

CLAIMS

1. Use of an anti-A β protofibril antibody in the manufacture of a medicament for treating a subject having, suspected of having, or at risk for developing Alzheimer's disease (AD), characterized in that:

the subject has an A β 42/40 ratio that indicates amyloid positive status, wherein the A β 42/40 ratio is determined by measuring a concentration of amyloid β 1-42 (A β 42) and a concentration of amyloid β 1-40 (A β 40) in a blood and/or CSF sample obtained from the subject; and

the medicament is adapted to be administered at a therapeutically effective dose of the anti-A β protofibril antibody,

wherein the anti-A β protofibril antibody comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 7 and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 8.

2. Use of an anti-A β protofibril antibody in the manufacture of a medicament for treating a subject having, suspected of having, or at risk for developing AD, characterized in that:

the subject has a first A β 42/40 ratio determined by measuring a first concentration of A β 42 and a concentration of A β 40 in a first blood and/or CSF sample obtained from the subject prior to treatment with the anti-A β protofibril antibody; and

the subject has a second A β 42/40 ratio determined by measuring a second concentration of A β 42 and a concentration of A β 40 in a second blood and/or CSF sample obtained from the subject during or after treatment with the anti-A β protofibril antibody,

wherein the medicament is adapted to be administered at a therapeutically effective dose of the anti-A β protofibril antibody when the second A β 42/40 ratio is elevated as compared to the first A β 42/40 ratio,

wherein the anti-A β protofibril antibody comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 7 and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 8.

3. Use of a reagent in the manufacture of a kit for selecting a subject for treatment with an A β protofibril antibody, characterized in that the kit comprises:

a reagent for measuring a concentration of amyloid β 1-42 (A β 42) and a concentration of amyloid β 1-40 (A β 40) in a blood and/or CSF sample obtained from the subject; and instructions for determining a ratio of A β 42 to A β 40 (A β 42/40 ratio),

wherein if the A β 42/40 ratio indicates amyloid positive status, the subject is selected for treatment with the anti-A β protofibril antibody; and wherein the anti-A β protofibril antibody comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 7 and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 8.

4. An *in vitro* method of selecting a subject for treatment with an anti-A β protofibril antibody, wherein the method comprises:

a. measuring a concentration of amyloid β 1-42 (A β 42) and a concentration of amyloid β 1-40 (A β 40) in a blood and/or CSF sample obtained from the subject to determine a ratio of A β 42 to A β 40 (A β 42/40 ratio); and

b. selecting the subject for treatment if the ratio indicates amyloid positive status, wherein the anti-A β protofibril antibody comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 7 and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 8.

5. Use of an anti-A β protofibril antibody in the manufacture of a medicament for treating a subject having, suspected of having, or at risk for developing AD, characterized in that:

the subject has a first A β 42/40 ratio determined by measuring a first concentration of A β 42 and a concentration of A β 40 in a first blood and/or CSF sample obtained from the subject prior to treatment with the anti-A β protofibril antibody; and

the subject has a second A β 42/40 ratio determined by measuring a second concentration of A β 42 and a concentration of A β 40 in a second blood and/or CSF sample obtained from the subject during or after treatment with the anti-A β protofibril antibody,

wherein the medicament is adapted to be administered at a therapeutically effective dose of the anti-A β protofibril antibody, and wherein an increase in the second A β 42/40 ratio compared to the first A β 42/40 ratio indicates effective treatment,

wherein the anti-A β protofibril antibody comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 7 and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 8

6. An *in vitro* method of monitoring efficacy of treatment with an anti-A β protofibril antibody in a subject having, suspected of having, or at risk for developing AD, comprising:
- a. measuring a first concentration of A β 42 and A β 40 in a blood and/or CSF sample obtained from the subject prior to treatment with a therapeutically effective amount of the anti-A β protofibril antibody to determine a first A β 42/A β 40 ratio;
 - b. measuring a second concentration of A β 42 and A β 40 in a blood and/or CSF sample obtained from the subject during or after treatment to determine a second A β 42/A β 40 ratio, and
 - c. comparing the first A β 42/A β 40 ratio to the second A β 42/A β 40 ratio, wherein an elevated second A β 42/40 ratio as compared to the first A β 42/40 ratio indicates an effective treatment;

wherein the anti-A β protofibril antibody comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 7 and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 8.

7. Use of a reagent in the manufacture of a kit for monitoring efficacy of treatment with an anti-A β protofibril antibody in a subject having, suspected of having AD, or at risk for developing AD, characterized in that the kit comprises:
- a. a first reagent for measuring a first concentration of A β 42 and of A β 40 in a blood and/or CSF sample obtained from the subject prior to treatment, and instructions for determining a first A β 42/40 ratio;
 - b. a second reagent for measuring a second concentration of A β 42 and of A β 40 in a blood and/or CSF sample obtained from the subject during or after administering a therapeutically effective amount of the anti-A β protofibril antibody, and instructions for determining a second A β 42/40 ratio,
- wherein an elevated second A β 42/40 ratio as compared to the first A β 42/40 ratio indicates an effective treatment; and

wherein the anti-A β protofibril antibody comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 7 and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 8.

8. The use of claim 5, wherein an elevated A β 42/40 ratio in the second sample relative to the first sample indicates a decrease of brain amyloid β in the subject.

9. The *in vitro* method of claim 6, wherein a reduced concentration in the second sample relative to the first sample indicates a decrease of brain amyloid β in the subject.

10. The use of claim 1 or 3, or the method of claim 4, wherein the A β 42/40 ratio that indicates amyloid positive status is at most 0.1, e.g., 0.099, 0.098, 0.097, 0.096, 0.095, 0.094, 0.093, 0.092, 0.091, or 0.09.

11. The use or method of claim 10, wherein the A β 42/40 ratio that indicates amyloid positive status is 0.092 to 0.094.

12. The use or the method of any one of claims 2, 5, or 6, wherein an increase in the A β 42/40 ratio above 0.092 to 0.094 indicates a treatment effect.

13. The use of any one of claims 1-3, 5, 7, 8, or 10-12, or the method of any one of claims 4, 6, or 9-12, wherein the subject has AD.

14. The use of any one of claims 1-3, 5, 7, 8, or 10-13, or the method of any one of claims 4, 6, or 9-13, wherein the subject has early AD.

15. The use of any one of claims 1-3, 5, 7, 8, or 10-12, or the method of any one of claims 4, 6, or 9-12, wherein the subject has pre-Alzheimer's disease (pre-AD).

16. The use of any one of claims 1-3, 5, 7, 8, 10-12, or 15, or the method of any one of claims 4, 6, 9-12, or 15, wherein the subject is cognitively normal but exhibits at least one biomarker of AD.
17. The use of any one of claims 1-3, 5, 7, 8, or 10-14, or the method of any one of claims 4, 6, or 9-14, wherein the subject has been diagnosed with
- a. mild cognitive impairment due to AD - intermediate likelihood and/or has been diagnosed as having mild AD dementia;
 - b. mild cognitive impairment due to Alzheimer's disease - intermediate likelihood by National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria;
 - c. mild cognitive impairment due to Alzheimer's disease - intermediate likelihood by a CDR global score of 0.5 and a Memory Box score of 0.5 or greater before treatment;
 - d. mild cognitive impairment due to AD - intermediate likelihood by a history of subjective memory decline with gradual onset and slow progression over the last 1 year before treatment, e.g., as corroborated by an informant;
 - e. mild AD dementia by the NIA-AA core clinical criteria for probable Alzheimer's disease dementia; or
 - f. mild AD dementia by a CDR score of 0.5 to 1.0 and a Memory Box score of 0.5 or greater before treatment.
18. The use of any one of claims 1, 3, or 10-17, or the method of any one of claims 4, or 9-17, wherein an amyloid-positive status is confirmed by a PET assessment, a CSF assessment of A β (1-42), MRI, retinal amyloid accumulation, and/or specific behavioral/cognitive phenotypes.
19. The use of any one of claims 1, 3, 5, 7, 8, 10-18, or the method of any one of claims 4, 6, or 9-18, wherein the subject has at least one copy of the ApoE4 gene.
20. The use of any one of claims 1-3, 5, 7, 8, 10-18, or the method of any one of claims 4, 6, or 9-19, wherein the A β 42/40 ratio is measured using an LC MS/MS platform.

21. The use of any one of claims 2, 5, 7, 8, or 13-20, or the method of any one of claims 6 or 13-20, wherein an elevated A β _{42/40} ratio above 0.092 to 0.094 indicates that the treatment has converted the subject from amyloid-positive to amyloid-negative status.
22. The use of any one of claims 2, 5, 7, 8, or 13-20, or the method of any one of claims 6 or 13-20, wherein the treatment is discontinued if it does not result in an A β _{42/40} ratio that indicates a conversion to amyloid negative status.
23. The use of any one of claims 1-3, 5, 7, 8, or 10-22, or the method of any one of claims 4, 6, or 9-22, wherein the treatment comprises an intravenous administration of the anti-A β protofibril antibody at a therapeutically effective dose of 10 mg/kg relative to the weight of the subject.
24. The use or the method of claim 23, wherein the therapeutically effective dose is to be administered every 2 weeks.
25. The use of any one of claims 1-3, 5, 7, 8, or 10-22, or the method of any one of claims 4, 6, or 9-22, wherein the treatment comprises a subcutaneous administration of a therapeutically effective dose of the anti-A β protofibril antibody.
26. The use of claim 26, wherein the therapeutically effective dose of the anti-A β protofibril antibody is 720 mg.
27. The use or the method of claim 25 or claim 26, wherein the therapeutically effective dose is to be administered weekly.
28. The use or the method of any one of claims 23-27, wherein the frequency of administration is reduced after 18 months or 24 months of treatment.
29. The use or method of any one of claims 23-28, wherein the dosage of the anti-A β protofibril antibody is reduced after 18 months or 24 months of treatment.

30. The use or method of any one of claims 23-29, wherein the subject is switched to a maintenance dosing regimen after 18 months or 24 months of treatment.
31. The use or method of any one of claims 23-30, wherein the subject is switched to a maintenance dosing regimen when the A β _{42/40} ratio indicates amyloid negative status.
32. The use or method of claim 31, wherein the A β _{42/40} ratio that indicates amyloid negative status is 0.092.
33. The use or the method of any one of claims 30-32, wherein the maintenance dosing regimen comprises an intravenous infusion of the anti-A β protofibril antibody at a therapeutically effective dose of 10 mg/kg relative to the weight of the subject, to be administered monthly.
34. The use or the method of any one of claims 30-32, wherein the maintenance dosing regimen comprises subcutaneous administration of the anti-A β protofibril antibody at a therapeutically effective dose of 360 mg, to be administered weekly, or at a dose that is 50% of the dose administered during the treatment period.
35. The use or the method of any one of claims 30-34, wherein a decrease in p-tau₁₈₁ or p-tau₂₁₇ is detected in a blood and/or CSF sample from the subject before switching to a maintenance dose.
36. The use or the method of any one of claims 30-35, wherein a brain amyloid negativity as measured by PET SUVR is detected in the subject before switching to a maintenance dose, e.g., a florbetapir PET SUVR level at or below 1.17.
37. The use or the method of any one of claims 30-36, wherein the maintenance dose is to be administered at a dose and/or frequency selected to maintain

a. an A β 42/40 ratio in a blood and/or CSF sample from the patient that indicates amyloid negative status; and/or

b. a florbetapir PET SUVR level at or below 1.17.

38. The use of any one of claims 1-3, 5, 7, 8, or 10-37, or the method of any one of claims 4, 6, or 9-37, wherein the subject is sequentially or simultaneously to be administered at least one additional AD medication, e.g., E2814.

39. The use of any one of claims 1-3, 5, 7, 8, or 10-38, or the method of any one of claims 4, 6, or 9-38, wherein the treatment results in:

a. a reduction or a slowing of increase of cerebrospinal fluid biomarkers, e.g., total tau, phosphorylated tau, neurogranin, neurofilament light peptide; and/or

b. a reduction or a slowing of increase of plasma or serum biomarkers, e.g., total tau, phosphorylated tau, p-tau 181, p-tau217, p-tau231, glial fibrillary acidic protein (GFAP), neurofilament light (NfL); and/or

c. an increase or a slowing of decrease of A β 1-42,
as compared to before treatment.

40. The use of any one of claims 1-3, 5, 7, 8, or 10-39, or the method of any one of claims 4, 6, or 9-39, wherein the treatment

a. delays clinical decline as determined by ADCOMS;

b. delays clinical decline as determined by ADAS MCI-ADL;

c. delays clinical decline as determined by modified iADRS;

d. delays clinical decline as measured by a CDR-SB; or

e. delays clinical decline as measured by an ADAS-Cog.

41. The use of any one of claims 1-3, 5, 7, 8, or 10-40, or the method of any one of claims 4, 6, or 9-40, further comprising monitoring for ARIA, e.g., ARIA-E and/or ARIA-H, e.g., as observed by MRI.

42. The use of any one of claims 1-3, 5, 7, 8, or 10-41, or the method of any one of claims 4, 6, or 9-41, wherein the use does not require a titration step prior to administering to the subject a first therapeutically effective dose of the anti-A β protofibril antibody.

43. The use of any one of claims 1-3, 5, 7, 8, or 10-42, or the method of any one of claims 4, 6, or 9-42, wherein prior to treatment, the subject has intermediate brain amyloid, e.g., as measured by PET SUVR.

44. The use of any one of claims 1-3, 5, 7, 8, or 10-43, or the method of any one of claims 4, 6, or 9-44, wherein the anti-A β protofibril antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 9 and a light chain comprising an amino acid sequence of SEQ ID NO: 10.

45. The use of any one of claims 1-3, 5, 7, 8, or 10-44, or the method of any one of claims 4, 6, or 9-44, wherein the concentration of amyloid β 1-42 (A β 42) and a concentration of amyloid β 1-40 (A β 40) is measured in a blood sample obtained from the subject.