

CLAIMS

1. Use of a binding member that selectively binds human amyloid beta 1-42 peptide ($A\beta$ 1-42) in the manufacture of a medicament for treating Alzheimer's disease (AD) in a patient, wherein a therapeutically effective amount of the binding member is to be administered to the patient, and wherein the binding member decreases the level of neurofilament light chain (NfL) in the patient compared with the level of NfL in the patient pre-treatment with the binding member.
2. Use of a binding member that selectively binds human amyloid beta 1-42 peptide ($A\beta$ 1-42) in the manufacture of a medicament for preventing neuronal axonal damage in a patient, wherein a therapeutically effective amount of the binding member is to be administered to the patient having or at risk of neuronal axonal damage, and
wherein the binding member decreases the level of neurofilament light chain (NfL) in the patient compared with the level of NfL in the patient pre-treatment with the binding member.
3. The use of claim 1 or 2, wherein the binding member decreases the level of NfL in the plasma of the patient.
4. The use of any one of claims 1 to 3, wherein the binding member decreases the level of NfL in the cerebrospinal fluid (CSF) of the patient.
5. The use of any one of claims 1 to 4, wherein the binding member decreases the level of NfL by at least 10%, preferably at least 20%, more preferably at least 30%, even more preferably at least 50% compared with the level of NfL in the patient pre-treatment with said binding member.
6. The use of any one of the preceding claims, wherein the NfL level is measured by ELISA, optionally SIMOA-HD1.

7. The use of any one of the preceding claims, wherein the patient is positive for amyloid, and wherein optionally the patient is:

- (a) negative for tau;
- (b) negative for neurodegeneration;
- (c) negative for tau and negative for neurodegeneration;
- (d) positive for tau;
- (e) positive for neurodegeneration;
- (f) positive for tau and positive for neurodegeneration;
- (g) positive for tau and negative for neurodegeneration; or
- (h) negative for tau and positive for neurodegeneration.

8. The use of claim 7, further comprising identifying the patient as amyloid positive, and optionally identifying the patient as:

- (a) negative for tau;
- (b) negative for neurodegeneration;
- (c) negative for tau and negative for neurodegeneration;
- (d) positive for tau;
- (e) positive for neurodegeneration;
- (f) positive for tau and positive for neurodegeneration;
- (g) positive for tau and negative for neurodegeneration; or
- (h) negative for tau and positive for neurodegeneration.

9. The use of claim 7 or 8 wherein a patient's status as (i) amyloid positive or negative; (ii) tau positive or negative; and/or (iii) neurodegeneration positive or negative; is independently determined on the basis of:

- (a) a CSF marker;
- (b) a plasma marker; and/or
- (c) an imaging marker.

10. The use of claim 9, wherein:

- (a) (i) the CSF marker for amyloid is CSF A β 1-42; (ii) the CSF marker for tau is CSF phospho-tau; and/or (iii) the CSF marker for neurodegeneration is CSF total tau; and/or
 - (b) (i) the imaging marker for amyloid is amyloid imaging; (ii) the imaging marker for tau is tau imaging; and/or (iii) the imaging marker for neurodegeneration is magnetic resonance imaging or fluorodeoxyglucose positron emission tomography.
- 11. The use of any one of the preceding claims, wherein the binding member that selectively binds human A β 1-42 is an antibody.
- 12. The use of claim 11, wherein the antibody that selectively binds human A β 1-42 binds to A β 1-42 with a dissociation constant (K_D) of 500 pM or less and either does not bind to A β 1-40 or binds A β 1-40 with a K_D greater than 1 mM.
- 13. The use of claim 11 or 12, wherein the antibody comprises:
 - (a) a VH domain comprising the MEDI1814 set of HCDRs, wherein the amino acid sequences of the Abet0380 HCDRS are
 - HCDR1 SEQ ID NO: 1
 - HCDR2 SEQ ID NO: 2
 - HCDR3 SEQ ID NO: 3or comprising the MEDI1814 set of HCDRs with one or two amino acid mutations; and
 - (b) a VL domain comprising the MEDI1814 set of LCDRs, wherein the amino acid sequences of the MEDI1814 LCDRS are
 - LCDR1 SEQ ID NO: 4
 - LCDR2 SEQ ID NO: 5
 - LCDR3 SEQ ID NO: 6or comprising the MEDI1814 set of LCDRs with one or two amino acid mutations.
- 14. The use of claim 13, wherein the antibody comprises:

- (a) (i) a MEDI1814 VH domain amino acid sequence of SEQ ID NO: 9, or comprising that amino acid sequence with one or two amino acid mutations; and a MEDI1814 VL domain amino acid sequence of SEQ ID NO: 10, or comprising that amino acid sequence with one or two amino acid mutations; or
- (b) (i) a Abet0380 VH domain amino acid sequence of SEQ ID NO: 7, or a germlined version thereof, or comprising that amino acid sequence with one or two amino acid mutations; and (ii) a Abet0380 VL domain amino acid sequence of SEQ ID NO: 8, or a germlined version thereof, or comprising that amino acid sequence with one or two amino acid mutations.

15. The use of any one of claims 11 to 14, wherein the antibody comprises a VH and a VL domain encoded by the Abet0380-GL nucleic acid sequence deposited under accession number 41890.

16. The use of any one claims 11 to 15, wherein the antibody is a human IgG, optionally a human IgG1 or human IgG2.

17. The use of claim 16, wherein the antibody is a human IgG1-TM, IgG1-YTE or IgG1-TM-YTE.

18. The use of any one claims 11 to 17, wherein the antibody is to be administered at a dose of ≥ 200 mg, optionally wherein the antibody is to be administered at a dose of about 200 mg, more preferably at a dose of about 300 mg, even more preferably at a dose of about 900 mg or even more preferably at a dose of about 1800 mg.

19. The use of any one of claims 11 to 18, wherein the antibody is to be administered at intervals of 3.5 to 4.5 weeks; optionally wherein the antibody is to be administered at intervals of 4 weeks (Q4W).

20. The use of any one of the preceding claims, wherein the binding member is to be administered intravenously or subcutaneously to the patient.

21. The use of any one of claims 2 to 20, wherein the neuronal axonal damage is associated with Alzheimer's Disease (AD), optionally mild-to-moderate AD, pre-symptomatic AD, and/or mild cognitive impairment due to AD.
22. The use of any one of the preceding claims, wherein the binding member decreases the level of pTau217 in the patient compared with the level of pTau217 in the patient pre-treatment with the binding member.
23. The use of any one of the preceding claims, wherein the binding member: (i) decreases the level of free A β 1-42 in the patient compared with the level of free A β 1-42 in the patient pre-treatment with the binding member; and/or increases the level of total A β 1-42 in the patient compared with the level of total A β 1-42 in the patient pre-treatment with the binding member.
24. The use of any one of the preceding claims, wherein the binding member is comprised within a pharmaceutical composition.
25. A binding member that selectively binds human amyloid beta 1-42 peptide (A β 1-42) for use in therapy, wherein the binding member decreases the level of neurofilament light chain (NfL) in the patient compared with the level of NfL in the patient pre-treatment with the binding member.
26. A method for assessing the efficacy of a binding member that selectively binds human amyloid beta 1-42 peptide (A β 1-42) for treating Alzheimer's disease, or for preventing neuronal axonal damage, the method comprising determining the level of NfL in a patient pre-treatment with the binding member and after treatment with the binding member, wherein the prevention of neuronal axonal damage is efficacious if the level of NfL in the patient is decreased after treatment with the binding member compared with the NfL level in the patient pre-treatment with the binding member.
27. The method of claim 26, wherein the treatment of Alzheimer's disease or the prevention of neuronal axonal damage is efficacious if the level of NfL in the plasma of the patient is decreased after treatment with the binding member, optionally wherein the decrease in the plasma level of NfL is a decrease of at least 30%.

28. The method of claim 26 or 27, wherein the treatment of Alzheimer's disease or the prevention of neuronal axonal damage is efficacious if the level of NfL in the CSF of the patient is decreased after treatment with the binding member, optionally wherein the decrease in the CSF level of NfL is a decrease of at least 30%.

29. A method for identifying a patient as suitable for the use of any one of claims 1 and 3 to 24, or the use of any one of claims 2 to 24, the method comprising assessing the amyloid status of a patient using a CSF marker, a plasma marker and/or an imaging marker pre-treatment with the binding member, and wherein the patient is identified as suitable for the treatment of Alzheimer's disease or the prevention of neuronal axonal damage wherein the amyloid status of the patient is amyloid positive.

30. The method of claim 29, wherein the method further comprises assessing (i) the tau status; (ii) the neurodegeneration status; or (iii) the tau status and the neurodegeneration status of the patient pre-treatment with the binding member, wherein a CSF marker and/or an imaging marker is independently selected for tau and/or neurodegeneration, and wherein the patient is identified as suitable for the treatment of Alzheimer's disease or the prevention of neuronal axonal damage wherein the patient is:

- (a) negative for tau;
- (b) negative for neurodegeneration;
- (c) negative for tau and negative for neurodegeneration;
- (d) positive for tau;
- (e) positive for neurodegeneration;
- (f) positive for tau and positive for neurodegeneration;
- (g) positive for tau and negative for neurodegeneration; or
- (h) negative for tau and positive for neurodegeneration.

31. The method of claim 29 or 30, wherein:

- (a) (i) the CSF marker for amyloid is CSF A β 1-42; (ii) the CSF marker for tau is CSF phospho-tau; and/or (iii) the CSF marker for neurodegeneration is CSF total tau; and/or
- (b) (i) the imaging marker for amyloid is amyloid imaging; (ii) the imaging marker for tau is tau imaging; and/or (iii) the imaging marker for neurodegeneration is magnetic resonance imaging or fluorodeoxyglucose positron emission tomography.

32. A kit comprising (i) a binding member that selectively binds human amyloid beta 1-42 peptide (A β 1-42); and (ii) an antibody that specifically binds to NfL; wherein optionally the binding member that selectively binds human A β 1-42 is an antibody as defined in any one of claims 12 to 17.