CLAIMS

1. Use of an anti-Aβ protofibril antibody in the manufacture of a medicament for treatment of a disorder in a subject having, suspected of having, or at risk for developing Alzheimer's disease (AD), wherein the medicament is adapted to be administered according to a dosage regimen comprising:

(a) an initiation dose comprising

(i) subcutaneous administration of the antibody weekly at a dose of 500 mg, or

(ii) intravenous administration of the antibody biweekly at a dose of 10 mg/kg

relative to the weight of the subject; and

(b) a maintenance dose comprising subcutaneous administration of the antibody weekly or biweekly at a dose of 250 mg,

wherein the anti-Aβ protofibril antibody comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO: 5 (HCDR1), SEQ ID NO: 6 (HCDR2), and SEQ ID NO: 7 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO: 8 (LCDR1), SEQ ID NO: 9 (LCDR2), and SEQ ID NO: 10 (LCDR3).

2. Use of the anti-Aβ protofibril antibody for the manufacture of a medicament according to claim 1, wherein treatment of a disorder in the subject comprises at least one of delaying clinical decline, reducing a brain amyloid level, and converting amyloid status from amyloid positive to amyloid negative in the subject.

3. Use of the anti-Aβ protofibril antibody for the manufacture of a medicament according to claim 1 or 2, wherein the medicament is adapted to be administered as an initiation dose comprising subcutaneous administration weekly for at least 18 months, optionally, using an autoinjector (AI) or vial-syringe.

4. Use of the anti-Aβ protofibril antibody for the manufacture of a medicament according to claim 1 or 2, wherein the medicament is adapted to be administered as an initiation dose comprising intravenous administration biweekly for at least 6 months, at least 12 months, at least 18 months, or at least 24 months.

5. Use of the anti-Aβ protofibril antibody for the manufacture of a medicament according to any one of claims 1-4, wherein the medicament is adapted to be administered as a maintenance dose comprising subcutaneous administration weekly, optionally, using an autoinjector (AI) or a vial-syringe.

6. Use of the anti-Aβ protofibril antibody for the manufacture of a medicament according to any one of claims 1-5, wherein (a) the anti-Aβ protofibril antibody comprises a heavy chain variable region comprising SEQ ID NO: 1 and a light chain variable region comprising SEQ ID NO: 2; or (b) the anti-Aβ protofibril antibody is BAN2401 (lecanemab).

7. Use of the anti-Aβ protofibril antibody for the manufacture of a medicament according to any one of claims 1-6, wherein the subject shows a change in at least one biomarker associated with AD pathology prior to treatment and/or a change in at least one biomarker associated with AD pathology during and/or after treatment as compared to a baseline made prior to treatment.

8. Use of the anti-Aβ protofibril antibody for the manufacture of a medicament according to claim 7, wherein the change in the biomarker prior to treatment is selected from:

(a) increased amyloid in the brain, e.g., as measured by amyloid PET (e.g., a centiloid measure of about 20–40, e.g., 20–32),

(b) increased tau in the brain, e.g., as measured by positron emission tomography (PET),

(c) decreased cerebrospinal fluid levels of a ratio of Aβ1–42/1–40 and/or increased total tau, p-tau (e.g., p-tau181, p-tau217, p-tau231), ratios of p-tau/np-tau, neurogranin, and/or neurofilament light chain (NfL), or

(d) decreased blood serum or plasma levels of a ratio of Aβ1–42/1–40 and/or increased total tau, phosphorylated tau (P-tau) isoforms (e.g., P-tau181, P-tau217, P-tau231), ratios of p-tau/np-tau, GFAP, and/or neurofilament light chain (NfL).

9. Use of the anti-Aβ protofibril antibody for the manufacture of a medicament according to claim 7 or 8, wherein the change and/or difference in the measurement during or after treatment is selected from:

(a) decreased amyloid in the brain, e.g., as measured by amyloid PET,

(b) decreased tau in the brain, e.g., as measured by PET,

(c) increased cerebrospinal fluid Aβ1–42/1–40 and/or decreased total tau, p-tau (e.g., p-tau181, p-tau217, p-tau231), ratios of p-tau/np-tau, neurogranin, and/or NfL, or

(d) increased blood serum or plasma Aβ1–42/1–40 and/or decreased total tau, phosphorylated tau (P-tau) isoforms (e.g., P-tau181, P-tau217, P-tau231), ratios of p-tau/np-tau, GFAP, and/or NfL.

10. Use of the anti-Aβ protofibril antibody for the manufacture of a medicament according to any one of claims 1-9, wherein the subject is:

(a) amyloid-positive prior to administration;

(b) ApoE4-positive;

(c) 65 to 80 years old; or

(d) 55 to 64 years old and has at least one risk factor selected from:

(i) a first-degree relative diagnosed with dementia onset before age 75;

(ii) at least one apolipoprotein E4 (APOE4) allele; and

(iii) elevated brain amyloid according to PET or CSF testing prior to said administration.

11. Use of the anti-Aβ protofibril antibody for the manufacture of a medicament according to any one of claims 1-10, wherein the subject:

(a) has Alzheimer's disease;

(b) has early Alzheimer's disease;

(c) is suspected of having Alzheimer's disease;

(d) is at risk for developing Alzheimer's disease; or

(e) has pre-AD.

12. Use of the anti-Aβ protofibril antibody for the manufacture of a medicament according to any one of claims 1-11, wherein the subject does not have cognitive impairment, or the subject has been diagnosed with:

(a) mild cognitive impairment due to Alzheimer's disease – intermediate likelihood and/or mild Alzheimer's disease dementia;

(b) mild cognitive impairment due to Alzheimer's disease – intermediate likelihood by NIA-AA criteria;

(c) mild cognitive impairment due to Alzheimer's disease – intermediate likelihood by CDR 0.5 and Memory Box score ≥0.5;

(d) mild cognitive impairment due to Alzheimer's disease – intermediate likelihood based on subjective memory decline over the prior year;

(e) mild Alzheimer's disease dementia by NIA-AA criteria; or

(f) mild Alzheimer's disease dementia by CDR 0.5–1.0 and Memory Box score ≥0.5.

13. Use of the anti-Aβ protofibril antibody for the manufacture of a medicament according to any one of claims 1-12, wherein, prior to administration, the subject has:

a. a Global Clinical Dementia Rating (CDR) score of 0;

b. a Mini-Mental State Examination (MMSE) score ≥27, with educational adjustments;

c. a Wechsler Memory Scale-Revised Logical Memory subscale II (WMS-R LM II) score of at least one standard deviation below age-adjusted mean in the WMS-IV LMII of less than or equal to 15 for a subject of age ranging from 50 to 64 years, of less than or equal to 12 for a subject of age ranging from 65 to 69 years, of less than or equal to 11 for a subject of age ranging from 70 to 74

years, of less than or equal to 9 for a subject of age ranging from 75 to 79 years, and of less than or equal to 7 for a subject of age ranging from 80 to 90 years.

14. Use of the anti-Aβ protofibril antibody for the manufacture of a medicament according to any one of claims 1-13, wherein the subject is receiving

(a) a thrombolytic, optionally selected from aspirin or a fibrinolytic agent; or

(b) an anti-platelet agent,

wherein the subject is not receiving an anticoagulant.

15. Use of the anti-Aβ protofibril antibody for the manufacture of a medicament according to any one of claims 1-14, wherein the subject:

(a) is monitored for development of ARIA, optionally wherein the dose of the anti-Aβ protofibril antibody at a subcutaneous dose of 500 mg reduces the risk for developing ARIA relative to a higher dose of the antibody, such as a subcutaneous dose of 720 mg;

(b) has not had a brain hemorrhage event, e.g., a microhemorrhage or intracerebral hemorrhage, or an ARIA event, prior to treatment; or

(c) has had or is at an increased risk for a brain hemorrhage event, e.g., a microhemorrhage or intracerebral hemorrhage, or an ARIA event, prior to treatment.

16. Use of the anti-Aβ protofibril antibody for the manufacture of a medicament according to any one of claims 1-15, wherein the subject previously received a first anti-Aβ antibody.

17. Use of a second anti-Aβ antibody for the manufacture of a medicament for treating a subject having early AD, suspected of having early AD, or at risk for early AD, who has received a first anti-Aβ antibody in an initiation dose, wherein the second anti-Aβ antibody is formulated for subcutaneous administration of the antibody weekly or biweekly in a maintenance dose of 250 mg, wherein the second anti-Aβ antibody comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO: 5 (HCDR1), SEQ ID NO: 6 (HCDR2), and SEQ ID NO: 7 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO: 8 (LCDR1), SEQ ID NO: 9 (LCDR2), and SEQ ID NO: 10 (LCDR3).

18. Use of the antibody for the manufacture of a medicament according to claim 16 or 17, wherein the first anti-Aβ antibody is aducanumab, bapineuzumab, crenezumab, donanemab, gantenerumab, lecanemab, or solanezumab, preferably donanemab.

19. Use of an anti-Aβ protofibril antibody for the manufacture of a medicament for treating a subject having early AD, suspected of having early AD, or at risk for early AD, wherein the medicament is adapted to be administered according to a dosage regimen comprising:

(a) a first initiation dose comprising intravenous administration of the antibody biweekly at a dose of 10 mg/kg relative to the weight of the subject; and

(b) a second initiation dose comprising subcutaneous administration of the antibody weekly at a dose of 720 mg or 500 mg; and

(a) a maintenance dose comprising subcutaneous administration of the antibody weekly at a maintenance dose of 250 mg, after 18 months or 24 months on the first and second initiation doses,

wherein the anti-Aβ protofibril antibody comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO: 5 (HCDR1), SEQ ID NO: 6 (HCDR2), and SEQ ID NO: 7 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO: 8 (LCDR1), SEQ ID NO: 9 (LCDR2), and SEQ ID NO: 10 (LCDR3).