 nM or less.
19. The method of any one of claims 1 to 17, wherein the anti-amyloid β antibody or an antigen-binding fragment thereof binds to amyloid β_{1-42} protofibrils with an apparent KD of about 1 nM or less.
20. The method of any one of claims 1 to 19, wherein the anti-amyloid β antibody or an antigen-binding fragment thereof binds to amyloid β_{1-28} monomers with an apparent KD of about 10 nM or less.
21. The method of any one of claims 1 to 20, wherein the anti-amyloid β antibody or antigen-binding fragment thereof is administered as a pharmaceutical composition comprising the anti-amyloid β antibody or antigen-binding fragment thereof and a pharmaceutically acceptable diluent.
22. The method of any one of claims 1 to 21, wherein the administration is intravenous or subcutaneous.
23. The method of claim 22, wherein the administration is subcutaneous.
24. The method of any one of claims 1 to 23, wherein the anti-amyloid β antibody or antigen-binding fragment thereof comprises a heavy chain variable region comprising heavy chain CDR1, CDR2, and CDR3 and a light chain variable region comprising light chain CDR1, CDR2, and CDR3, wherein
- heavy chain CDR1 comprises the amino acid sequence of SEQ ID NO: 3,
 - heavy chain CDR2 comprises the amino acid sequence of SEQ ID NO: 4,
 - heavy chain CDR3 comprises the amino acid sequence of SEQ ID NO: 5,
 - light chain CDR1 comprises the amino acid sequence of SEQ ID NO: 6,
 - light chain CDR2 comprises the amino acid sequence of SEQ ID NO: 7, and
 - light chain CDR3 comprises the amino acid sequence of SEQ ID NO: 8.

25. The method of claim 24, wherein the heavy chain variable region, excluding the CDRs, is at least 95% identical to the amino acid sequence of SEQ ID NO: 1, and the light chain variable region, excluding the CDRs, is at least 95% identical to the amino acid sequence of SEQ ID NO: 2.
26. The method of claim 25, wherein the heavy chain variable region, excluding the CDRs, is at least 98% identical to the amino acid sequence of SEQ ID NO: 1, and the light chain variable region, excluding the CDRs, is at least 98% identical to the amino acid sequence of SEQ ID NO: 2.
27. The method of claim 26, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 1, and wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 2.
28. The method of claim 24, wherein the heavy chain variable region consists of SEQ ID NO: 1, and wherein the light chain variable region consists of the amino acid sequence of SEQ ID NO: 2.
29. The method of any one of claims 1 to 28, wherein the anti-amyloid β antibody is a humanized IgG1.
30. The method of any one of claims 1 to 28, wherein the anti-amyloid β antibody is a full antibody, a chimeric antibody, a CDR-grafted antibody, or a recombinant antibody.
31. The method of any one of claims 1 to 30, wherein the anti-amyloid β antibody or antigen-binding fragment thereof further comprises a heavy chain constant region comprising an amino acid sequence at least 95% identical to SEQ ID NO: 9 and/or a light chain constant region comprising an amino acid sequence at least 95% identical to SEQ ID NO: 10.
32. The method of any one of claims 1 to 31, wherein the anti-amyloid β antibody or antigen-binding fragment thereof further comprises a heavy chain constant region comprising an amino acid sequence at least 98% identical to SEQ ID NO: 9 and/or a light chain constant region comprising an amino acid sequence at least 98% identical to SEQ ID NO: 10.

33. The method of any one of claims 1 to 32, wherein the anti-amyloid β antibody comprises a heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 9, with or without the C-terminal lysine, and a light chain constant region comprising an amino acid sequence of SEQ ID NO: 10.
34. The method of any one of claims 1 to 33, wherein the anti-amyloid β antibody comprises a heavy chain constant region consisting essentially of an amino acid sequence of SEQ ID NO: 9, with or without the C-terminal lysine, and a light chain constant region consisting essentially of an amino acid sequence of SEQ ID NO: 10.
35. The method of any one of claims 1 to 34, wherein the anti-amyloid β antibody comprises a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.
36. The method of any one of claims 1 to 35, wherein the anti-amyloid β antibody is h2731.
37. A method of treating Alzheimer's disease in a subject, the method comprising subcutaneously administering to the subject about 300 mg of an anti-amyloid β antibody once about every 4 weeks; the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.
38. A method of treating Alzheimer's disease in a subject, the method comprising subcutaneously administering to the subject about 350 mg of an anti-amyloid β antibody once about every 4 weeks; the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.
39. A method of treating Alzheimer's disease in a subject, the method comprising subcutaneously administering to the subject about 400 mg of an anti-amyloid β antibody once about every 4 weeks; the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

40. A method of treating Alzheimer's disease in a subject, the method comprising subcutaneously administering to the subject about 200 mg of an anti-amyloid β antibody once about every 2 weeks; the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

41. A method of reducing amyloid plaque in a subject, the method comprising subcutaneously administering to the subject about 300 mg of an anti-amyloid β antibody once about every 4 weeks; the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

42. A method of reducing amyloid plaque in a subject, the method comprising subcutaneously administering to the subject about 350 mg of an anti-amyloid β antibody once about every 4 weeks; the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

43. A method of reducing amyloid plaque in a subject, the method comprising subcutaneously administering to the subject about 400 mg of an anti-amyloid β antibody once about every 4 weeks; the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

44. A method of reducing amyloid plaque in a subject, the method comprising subcutaneously administering to the subject about 200 mg of an anti-amyloid β antibody once about every 2 weeks; the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

45. A method of treating Alzheimer's disease in a subject, comprising subcutaneously administering to the subject a dose of an anti-A β antibody sufficient to achieve an average concentration over the dosing interval (C_{ave} value) of about 20 $\mu\text{g/mL}$ to about 40 $\mu\text{g/mL}$, the anti-A β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

46. A method of treating Alzheimer's disease in a subject, comprising subcutaneously administering to the subject a dose of an anti-A β antibody sufficient to achieve an area under

the concentration-time curve for dosing interval value ($AUC_{0-\tau}$ value) of about 15,000 hr* $\mu\text{g/mL}$ to about 30,000 hr* $\mu\text{g/mL}$, the anti-A β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

47. The method of any one of claims 1 to 46, wherein a maximum concentration over a dosing interval ($C_{\max}$) of the anti-amyloid β antibody or antigen binding fragment thereof in the subject is about 30 $\mu\text{g/mL}$ to about 60 $\mu\text{g/mL}$.

48. The method of any one of claims 1 to 46, wherein a $C_{\max}$ value of the anti-amyloid β antibody or antigen binding fragment thereof in the subject is about 50 $\mu\text{g/mL}$ to about 60 $\mu\text{g/mL}$.

49. The method of any one of claims 1 to 46, wherein a $C_{\max}$ value of the anti-amyloid β antibody or antigen binding fragment thereof in the subject does not exceed about 60 $\mu\text{g/mL}$.

50. The method of any one of claims 47 to 49, wherein the $C_{\max}$ value is a serum $C_{\max}$ value.

51. The method of any one of claims 47 to 49, wherein the $C_{\max}$ value is a plasma $C_{\max}$ value.

52. The method of any one of claims 1 to 51, wherein a C_{ave} value of the anti-amyloid β antibody or antigen binding fragment thereof in the subject is about 20 $\mu\text{g/mL}$ to about 40 $\mu\text{g/mL}$.

53. The method of any one of claims 1 to 51, wherein a C_{ave} value of the anti-amyloid β antibody or antigen binding fragment thereof in the subject is about 30 $\mu\text{g/mL}$ to about 40 $\mu\text{g/mL}$.

54. The method of any one of claims 1 to 51, wherein a C_{ave} value of the anti-amyloid β antibody or antigen binding fragment thereof in the subject does not exceed about 40 $\mu\text{g/mL}$.

55. The method of any one of claims 45 and 52 to 54, wherein the C_{ave} value is a serum C_{ave} value.
56. The method of any one of claims 45 and 52 to 54, wherein the C_{ave} value is a plasma C_{ave} value.
57. The method of any one of claims 1 to 56, wherein an AUC_{0-tau} value of the anti-amyloid β antibody or antigen binding fragment thereof in the subject is about 15,000 $hr*\mu g/mL$ to about 30,000 $hr*\mu g/mL$.
58. The method of any one of claims 1 to 57, wherein an AUC_{0-tau} value of the anti-amyloid β antibody or antigen binding fragment thereof in the subject is about 20,000 $hr*\mu g/mL$ to about 30,000 $hr*\mu g/mL$.
59. The method of any one of claims 1 to 58, wherein an AUC_{0-tau} value of the anti-amyloid β antibody or antigen binding fragment thereof in the subject does not exceed about 30,000 $hr*\mu g/mL$.
60. The method of any one of claims 46 and 57 to 59, wherein the AUC_{0-tau} value is a serum AUC_{0-tau} value.
61. The method of any one of claims 46 and 57 to 59, wherein the AUC_{0-tau} value is a plasma AUC_{0-tau} value.
62. The method of any one of claims 1 to 61, wherein brain amyloid beta plaque in the subject is reduced.
63. The method of any one of claims 2, 3, and 62, wherein the reduction of brain amyloid beta plaque comprises a reduction of at least about 30 centiloids to about 70 centiloids.
64. The method of any one of claims 2, 3, and 62, wherein the reduction of brain amyloid beta plaque comprises a reduction of from about 45 centiloids to about 80 centiloids.

65. The method of any one of claims 2, 3, and 62, wherein the reduction of brain amyloid beta plaque comprises a reduction of about 50 centiloids to about 85 centiloids.
66. The method of any one of claims 2, 3, and 62, wherein the reduction of brain amyloid beta plaque comprises a reduction of at least about 40% to about 90%.
67. The method of any one of claims 2, 3, and 62, wherein the reduction of brain amyloid beta plaque comprises a reduction of from about 60% to about 100%.
68. The method of any one of claims 2, 3, and 62, wherein the reduction of brain amyloid beta plaque comprises a reduction of about 65% to about 100%.
69. The method of any one of claims 2, 3, and 62 to 68, wherein the reduction of brain amyloid beta plaque is a reduction compared to baseline.
70. The method of any one of claims 2, 3, and 62 to 69, wherein the reduction of brain amyloid beta plaque is a reduction compared to the subject prior to the administration of the anti-amyloid β antibody.
71. The method of any one of claims 2, 3, and 62 to 70, wherein the reduction of brain amyloid beta plaque is achieved after about 6 months of treatment.
72. The method of any one of claims 2, 3, and 62 to 70, wherein the reduction of brain amyloid beta plaque is achieved after about 12 months of treatment.
73. The method of any one of claims 2, 3, and 62 to 70, wherein the reduction of brain amyloid beta plaque is achieved after about 18 months of treatment.
74. The method of any one of claims 2, 3, and 62 to 73, wherein the reduction of brain amyloid beta plaque is assessed by Positron Emission Tomography (PET).
75. The method of any one of claims 1 to 74, wherein the subject is converted from amyloid positive to amyloid negative.

76. The method of any one of claims 1 to 75, wherein treating comprises increasing a probability of converting the subject from amyloid positive to amyloid negative.
77. The method of any one of claims 1 to 76, wherein treating comprises a probability of converting the subject from amyloid positive to amyloid negative by about 10% to about 40%.
78. The method of any one of claims 1 to 76, wherein treating comprises a probability of converting the subject from amyloid positive to amyloid negative by about 30% to about 60%.
79. The method of any one of claims 1 to 76, wherein treating comprises a probability of converting the subject from amyloid positive to amyloid negative by about 40% to about 80%.
80. The method of any one of claims 77 to 79, wherein the probability of converting the subject from amyloid positive to amyloid negative is a probability after about 6 months of treatment.
81. The method of any one of claims 77 to 79, wherein the probability of converting the subject from amyloid positive to amyloid negative is a probability after about 12 months of treatment.
82. The method of any one of claims 77 to 79, wherein the probability of converting the subject from amyloid positive to amyloid negative is a probability after about 18 months of treatment.
83. The method of any one of claims 1 to 82, wherein treating comprises slowing, halting, or reversing decline in cognitive function.
84. The method of claim 83, wherein treating comprises slowing decline in cognitive function.

85. The method of claim 83 or 84, wherein cognitive function is measured by at least one of the following CRD-SB, ADAS-Cog14, ADCOMS, and ADCS MCI-ADL.

86. The method of claim 85, wherein cognitive function is measured by ADCOMS.

87. A method of modulating a biomarker in a subject, comprising administering to the subject from about 205 mg to about 400 mg of an anti-amyloid β antibody once about every 3-5 weeks, the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

88. A method of increasing a ratio of A β 42/40 in a subject, comprising administering to the subject about 205 mg to about 400 mg of an anti-amyloid β antibody once about every 3-5 weeks, the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

89. A method of decreasing an amount of phospho-tau in a subject, comprising administering to the subject about 205 mg to about 400 mg of an anti-amyloid β antibody thereof once about every 3-5 weeks, the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

90. A method of decreasing an amount of phospho-tau in a subject, comprising administering to the subject about 100 mg to about 200 mg of an anti-amyloid β antibody thereof twice about every 3-5 weeks, the anti-amyloid β antibody comprising a heavy chain of SEQ ID NO: 11, with or without the C-terminal lysine, and a light chain of SEQ ID NO: 12.

91. The method of any one of claims 87 to 90, wherein the administration comprises a subcutaneous injection.

92. The method of any one of claims 1 to 91, wherein a biomarker in the subject is modulated.

93. The method of claim 92, wherein the biomarker in the subject is modulated compared to baseline.

94. The method of any one of claims 1 to 93, wherein the method further comprises detecting a biomarker in a sample collected from the subject.
95. The method of any one of claims 1 to 94, wherein the method further comprises quantifying a biomarker in a sample collected from the subject.
96. The method of any one of claims 87 and 92 to 95, wherein the biomarker comprises the ratio of A β 42/40 in the subject.
97. The method of any one of claims 88 and 96, wherein the ratio of A β 42/40 in the subject increases at least 25%.
98. The method of any one of claims 88 and 96, wherein the ratio of A β 42/40 in the subject increases at least 50%.
99. The method of any one of claims 88 and 96, wherein the ratio of A β 42/40 in the subject increases about 25% to about 100%.
100. The method of any one of claims 88 and 96, wherein the ratio of A β 42/40 in the subject increases about 50% to about 100%.
101. The method of any one of claims 87 and 92 to 95, wherein the biomarker comprises a phospho-tau value.
102. The method of any one of claims 89, 90, and 101, wherein the phospho-tau value comprises at least one of the following: a p181-tau value, a p212-tau value, p217-tau value, a p231-tau value, and a p235-tau value.
103. The method of any one of claims 89, 90, and 101, wherein the phospho-tau value comprises a p181-tau value.
104. The method of any one of claims 89, 90, and 101, wherein the phospho-tau value comprises a p212-tau value.

105. The method of any one of claims 89, 90, and 101, wherein the phospho-tau value comprises a p217-tau value.
106. The method of any one of claims 89, 90, and 101, wherein the phospho-tau value comprises a p231-tau value.
107. The method of any one of claims 89, 90, and 101, wherein the phospho-tau value comprises a p235-tau value.
108. The method of any one of claims 89, 90, and 101 to 107, wherein the phospho-tau value decreases.
109. The method of any one of claims 89, 90, and 108, wherein the phospho-tau value decreases at least about 10%.
110. The method of any one of claims 89, 90, and 108, wherein the phospho-tau value decreases about 10% to about 30%.
111. The method of any one of claims 89, 90, and 108, wherein the phospho-tau value decreases about 20% to about 30%.
112. The method of any one of claims 94 and 95, wherein the sample comprises blood or a portion thereof collected from the subject.
113. The method of any one of claims 94 and 95, wherein the sample comprises plasma collected from the subject.
114. The method of any one of claims 94 and 95, wherein the sample comprises serum collected from the subject.
115. The method of any one of claims 94 and 95, wherein the sample comprises cerebral spinal fluid ("CSF") collected from the subject.

116. The method of any one of claims 1 to 115, wherein the method comprises a risk of ARIA-E that is less than about 45%.

117. The method of any one of claims 1 to 115, wherein the method comprises a risk of ARIA-E from about 25% to about 45%.

118. The method of any one of claims 1 to 115, wherein the method comprises a risk of ARIA-E of less than about 75%.

119. The method of any one of claims 1 to 115, wherein the method comprises a risk of ARIA-E of about 50% to about 75%.

120. The method of any one of claims 1 to 115, wherein the method comprises a risk of symptomatic ARIA-E that is less than about 15%.

121. The method of any one of claims 1 to 115, wherein the method comprises a risk of symptomatic ARIA-E that is less than about 30%.

122. The method of any one of claims 116 to 121, wherein the risk of ARIA-E is a risk of severe ARIA-E.

123. The method of any one of claims 116 to 122, wherein the risk of ARIA-E is the risk after about 6 months of treatment.

124. The method of any one of claims 116 to 122, wherein the risk of ARIA-E is the risk after about 12 months of treatment.

125. The method of any one of claims 116 to 122, wherein the risk of ARIA-E is the risk after about 18 months of treatment.

126. The method of any one of claims 1 to 125, wherein the subject does not experience symptomatic ARIA-E during treatment.

127. The method of any one of claims 1 to 126, wherein the method comprises a risk of ARIA-H that is less than about 35%.

128. The method of any one of claims 1 to 126, wherein the method comprises a risk of ARIA-H from about 10% to about 35%.

129. The method of claim 127 or 128, wherein the risk of ARIA-H is a risk of severe ARIA-H.

130. The method of any one of claims 127 to 129, wherein the risk of ARIA-H is the risk after about 6 months of treatment.

131. The method of any one of claims 1 to 130, wherein the subject does not experience symptomatic ARIA-H during treatment.

132. The method of any one of claims 116 to 131, wherein ARIA-E and/or ARIA-H is assessed by Magnetic Resonance Imaging ("MRI").

133. The method of any one of claims 1 to 132, wherein the subject is an APOE4 homozygous subject.

134. The method of any one of claims 1 to 132, wherein the subject is an APOE4 heterozygous subject or an APOE4 noncarrier.

135. The method of any one of claims 1 to 134, wherein the method further comprises determining the APOE4 status of the subject prior to administration.

136. The method of any one of claims 1 to 135, wherein the duration of the treatment is at least 6 months.

137. The method of any one of claims 1 to 135, wherein the duration of the treatment is at least 12 months.

138. The method of any one of claims 1 to 135, wherein the duration of the treatment is at least 18 months.

139. The method of any one of claims 1 to 138, wherein the administration is performed using a syringe.

140. The method of any one of claims 1 to 138, wherein the administration is performed using an autoinjector.

141. The method of any one of claims 1 to 140, wherein the subject is a mammal.

142. The method of any one of claims 1 to 141, wherein the subject is a human.