

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 a level of p-tau181 in a blood and/or CSF sample that indicates amyloid positive status; 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 level of p-tau181 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 level of p-tau181 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 level of p-tau181 is reduced as compared to the first level of p-tau181,

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. 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 level of p-tau181 in a blood and/or CSF sample; and

instructions for selecting the subject for treatment with the anti-A β protofibril antibody if the level of p-tau181 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.

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 level of p-tau181 in a blood and/or CSF sample obtained from the subject to determine a level of p-tau181; and

b. selecting the subject for treatment with the anti-A β protofibril antibody if the level of p-tau181 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. 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 level of p-tau181 in a first blood and/or CSF sample obtained from the subject prior to treatment with a therapeutically effective amount of the anti-A β protofibril antibody;

b. measuring a second level of p-tau181 in a second blood and/or CSF sample obtained from the subject during or after treatment, and

c. comparing the first level of p-tau181 to the second level of p-tau181, wherein a decrease in the second level of p-tau181 as compared to the first level of p-tau181 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.

6. 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 level of p-tau181 in a blood and/or CSF sample obtained from the subject prior to treatment;
- b. a second reagent for measuring a second level of p-tau181 in a blood and/or CSF sample obtained from the subject during and/or after treatment; and
- b. instructions for use in monitoring efficacy of treatment, comprising determining the first level of p-tau181 from the subject prior to treatment, determining the second level of p-tau181 from the subject during or after treatment with a therapeutically effective amount of the anti-A β protofibril antibody, and comparing the second level of p-tau181 to the first level of p-tau181, wherein a decrease in the second level of p-tau181 as compared to the first level of p-tau181 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.

7. The use according to claim 1, the kit according to claim 3, or the method according to claim 4, wherein the level of p-tau181 that indicates amyloid positive status is at or above about 2.2 pg/mL.

8. The use or the method of claim 7, wherein the level of p-tau181 that indicates amyloid positive status is at or above about 2.3 pg/mL.

9. The use according to claim 1 or claim 2, the kit according to claim 3 or claim 6, or the method according to claim 4 or claim 5, wherein the subject has:

- (a) Alzheimer's disease;
- (b) early Alzheimer's disease;
- (c) pre-Alzheimer's disease (pre-AD); or
- (d) is cognitively normal but exhibits at least one biomarker of AD

10. The use according to claim 1 or claim 2, the kit according to claim 3 or claim 6, or the method according to claim 4 or claim 5, wherein the subject has been diagnosed with
- a. mild cognitive impairment due to Alzheimer's disease - intermediate likelihood and/or has been diagnosed as having mild Alzheimer's disease 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 Alzheimer's disease - 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 Alzheimer's disease dementia by the NIA-AA core clinical criteria for probable Alzheimer's disease dementia; or
 - f. mild Alzheimer's disease dementia by a CDR score of 0.5 to 1.0 and a Memory Box score of 0.5 or greater before treatment.
11. The use according to claim 1, the kit according to claim 3, or the method according to claim 4, 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.
12. The use according to claim 1 or claim 2, the kit according to claim 3 or claim 6, or the method according to claim 4 or claim 5, wherein the subject has at least one copy of the ApoE4 gene.
13. The use according to claim 1 or claim 2, the kit according to claim 3 or claim 6, or the method according to claim 4 or claim 5, wherein the level of p-tau181 is measured using an LC MS/MS platform.

14. The use according to claim 1, the kit according to claim 3, or the method according to claim 4, wherein a decreased level of p-tau181 indicates that the treatment has converted the subject from amyloid-positive to amyloid-negative status.

15. The use according to claim 1 or claim 2, the kit according to claim 3 or claim 6, or the method according to claim 4 or claim 5, 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 every 2 weeks.

16. The use according to claim 1 or claim 2, the kit according to claim 3 or claim 6, or the method according to claim 4 or claim 5, wherein the treatment comprises a subcutaneous administration of a therapeutically effective dose of the anti-A β protofibril antibody of 720 mg of the anti-A β protofibril antibody, weekly.

17. The use according to claim 1 or claim 2, the kit according to claim 3 or claim 6, or the method according to claim 4 or claim 5, wherein the subject is switched to a maintenance dosing regimen

(a) after 18 months or 24 months of treatment, or

(b) when the level of p-tau181 in the subject indicates amyloid negative status.

18. The use, the kit, or the method of claim 17, wherein the maintenance dosing regimen comprises (i) 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, administered every 4 weeks, or (ii) a subcutaneous administration of the anti-A β protofibril antibody, optionally at a therapeutically effective dose of either 360 mg, administered weekly, or at a dose that is 50% of the dose administered during the treatment period.

19. The use, the kit, or the method of claim 17, wherein, before switching to a maintenance dose, at least one of the following is detected in the subject:

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 and/or A β 42/40 ratio, as compared to before treatment.

20. The use, the kit, or the method of claim 17, 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.

21. The use, the kit, or the method of claim 17, wherein the maintenance dose is administered at a dose and/or frequency selected to maintain

a. a level of p-tau181 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.

22. The use according to claim 1 or claim 2, the kit according to claim 3 or claim 6, or the method according to claim 4 or claim 5, wherein the subject is sequentially or simultaneously administered at least one additional AD medication, e.g., E2814.

23. The use according to claim 1 or claim 2, the kit according to claim 3 or claim 6, or the method according to claim 4 or claim 5, 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 and/or A β 42/40 ratio, as compared to before treatment.

24. The use according to claim 1 or claim 2, the kit according to claim 3 or claim 6, or the method according to claim 4 or claim 5, 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.
25. The use according to claim 1 or claim 2, the kit according to claim 3 or claim 6, or the method according to claim 4 or claim 5, further comprising monitoring for ARIA, e.g., ARIA-E and/or ARIA-H, e.g., as observed by MRI.
26. The use according to claim 1 or claim 2, the kit according to claim 3 or claim 6, or the method according to claim 4 or claim 5, wherein prior to treatment, the subject has intermediate brain amyloid, e.g., as measured by PET SUVR.
27. The use according to claim 1 or claim 2, the kit according to claim 3 or claim 6, or the method according to claim 4 or claim 5, 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.
28. The use according to claim 1 or claim 2, the kit according to claim 3 or claim 6, or the method according to claim 4 or claim 5, wherein the concentration of level of p-tau181 is measured in a blood sample obtained from the subject.