# ANTI-N3pGlu AMYLOID BETA PEPTIDE ANTIBODIES AND USES THEREOF

The present invention relates to treatment of a disease with anti-N3pGlu Aβ antibodies, wherein the disease is characterized by deposition of Amyloid Beta (Aβ) in a patient. More specifically, the present invention relates to a short term induction treatment with N3pGlu Aβ antibodies of a disease characterized by deposition of Aβ in the brain, including Alzheimer's disease (AD), Down's syndrome, and cerebral amyloid angiopathy (CAA).

The deposits found in plaques of human patients are comprised of a heterogeneous mixture of Aβ peptides. N3pGlu Aβ, also referred to as N3pE Aβ, Aβ pE3-42, or $A\beta_{p3\text{-}42}$, is a truncated form of Aβ peptide and is found only in plaques. N3pGlu Aβ lacks the first two amino acid residues at the N-terminus of human Aβ and has a pyroglutamate which was derived from the glutamic acid at the third amino acid position. Although N3pGlu Aβ peptide is a minor component of the deposited Aβ in the brain, studies have demonstrated that N3pGlu Aβ peptide has aggressive aggregation properties and accumulates early in the deposition cascade.

Antibodies to N3pGlu Aβ are known in the art. For example, U.S. Patent Number 8,679,498 discloses anti-N3pGlu Aβ antibodies and methods of treating diseases such as Alzheimer's disease, with the antibodies. Passive immunization by long term chronic administration of antibodies against the Aβ, including N3pGlu Aβ, found in deposits has been shown to disrupt the Aβ aggregates and promote the clearance of plaques in the brain in various animal models. However, in humans long term chronic administration of Aβ antibodies has led to adverse events that include amyloid-related imaging abnormalities (ARIA), suggestive of vasogenic edema and sulcal effusions (ARIA-E), as well as microhaemorrhages and haemosiderin deposits (ARIA-H) as well as infusion site reactions and risk of immunogenicity. See Piazza and Winblad, "Amyloid-Related Imaging Abnormalities (ARIA) in Immunotherapy Trials for Alzheimer's Disease: Need for Prognostic Biomarkers?" Journal of Alzheimer's Disease, 52 (2016) 417-420.

Summary

In one aspect of the present disclosure, there is provided a use of an anti-N3pGlu Aβ antibody in the manufacture of a medicament for treating or preventing the progression of a disease characterized by amyloid beta (Aβ) deposits in the brain of a patient, wherein an induction dose of 10 to 60 mg/kg for a period of 6 months or less is to be administered to the patient, and wherein the anti-N3pGlu Aβ antibody comprises a light chain variable region (LCVR) and a

heavy chain variable region (HCVR), wherein said LCVR and HCVR are selected from the group consisting of:

a) LCVR of SEQ ID NO: 25 and HCVR of SEQ ID NO: 26;
b) LCVR of SEQ ID NO: 25 and HCVR of SEQ ID NO: 27;
c) LCVR of SEQ ID NO: 32 and HCVR of SEQ ID NO: 34;
d) LCVR of SEQ ID NO: 9 and HCVR of SEQ ID NO: 8; and
e) LCVR of SEQ ID NO: 10 and HCVR of SEQ ID NO: 8.

WE CLAIM:

1. Use of an anti-N3pGlu Aβ antibody in the manufacture of a medicament for treating or preventing the progression of a disease characterized by amyloid beta (Aβ) deposits in the brain of a patient, wherein an induction dose of 10 to 60 mg/kg for a period of 6 months or less is to be administered to the patient,

and wherein the anti-N3pGlu Aβ antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein said LCVR and HCVR are selected from the group consisting of:

a) LCVR of SEQ ID NO: 25 and HCVR of SEQ ID NO: 26;
b) LCVR of SEQ ID NO: 25 and HCVR of SEQ ID NO: 27;
c) LCVR of SEQ ID NO: 32 and HCVR of SEQ ID NO: 34;
d) LCVR of SEQ ID NO: 9 and HCVR of SEQ ID NO: 8; and
e) LCVR of SEQ ID NO: 10 and HCVR of SEQ ID NO: 8.

2. The use according to claim 1, wherein the anti-N3pGlu Aβ antibody comprises a light chain (LC) and a heavy chain (HC), wherein said LC and HC are selected from the group consisting of:

a) LC of SEQ ID NO: 28 and HC of SEQ ID NO: 29;
b) LC of SEQ ID NO: 28 and HC of SEQ ID NO:30;
c) LC of SEQ ID NO: 33 and HC of SEQ ID NO: 35;
d) LC of SEQ ID NO: 12 and HC of SEQ ID NO: 11; and
e) LC of SEQ ID NO: 13 and HC of SEQ ID NO: 11.

3. The use according to claim 2, wherein the anti-N3pGlu Aβ antibody comprises a light chain (LC) of SEQ ID NO: 28 and a heavy chain (HC) of SEQ ID NO: 29.

4. The use according to claim 1, wherein the anti-N3pGlu Aβ antibody is to be administered one-time.

5. The use according to claim 1, wherein the anti-N3pGlu Aβ antibody is to be administered every two weeks for a period of 6 months.

6. The use according to claim 1, wherein the anti-N3pGlu Aβ antibody is to be administered monthly for a period of 6 months.

7. The use according to claim 1, wherein the disease characterized by Aβ deposit in the brain of a patient is selected from preclinical or clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy.

8. The use according to claim 1, wherein the disease characterized by Aβ deposit in the brain of a patient is selected from preclinical AD, prodromal AD, mild AD, moderate AD and severe AD.

9. The use according to claim 1, wherein the induction dose of the anti-N3pGlu Aβ antibody to be administered to the patient is 10 to 40 mg/kg.

10. The use according to claim 1, wherein the induction dose of the anti-N3pGlu Aβ antibody to be administered to the patient is 10 to 20 mg/kg.

11. The use according to claim 1, wherein the induction dose of the anti-N3pGlu Aβ antibody to be administered to the patient is 15 to 30 mg/kg.

12. The use according to claim 1, wherein the induction dose of the anti-N3pGlu Aβ antibody to be administered to the patient is selected from 10 mg/kg, 15 mg/kg, 20 mg/kg and 40 mg/kg.

13. The use according to claim 1, wherein the induction dose of the anti-N3pGlu Aβ antibody to be administered to the patient is 10 mg/kg.

14. The use according to claim 1, wherein the induction dose of the anti-N3pGlu Aβ antibody to be administered to the patient is 20 mg/kg.

15. The use according to claim 1, wherein the induction dose of the anti-N3pGlu Aβ antibody to be administered to the patient is 40 mg/kg.

16. The use according to claim 1, wherein the induction dose which is to be administered to the patient is to be followed by a maintenance dose with the same anti-N3pGlu Aβ antibody every 2, 3, 5 or 10 years post completion of the induction dose treatment.