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(54) Title: ANTI-N3pGlu AMYLOID BETA ANTIBODIES, DOSES, AND USES THEREOF

(57) Abstract: The treatment or prevention of a disease characterized by deposition of amyloid beta (Aβ) plaques in the brain of a human subject, in particular intravenous and subcutaneous doses and dosing regimens of anti-N3pG antibodies.

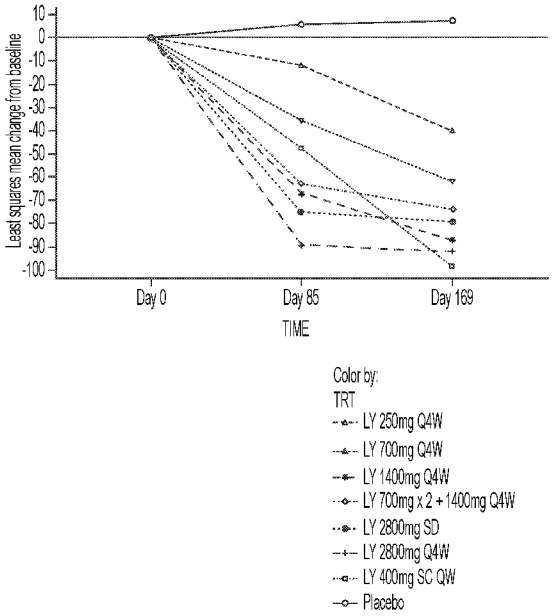

FIG. 1

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[Continued on next page]

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ANTI-N3pGlu AMYLOID BETA ANTIBODIES, DOSES, AND USES THEREOF

REFERENCE TO SEQUENCE LISTING

[001] The instant application contains a Sequence Listing which has been submitted electronically in ST.26 XML format and is hereby incorporated by reference in its entirety. Said ST.26 XML Sequence Listing was created on October 23, 2023, is named 30394.xml and is 15,353 bytes in size.

FIELD OF THE INVENTION

[002] The present invention is related to anti-N3pGlu Aβ antibodies, their doses, their dosing regimens, and methods of using such antibodies, including uses for the treatment or prevention of a disease characterized by deposition of Aβ in the brain of a subject. The diseases that can be treated or prevented using antibodies, dosing regimens, or methods disclosed herein include, e.g., Alzheimer's disease (AD), Down's syndrome, and cerebral amyloid angiopathy (CAA).

BACKGROUND

[003] Alzheimer's disease (AD) is an age-related neurodegenerative disorder, characterized by a progressive decline in cognitive function and ability to perform activities of daily living that can ultimately lead to death due to complications of the disease. Pathological hallmarks of AD, identified at autopsy, include the presence of neuritic Aβ plaques, neurofibrillary tangles (Selkoe, "The Molecular Pathology of Alzheimer's Disease," Neuron 6(4):487-498 (1991); Hyman et al., "National Institute on Aging–Alzheimer's Association Guidelines on Neuropathologic Assessment of Alzheimer's Disease," Alzheimers Dement. 8(1):1-13 (2012)), and neuronal loss in brain regions important for cognition, such as the hippocampus and temporal cortex (Padurariu et al., "Hippocampal Neuronal Loss in the CA1 and CA3 Areas of Alzheimer's Disease Patients," Psychiatr Danub. 24(2):152 158 (2012).

[004] The amyloid hypothesis of AD states that the production and deposition of Aβ are early and necessary events in the pathogenesis of AD (Hardy and Selkoe, "The Amyloid Hypothesis of Alzheimer's Disease: Progress and Problems on the Road to Therapeutics," Science 297(5580):353-356 (2002)). Amyloid beta is formed by the

proteolytic cleavage of a larger glycoprotein called amyloid precursor protein (APP). APP is an integral membrane protein expressed in many tissues, but especially in neuron synapses. APP is cleaved by γ-secretase to release the Aβ peptide, which encompasses a group of peptides ranging in size from 37-49 amino acid residues. Aβ monomers aggregate into various types of higher order structures including oligomers, protofibrils, and amyloid fibrils. Amyloid oligomers are soluble and may spread throughout the brain, while amyloid fibrils are larger and insoluble and can further aggregate to form amyloid plaques. The amyloid plaques found in human patients include a heterogeneous mixture of Aβ peptides, some of which include N-terminal truncations and further may include N-terminal modifications such as an N-terminal pyroglutamate residue (pGlu).

[005] The role for amyloid plaques in driving disease progression is supported by study of uncommon genetic variants that either increase or decrease Aβ deposition (Fleisher et al., "Associations Between Biomarkers and Age in the Presenilin 1 E280A Autosomal Dominant Alzheimer Disease Kindred: A Cross-sectional Study," JAMA Neurol 72:316-24 (2015); Jonsson et al., "A Mutation in APP Protects Against Alzheimer's Disease and Age-related Cognitive Decline," Nature 488:96-9 (2012)). In addition, presence of amyloid plaques early in the disease increases the likelihood of progression of mild cognitive impairment (MCI) to AD dementia (Doraiswamy et al., "Amyloid-β Assessed by Florbetapir F18 PET and 18-month Cognitive Decline: A Multicenter Study," Neurology 79:1636-44 (2012)). Another hallmark neuropathological lesion of AD is comprised of intraneuronal, neurofibrillary tangles consisting of tau proteins, which spread through the brain and mark disease progression (Braak and Braak, "Evolution of the Neuropathology of Alzheimer's Disease," Acta Neurol Scand Suppl. 165:3-12 (1996). The presence of both is necessary for the diagnosis of definite AD, although scientific understanding of the relationship between these 2 pathologies is still evolving.

[006] Interventions or therapies aiming at removal of Aβ plaques are hypothesized to slow the clinical progression of AD. Antibodies targeting Aβ have shown promise as a therapeutic for Alzheimer's disease in both preclinical and clinical studies. Despite this promise, many antibodies targeting amyloid have failed to meet therapeutic endpoints in multiple clinical trials. The history of anti-amyloid clinical trials spans almost two decades and has, for the most part, cast doubt on the potential of such therapies to

effectively treat AD (Aisen et al., "The Future of Anti-amyloid Trials," The Journal of Prevention of Alzheimer's Disease 7:146-151 (2020), Budd et al., "Clinical Development of Aducanumab, an Anti-Aβ Human Monoclonal Antibody Being Investigated for the Treatment of Early Alzheimer's Disease," The Journal of Prevention of Alzheimer's Disease 4(4):255-263 (2017) and Klein et al., "Gantenerumab Reduces Amyloid-β Plaques in Patients with Prodromal to Moderate Alzheimer's Disease: A PET Substudy Interim Analysis," Alzheimer's Research & Therapy 11.1: 1-12 (2019)).

[007] Moreover, some of the anti-amyloid monoclonal antibodies come with significant safety risks. Administration of Aβ antibodies has led to adverse events in humans, such as amyloid-related imaging abnormalities (ARIA), suggestive of vasogenic edema and sulcal effusions (ARIA-E), microhemorrhages and haemosiderin deposits (ARIA-H), infusion site reactions, and risk of immunogenicity. See, e.g., Piazza and Winblad, "Amyloid-Related Imaging Abnormalities (ARIA) in Immunotherapy Trials for Alzheimer's Disease: Need for Prognostic Biomarkers?" Journal of Alzheimer's Disease, 52:417-420 (2016); Sperling, et al., "Amyloid-related Imaging Abnormalities in Patients with Alzheimer's Disease Treated with Bapineuzumab: A Retrospective Analysis," The Lancet Neurology 11.3: 241-249 (2012); Brashear et al., "Clinical Evaluation of Amyloid-related Imaging Abnormalities in Bapineuzumab Phase III Studies," J. of Alzheimer's Disease 66.4:1409-1424 (2018); Budd et al., "Clinical Development of Aducanumab, an Anti-Aβ Human Monoclonal Antibody Being Investigated for the Treatment of Early Alzheimer's Disease," The Journal of Prevention of Alzheimer's Disease 4.4: 255 (2017). ARIA is the most common side effect of this class of drugs. ARIA is usually asymptomatic and can be detected using brain MRI. ARIA can lead to symptoms such as headache, confusion, dizziness, visual disturbances, nausea, and seizures. The relationship between the stage of Alzheimer's progression, targeted population of Alzheimer's patients, the rate of clearance of amyloid plaques by anti-amyloid antibody treatment, and the rate of occurrence of ARIA upon treatment is not well understood.

[008] Several therapeutic amyloid targeted antibodies have demonstrated dose-response related increases in ARIA-E. See, e.g., Brashear et al., "Clinical Evaluation of Amyloid-related Imaging Abnormalities in Bapineuzumab Phase III Studies," J. of Alzheimer's Disease 66.4:1409-1424 (2018); Budd et al., "Clinical Development of

Aducanumab, an Anti-Aβ Human Monoclonal Antibody Being Investigated for the Treatment of Early Alzheimer's Disease," The Journal of Prevention of Alzheimer's Disease 4.4: 255 (2017). In some instances, there is a higher incidence rate of ARIA-E in patients harboring the epsilon-4 allele of apolipoprotein E (referred to herein as APOE4, apoE4, or ApoE-e4).

[009] To decrease the rate of ARIA-E adverse events while maintaining plaque clearance, some antibody treatment programs implement dose-titration schemes that included multiple dose escalations (3-4 steps) over a period of ~6-months prior to reaching their efficacious dose level. See, e.g., Budd et al., "Clinical Development of Aducanumab, an Anti-Aβ Human Monoclonal Antibody Being Investigated for the Treatment of Early Alzheimer's Disease," The Journal of Prevention of Alzheimer's Disease 4.4:255 (2017) and Klein et al., "Gantenerumab Reduces Amyloid-β Plaques in Patients with Prodromal to Moderate Alzheimer's Disease: a PET Substudy Interim Analysis," Alzheimer's Research & Therapy 11.1:101 (2019). Such treatment regimens may not fully clear amyloid plaques or may delay clearance of amyloid plaque.

[0010] Thus, a need exists for improved doses, dosing regimens, or methods that properly treat subjects without causing or increasing problematic adverse events.

BRIEF SUMMARY

[0011] The present disclosure is related to anti-N3pGlu Aβ antibodies that exhibit a surprisingly fast rate of amyloid clearance upon administration to a human subject in need thereof without causing or increasing problematic adverse events. In one embodiment, the anti-N3pGlu Aβ antibody of the present disclosure is remternetug (LY3372993). Remternetug is an IgG1 antibody directed at the pyroglutamate modification of the third amino acid of the amyloid-beta peptide (N3pG Aβ) that is present only in brain amyloid plaques. The mechanism of action of remternetug is to target and remove deposited amyloid plaque, a key pathological hallmark of AD, via microglial-mediated phagocytosis.

[0012] Remternetug has a relatively long half-life, reduced risk of immunogenicity, and robust amyloid plaque clearance that allows flexibility in dosing regimens. Such flexibility is not achievable with other anti-amyloid antibodies, such as, donanemab. Remternetug can be given less frequently (longer window between doses) while

achieving robust and fast amyloid plaque clearance. In some embodiments, remternetug can be administered intravenously (IV) at 8 weeks (Q8W) to 12 weeks (Q12W) dosing intervals. Such intervals allow time for adverse events, e.g., asymptomatic ARIA to resolve without interrupting dosing. In some embodiments, remternetug can be administered subcutaneously (SC). SC doses can be administered either weekly (Q1W), once every two weeks (Q2W), or bi-monthly. Collectively, these dosing regimens provide for fast and robust amyloid clearance, mitigate risk of adverse events, and reduce participant burden by allowing for less frequent dosing and/or reduced number of doses. As remternetug can be administered intravenously or subcutaneously, a dosing regimen can be selected based on the patient's preference or requirement, thereby potentially increasing compliance, and adherence to therapy. SC dosing may also mitigate the potential for ARIA risk due to lower Cmax observed with dosing. Another advantage of remternetug is that it can administered in low doses and/or less frequently to achieve rapid and complete amyloid plaque clearance. High amounts of remternetug can achieve population amyloid plaque clearance levels greater than 90%, which represents a best-in-class treatment option. Remternetug and donanemab both target an epitope of amyloid peptide that is only present in the brain amyloid plaque and can achieve robust clearance of amyloid plaque from the brain. Since amyloid plaque can be cleared by both of these antibodies, dosing regimens are fixed thereby positively impacting dosing regimen compliance and adherence compared to treatments administered over the life of a patient. Considering remternetug robust amyloid plaque clearance, fewer doses of remternetug can be given compared to any other amyloid plaque lowering therapy currently being explored in clinical trial development.

[0013] In some embodiments, the disease characterized by Aβ plaques in the brain of the human subject preclinical Alzheimer's disease (AD), clinical AD, prodromal AD, mild AD, moderate AD, severe AD, Down's syndrome, clinical cerebral amyloid angiopathy, or pre-clinical cerebral amyloid angiopathy. In one embodiment, the disease is preclinical AD. In some embodiments, the disease is prodromal AD. In some embodiments, the disease is mild dementia due to AD.

[0014] In some embodiments, the antibodies, the methods, or the dosing regimens identified in the present disclosure result in the treatment or prevention of Alzheimer's disease. In some embodiments, the antibodies, the methods, or the dosing regimens

identified in the present disclosure causes: i) reduction of Aβ plaques in the brain of the human subject; ii) slowing of cognitive decline in the human subject; or iii) slowing of functional decline in the human subject.

[0015] The anti-N3pGlu Aβ antibodies described in various aspects of the present disclosure include:

an anti-N3pGlu Aβ antibody comprising: light chain complementarity determining region 1 (LCDR1) having an amino acid sequence of SEQ ID NO: 4, light chain complementarity determining region 2 (LCDR2) having an amino acid sequence of SEQ ID NO: 5, and light chain complementarity determining region 3 (LCDR3) having an amino acid sequence of SEQ ID NO: 6 or an amino acid sequence having at least 95% homology to LCDR1 of SEQ ID NO: 4, an amino acid sequence having at least 95% homology to LCDR2 of SEQ ID NO: 5, and an amino acid sequence having at least 95% homology to LCDR3 of SEQ ID NO: 6;

an anti-N3pGlu Aβ antibody comprising: heavy chain complementarity determining region 1 (HCDR1) having an amino acid sequence of SEQ ID NO: 1, heavy chain complementarity determining region 2 (HCDR2) having an amino acid sequence of SEQ ID NO: 2, and heavy chain complementarity determining region 3 (HCDR3) having an amino acid sequence of SEQ ID NO: 3 or an amino acid sequence having at least 95% homology to HCDR1 of SEQ ID NO: 1, an amino acid sequence having at least 95% homology to HCDR2 of SEQ ID NO: 2, and an amino acid sequence having at least 95% homology to HCDR3 of SEQ ID NO: 3;

an anti-N3pGlu Aβ antibody comprising: LCDR1 having an amino acid sequence of SEQ ID NO: 4, LCDR2 having an amino acid sequence of SEQ ID NO: 5, LCDR3 having an amino acid sequence of SEQ ID NO: 6, HCDR1 having an amino acid sequence of SEQ ID NO: 1, HCDR2 having an amino acid sequence of SEQ ID NO: 2, and HCDR3 having an amino acid sequence of SEQ ID NO: 3 or amino acid sequence having at least 95% homology to LCDR1 of SEQ ID NO: 4, amino acid sequence having at least 95% homology to LCDR2 of SEQ ID NO: 5, amino acid sequence having at least 95% homology to LCDR3 of SEQ ID NO: 7, amino acid sequence having at least 95% homology to HCDR1

of SEQ ID NO: 8, amino acid sequence having at least 95% homology to HCDR2 of SEQ ID NO: 9, and amino acid sequence having at least 95% homology to HCDR3 of SEQ ID NO: 10;

an anti-N3pGlu Aβ antibody comprising: a LCVR and a HCVR, wherein said LCVR comprises: LCDR1, LCDR2 and LCDR3 and HCVR comprises HCDR1, HCDR2 and HCDR3, which are selected from the group consisting of LCDR1 is SEQ ID NO: 4, LCDR2 is SEQ ID NO: 5, LCDR3 is SEQ ID NO: 6, HCDR1 is SEQ ID NO: 1, HCDR2 is SEQ ID NO: 2, and HCDR3 is SEQ ID NO: 3 or a LCVR and a HCVR, wherein said LCVR comprises LCDR1, LCDR2 and LCDR3 and HCVR comprises HCDR1, HCDR2 and HCDR3, which are selected from the group consisting of LCDR1 having at least 95% homology to SEQ ID NO: 4, LCDR2 having at least 95% homology to SEQ ID NO: 5, LCDR3 having at least 95% homology to SEQ ID NO: 6, HCDR1 having at least 95% homology to SEQ ID NO: 1, HCDR2 having at least 95% homology to SEQ ID NO: 2, and HCDR3 having at least 95% homology to SEQ ID NO: 3.

an N3pGlu Aβ antibody comprising a light chain (LC) comprising: the amino acid sequence of SEQ ID NO: 10 or amino acid sequence having at least 95% homology to SEQ ID NO: 10;

an N3pGlu Aβ antibody comprising a heavy chain (HC) comprising: the amino acid sequence of SEQ ID NO: 9 or amino acid sequence having at least 95% homology to SEQ ID NO: 9;

an anti-N3pGlu Aβ antibody comprising a LC and a HC, wherein the LC comprises the amino acid sequence of SEQ ID NO: 10 and the HC comprises the amino acid sequence of SEQ ID NO: 9 or wherein the LC comprises amino acid sequence having at least 95% homology to SEQ ID NO: 10 and the HC comprises amino acid sequence having at least 95% homology to SEQ ID NO: 9;

an anti-N3pGlu Aβ antibody comprising two light chains and two heavy chains, wherein the LC comprises amino acid sequence of SEQ ID NO: 10 or amino acid sequence having at least 95% homology to SEQ ID NO: 10 and the HC comprises the amino acid sequence of SEQ ID NO: 9 or amino acid sequence having at least 95% homology to SEQ ID NO: 9.

an N3pGlu Aβ antibody comprising a LCVR comprising the amino acid sequence of SEQ ID NO: 8 or amino acid sequence having at least 95% homology to SEQ ID NO: 8;

an N3pGlu Aβ antibody comprising a HCVR comprising the amino acid sequence of SEQ ID NO: 7 or amino acid sequence having at least 95% homology to SEQ ID NO: 7.

an N3pGlu Aβ antibody comprising a LCVR and a HCVR wherein the LCVR comprises the amino acid sequence of SEQ ID NO: 8 or amino acid sequence having at least 95% homology to SEQ ID NO: 8; and the HCVR comprises the amino acid sequence of SEQ ID NO: 7 or amino acid sequence having at least 95% homology to SEQ ID NO: 7.

[0016] In some embodiments, the anti-N3pGlu Aβ antibodies of the present disclosure include kappa LC and IgG HC. In a particular embodiment, the anti-N3pGlu Aβ antibodies of the present disclosure are of the human IgG1 isotype.

[0017] In an embodiment, the anti-N3pGlu Aβ antibody of the present disclosure is Remternetug. Remternetug is a monoclonal antibody directed at the N3pG Aβ that is present only in deposited amyloid plaques. Remternetug includes two light chains and two heavy chains, wherein the LC comprises amino acid sequence of SEQ ID NO: 10 and the HC comprises the amino acid sequence of SEQ ID NO: 9. Remternetug is an IgG1 monoclonal antibody consisting of 2 identical light chain polypeptides composed of 214 amino acids each and 2 identical heavy chain polypeptides composed of 451 amino acids each. Each heavy chain contains a single, N-linked glycosylation site at Asn302. Remternetug binds specifically to the aggregated N3pG Aβ peptide with high-affinity (apparent dissociation constant approximately 45.7 nM). Remternetug selectively targets deposited plaque in the AD brain and has been engineered to maximize high effector function, including, target engagement, and microglia-mediated phagocytosis of the plaque.

[0018] In some embodiments, the doses of antibody of the present disclosure are administered to subject for a duration sufficient to treat or prevent the disease. In some embodiments, the antibody doses are administered to the subject until the Aβ plaques in the brain of the human subject are cleared. In some embodiments, the antibody is administered until at least one of the following occurs: i) the Aβ plaques in the brain of

the human subject are 24.1 centiloids or lower as measured by two consecutive amyloid PET imaging scans, wherein the two consecutive amyloid PET imaging scans are at least 6 months apart; or ii) the Aβ plaques in the brain of the human subject are 11 centiloids or lower as measured by a single amyloid PET imaging scan. In some embodiments, the antibody is administered to the subject until the subject is amyloid negative. In some embodiments, the antibody is administered to the subject until the Aβ plaque level of <24.1 CL is reached as measured by amyloid PET imaging scan.

[0019] In some embodiments, the human subject of the present disclosure is administered one or more intravenous doses of from about 200 mg to about 3000 mg of the anti-N3pGlu Aβ antibody as described herein. In some embodiments, the human subject is administered at least a dose of 200 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1050 mg, 1100 mg, 1150 mg, 1200 mg, 1250 mg, 1300 mg, 1350 mg, 1400 mg, 1450 mg, 1500 mg, 1550 mg, 1600 mg, 1650 mg, 1700 mg, 1750 mg, 1800 mg, 1850 mg, 1900 mg, 1950 mg, 2000 mg, 2050 mg, 2100 mg, 2150 mg, 2200 mg, 2250 mg, 2300 mg, 2350 mg, 2400 mg, 2450 mg, 2500 mg, 2550 mg, 2600 mg, 2650 mg, 2700 mg, 2750 mg, 2800 mg, 2850 mg, 2900 mg, 2950 mg, or 3000 mg of the anti-N3pGlu Aβ antibody as described herein.

[0020] In some embodiments, the intravenous dose of the anti-N3pGlu Aβ antibody is administered to the human subject at a frequency of once every week, once every two weeks, once every four weeks, once every six weeks, once every eight weeks, once every twelve weeks, or once every 16 weeks. In some embodiments, the intravenous dose is administered at a frequency of once every twelve weeks. In some embodiments, the intravenous dose is administered at a frequency of once every eight weeks. In some embodiments, the intravenous dose is administered at a frequency of once every four weeks. In some embodiments, the intravenous dose is administered at a frequency of once every two weeks.

[0021] In some embodiments, from about one to about twenty intravenous doses of the anti-N3pGlu Aβ antibody are administered to the human subject. In some embodiments, from about one to about 10 intravenous doses are administered to the human subject. In some embodiments, from about one to about five intravenous doses are administered to the human subject. In some embodiments, at least one intravenous dose of the anti-

N3pGlu Aβ antibody is administered to the subject. In some embodiments, two doses, three doses, four doses, five doses, six doses, seven doses, eight doses, nine doses, ten doses, eleven doses, twelve doses, thirteen doses, fourteen doses, fifteen doses, sixteen doses, seventeen doses, eighteen doses, nineteen doses, or twenty doses of the anti-N3pGlu Aβ antibody are administered to the human subject.

[0022] In some embodiments, the human subject is suffering from early symptomatic AD and is administered i) from about 1 to about 20 intravenous doses; ii) from about 1 to about 10 intravenous doses; or iii) from about 1 to about 5 intravenous doses of 2300 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 12 weeks (Q12W). In some embodiments, the human subject is suffering from early symptomatic AD and is administered about 3 intravenous doses of 2300 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 12 weeks (Q12W).

[0023] In some embodiments, the human subject is suffering from early symptomatic AD and is administered i) from about 1 to about 20 intravenous doses; ii) from about 1 to about 10 intravenous doses; or iii) from about 1 to about 5 intravenous doses of 1500 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 12 weeks (Q12W). In some embodiments, the human subject is suffering from early symptomatic AD and is administered about 4 intravenous doses of 1500 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 12 weeks (Q12W).

[0024] In some embodiments, the human subject is suffering from early symptomatic AD and is administered i) from about 1 to about 20 intravenous doses; ii) from about 1 to about 10 intravenous doses; or iii) from about 1 to about 5 intravenous doses of 800 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 8 weeks (Q8W). In some embodiments, the human subject is suffering from early symptomatic AD and is administered about 7 intravenous doses of 800 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 8 weeks (Q8W).

[0025] In some embodiments, the human subject is suffering from early symptomatic AD and is administered i) from about 1 to about 20 intravenous doses; ii) from about 1 to about 10 intravenous doses; or iii) from about 1 to about 5 intravenous doses of 800 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 4 weeks (Q4W). In some embodiments, the human subject is suffering from early symptomatic AD and is

administered about 7 intravenous doses of 800 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 4 weeks (Q4W).

[0026] In some embodiments, the human subject is suffering from early symptomatic AD and is administered about 3 intravenous doses of 2300 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 12 weeks (Q12W). In some embodiments, the human subject is suffering from early symptomatic AD and is administered about 4 intravenous doses of 1500 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 12 weeks (Q12W). In some embodiments, the human subject is suffering from early symptomatic AD and is administered about 7 intravenous doses of 800 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 8 weeks (Q8W). In some embodiments, the human subject is suffering from early symptomatic AD and is administered about 7 intravenous doses of 800 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 4 weeks (Q4W). In some embodiments, the human subject is suffering from early symptomatic AD and is administered about 12 intravenous doses of 400 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 4 weeks (Q4W). In some embodiments, the human subject is suffering from early symptomatic AD and is administered about 19 intravenous doses of 400 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 4 weeks (Q4W).

[0027] In some embodiments, the human subject is suffering from early symptomatic AD and is administered about 36 subcutaneous doses of 400 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every week (Q1W). In some embodiments, the human subject is suffering from early symptomatic AD and is administered about 52 subcutaneous doses of 400 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every week (Q1W). In some embodiments, the human subject is suffering from early symptomatic AD and is administered about 76 subcutaneous doses of 400 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every week (Q1W). In some embodiments, the human subject is suffering from early symptomatic AD and is administered about 36 subcutaneous doses of 400 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every two weeks (Q2W). In some embodiments, the human subject is suffering from early symptomatic AD and is administered about 52 subcutaneous doses of 400 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every two weeks (Q2W). In some embodiments, the human subject is suffering from

early symptomatic AD and is administered about 76 subcutaneous doses of 400 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every two weeks (Q2W). In some embodiments, the human subject is suffering from early symptomatic AD and is administered about 9 subcutaneous doses of 800 mg (or 2 x 400 mg, e.g., two injections of 400 mg) of the anti-N3pGlu Aβ antibody of the present disclosure once every four weeks (Q4W). In some embodiments, the human subject is suffering from early symptomatic AD and is administered about 12 subcutaneous doses of 800 mg (or 2 x 400 mg, e.g., two injections of 400 mg) of the anti-N3pGlu Aβ antibody of the present disclosure once every four weeks (Q4W).

[0028] In some embodiments, the human subject is suffering from preclinical AD and is administered i) from about 1 to about 20 intravenous doses; ii) from about 1 to about 10 intravenous doses; or iii) from about 1 to about 5 intravenous doses of 2300 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 12 weeks (Q12W). In some embodiments, the human subject is suffering from preclinical AD and is administered about 2 intravenous doses of 2300 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 12 weeks (Q12W).

[0029] In some embodiments, the human subject is suffering from preclinical AD and is administered i) from about 1 to about 20 intravenous doses; ii) from about 1 to about 10 intravenous doses; or iii) from about 1 to about 5 intravenous doses of 1500 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 12 weeks (Q12W). In some embodiments, the human subject is suffering from preclinical AD and is administered about 3 intravenous doses of 1500 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 12 weeks (Q12W).

[0030] In some embodiments, the human subject is suffering from preclinical AD and is administered i) from about 1 to about 20 intravenous doses; ii) from about 1 to about 10 intravenous doses; or iii) from about 1 to about 5 intravenous doses of 800 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 8 weeks (Q8W). In some embodiments, the human subject is suffering from preclinical AD and is administered about 5 or about 6 intravenous doses of 800 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 8 weeks (Q8W).

[0031] In some embodiments, the human subject is suffering from preclinical AD and is administered i) from about 1 to about 20 intravenous doses; ii) from about 1 to about 10

intravenous doses; or iii) from about 1 to about 5 intravenous doses of 800 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 4 weeks (Q4W). In some embodiments, the human subject is suffering from preclinical AD and is administered about 5 or about 6 intravenous doses of 800 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 4 weeks (Q8W).

[0032] In some embodiments, the human subject of the present disclosure is administered one or more subcutaneous doses of from about 20 mg to about 1000 mg of the anti-N3pGlu Aβ antibody as described herein. In some embodiments, the human subject of the present disclosure is administered one or more subcutaneous doses of from about 250 mg to about 500 mg of the anti-N3pGlu Aβ antibody as described herein. In some embodiments, the human subject is administered at least one subcutaneous dose of 20 mg, 40 mg, 60 mg, 80 mg, 100 mg, 120 mg, 140 mg, 160 mg, 180 mg, 200 mg, 220 mg, 240 mg, 260 mg, 280 mg, 300 mg, 320 mg, 340 mg, 360 mg, 380 mg, 400 mg, 420 mg, 440 mg, 460 mg, 480 mg, 500 mg, 520 mg, 540 mg, 560 mg, 580 mg, 600 mg, 620 mg, 640 mg, 660 mg, 680 mg, 700 mg, 720 mg, 740 mg, 760 mg, 780 mg, 800 mg, 820 mg, 840 mg, 860 mg, 880 mg, 900 mg, 920 mg, 940 mg, 960 mg, 980 mg, or 1000 mg.

[0033] In some embodiments, the subcutaneous dose of the anti-N3pGlu Aβ antibody is administered to the human subject at a frequency of once every week, once every two weeks, once every four weeks, once every six weeks, once every eight weeks, or once every twelve weeks. In some embodiments, the subcutaneous dose is administered at a frequency of once every week. In some embodiments, the subcutaneous dose is administered at a frequency of once every two weeks. In some embodiments, the subcutaneous dose is administered at a frequency of once every four weeks. In some embodiments, the subcutaneous dose is administered at a frequency of once every six weeks. In some embodiments, the subcutaneous dose is administered at a frequency of once every eight weeks.

[0034] In some embodiments, from about one to about a hundred subcutaneous doses of the anti-N3pGlu Aβ antibody are administered to the human subject. In some embodiments, from about one to about 90 subcutaneous doses are administered to the human subject. In some embodiments, from about one to about 80 subcutaneous doses are administered to the human subject. In some embodiments, from about one to about 70 subcutaneous doses are administered to the human subject. In some embodiments, from

about one to about 60 subcutaneous doses are administered to the human subject. In some embodiments, from about one to about 50 subcutaneous doses are administered to the human subject. In some embodiments, from about one to about 40 subcutaneous doses are administered to the human subject. In some embodiments, from about one to about 30 subcutaneous doses are administered to the human subject. In some embodiments, from about one to about 20 subcutaneous doses are administered to the human subject. In some embodiments, from about one to about 10 subcutaneous doses are administered to the human subject. In some embodiments, at least one subcutaneous dose of the anti-N3pGlu Aβ antibody is administered to the subject. In some embodiments, 10 doses, 20 doses, 30 doses, 40 doses, 50 doses, 60 doses, 70 doses, 80 doses, 90 doses, or 100 doses of the anti-N3pGlu Aβ antibody are administered to the human subject. In some embodiments, about 24 subcutaneous doses are administered to the human subject. In some embodiments, about 36 subcutaneous doses are administered to the human subject. In some embodiments, about 52 subcutaneous doses are administered to the human subject. In some embodiments, about 76 subcutaneous doses are administered to the human subject.

[0035] In some embodiments, the human subject is suffering from early symptomatic AD and is administered i) from about 1 to about 90 subcutaneous doses; ii) from about 1 to about 60 subcutaneous doses; or iii) from about 1 to about 30 subcutaneous doses of 400 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every week (Q1W). In some embodiments, the human subject is suffering from early symptomatic AD and is administered about 36 subcutaneous doses of 1500 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every week (Q1W).

[0036] In some embodiments, the human subject is suffering from early symptomatic AD and is administered i) from about 1 to about 90 subcutaneous doses; ii) from about 1 to about 60 subcutaneous doses; or iii) from about 1 to about 30 subcutaneous doses of 400 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 2 weeks (Q2W). In some embodiments, the human subject is suffering from early symptomatic AD and is administered about 52 subcutaneous doses of 400 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 2 weeks (Q2W). In some embodiments, the human subject is suffering from early symptomatic AD and is administered about 76

subcutaneous doses of 400 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 2 weeks (Q2W).

[0037] In some embodiments, the human subject is suffering from preclinical AD and is administered about 2 intravenous doses of 2300 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 12 weeks (Q12W). In some embodiments, the human subject is suffering from preclinical AD and is administered about 3 intravenous doses of 1500 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 12 weeks (Q12W). In some embodiments, the human subject is suffering from preclinical AD and is administered about 5 intravenous doses of 800 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 8 weeks (Q8W). In some embodiments, the human subject is suffering from preclinical AD and is administered about 6 intravenous doses of 800 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 8 weeks (Q8W). In some embodiments, the human subject is suffering from preclinical AD and is administered about 5 intravenous doses of 800 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 4 weeks (Q4W). In some embodiments, the human subject is suffering from preclinical AD and is administered about 6 intravenous doses of 800 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every 4 weeks (Q4W).

[0038] In some embodiments, the human subject is suffering from preclinical AD and is administered i) from about 1 to about 60 subcutaneous doses; ii) from about 1 to about 30 subcutaneous doses; or iii) from about 1 to about 10 subcutaneous doses of 400 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every week (Q1W). In some embodiments, the human subject is suffering from preclinical AD and is administered about 24 subcutaneous doses of 400 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every week (Q1W). In some embodiments, the human subject is suffering from preclinical AD and is administered about 36 subcutaneous doses of 400 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every week (Q1W). In some embodiments, the human subject is suffering from preclinical AD and is administered about 52 subcutaneous doses of 400 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every week (Q1W). In some embodiments, the human subject is suffering from preclinical AD and is administered about 24 subcutaneous doses of 400 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every week (Q1W). In some embodiments, the human subject is suffering from preclinical AD and is

administered about 12 subcutaneous doses of 400 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every two weeks (Q2W). In some embodiments, the human subject is suffering from preclinical AD and is administered about 18 subcutaneous doses of 400 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every two weeks (Q2W). In some embodiments, the human subject is suffering from preclinical AD and is administered about 26 subcutaneous doses of 400 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every two weeks (Q2W). In some embodiments, the human subject is suffering from preclinical AD and is administered about 6 subcutaneous doses of 800 mg (or 2 x 400 mg, e.g., two injections of 400 mg) of the anti-N3pGlu Aβ antibody of the present disclosure once every four weeks (Q4W). In some embodiments, the human subject is suffering from preclinical AD and is administered about 8 subcutaneous doses of 800 mg (or 2 x 400 mg, e.g., two injections of 400 mg) of the anti-N3pGlu Aβ antibody of the present disclosure once every four weeks (Q4W). In some embodiments, the human subject is suffering from preclinical AD and is administered about 9 subcutaneous doses of 800 mg (or 2 x 400 mg, e.g., two injections of 400 mg) of the anti-N3pGlu Aβ antibody of the present disclosure once every four weeks (Q4W). In some embodiments, the human subject is suffering from preclinical AD and is administered about 12 subcutaneous doses of 800 mg (or 2 x 400 mg, e.g., two injections of 400 mg) of the anti-N3pGlu Aβ antibody of the present disclosure once every four weeks (Q4W).

[0039] In some embodiments, the human subject is suffering from preclinical AD and is administered i) from about 1 to about 60 subcutaneous doses; ii) from about 1 to about 30 subcutaneous doses; or iii) from about 1 to about 10 subcutaneous doses of 400 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every two weeks (Q2W). In some embodiments, the human subject is suffering from preclinical AD and is administered about 24 subcutaneous doses of 400 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every two weeks (Q2W). In some embodiments, the human subject is suffering from preclinical AD and is administered about 36 subcutaneous doses of 400 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every two weeks (Q2W). In some embodiments, the human subject is suffering from preclinical AD and is administered about 52 subcutaneous doses of 400 mg of the anti-N3pGlu Aβ antibody of the present disclosure once every two weeks (Q2W).

[0040] In some embodiments, the dosing regimen of the present disclosure includes one or more additional doses (also referred to as maintenance doses) that may be administered after the completion (e.g., after the subject's amyloid beta is cleared) of the IV dosing regimen or the subcutaneous dosing regimen as described herein. For instance, in some embodiments, the subject may be administered one or more maintenance doses to reduce the deposition of Aβ in the brain of the subject, prevent further deposition of Aβ in the brain of the subject, prevent further cognitive decline, prevent further memory loss, or prevent further functional decline. An intravenous maintenance dose could be from about 250 mg to about 3000 mg of the anti-N3pGlu Aβ antibody. In some embodiments, the subcutaneous maintenance dose could be from about 20 mg to about 1000 mg of the anti-N3pGlu Aβ antibody.

[0041] Some embodiments of the present disclosure includes a method of treating or preventing a disease characterized by deposition of amyloid beta (Aβ) plaques in the brain of a human subject in need thereof comprising: administering to the subject one or more intravenous (IV) doses from about 250 mg to about 3000 mg of an anti-N3pG Aβ antibody at a frequency of: i) about once every twelve weeks (Q12W); ii) about once every eight weeks (Q8W); or iii) about once every four weeks (Q4W); subsequently administering one or more maintenance doses of about 250 mg to about 3000 mg of the anti-N3pGlu Aβ antibody; wherein the anti-N3pGlu Aβ antibody comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 8 and a heavy chain variable region (HCVR), comprising the amino acid sequence of SEQ ID NO: 7.

[0042] In some embodiments, the present disclosure includes a method of treating or preventing a disease characterized by deposition of amyloid beta (Aβ) plaques in the brain of a human subject in need thereof comprising: administering to the subject one or more subcutaneous doses from about 20 mg to about 1000 mg of an anti-N3pG Aβ antibody at a frequency of about once every week, about once every 2 weeks, or once every four weeks; subsequently administering one or more maintenance doses of about 20 mg to about 1000 mg of the anti-N3pGlu Aβ antibody; wherein the anti-N3pGlu Aβ antibody comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 8 and a heavy chain variable region (HCVR), comprising the amino acid sequence of SEQ ID NO: 7.

[0043] In some embodiments, one or more maintenance doses of the anti-N3pGlu Aβ antibodies of the present disclosure can be administered to the subject every 2, every 4 weeks, every 8 weeks, every 12 weeks, every month, every 1 year, every 2 years, every 3 years, every 4 years, every 5 years, or every 10 years. In some embodiments, the maintenance dose is given every year. In an embodiment, the maintenance dose is given every 2 years. In another embodiment, the maintenance dose is given every 3 years. In another embodiment, the maintenance dose of the antibody is given every 5 years. In another embodiment, the maintenance dose of the antibody is given every 10 years. In another embodiment, the maintenance dose of the antibody is given every 2 to 5 years. In another embodiment, the maintenance dose of the antibody is given every 5 to 10 years.

[0044] In some aspects, the present disclosure is related to a method of treating or preventing a disease characterized by deposition of amyloid beta (Aβ) plaques in the brain of a human subject comprising: i) administering to the subject one or more anti-N3pGlu Aβ antibody doses as disclosed in the present application; ii) evaluating magnetic resonance image (MRI) scan of the subject's brain, after the administration of a dose of the antibody and prior to the administration of a subsequent dose, for amyloid-related imaging abnormality (ARIA); wherein administration of the subsequent dose is temporarily withheld if symptoms consistent with ARIA occur; and wherein the anti-N3pGlu Aβ antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR consists of the amino acid sequence of SEQ ID NO: 8 and the HCVR consists of the amino acid sequence of SEQ ID NO: 7. In some embodiments, the administration of the subsequent dose (as well as other subsequent doses as identified in the present application) is re-initiated after resolution of ARIA symptoms or radiographic stabilization on MRI. In some embodiments, the subsequent dose(s) is withheld, and corticosteroids are administered to the subject. In some embodiments, the disease characterized by deposition of amyloid beta (Aβ) plaques in the brain of a human subject is Alzheimer's disease. In some embodiments, the antibody is remternetug.

[0045] In some aspects, the present disclosure is related to a method of treating or preventing a disease characterized by deposition of amyloid beta plaques in the brain of a human subject in need thereof comprising: i) administering to the subject one or more anti-N3pGlu Aβ antibody doses as disclosed in the present application; ii) evaluating

magnetic resonance image (MRI) scan of the subject's brain for ARIA, after the administration of a dose and prior to the administration of a subsequent dose; wherein the administration of the subsequent dose is discontinued if symptoms consistent with severe or symptomatic ARIA occur; and wherein the anti-N3pGlu Aβ antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR consists of the amino acid sequence of SEQ ID NO: 8 and the HCVR consists of the amino acid sequence of SEQ ID NO: 7. In some embodiments, the administration of one or more subsequent doses is discontinued, and corticosteroids are administered to the subject. In some embodiments, the disease characterized by deposition of amyloid beta (Aβ) plaques in the brain of a human subject is Alzheimer's disease. In some embodiments, the antibody is remternetug.

[0046] In some embodiments, the present disclosure is related to a method of treating or preventing a disease characterized by deposition of amyloid beta plaques in a subject until symptoms consistent with ARIA-E occur comprising: i) administering to the subject one or more anti-N3pGlu Aβ antibody doses as disclosed in the present application; wherein the anti-N3pGlu Aβ antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR consists of the amino acid sequence of SEQ ID NO: 8 and the HCVR consists of the amino acid sequence of SEQ ID NO: 7. In some embodiments, the symptoms of ARIA are detected by MRI or are presented in the subject. In some embodiments, the disease characterized by deposition of amyloid beta (Aβ) plaques in the brain of a human subject is Alzheimer's disease. In some embodiments, the antibody is remternetug.

[0047] In some embodiments, the present disclosure is related to a method for treating a subject suffering from Alzheimer's disease with remternetug, the method comprising the steps of: a) administering remternetug to the subject; b) determining whether the subject has symptoms of ARIA-E i) by performing or having performed an MRI or ii) if clinical symptoms consistent with ARIA-E occur; and c) if the patient has moderate symptoms of ARIA-E, temporarily discontinuing treatment with remternetug; and d) if the patient does not have symptomatic ARIA-E, administering remternetug to the patient until brain amyloid is cleared, is negative, or is <24.1 CL. In some embodiments, the subsequent dose is withheld, and corticosteroids are administered to the subject. In some embodiments, the disease characterized by deposition of amyloid beta (Aβ) plaques in the

brain of a human subject is Alzheimer's disease. In some embodiments, the antibody is remternetug.

[0048] In some embodiments, the present disclosure is related to an improved method for treating a subject suffering from Alzheimer's disease with remternetug, wherein the method comprises: a) administering remternetug to the subject; b) determining whether the subject has symptoms of ARIA-E i) by performing or having performed an MRI or ii) if clinical symptoms consistent with ARIA-E occur; and c) if the patient has moderate symptoms of ARIA-E, temporarily discontinuing treatment with remternetug; and d) if the patient does not have symptomatic ARIA-E, administering remternetug to the subject until brain amyloid is cleared, is negative, or is <24.1 CL. In some embodiments, the subsequent dose is withheld, and corticosteroids are administered to the subject. In some embodiments, the disease characterized by deposition of amyloid beta (Aβ) plaques in the brain of a human subject is Alzheimer's disease. In some embodiments, the antibody is remternetug.

[0049] In some embodiments, the present disclosure is related to an improved method for treating a subject suffering from Alzheimer's disease with remternetug, wherein the method comprises: a) administering remternetug to the subject; b) determining whether the subject has symptoms of ARIA-E i) by performing or having performed an MRI or ii) if clinical symptoms consistent with ARIA-E occur; and c) if the patient has moderate symptoms of ARIA-E, temporarily discontinuing treatment with remternetug; and d) if the patient does not have symptomatic ARIA-E, administering remternetug to the subject until brain amyloid is cleared, is negative, or is <24.1 CL. In some embodiments, the subsequent dose is withheld, and corticosteroids are administered to the subject. In some embodiments, the disease characterized by deposition of amyloid beta (Aβ) plaques in the brain of a human subject is Alzheimer's disease. In some embodiments, the antibody is remternetug.

[0050] In some embodiments, the present disclosure is related to an improved method for treating a subject suffering from Alzheimer's disease with remternetug, wherein the method comprises: a) administering or having administered remternetug to the subject; b) determining whether the patient has symptoms of ARIA-E i) by performing or having performed an MRI or ii) if clinical symptoms consistent with ARIA-E occur; and c) if the patient does not have symptomatic ARIA-E, further administering remternetug to the

patient. In some embodiments, the subsequent dose is withheld, and corticosteroids are administered to the subject. In some embodiments, the disease characterized by deposition of amyloid beta (Aβ) plaques in the brain of a human subject is Alzheimer's disease. In some embodiments, the antibody is remternetug.

[0051] In some embodiments, the present disclosure is related to an improved method for treating a subject suffering from Alzheimer's disease with remternetug, wherein the method comprises: a) administering or having administered remternetug to the subject; b) discontinuing treatment if the patient has moderate symptoms of ARIA-E; and c) continuing treatment once ARIA-E resolves by administering remternetug to the patient until brain amyloid is cleared, is negative, is <24.1 CL, or ARIA-E symptoms reappear. In some embodiments, the symptoms or ARIA-E are confirmed or are determined by an MRI scan.

[0052] In some embodiments, the treatment with remternetug is withheld or discontinued due to or upon occurrence of severe or symptomatic ARIA-E. In some embodiments, upon occurrence of mild or moderate asymptomatic ARIA-E in subjects, treatment with remternetug may be temporarily withheld or interrupted. In some embodiments, upon occurrence of mild or moderate asymptomatic ARIA-E in subjects, the dose of remternetug may be temporarily reduced. In some embodiments—upon occurrence of ARIA-E—supportive therapy including corticosteroids may be administered to the patient. In some embodiments, treatment with remternetug may be re-initiated after resolution of symptoms or radiographic stabilization on abnormal brain MRI.

[0053] If symptoms of ARIA-H occur, it is often in the presence of ARIA-E and managed accordingly as for ARIA-E. In some embodiments, a brain MRI of a patient is obtained prior to dosing with remternetug or if symptoms consistent with ARIA-H occur. In some embodiments, the treatment with remternetug is withheld or discontinued due to or upon occurrence of ARIA-H. In some embodiments—upon occurrence of ARIA-H in patients—treatment with remternetug may be temporarily interrupted, e.g., when ARIA-H symptoms are mild or moderate. In some embodiments, upon occurrence of mild or moderate asymptomatic ARIA-H in patients, the dose of remternetug may be temporarily reduced. In some embodiments, upon occurrence of ARIA-H supportive therapy including corticosteroids may be administered to the patient. In some embodiments,

treatment with remternetug may be temporarily discontinued until symptoms of ARIA-E or ARIA-H improve.

[0054] Some aspects of the present disclosure are related to identifying, monitoring, or evaluating a human subject for Amyloid Related Imaging Abnormalities (ARIA) before or after the subject is administered the anti-N3pGlu Aβ antibodies of the present disclosure. In some embodiments, the present disclosure is related to identifying, monitoring, or evaluating a human subject for ARIA while the subject is being treated with the anti-N3pGlu Aβ antibodies of the present disclosure. In some embodiments, ARIA includes both ARIA-E and ARIA-H. ARIA-E refers to cerebral edema, involving the breakdown of the tight endothelial junctions of the blood-brain barrier and subsequent accumulation of fluid. ARIA-H refers to cerebral microhemorrhages (mH), small hemorrhages on the brain, often accompanied by hemosiderosis.

[0055] In some embodiments, the brain MRI scan can be administered to the human subject to diagnose/evaluate/monitor adverse event(s) caused by administration of the anti-N3pGlu Aβ antibody. For example, a brain Magnetic Resonance Imaging (MRI) scan may be administered to the human subject to identify, monitor, or evaluate the human subject for ARIA, including, e.g., ARIA-E or ARIA-H.

[0056] In some embodiments, the methods of the present disclosure include a step of excluding a subject from treatment with the anti-N3pGlu Aβ antibody, if upon screening (i.e., before treatment with the antibody), the subject is identified as having ARIA.

[0057] In some embodiments, a baseline brain MRI is obtained or evaluated prior to initiating treatment with the anti-N3pGlu Aβ antibodies. The human subject may be administered a brain MRI scan in between administration of doses of the anti-N3pGlu Aβ antibody (e.g., once every week, once every two weeks, once every 4 weeks, or once every 12 weeks). In some embodiments, the human subject is administered a brain MRI scan before administering an intravenous or subcutaneous dose of the anti-N3pGlu Aβ antibody. In some embodiments, the human subject is administered a brain MRI scan after a first dose of the anti-N3pGlu Aβ antibody is administered to the patient. In some embodiments, the human subject is administered a brain MRI scan after two or three doses of the anti-N3pGlu Aβ antibody have been administered.

[0058] In some embodiments, the human subject is administered a brain MRI scan after the first week or first four weeks of treatment. In some embodiments, the human subject

is administered a brain MRI scan after the first 12 weeks of initiation of treatment. In some embodiments, the human subject is administered a brain MRI scan after the last dose. In some embodiments, the human subject is administered a brain MRI scan and evaluated for ARIA upon physician's recommendation or upon suspicion of ARIA. In some embodiments, the subject is not administered the antibody of the present disclosure if a centrally read MRI demonstrates the presence of ARIA-E, >4 cerebral microhemorrhages, more than 1 area of superficial siderosis, any macrohemorrhage, or severe white matter disease at screening prior to start of therapy.

[0059] In some embodiments, the anti-N3pGlu Aβ antibody of the present disclosure can be administered in simultaneous, separate, or sequential combination with an effective amount of an agent to treat Alzheimer's disease. Symptomatic agents can be selected from cholinesterase inhibitors (ChEIs) and/or a partial N-methyl-D-aspartate (NMDA) antagonist. In a preferred embodiment the agent is a ChEI. In another preferred embodiment the agent is a NMDA antagonist or a combination agent comprising a ChEI and NMDA antagonist. In some embodiments, the anti-N3pGlu Aβ antibody of the present disclosure can be administered in simultaneous, separate, or sequential combination with another anti-Aβ antibody or another anti-N3pGlu Aβ antibody. In some embodiments, the anti-N3pGlu Aβ antibody of the present disclosure is administered in combination with donanemab, solanezumab, aducanumab, lecanemab, or gantenerumab.

[0060] As used herein, "anti-N3pGlu Aβ antibody," "anti-N3pG antibody," or "anti-N3pE antibody," used interchangeably, refer to an antibody that binds preferentially to N3pGlu Aβ over Aβ1-40 or Aβ1-42. As used herein, an "antibody" is an immunoglobulin molecule comprising two HC and two LC interconnected by disulfide bonds. The amino terminal portion of each LC and HC includes a variable region responsible for antigen recognition via the complementarity determining regions (CDRs) contained therein. The CDRs are interspersed with regions that are more conserved, termed framework regions. Assignment of amino acids to CDR domains within the LCVR and HCVR regions of the antibodies of the present disclosure is based on the following: Kabat numbering convention (Kabat, et al., Ann. NY Acad. Sci. 190:382-93 (1971); Kabat et al., Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242 (1991)), and

North numbering convention (North et al., A New Clustering of Antibody CDR Loop Conformations, Journal of Molecular Biology, 406:228-256 (2011)). Following the above method, the CDRs of the antibodies of the present disclosure were determined.

[0061] The antibodies of the present disclosure are monoclonal antibodies ("mAbs"). Monoclonal antibodies can be produced, for example, by hybridoma technologies, recombinant technologies, phage display technologies, synthetic technologies, e.g., CDR-grafting, or combinations of such or other technologies known in the art. The monoclonal antibodies of the present disclosure are human or humanized. Humanized antibodies can be engineered to contain one or more human framework regions (or substantially human framework regions) surrounding CDRs derived from a non-human antibody. Human framework germline sequences can be obtained from ImunoGeneTics (INGT) via their website, http://imgt.cines.fr, or from The Immunoglobulin FactsBook by Marie-Paule Lefranc and Gerard Lefranc, Academic 25 Press, 2001, ISBN 012441351. Techniques for generating human or humanized antibodies are well known in the art. The present disclosure includes the antibody or a nucleic acid encoding the antibody. In some embodiments, the antibody or the nucleic acid is provided in isolated form. As used herein, the term "isolated" refers to a protein, peptide, or nucleic acid that is not found in nature and is free or substantially free from other macromolecular species found in a cellular environment. "Substantially free", as used herein, means the protein, peptide or nucleic acid of interest comprises more than 80% (on a molar basis) of the macromolecular species present, preferably more than 90% and more preferably more than 95%.

[0062] The anti-N3pGlu Aβ antibody of the present disclosure may be administered as a pharmaceutical composition. The pharmaceutical composition comprising an antibody of the present disclosure can be administered to a subject at risk for, or exhibiting, diseases or disorders as described herein by parenteral routes (e.g., subcutaneous, intravenous). Subcutaneous and intravenous routes are preferred. In some embodiments, the anti-N3pGlu Aβ antibody is administered by intravenous infusion. In some embodiments, the anti-N3pGlu Aβ antibody is administered by subcutaneous infusion.

BRIEF DESCRIPTION OF THE DRAWINGS

[0063] FIG. 1 is a graph illustrating least square mean change from baseline of cerebral amyloid plaque to day 169 represented by dosing groups, where LY = LY3372993/remternetug; MMRM = mixed model for repeated measures; Q4W = once every 4 weeks; QW = once every week; SC = subcutaneous; SD = single dose; TRT = treatment.

[0064] FIG. 2 is amyloid PET scan images from a LAKB participant within Cohort 12 who received a single dose of 2800 mg remternetug showing representative amyloid reduction through day 85 wherein the X-axis is standardized uptake values (SUV); this shows an amyloid reduction of 144 CL at day 85; brain regions labelled "A" for anterior, "P" for posterior, "L" for left side, and "R" for right side.

[0065] FIG. 3 provides a representation of the study schema for addendum 1 of LAKC as described in Example 5, where IV = intravenous; Q12W = every 12 weeks; V = visit; and V1 occurs up to 49 days prior to V2 (represented as "a").

[0066] FIG. 4 provides a representation of the study schema for addendum 3 of LAKC as described in Example 5, where IV = intravenous; Q4W = every 4 weeks; Q8W = every 8 weeks; V = visit; and V1 occurs up to 49 days prior to the start of study intervention at V2 (represented as "a").

[0067] FIG. 5 provides a representation of the study schema for addendum 4 of LAKC as described in Example 5, where SC = subcutaneous; QW = every week; Q4W = every 4 weeks; V1 occurs up to 49 days prior to V2 (represented as "a").

[0068] FIG. 6 provides a representation of the study schema for addendum 4 of LAKC as described in Example 5, where SC = subcutaneous; Visit 1 occurs up to 49 days before the start of study intervention at Visit 2 (represented as "a"); Visit 801 occurs 20 weeks after the last dose (represented as "b").

[0069] FIG. 7 provides a representation of the study schema for main protocol of study LAKC as described in Example 5, where V601 occurs up to 30 days prior to V1 (represented as "a"); V1 occurs up to 49 days prior to V2 (represented as "a"); participants in 400 mg QW SC cohort are dose adjusted to 800 mg SC Q4W or placebo following a minimum 4-week treatment pause (represented as "b").

[0070] FIG. 8 provides a representation of the study schema for study LAKD as described in Example 6, where SC = subcutaneous; V601 occurs up to 30 days prior to V1 (represented as "a"); and V1 occurs up to 63 days prior to V2 (represented as "a").

[0071] FIG. 9 provides a representation of the study schema for study LAKE as described in Example 7.

[0072] FIG. 10 provides a representation of the study schema for study LAKE as described in Example 8, where IV = intravenous; V601 occurs up to 30 days prior to V1 (represented as "a"); and V1 occurs up to 63 days prior to V2 (represented as "a").

[0073] FIG. 11 provides a schematic of tau stratification for LAKD and LAKF of Example 9.

DETAILED DESCRIPTION

[0074] The terms "treatment," "treating" or "to treat," as used herein, include restraining, slowing, or stopping the progression or severity of an existing symptom, condition, disease, or disorder in a subject.

[0075] The term "subject" refers to a human.

[0076] The term "prevention" means prophylactic administration of the antibody of the present disclosure to an asymptomatic subject or a subject with pre-clinical Alzheimer's disease to prevent onset or progression of the disease.

[0077] The terms "disease characterized by deposition of Aβ" or a "disease characterized by Aβ plaques" are used interchangeably and refer to a disease that is pathologically characterized by Aβ plaques in the brain or in brain vasculature. This includes diseases such as Alzheimer's disease, Down's syndrome, and cerebral amyloid angiopathy. A clinical diagnosis, staging or progression of Alzheimer's disease can be readily determined by the attending diagnostician or health care professional, as one skilled in the art, by using known techniques and by observing results. This generally includes brain plaque imaging, mental or cognitive assessment (e.g., Clinical Dementia Rating – summary of boxes (CDR-SB), Mini-Mental State Exam (MMSE) or Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog)) or functional assessment (e.g., Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL). The cognitive and functional assessment can be used to determine changes in a patient's cognition (e.g., cognitive decline) and function (e.g., functional decline). "Clinical

Alzheimer's disease" as used herein is a diagnosed stage of Alzheimer's disease. It includes conditions diagnosed as prodromal Alzheimer's disease, mild Alzheimer's disease, moderate Alzheimer's disease, and severe Alzheimer's disease. The term "pre-clinical Alzheimer's disease" is a stage that precedes clinical Alzheimer's disease, where measurable changes in biomarkers (such as CSF Aβ42 levels or deposited brain plaque by amyloid PET) indicate the earliest signs of a subject with Alzheimer's pathology, progressing to clinical Alzheimer's disease. This is usually before symptoms such as memory loss and confusion are noticeable. Pre-clinical Alzheimer's disease also includes pre-symptomatic autosomal dominant carriers, as well as patients with higher risk for developing AD by virtue of carrying one or two APOE4 alleles.

[0078] A reduction or slowing of cognitive decline can be measured by cognitive assessments such as Clinical Dementia Rating – summary of boxes, Mini-Mental State Exam or Alzheimer's Disease Assessment Scale-Cognitive. A reduction or slowing of functional decline can be measured by functional assessments such as ADCS-ADL.

[0079] In some embodiments, the subject/patient of the present disclosure has a very low tau burden. As used herein, a human subject has "very low tau" burden if the tau burden is less than 1.10 SUVr (<1.10 SUVr, Standardized Uptake Value ratio) using ^{18}F-flortaucipir based quantitative analysis where quantitative analysis refers to calculation of SUVr and SUVr represents counts within a specific target region of interest in the brain (multiblock barycentric discriminant analysis or MUBADA, see Devous et al, "Test-Retest Reproducibility for the Tau PET Imaging Agent Flortaucipir F18," J. Nucl. Med. 59:937–943 (2018)) when compared with a reference region (parametric estimate of reference signal intensity or PERSI, see, Southekal et al., "Flortaucipir F 18 Quantitation Using Parametric Estimation of Reference Signal Intensity," J. Nucl. Med. 59:944–951 (2018)).

[0080] In some embodiments, the subject/patient of the present disclosure has a very low tau to moderate tau burden. As used herein, a human subject has "very low tau to moderate tau" burden if the tau burden is less than or equal to 1.46 SUVr (i.e., ≤1.46 SUVr) using ^{18}F-flortaucipir based quantitative analysis where quantitative analysis refers to calculation of SUVr and SUVr represents counts within a specific target region of interest in the brain (MUBADA, see Devous et al, "Test-Retest Reproducibility for the Tau PET Imaging Agent Flortaucipir F18," J. Nucl. Med. 59:937–943 (2018)) when

compared with a reference region (PERSI, see, Southekal et al., "Flortaucipir F 18 Quantitation Using Parametric Estimation of Reference Signal Intensity," J. Nucl. Med. 59:944–951 (2018)).

[0081] In some embodiments, the subject/patient of the present disclosure has a low tau to moderate tau burden. As used herein, a human subject has "low tau to moderate tau" burden if the tau burden is from greater than or equal to 1.10 to less than or equal to 1.46 (i.e., ≥1.10 SUVr to ≤1.46 SUVr) using ^{18}F-flortaucipir based quantitative analysis where quantitative analysis refers to calculation of SUVr and SUVr represents counts within a specific target region of interest in the brain (MUBADA, see Devous et al, "Test-Retest Reproducibility for the Tau PET Imaging Agent Flortaucipir F18," J. Nucl. Med. 59:937–943 (2018)) when compared with a reference region (PERSI, see, Southekal et al., "Flortaucipir F 18 Quantitation Using Parametric Estimation of Reference Signal Intensity," J. Nucl. Med. 59:944–951 (2018)). "Low tau to moderate tau" burden can also be referred to as "intermediate" tau burden.

[0082] In some embodiments, the subject/patient of the present disclosure has a high tau burden. As used herein, a human subject has "high tau" burden if the tau burden is greater than 1.46 SUVr (i.e., >1.46 SUVr) using ^{18}F-flortaucipir based quantitative analysis where quantitative analysis refers to calculation of SUVr and SUVr represents counts within a specific target region of interest in the brain (MUBADA, see Devous et al, "Test-Retest Reproducibility for the Tau PET Imaging Agent Flortaucipir F18," J. Nucl. Med. 59:937–943 (2018)) when compared with a reference region (PERSI, see, Southekal et al., "Flortaucipir F 18 Quantitation Using Parametric Estimation of Reference Signal Intensity," J. Nucl. Med. 59:944–951 (2018)).

[0083] The antibodies, doses, dosing regimens, or methods disclosed herein can be used to treat or prevent early symptomatic Alzheimer's disease. As used herein, early symptomatic Alzheimer's disease encompasses the mild cognitive impairment stage of AD (also known as prodromal AD) and the mild dementia stage of AD. The National Institute on Aging and Alzheimer's Association (NIA-AA) created a framework to help define Alzheimer's disease (see, Jack et al., "NIA-AA Research Framework: Toward a Biological Definition of Alzheimer's Disease," Alzheimer's & Dementia: The Journal of the Alzheimer's Association 14(4) 535-562 (2018), which is hereby incorporated by reference in its entirety).

[0084] The term "with chronic administration" means throughout the subject's lifetime.

[0085] As used herein, mild cognitive impairment is defined as cognitive performance below expected range for that individual based on all available information. This may be based on clinical judgment and/ or on cognitive test performance. Cognitive performance is usually in the impaired/abnormal range based on population norms, but this is not required as long as the performance is below the range expected for that individual. In addition to evidence of cognitive impairment, evidence of decline in cognitive performance from baseline must also be present. This may be reported by the individual or by an observer or observed by change on longitudinal cognitive testing/behavioral assessments or by a combination of these. In this stage, the individual performs daily life activities independently, but cognitive difficulty may result in detectable but mild functional impact on the more complex activities of daily life, either self-reported or corroborated by a study partner.

[0086] As used herein, mild dementia is defined as substantial progressive cognitive impairment affecting several domains, and/or neurobehavioral disturbance. This is documented by the individual's report or by observer (e.g., study partner) report or by change on longitudinal cognitive testing. This stage includes clear functional impact on daily life, affecting mainly instrumental activities, and the individual is no longer fully independent/requires occasional assistance with daily life activities. An individual no longer is considered to have mild AD dementia when the AD has worsened to the point of a) extensive functional impact on daily life with impairment in basic activities and b) is no longer independent and requires frequent assistance with daily life activities.

[0087] As used herein, the term "about" means up to ±10%.

[0088] The terms "subject" and "patient" are used interchangeably in the present disclosure.

[0089] The phrases "slowing of decline" and "slowing disease progression" are used interchangeably in the present disclosure.

[0090] As used herein, "methods of treatment" are equally applicable to use of a composition for treating the diseases or disorders described herein and/or compositions for use and/or uses in the manufacture of a medicaments for treating the diseases or disorders described herein.

EXAMPLES

[0091] The following Examples further illustrate the present disclosure. It should be understood however, that the Examples are set forth by way of illustration and not limitation, and that various modifications may be made by one of ordinary skill in the art.

[0092] The following table provides some examples of dosing regimens of remternetug provided by the present disclosure:

Delivery	**Dose (mg)**	**Dose Freq.**	**# of doses**	**Dose administration times shown by week numbers**	**Indication**
IV	2300	Q12W	3	0,12,24	Treatment or prevention of Early Symptomatic AD[a]
IV	1500	Q12W	4	0,12,24,36	
IV	800	Q8W	7	0,8,16,24,32,40,48	
IV	400; 800[c]	Q4W; Q8W	3; 5	0,4,8,16,24,32,40,48	
IV	400	Q4W	13	0,4,8,12,16,20,24,28,32,36,40,44 ,48,52	
SC	400	Q1W	36	0,1,2,3…,36	
SC	800	Q4W	13	0,4,8,12,16,20,24,28,32,36,40,44 ,48	
SC	400; 800[d]	Q4W	3; 10	0,4,8,12,16,20,24,28,32,36,40,44 , 48	
IV	200 400 800	Q8W	2; 2; 3 (or 6)	0, 8, 16, 24, 32, 40, 48 (or up to 72 weeks)	
SC	400 800 800	Q8W Q8W Q4W	3; 3; 7	0, 8, 16, 24, 32, 40, 48, 52, 56, 60, 64, 68, 72	
IV	2300	Q12W	2	0,12	Treatment or prevention of Preclinical AD[b]
IV	1500	Q12W	3	0,12,24	
IV	800	Q8W	5	0,8,16,24,32	
IV	400; 800[e]	Q4W; Q8W	3; 3	0,4,8,16,24,32	
IV	400; 800[f]	Q4W; Q8W	3; 4	0,4,8,16,24,32,40	
IV	400	Q4W	10	0,4,8,12,16,20,24,28,32,36	
SC	400	Q1W	36	0,1,2,3…35	
SC	800	Q4W	13	0,4,8,12,16…48	

SC	400; 800[g]	Q4W	3; 8	0,4,8,12,16,20,24,28,32,36,40	
SC	100 400 800 800	Q8W Q8W Q8W Q4W	2 2 2 7	0, 8, 16, 24, 32…72	
SC	200 400 800 800	Q8W Q8W Q8W Q4W	1 2 1 9-11	0, 8, 16, 24, 32, 36, 40, 44, 48, 52, 56, 60, 64 (or up to 72)	
SC	400 800 800	Q8W Q8W Q4W	2 1 7-13	0, 8, 16, 24, 28, 32, 36, 40, 44, 48 (or up to 72)	
SC	400 800 800	Q12W Q8W Q4W	2 1 9-11	0, 12, 24, 32, 36, 40, 44, 48, 52, 56, 60, 64 (or up to 72)	

"a" treatment or prevention also causes i) reduction of Aβ plaques in the brain of the human subject, ii) slowing of cognitive decline in the human subject, or iii) slowing of functional decline in the human subject.
"b" treatment or prevention also causes i) reduction of Aβ plaques in the brain of the human subject, ii) slowing of cognitive decline in the human subject, or iii) slowing of functional decline in the human subject.
"c" indicates that a total of 3 doses of 400 mg are delivered to the patient at a frequency of one dose every 4 weeks (Q4W) followed by a total of 5 doses of 800 mg where each dose is delivered at a frequency of one dose every 8 weeks (Q8W).
"d" indicates that a total of 3 doses of 400 mg are delivered to the patient at a frequency of one dose every 4 weeks (Q4W) followed by a total of 10 doses of 800 mg where each dose is delivered at a frequency of one dose every 4 weeks (Q4W).
"e" indicates that a total of 3 doses of 400 mg are delivered to the patient at a frequency of one dose every 4 weeks (Q4W) followed by a total of 3 doses of 800 mg where each dose is delivered at a frequency of one dose every 8 weeks (Q8W).
"f" indicates that a total of 3 doses of 400 mg are delivered to the patient at a frequency of one dose every 4 weeks (Q4W) followed by a total of 4 doses of 800 mg where each dose is delivered at a frequency of one dose every 8 weeks (Q8W).
"g" indicates that a total of 3 doses of 400 mg are delivered to the patient at a frequency of one dose every 4 weeks (Q4W) followed by a total of 8 doses of 800 mg where each dose is delivered at a frequency of one dose every 4 weeks (Q4W).

Example 1: Non-clinical Studies.

[0093] Non-clinical ADME: The nonclinical pharmacokinetics (PK) of remternetug was characterized following a single intravenous (IV) or subcutaneous (SC) dose in cynomolgus monkeys. Multiple-dose toxicokinetics were characterized in cynomolgus monkeys following twice-weekly IV doses for 6 weeks. Serum concentrations of

remternetug were determined by validated ELISA, which employed immobilized ligand N3pG Aβ to capture remternetug.

[0094] Remternetug PK was described by low CL, small Vss, and a terminal $t_{1/2}$ of elimination of 329 to 390 hours (approximately 14 to 16 days) in monkeys. Subcutaneous bioavailability in monkeys was approximately 74%. Following twice-weekly IV dosing in cynomolgus monkeys for 6 weeks, exposure to remternetug increased with increasing dose between 20 and 200 mg/kg in a roughly dose-proportional manner. An approximately 3- to 4-fold accumulation in exposures was observed. Antidrug antibodies were not detected following administration of remternetug in single or repeat-dose studies.

[0095] Single-Dose Pharmacokinetics: The serum PK of remternetug in cynomolgus monkeys was characterized following a single bolus administration of 1 mg/kg (IV) or 40 mg/kg (IV and SC) as shown in Table 1.

Table 1. Summary of Pharmacokinetic Parameters of Remternetug in Cynomolgus Monkeys following a Single IV or SC Administration

Parameter[a]	IV	IV	SC
	1 mg/kg	40 mg/kg	40 mg/kg
	N = 2 Animals	N = 3 Animals	N = 3 Animals
C_0 (mg/mL)	28	984 ± 108	NA
T_{max} (hr)	NA	6.00 ± 0.00[b]	128 ± 36.7
C_{max} (mg/mL)	27	915 ± 68.2	372 ± 45.3
$AUC_{0-\infty}$ (mg·hr/mL)	7380	282,000 ± 52,200	20,6000 ± 15,800
$t_{1/2}$ (hr)	390	377 ± 128	329 ± 75.2
CL (mL/hr/kg)	0.14	0.145 ± 0.0280	NA
CL/F (mL/hr/kg)	NA	NA	0.195 ± 0.0156
V_{SS} (mL/kg)	69	ND	ND
%F	NA	NA	74

Abbreviations: $AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity; C_0 = estimated serum concentration at time zero; CL = clearance; CL/F = relative clearance ; C_{max} = maximum observed serum concentration; %F = percent bioavailability; IV = intravenous; SC = subcutaneous; N3pG Aβ = pyroglutamate modification of the third amino acid of amyloid-beta peptide; N = number of determinations; NA = not applicable; ND= not determined; $t_{1/2}$ = terminal half-life; T_{max} = time to maximum serum concentration; V_{ss} = steady-state volume of distribution.

a Parameters were calculated based on concentrations determined by N3pG Aβ antigen-capture enzyme-linked immunosorbent assay. Mean (n = 2) or mean +/- standard deviation (n = 3) of values is presented.

b The first time point collected was 6 hours postdose.

[0096] Serum concentrations of remternetug were determined by an ELISA, which employed immobilized ligand N3pG Aβ to capture remternetug. For each time point, samples were collected from 2 or 3 animals. Remternetug PK exhibited low CL and a small Vss, consistent with reported blood volume for cynomolgus monkeys, indicating that remternetug is largely distributed within the vascular system. The mean elimination $t_{1/2}$ ranged from 329 to 390 hours (approximately 14 to 16 days). When comparing the 1- and 40-mg/kg IV doses, Cmax and AUC were dose proportional; bioavailability following SC administration was 74%. There were no injection site reactions (clinical observation of injection site and microscopic evaluation of skin biopsies).

[0097] Multiple-Dose Toxicokinetics: A toxicology study was conducted in cynomolgus monkeys, with dosing twice weekly for 6 weeks. Repeat-dose serum toxicities of remternetug were determined as part of the GLP toxicology study. Remternetug was administered at 20 or 200 mg/kg to 6 animals per group. Serum concentrations of remternetug were determined by validated ELISA, which employed immobilized ligand N3pG Aβ to capture remternetug, and detection through horseradish peroxidase-labeled antihuman IgG. Serum toxicokinetics in cynomolgus monkeys are described in Table 2.

Table 2: Serum Toxicokinetics Parameters (Mean ± SD) of Remternetug in Cynomolgus Monkeys following Twice-Weekly Intravenous Administration for 6 Weeks

Administered Dose (mg/kg)	20	200
N	6	6
Day 1		
C_0 (µg/mL)	541 ± 73.3	5290 ± 506
C_{max} (µg/mL)	519 ± 67.0	5070 ± 401
T_{max} (hr)	1.00 ± 0.00	1.00 ± 0.00
AUC_{0-96} (µg□h/mL)	29,300 ± 2200	288,000 ± 11,500
Day 39		
C_0 (µg/mL)	1590 ± 258	13,900 ± 695
C_{max} (µg/mL)	1580 ± 254	13,600 ± 751
T_{max} (hr)	2.17 ± 2.86	1.00 ± 0.00
AUC_{0-96} (µg□h/mL)	123,000 ± 23,800	941,000 ± 54,300

Abbreviations: AUC_{0-96} = area under the curve during the dosing interval; C_0 = back-extrapolated concentration at time 0; Cmax = maximum observed concentration; F = female; M = male; MF = male and female combined; N = number of animals; SD = standard deviation; Tmax = time of maximum observed concentration.

[0098] Samples from all study animals were tested for the presence of ADAs, and no treatment-emergent ADAs were detected following administration of remternetug for 6 weeks.

[0099] Exposure to remternetug, as assessed by area under the curve during the dosing interval (AUC096), back-extrapolated concentration at time 0 (C0), and Cmax increased with increasing dose on all days evaluated and were roughly dose proportional between 20 and 200 mg/kg. Values for Cmax and AUC_{0-96} were approximately 3- to 4-fold higher on Day 39 than on Day 1, indicating accumulation of remternetug in monkey serum after multiple doses. Concentrations at pre-dose and 1-hour postdose on Day 22 were comparable with those on Day 39 at corresponding groups and timepoints. Antidrug antibodies were not detected in all samples.

[00100] Non-clinical Safety Pharmacology and Toxicology:

[00101] The safety of remternetug was assessed in a 6-week toxicity study in cynomolgus monkeys with evaluations of safety pharmacology and toxicology. No adverse or important drug related findings were found.

[00102] The overall nonclinical safety profile of remternetug is supportive of clinical studies in humans (see Tables 3 and 4).

Table 3: Margin of Safety for Single Intravenous Administration of Remternetug Based on Administered Dose and Exposure

Species **Dose level**	**Human Dose (mg/kg)**	**Dose Multiple[a]**	**AUC (µg•h/mL)**	**AUC Exposure Multiple[b]**	**C_{max} (µg/mL)**	**Cmax Exposure Multiple[b]**
Cynomolgus Monkey						
200 mg/kg twice-weekly NOAEL[c]	-	-	941,000	-	13,600	-
Human Starting Dose						
20 mg (single dose)	0.29	690×	3450	273×	6.39	2128×
Human Highest Dose						
2800 mg (highest dose)	10	20×	152,000	6.2×	631	22×

Abbreviations: AUC = area under the serum concentration versus time curve; $AUC_{0\text{-}96h}$ = AUC from time zero to 96 hours postdose; $AUC_{0\text{-}\infty}$ = area under concentration versus time curve from zero to infinity; C_{max} = maximum serum concentration; NOAEL = no-observed-adverse-effect level.

a Dose multiple is the dose at the NOAEL (200 mg/kg) in monkeys/dose in humans based on mg/kg (assuming 70 kg as the subject weight). For biological products administered intravenously with a molecular weight >100,000 Da, scaling doses on a mg/kg basis is the preferred approach (FDA 2005).

b Exposure multiple is the calculated $AUC_{0\text{-}96h}$ (or C_{max}) in animals after 6 weeks of treatment (Day 36)/$AUC_{0\text{-}\infty}$ (or C_{max}) in humans after a single dose from Study LAKB (NCT04451408, clinicaltrials.gov).

c NOAEL determined in a 6-week, repeat-dose toxicity study in the cynomolgus monkey.

Table 4: Margin of Safety for Repeat Intravenous or SC Administration of Remternetug.

Species Dose Level	Dose mg/kg /week	Dose Multiple Per Week[a]	$C_{av,ss}$[b] (mg/mL)	$C_{av,ss}$[c] Exposure Multiple	C_{max}[b] (mg/mL)	C_{max} Exposure[c] Multiple
Cynomolgus monkey 200 mg/kg twice weekly[d]	400	NA	9802	NA	13,600	NA
Human SC Dose, 400 mg QW	5.7	70	242	41	252	54
Human IV Dose (Titration)[e]	1.4	286	70	140	351	39
Human IV Dose, 2300 mg Q12W	2.7	146	202	49	1010	13
Human Highest Dose 2800 mg Q4W (Study LAKB)[f]	10	40	368	27	834	16

Abbreviations: $C_{av,ss}$ = average steady-state serum concentration; C_{max} = maximal serum concentration; $C_{max,ss}$ = maximum observed drug concentration at steady state; NA = not applicable; NOAEL = no-observed-adverse-effect level; PK = pharmacokinetic; Q4W = once every 4 weeks; Q12W = once every 12 weeks; SC = subcutaneous.

a Dose multiple is the total weekly dose at the NOAEL (200 mg/kg twice weekly for a total of 400 mg/week) in monkeys divided by the weekly drug dose in humans based on mg/kg (assuming 70 kg as the subject weight and dividing the human dose by the weeks in the dosing interval).

b Cynomolgus monkey $C_{av,ss}$ was calculated by dividing mean Day 39 tox study AUC_{0-96} by 96 hours; monkey C_{max} was the mean C_{max} value observed on Day 39. Human

$C_{av,ss}$ and C_{max} values for SC and IV dosing were derived from the population PK model, 30 May 2022 data cutoff.

c $C_{av,ss}$ or C_{max} exposure multiple is the monkey $C_{av,ss}$ or C_{max} Day 36 divided by the model-predicted $C_{av,ss}$ (or $C_{max,ss}$) in humans.

d NOAEL determined in a 6-week, repeat-dose toxicity study in the cynomolgus monkey.

e IV titration of 200 mg Q8W x 2, 400 mg Q8W x 2, and 800 mg Q8W x 3 doses.

f Highest administered clinical dose (2800 mg given intravenously Q4W).

[00103] Tissue cross-reactivity studies with human and cynomolgus tissues were also conducted. Remternetug produced immunoreactivity in plaques in cerebellum or cerebrum, extracellular material in the walls of small blood vessels, and glial cells in the human brain. Additionally, binding with remternetug was observed in several epithelial cell types and in spermatogenic cells in the human testis. In cynomolgus monkey tissues, binding with remternetug was present only in epithelial cells in the skin and in stromal cells in the decidual plate of the placenta. The immunoreactivity observed with remternetug in plaques in the human brain was expected based on the known diagnosis of AD in 1 donor, or the age of the other donor (86 years) even without a diagnosis of AD. Plaques were not expected to be present in the cynomolgus monkey brain samples because these samples were obtained from young adults. All other immunoreactivity observed with remternetug in the human and cynomolgus monkey tissue panels was unexpected, because the target epitope is AD plaque-specific and has not been reported to be expressed in normal tissues or demonstrated in physiologic fluids. However, all cellular binding in the human and cynomolgus monkey tissue panels in the current study was cytoplasmic in nature. The monoclonal antibody binding to cytoplasmic sites generally is considered of little to no toxicological significance because cytoplasm/cytoplasmic structures are considered to be unavailable to monoclonal antibodies in vivo.

Example 2: Clinical Studies.

Dose Considerations for Participants with Early Symptomatic AD and / or Pre-Symptomatic AD (Preclinical AD)

[00104] Selecting a dose for administration to human participants seeks to address one or both of: (i) achieving robust amyloid plaque clearance in participants, namely, amyloid

plaque clearance (<24.1 centiloids) in about 80-90% of participants (i.e. within 52 or 72 weeks of treatment or less); and (ii) lowering risk for ARIA development while maintaining robust plaque clearance. Implementation of dosing at 4-, 8-, and 12-week intervals, or combinations thereof, are contemplated herein seeking to allow time for any asymptomatic ARIA to resolve without interrupting dosing and also decrease the risk of ARIA exacerbation. A titration scheme is also contemplated herein for reducing incidence and severity of observed ARIA (Salloway et al. 2022).

[00105] Subcutaneous dosing is contemplated herein for allowing a slower increase in serum concentrations with a lower Cmax as compared to IV administration. It has been hypothesized that a lower Cmax and a slower increase in serum concentration may reduce ARIA risk. (Hayato et al. 2020; Salloway et al. 2022). Implementation of dosing at 4-, 8-, and 12-week dosing intervals, or combinations thereof, are contemplated herein seeking to allow time for any asymptomatic ARIA to resolve without interrupting dosing and also potentially decrease the risk of ARIA exacerbation. A titration scheme is also contemplated herein for subcutaneous dosing for reducing incidence and severity of observed ARIA.

[00106] Intravenous and subcutaneous dose regimens also seek to provide acceptable preparation and convenience for patients. Dose regimens provided herein account for remternetug's relatively long half-life, reduced risk of immunogenicity, and robust amyloid plaque clearance, attributes which are not applicable to other anti-N3pGlu Aβ antibodies. Such attributes seek to achieve robust amyloid plaque clearance, with less frequent dosing (e.g., 4-, 8-, and 12-week, or combinations thereof, dosing intervals for either IV or SC dosing); dosing intervals allowing for any asymptomatic ARIA to resolve without interrupting dosing; and SC dosing which may mitigate the potential for ARIA risk due to lower Cmax observed with dosing as well as reduce participant burden.

[00107] Remternetug targets amyloid beta peptide wherein the peptide is modified at the third position with pyroglutamate. The pyroglutamate modified Aβ is only present in the brain amyloid plaque. Remternetug can achieve robust clearance of amyloid plaque from the brain. Dosing regimens provided herein may be a fixed duration, which positively impacts dosing regimen compliance and adherence compared to treatments administered over the life of a patient.

Example 3: A Single-Dose, Dose-Escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of remternetug in Healthy Participants.

[00108] Study LAKA (NCT03720548, clinicaltrials.gov) was the first-in-human administration of remternetug. This completed single-ascending dose (SAD) Phase 1 study was conducted in healthy participants to evaluate safety, tolerability, pharmacokinetics (PK), and immunogenicity of remternetug. Study LAKA was designed as a single- and multiple-ascending dose study, but only the SAD part was conducted.

[00109] Trial Design Synopsis: Participants received a single dose of remternetug or placebo and were monitored for approximately 12 weeks postdose for safety assessments, and collection of PK and immunogenicity samples. Four dose levels were evaluated (i.e., 20, 75, 250, and 700 mg).

[00110] Primary Objectives: The primary objectives of Study LAKA were to evaluate the safety and tolerability of remternetug in healthy participants and patients with Alzheimer's disease (AD).

[00111] Secondary Objectives: Secondary objectives of Study LAKA were: i) to assess the serum PK of remternetug after a single intravenous (IV) infusion in healthy participants and multiple IV infusions in patients with AD; and ii) to evaluate the effect of remternetug on brain amyloid load in patients with AD.

[00112] Patient Population: Study LAKA consisted of healthy males and females between 18 and 45 years old, inclusive, with a body mass index (BMI) between 18.0 and 32.0 kg/m2, inclusive. Participants who had evidence of cognitive impairment (a Mini-Mental State Examination [MMSE] total score less than 29), a brain magnetic resonance imaging (MRI) scan that demonstrated clinically significant findings, or a family history of early onset AD were excluded.

[00113] Safety and Tolerability Results: There were no deaths or other serious adverse events (SAEs), and no participants were discontinued due to an adverse event (AE). Twelve (33.3%) participants reported a total of 15 adverse events with no apparent treatment-related trends. All AEs reported were mild in intensity. Only 1 AE (dizziness following administration of 700 mg remternetug) was considered to be related to the study treatment. No infusion-related reactions or hypersensitivity events were observed.

[00114] Immunogenicity Results: No participant had treatment-emergent antidrug antibodies (treatment-induced or treatment-boosted) following administration of remternetug.

[00115] Pharmacokinetic (PK) Results: The PK of remternetug was assessed up to 12 weeks after a single IV dose in healthy participants at a dose range of 20 to 700 mg in Study LAKA. The PK parameters of remternetug are presented in Table 5 below.

Table 5: Mean (% CV) Noncompartmental Pharmacokinetic Parameters Following a Single Intravenous Dose of Remternetug in Healthy Participants.

	Single-Dose Cohort			
Treatment	**20 mg IV**	**75 mg IV**	**250 mg IV**	**700 mg IV**
N	7	7	7	7
Cmax	6.39	23.4	77.3	208
(µg/mL)	(29)	(15)	(22)	(28)
$t_{1/2}$	28.2	23.0	22.3	24.2
(day)	(17.3-61.6)	(6.27-41.0)	(18.7-30.7)	(20.0-30.6)
AUC(0-∞)	3450	9860	32,700	73,300
(µg•hr/mL)	(38)	(48)	(17)	(14)
CL	0.139	0.183	0.183	0.229
(L/day)	(38)	(48)	(17)	(14)

Abbreviations: $AUC_{(0-\infty)}$ = area under the concentration versus time curve from zero to infinity; C_{max} = maximum observed drug concentration; CV = coefficient of variation; CL = total body clearance of drug calculated after IV administration; IV = intravenous; N = number of participants; $t_{1/2}$ = half-life associated with the terminal rate constant.

[00116] Pharmacodynamic Results: Study LAKA was designed with a multiple-ascending dose (MAD) part to investigate pharmacodynamic (PD) results; however, only the SAD part was conducted. Thus, no PD results were available for this study.

[00117] Conclusions: Single IV doses up to 700 mg remternetug were safe and well-tolerated following administration to healthy participants. No participants developed treatment-emergent antidrug antibodies up to 12 weeks following a single dose of

remternetug. The PK of remternetug was generally linear and exhibited a long $t_{1/2}$, typical of monoclonal antibodies.

Example 4: A Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Remternetug in Participants with Alzheimer's Disease and Healthy Participants.

[00118] Study LAKB (NCT04451408, clinicaltrials.gov) is an ongoing Phase 1 study composed of two parts. Part A of the study is being conducted to investigate the safety and tolerability of remternetug after single and multiple doses (IV or subcutaneous (SC)) in participants with AD, including participants of Japanese descent, and to investigate the effects of remternetug on cerebral amyloid plaque level.

[00119] Part B of the study is being conducted in healthy participants, including participants of Japanese descent, to evaluate the safety, tolerability, and PK of up to 2800 mg remternetug following both IV and SC administration, and to explore any immunogenicity risks. The following Table 6 depicts cohorts of study LAKB:

Table 6: Overview of Clinical Pharmacology Studies.

Trial Alias	Countries	Participant Exposure
LAKB	United States, Japan	Remternetug multiple doses IV in participants with AD[a]: Cohort 1 (250 mg or PBO Q4W): 6 Cohort 2 (700 mg or PBO Q4W): 18 Cohort 3 (1400 mg or PBO Q4W): 16 Cohort 4 (2800 mg or PBO Q4W): 6 Cohort 7 (700 mg -1400 mg or PBO Q4W)[b]: 5 Cohort 12 (2800 mg or PBO single dose): 6 Remternetug multiple doses SC in participants with AD: Cohort 14 (400 mg or PBO): 18 Remternetug single dose in healthy participants: Cohort 5 (2800 mg or PBO IV): 12

		Japanese: 8 Non-Japanese: 4 Cohort 8 (400 mg or PBO SC): 20 Japanese: 6 Non-Japanese: 14 Cohort 9 (2000 mg or PBO SC): 14 Cohort 10 (2800 mg or PBO IV): 18 Japanese: 6 Non-Japanese: 12

Abbreviations: AD = Alzheimer's disease, IV = intravenous; PBO = placebo; Q4W = once every 4 weeks; SC = subcutaneous.

[a] Remternetug-to-placebo randomization ratio for all cohorts in Part A was 5:1.

[b] Cohort 7 was a titration cohort of 700 mg IV Q4W two doses, followed by 1400 mg IV Q4W.

[00120] Remternetug, as shown herein, demonstrated rapid and robust amyloid plaque clearance, and demonstrated acceptable safety and tolerability, in patient with AD.

[00121] Part A Trial Design Synopsis: Part A is composed of cohorts, each with a remternetug-to-placebo randomization ratio of 5:1. The decision for dose escalation is made after at least 6 participants in a particular cohort have been dosed and safety data through Day 29 have been evaluated from at least 4 participants administered with study intervention. Additional participants may be added to existing cohorts based on the review of safety, tolerability, PK, and PD data. All potential participants of Part A undergo screening procedures including a MMSE, screening magnetic resonance imaging (MRI), and screening florbetapir positron emission tomography (PET) scans.

[00122] Participants in Cohorts 1 to 4, 7, and 12 received their first dose of study intervention on Day 1 of the treatment period as an IV infusion and were under observation as an inpatient overnight after the first dose. Participants were monitored as outpatients and had repeat neurological examinations and MRI performed approximately 4 weeks after the first dose of study intervention. The remaining doses of study intervention are being administered IV on an outpatient basis approximately once every 4

weeks (Q4W); except participants randomized to Cohort 12 who received only a single dose of 2800 mg.

[00123] Participants in Cohort 14 received their first dose of study intervention on Day 1 of the treatment period as SC injection; participants were under observation for approximately 6 hours after completing each of the initial 4 doses and at least 2 hours after completing all subsequent dosing visits. Participants were monitored as outpatients and had repeat neurological examinations and MRI after the first dose of study intervention.

[00124] All participants in Part A are monitored for safety, particularly amyloid-related imaging abnormalities (ARIA) and hypersensitivity reactions, for at least 12 weeks after the last dose of study intervention with periodic outpatient visits.

[00125] Part B Study Design Synopsis: Part B is a SAD study conducted in healthy participants receiving remternetug either IV or SC administration. Participants receive a single dose of remternetug or placebo and are monitored for approximately 12 weeks post-dose for safety assessments, and collection of PK and immunogenicity samples.

[00126] Primary Objective: The primary objective of Study LAKB Part B is to evaluate the safety and tolerability of remternetug in participants with AD and healthy participants, including participants of Japanese descent, following IV or SC administration.

[00127] Secondary Objectives: Secondary objectives of Study LAKB Part B are: i) to assess the serum PK of remternetug in participants with AD, including participants of Japanese descent, after single or multiple IV infusions, or SC injection in healthy participants, including participants of Japanese descent, after a single dose IV infusion and a single dose SC administration; and ii) to evaluate the effect of remternetug on cerebral amyloid plaque level in participants with AD, including participants of Japanese descent.

[00128] Patient Population: Study LAKB Part A included males and females between 55 and 85 years old, inclusive, with gradual and progressive changes in memory function and a clinical diagnosis of mild cognitive impairment due to AD, or AD dementia. Participants also have evidence of amyloid brain pathology as determined by an amyloid PET scan and have a MMSE score greater than or equal to 16. Participants must have a study partner to participate. Participants who had serious disease (other than AD) that could interfere with study analyses or impact the ability of the participant to complete the

study were excluded. Participants that have a centrally read MRI that demonstrates the presence of ARIA-E, >4 cerebral microhemorrhages, >1 area of superficial siderosis, any macrohemorrhage, or severe white matter disease were excluded.

[00129] Study LAKB Part B includes healthy males and females between 18 and 45 years old, inclusive, with a BMI between 18.0 and 32.0 kg/m2, inclusive. Participants who had a brain magnetic resonance imaging scan that demonstrated clinically significant findings, or a family history of early onset AD were excluded.

[00130] Safety and Tolerability Results for Participants with Alzheimer's Disease: As of August 2023, a total of 75 participants with AD received at least 1 dose of remternetug or placebo.

[00131] Forty participants with AD (53.3%) reported at least 1 treatment-emergent AE (TEAE); most were mild or moderate in severity. ARIA-E (n = 16; 21.3%) was the most frequently reported TEAE. The incidence of ARIA-E appeared to be dose-dependent with intravenous dosing. ARIA-H was reported in 12 (16.0%) participants. No macrohemorrhages were observed. Three cases of ARIA-E (of 16 identified) were symptomatic. All but 6 patients experiencing ARIA were managed with temporary discontinuation (6 patients were discontinued from the study).Follow-up MRIs after temporary discontinuation of study intervention demonstrated partial or complete resolution of ARIA-E.

[00132] No participants with AD experienced injection site pain, pruritus, and edema. Two infusion-related reactions and a hypersensitivity event of contact dermatitis were observed; all three events were considered mild.

[00133] Safety and Tolerability Results for Healthy Participants: As of May 2022, a total of 64 healthy participants, 20 of Japanese descent, have received 1 dose of remternetug or placebo.

[00134] No deaths, SAEs, or early discontinuations due to AEs were observed. Twelve (18.8%) healthy participants reported at least 1 TEAE. The TEAE reported by at least 2 participants was COVID-19 infection. The overall incidence of TEAEs was similar between Japanese and non-Japanese participants. No TEAEs were considered by the investigator to be related to study treatment.

[00135] Injection site reactions were assessed prospectively after a single SC injection of 34 participants. Preliminary analysis showed mild injection site reactions. The findings

included: mild injection site erythema and induration in approximately 50% of healthy participants; mild injection site pain in 2 participants; and/or pruritus and edema in 1 participant each. Most of the injection site reactions lasted up to 4 hours after administration.

[00136] Immunogenicity Results: In this ongoing study, no participant has had treatment-emergent antidrug antibodies (treatment-induced or treatment-boosted) following administration of remternetug following single or multiple administration of remternetug as of August 2023.

[00137] Pharmacokinetic Results: PK following single dose of 2800 mg IV and 400 mg SC in healthy participants were evaluated up to 56 days after administration in Study LAKB. Bioavailability following SC administration was observed to be 61%. This was based on geometric mean observed $AUC_{0-\infty}$ following 2800 mg IV or 400 mg SC single dose administrations in healthy volunteers. PK results are shown in Table 7 below.

Table 7: Mean (% CV) Noncompartmental Pharmacokinetic Parameters Following Single Dose of either 2800 mg IV or 400 mg subcutaneous of Remternetug in Healthy Participants.

Parameter	Geometric Mean (CV%)	
	Single Dose IV 2800 mg (N=9)	Single Dose SC 400 mg (N=10)
C_{max} (µg/mL)	984 (24)	37.1 (29)
T_{max}[a] (h)	0.70 (0.68-6.02)	168 (96.15-339.1)
$AUC_{(0-672)}$ (µg·h/mL)	212000 (21)	17400 (24)
$AUC_{(0-1344)}$ (µg·h/mL)	308000 (25)	26800 (24)
$AUC_{(0-\infty)}$ (µg·h/mL)	394000 (24)	32100 (25)
CL (L/Day)	0.171 (24)	0.299 (25)
V_z (L)	6.13 (47)	6.98 (26)
Bioavailability (F%)	61	

Abbreviations: $AUC_{(0-672)}$ = dosing interval 672 hours (Month 1); $AUC_{(0-1344)}$ = dosing interval 672 hours = Month 2; $AUC_{(0-\infty)}$ = area under the concentration versus time curve from zero to infinity; Bioavailability = (Dose normalized Geomean AUCτ SC/ Dose normalized Geomean AUCτ IV) * 100; C_{max} = maximum observed drug concentration; CL = total body clearance after intravenous administration; CV = coefficient of variation; IV = intravenous; N = number of Participants; SC = subcutaneous; tmax = time of maximum observed drug concentration; V_z = apparent volume of distribution during the terminal phase.

[a] Median (range).

[00138] PK data of participants with AD from the ongoing studies LAKB and LAKC (Detailed in Examples 4 and 5) are reported below as of the data cut-off date of 24 March 2023. Cmax,ss and AUCτ,ss both increased with dose. In Study LAKB, there was accumulation with repeated monthly administration of remternetug, with accumulation ratio of approximately 1.6, 1.3, 1.0 and 1.9 following doses of 250 mg, 700 mg, 1400 mg, and 2800 mg Q4W IV, respectively. Preliminary population PK analyses were carried out using all observed LAKB and LAKC data (n = 451 participants). Intravenous and subcutaneous PK data were best described by a first order absorption, 2-compartment model with clearance and volume terms scaled to patient body weight with fixed exponents of 0.8 and 1, respectively (based on allometric principles). Age of Phase 1 (20 mg/mL) drug product was identified as a significant covariate, on exposure. Material age in Phase 1 study at the start of treatment (time, Day = 0) varied from 182 to 621 days. Exposure (LAKB) decreased linearly with age of the material over the range of 180 to 423 days. Investigation of the impact of material age indicated that age-related increases in oxidation were responsible for the PK changes. The Phase 3 drug product formulation incorporated modifications including increased remternetug concentration and inclusion of methionine, which stabilized against oxidation.

[00139] Based on LAKC PK data, serum exposure changes were not observed with Phase 3 material age. Based on the preliminary population PK model, bioavailability was estimated at 60% and mean absorption rate of remternetug following subcutaneous administration at 0.008 h-1. Maximum concentration (Cmax) is achieved at the end of the IV infusion (30 min to 3 hr) or at approximately 7 days following IV or SC administration, respectively. Central volume of distribution is 2.74 L with 38% inter-individual variability, while peripheral volume of distribution is 2.73 L with 28% inter-

individual variability. Serum clearance is 0.0053 L/h, with 54% between-participant variability.

[00140] Remternetug PK is dose proportional in dose range 250 mg to 2800 mg IV. There also are dose dependent increases in serum exposures following 400 mg and 800 mg SC dosing (limited data).

[00141] Pharmacodynamic Results: In study LAKB, ^{18}F-florbetapir PET scans were performed before, approximately 12 weeks and 24 weeks after initiation of IV administration of remternetug or placebo every 4 weeks, or a single dose or remternetug or placebo. For SC administration of remternetug, ^{18}F-florbetapir PET scans were performed 4 weeks, 12 weeks, and 24 weeks after initiation of weekly dosing of remternetug or placebo.

[00142] Florbetapir images of available cohorts were prepared substantially as described here. A composite SUVr was calculated using 6 target cortical regions and whole cerebellum as a reference region (Clark et al. 2011). This composite SUVr that measures cerebral Aβ plaque was converted to centiloid unit via the formula: Centiloid unit = 183.07*SUVr − 177.26 (Navitsky et al. 2018). As previously reported (Navitsky et al. 2018), the threshold of 24.1 centiloid unit (CL) discriminates neuropathologically verified none or sparse versus moderate to frequent plaques in autopsy-confirmed data. The threshold of 0 CL represents the average value in "high-certainty," amyloid-negative subjects i.e., young (≤45 years old) controls (Klunk et al. 2015).

[00143] Figure 1 describes the change from baseline of cerebral amyloid plaque up to Day 169 by individual participants and b y time point. For both IV and SC cohorts, time- and dose/concentration-dependent amyloid plaque lowering was observed. Amyloid plaque level <24.1 CL was used to define amyloid clearance (Navitsky et al. 2018; Mintun et al. 2021). The proportion of participants that achieved amyloid clearance increased with remternetug dose and time (see, **Error! Reference source not found.**). A similar trend was observed when amyloid plaque level <0 CL was used as threshold (see, Table 8a and b).

Table 8a: Overall Percentage of Participants Achieving Amyloid Clearance (CL<24.1) for Study LAKB

Treatment	Day 85 (n/s)	Day 169 (n/s)	Day 253 (n/s)
Placebo (N=13)	0/9 (0.00%)	0/9 (0.00%)	0/6 (0.00%)
LY 250mg Q4W (N=5)	0/4 (0.00%)	0/4 (0.00%)	1/4 (25.00%)
LY 700mg Q4W (N=15)	4/15 (26.67%)	8/14 (57.14%)	3/5 (60.00%)
LY 1400mg Q4W (N=13)	6/12 (50.00%)	10/10 (100.00%)	5/7 (71.43%)
LY 2800mg Q4W (N=5)	4/4 (100.00%)	4/4 (100.00%)	4/4 (100.00%)
LY 700mg x 2 + 1400mg	2/3 (66.67%)	2/2 (100.00%)	0/-
LY 2800mg SD (N=5)	3/5 (60.00%)	2/5 (40.00%)	3/5 (60.00%)
LY 400mg SC QW (N=15)	0/3 (0.00%)	2/2 (100.00%)	0/-

Table 8b: Overall Percentage of Participants Achieving Negative Centiloid Level for Study LAKB

Treatment	Day 85 (n/s)	Day 169 (n/s)	Day 253 (n/s)
Placebo (N=13)	0/9 (0.00%)	0/9 (0.00%)	0/6 (0.00%)
LY 250mg Q4W (N=5)	0/4 (0.00%)	0/4 (0.00%)	0/4 (00.00%)
LY 700mg Q4W (N=15)	1/15 (6.67%)	1/14 (7.14%)	1/5 (20.00%)
LY 1400mg Q4W (N=13)	3/12 (25.00%)	6/10 (60.00%)	3/7 (42.86%)
LY 2800mg Q4W (N=5)	4/4 (100.00%)	3/4 (75.00%)	4/4 (100.00%)

LY 700mg x 2 + 1400mg	1/3 (33.33%)	1/2 (50.00%)	0/-
LY 2800mg SD (N=5)	2/5 (40.00%)	2/5 (40.00%)	1/5 (20.00%)
LY 400mg SC QW (N=15)	0/3 (0.00%)	1/2 (50.00%)	0/-

Abbreviations: LY = remternetug; N = Number of randomized subjects; n = Subjects with Florbetapir F18 PET level meeting the criteria; s = Number of available Florbetapir F18 PET scans; Q4W = Once every 4 weeks; SD = Single Dose; SC = Subcutaneous; QW = Once every week.

[00144] Amyloid clearance was rapid and robust in some participants. An example of amyloid clearance is depicted in Figure 2 as a representative example from Study LAKB in a participant who received a single dose of 2800 mg and achieved amyloid clearance at the Day 85 visit. The X-axis of Figure 2 provides standardized uptake values (SUV) and Figures 2 reflects the participant experienced an amyloid reduction of 144 centiloids (CLs) at Day 85.

[00145] Pharmacokinetics/Pharmacodynamics: A PK/PD analysis of the relationship between serum remternetug concentrations and amyloid plaque (as measured using ^{18}F-florbetapir PET) found a linear model best described the treatment effect on reduction of amyloid plaque level over time. Time to achieve amyloid plaque clearance (levels of <24.1 CL) was dependent on dose and baseline amyloid plaque level. An exposure-response model was used to fit the amyloid plaque data over time. The model was parametrized in terms of natural degradation half-life of amyloid plaque, treatment effect, and baseline. The effect of remternetug PK was described using a linear model stimulating the degradation rate of plaque removal. The treatment effect represented by slope was also found to be correlated with the baseline amyloid plaque level. The exposure-amyloid plaque model suggested that:

with an increase in exposure there was a proportional increase in plaque removal rate. Although the data at the time of filing did not allow for estimation of maximum response and associated serum concentration required for half-maximum response, it was evident from observations that 2800 mg IV Q4W achieved the highest plaque removal within the dose range studied.

time to achieve amyloid plaque (<24.1 CL units) clearance was dependent on baseline amyloid plaque level. The higher the baseline value, the more time was needed to achieve amyloid plaque clearance.

ApoE4 carrier status (limited data) was examined as a potential covariate on both baseline and slope but was not identified as a significant covariate on this preliminary exposure-amyloid plaque model.

Example 5: Assessment of safety and efficacy measured by amyloid reduction of remternetug in early symptomatic Alzheimer's disease

[00146] Study LAKC (NCT04451408, clinicaltrials.gov) is an ongoing Phase 3 study composed of open-label addenda and a double-blind, placebo controlled, randomized clinical trial (i.e., the main protocol). The open-label addendum is collecting open-label safety data in participants with early symptomatic AD with evidence of amyloid pathology who receive IV or SC remternetug dosing regimens. The main protocol is evaluating remternetug administered IV and SC compared to placebo to measure amyloid plaque clearance in participants with early symptomatic AD.

[00147] Open-Label Addenda Trial Design Synopsis: The purpose of these addenda is to assess open-label safety in participants who receive remternetug IV or SC; no placebo dosing will be administered in these addenda.

[00148] Addenda 1, 3, and 4, set forth below, have been initiated. Participants are being assigned to

remternetug 2300 mg IV every 12 weeks for 3 doses,

remternetug 1500 mg IV every 12 weeks for 4 doses,

remternetug 800 mg IV every 8 weeks for 7 doses,

remternetug 400 mg IV every 4 weeks for 3 doses, administered at weeks 0, 4, and 8; and 800 mg IV every 8 weeks for 5 doses, administered at weeks 16, 24, 32, 40, and 48,

400 mg IV every 8 weeks for 2 doses, administered at weeks 0 and 8; and 800 mg IV every 8 weeks for 5 doses, administered at weeks 16, 24, 32, 40, and 48,

200 mg IV every 8 weeks for 2 doses, administered at weeks 0 and 8; 400 mg IV every 8 weeks for 2 doses, administered at weeks 16 and 24; and 800 mg IV every 8 weeks for 3 doses, administered at weeks 32, 40, and 48,

400 mg SC every week for 36 doses, or

400 mg SC every 4 weeks for 13 doses.

[00149] The study schema for addendum 1 is provided in Figure 3, the study schema for addendum 3 is provided in Figure 4, and the study schema for addendum 4 is provided in Figure 5.

[00150] Assessment of SC arms may also be performed substantially as provided herein, and pursuant to Addendum 5 (a study schema provided in Figure 6). Accordingly, participants will be randomized (1:1:1) to one the three following open-label subcutaneous dosing regimens:

Treatment group 1 (13 doses overall)

100 mg Q8W for 2 doses followed by

400 mg Q8W for 2 doses followed by

800 mg Q8W for 2 doses followed by

800 mg Q4W for up to 7 doses.

Treatment group 2 (15 doses overall)

200 mg Q8W for 1 dose followed by

400 mg Q8W for 2 doses followed by

800 mg Q8W for 1 dose followed by

800 mg Q4W for up to 11 doses.

Treatment group 3 (16 doses overall)

400 mg Q8W for 2 doses followed by

800 mg Q8W for 1 dose followed by

800 mg Q4W for up to 13 doses.

Further, a ***treatment group 4 (14 doses overall) may also be initiated substantially as described below:***

400 mg every 12 weeks for 2 doses followed by

800 mg Q8W for 1 dose followed by

800 mg Q4W for up to 11 doses.

[00151] Summary statistics and statistical analyses will be provided for the safety and exposure data that is collected in the addenda as defined in the statistical analysis plan. The analyses of the addenda will generally follow what is described in the statistical

analysis plan for the main protocol, with the exception that there will be no testing relative to the remternetug or placebo arms in the double-blind treatment phase.

[00152] Open-Label Addenda Objectives: The primary objectives of the addenda are to describe the safety of remternetug. Secondary objectives of the addenda are to assess peripheral PK and presence of anti-remternetug antibodies. Additionally, a secondary objective of addendum 4 is to assess the proportion of participants who reach brain amyloid clearance and the mean absolute change from baseline in brain amyloid plaque on amyloid PET scans.

[00153] Open-Label Addendum Patient Population: In general, an individual may take part in the Open-Label Addendum if they:

are 60 to 85 years of age, inclusive;

have gradual and progressive change in cognitive function;

have an MMSE score of 20 to 28, inclusive (Addendum 1, 3, and 4) or have an MMSE score of 22 to 30, inclusive (Addendum 5); and

have an amyloid PET scan result consistent with the presence of brain amyloid pathology (for example, has Aβ plaques in the brain above 24cL).

[00154] In LAKC Addendum 5, participants must also have a CDR-GS of 0.5 or 1 to be enrolled.

[00155] In general, an individual may not take part in the study if they:

have significant neurological disease or psychiatric diagnosis other than AD that may interfere with the analysis or ability to complete the study;

have any clinically important abnormality at screening that could be detrimental to the participant, could compromise the study, or show evidence of other etiologies for dementia;

have current serious or unstable illness or condition that could interfere with the analysis of the study; and/or

are a woman of childbearing potential.

[00156] Study LAKC (Main Protocol) Trial Design Synopsis: Study LAKC is an ongoing multicenter, randomized, double-blind, placebo-controlled, Phase 3 study of remternetug in participants with early symptomatic AD. Participants who meet entry criteria will be enrolled to one of the SC QW, SC Q4W, or IV cohorts, and randomly assigned in a 3:1 ratio of remternetug to placebo, respectively.

IV Cohort (N=~200)

remternetug 800 mg IV every 8 weeks for up to 7 doses, or

placebo IV

SC QW Cohort (N=~200)*

remternetug 400 mg SC weekly for 36 doses, or

placebo SC

SC Q4W Cohort (N=~200)

remternetug 800 mg SC Q4W for 13 doses, or

placebo SC

[00157] Participants previously enrolled and randomized into the SC QW cohort, dosing has been adjusted to 800 mg SC Q4W or placebo following a minimum 4-week treatment pause. A study schema for the main protocol is provided in Figure 7.

[00158] Randomization at a 3:1 ratio of remternetug to placebo, respectively, will be sought. Analyses for the primary and each of the key secondary endpoints in the trial will be conducted for each cohort. Superiority of each dosing regimen to placebo in proportion of participants who reach plaque clearance at Week 52 is a primary endpoint.

[00159] Study LAKC (Main Protocol) Study Objectives: The primary objective of the study is to test the hypothesis that at least one dosing regimen (SC or IV) of remternetug is superior to placebo on brain amyloid plaque clearance in participants with early symptomatic AD. The secondary objectives of the study are: i) to test the hypothesis that at least 1 dosing regimen (SC or IV) of remternetug is superior to placebo on degree of brain amyloid plaque reduction; ii) to test the hypothesis that at least 1 dosing regimen (SC or IV) of remternetug is superior to placebo on brain amyloid plaque clearance in participants with early symptomatic AD; and iii) to test the hypothesis that at least 1 dosing regimen (SC or IV) of remternetug is superior to placebo on degree of brain amyloid plaque reduction. Other secondary objectives of the study include: i) to describe the safety of remternetug and ii) to assess peripheral PK and presence of anti-remternetug antibodies.

[00160] Study LAKC (Main Protocol) Patient Population: In general, an individual may take part in the Study LAKC (Main Protocol) if they: are 60 to 85 years of age, inclusive; have gradual and progressive change in cognitive function; have an MMSE score of 20 to 28, inclusive; have a P-tau result consistent with the presence of brain amyloid pathology;

and have an amyloid PET scan result consistent with the presence of brain amyloid pathology.

[00161] In general, an individual may not take part in the study if they: have a significant neurological disease or psychiatric diagnosis other than AD that may affect cognition, interfere with the analysis of the study or ability to complete the study; have any clinically important abnormality at screening that could be detrimental to the participant, could compromise the study, or show evidence of other etiologies for dementia; have current serious or unstable illness or condition that could interfere with the analysis of the study; and/or are a woman of childbearing potential.

[00162] Study LAKC Dose Justification: Doses were selected in consideration of the following factors: Safety and tolerability data from Phase 1 development in participants with early symptomatic AD; Safety data from open-label addenda of LAKC in participants with early symptomatic AD; Observed bioavailability of SC drug product in healthy volunteers; PK exposure-amyloid plaque analysis of all available data across a wide dose range.

[00163] The inventors of the present disclosure provided herein, submit:

The 800 mg remternetug administered intravenously once every 8 weeks given over seven infusions (on weeks 0, 8, 16, 24, 32, 40, and 48) is anticipated to result in ≥80% of participants reaching amyloid plaque clearance at 52 weeks from the start of dosing while still allowing for built-in pauses to mitigate ARIA risk.

The 2300 mg remternetug administered once every 12 weeks given over three infusions (on weeks 0, 12, and 24) is anticipated to result in approximately 90% of participants reaching amyloid plaque clearance at 52 weeks from the start of dosing.

The 1500 mg remternetug administered once every 12 weeks given over three infusions (on weeks 0, 12, 24, and 36) is anticipated to result in approximately 90% of participants reaching amyloid plaque clearance at 52 weeks from the start of dosing.

The titration-based 400 mg remternetug administered intravenously once every 4 weeks given over three infusions (on weeks 0, 4, and 8) followed by 800 mg remternetug administered intravenously once every 8 weeks given over five infusions (on weeks 16, 24, 32, 40, and 48)is anticipated to result in ≥ 80% of participants reaching amyloid plaque clearance at 52 weeks from the start of dosing

while still allowing for built-in pauses at higher doses (i.e. 800 mg) to mitigate ARIA risk.

The titration-based 400 mg remternetug administered intravenously once every 4 weeks given over two infusions (on weeks 0 and 8) followed by 800 mg remternetug administered intravenously once every 8 weeks given over five infusions (on weeks 16, 24, 32, 40, and 48) is anticipated to result in ≥ 80% of participants reaching amyloid plaque clearance at 52 weeks from the start of dosing while still allowing for built-in pauses to mitigate ARIA risk.

The titration-based 200 mg remternetug administered intravenously once every 4 weeks given over two infusions (on weeks 0 and 8) followed by 400 mg remternetug administered intravenously once every 8 weeks given over two infusions (on weeks 16 and 24) followed by 800 mg remternetug administered intravenously once every 8 weeks given over three infusions (on weeks 32, 40, and 48) is anticipated to result in ≥ 60% of participants reaching amyloid plaque clearance at 52 weeks. An alternative scheme would follow 200 mg and 400 mg infusions with 800 mg remternetug administered intravenously once every 8 weeks given over 6 infusions (on weeks 32, 40, 48, 56, 64, and 72); this dosing regimen is anticipated to result in ≥ 90% of participants reaching amyloid plaque clearance at 76 weeks from the start of dosing while still allowing for built-in pauses to mitigate ARIA risk.

The fixed IV dosing regimens include built-in dosing pauses (2 to 3 months between infusions). These IV dosing regimens are also anticipated to result in robust plaque clearance with the pause between doses serving to minimize ARIA risk. Anticipated exposure range will be within that previously explored in Phase 1. It is hypothesized that 8 to 12-week dosing intervals will allow time for potential asymptomatic ARIA to resolve and may decrease the risk of ARIA exacerbation (Salloway et al. 2022).

The titration-based IV dosing regimens include built-in dosing pauses (2 months between infusions). It is hypothesized a titration scheme may reduce the severity of observed ARIA while the 8-week dosing pauses serve to minimize ARIA risk associated with dose escalation.

An alternative IV dosing regimen of 400 mg remternetug administered intravenously once every 4 weeks given over thirteen infusions (on weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48) is also being considered, with an expectation of ≥80% of participants reaching amyloid plaque clearance at 52 weeks from the start of dosing.

The SC dosing regimens of 400 mg administered weekly for 36 doses or 800 mg administered once every 4 weeks for 13 doses are anticipated to result in about 80 to 90% of participants reaching amyloid plaque clearance at week 52 from the start of dosing.

The SC dosing regimens are hypothesized to have a slower increase in serum concentrations with a lower C_{max} compared to those achieved after IV administration. C_{max} at steady state following subcutaneous administration will be achieved after approximately 4 months for both SC dosing regimens, providing a slower increase in serum concentration similar to that of a titration scheme. It is hypothesized that a lower C_{max} and a slower increase in serum concentration may reduce ARIA risk (Hayato et al., "OC14: BAN2401 and ARIA-E in Early Alzheimer's Disease: Pharmacokinetic/pharmacodynamic Time-to-event Analysis from the Phase 2 Study in Early Alzheimer's Disease," *J. Prev. Alzheimer's Dis.* 7(Suppl 1): 2–54 (2020); Salloway et al., "Amyloid-related Imaging Abnormalities in 2 Phase 3 Studies Evaluating Aducanumab in Patients with Early Alzheimer's Disease," *JAMA Neurol.* 79(1):13-21(2022); which are hereby incorporated by reference in their entireties).

Both SC dosing regimens are projected to achieve monthly serum exposures within the range of observed steady state exposures following 700 and 1400 mg IV Q4W from the Phase 1 Study. Once every four week and weekly SC dosing would be close to that lower and higher exposure range, respectively.

Titration-based SC dosing regimens with built-in pauses are being evaluated if C_{max} is not a predominant factor in ARIA development. A titration scheme may reduce the severity of observed ARIA while the initial 8- to 12- week dosing pauses serve to minimize ARIA risk associated with dose escalation. The following titration-based dosing regimens may be evaluated:

remternetug of 400 mg SC every 8 weeks for 2 doses, administered at weeks 0 and 8, with titration up to 800 mg of remternetug SC for 1 dose, administered at week 16, and administration of 800 mg remternetug SC every 4 weeks for 13 doses, administered at weeks 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72.

remternetug of 400 mg SC every 12 weeks for 2 doses, administered at weeks 0 and 12, with titration up to 800 mg of remternetug SC for 1 dose, administered at week 24, and administration of 800 mg remternetug SC every 4 weeks for 11 doses, administered at weeks 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72.

remternetug of 200 mg SC for 1 dose, administered at week 0, with titration up to 400 mg of remternetug SC every 8 weeks for 2 doses, administered at weeks 8 and 16, with titration up to 800 mg SC of remternetug for 1 dose, administered at week 24, and administration of 800 mg SC of remternetug every 4 weeks for 11 doses, administered at weeks 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72.

remternetug of 100 mg SC administered every 8 weeks for 2 doses, administered at weeks 0, and 8, with titration up to 400 mg of remternetug SC every 8 weeks administered for 2 doses, administered at weeks 16 and 24, with titration up to 800 mg SC of remternetug administered for 2 doses every 8 weeks, administered at weeks 32 and 40, and administration of 800 mg SC of remternetug every 4 weeks for 7 doses, administered at weeks 48, 52, 56, 60, 64, 68, and 72.

remternetug of 400 mg SC every 8 weeks for 3 doses, administered at weeks 0, 8 and 16, with titration up to 800 mg of remternetug SC for 3 doses, administered at weeks 24, 32 and 40, and administration of 800 mg remternetug SC every 4 weeks for 7 doses, administered at weeks 48, 52, 56, 60, 64, 68 and 72.

[00164] Safety Results of ongoing Phase 3 Study LAKC: To date (53.4%) participants reported at least 1 treatment-emergent adverse event (TEAEs). Of TEAEs, ARIA-E and ARIA-H have occurred in 10 or more out of 100 participants. Other TEAEs observed (occurring in 1 to 9 out of 100 participants) include, but not limited to, headache,

COVID-19, fall, upper respiratory tract infection, dizziness, urinary tract infection, diarrhea, and confusional state. Symptomatic ARIA-E has occurred in 1 to 9 out of 100 participants. Headache has occurred in approximately half of symptomatic cases. ARIA has been associated with SAEs and a death in participants receiving remternetug. The incidence of SAEs associated with ARIA was higher in participants with pre-existing superficial siderosis. Studies LAKB and LAKC were amended to exclude further participants with baseline superficial siderosis to enroll, and all randomized participants with baseline superficial siderosis have been discontinued from further study treatment.

[00165] In participants receiving study treatment, ARIA-E, if it occurred, generally developed within the first 12 weeks of dosing. Incidence of ARIA-E was higher in cohorts testing higher doses of remternetug administered intravenously whereas incidence was lower in participants receiving less frequent dosing administered subcutaneously (800 mg Q4W compared to 400 mg QW, for example) even though the initial dose was higher in the Q4W dosing regimen. The incidence of ARIA-E was higher in participants who are APOE ε4/ε4 compared to heterozygous or noncarriers of the APOE ε4 allele. Macrohemorrhage, although it has been observed in participants taking remternetug, such events were uncommon (less than 1 in 100 people).

[00166] Hypersensitivity events have occurred in less than 1 out of 100 participants. One report of infusion-related reaction has been reported. No anaphylaxis has been observed. In participants receiving SC remternetug or placebo, injection site reactions have occurred in 1 to 9 out of 100 participants. Injection site reactions have been mild to moderate in severity and erythema has been the predominant sign and symptom.

[00167] Pharmacodynamic Results: In a subset of study participants, florbetapir F18 PET scans were performed before and 24 weeks after initiation of open-label IV administration of remternetug. As of 22 September 2023, the following raw mean change from baseline at Week 24 were observed:

−81.9 CL for participants administered 2300 mg IV Q12W remternetug (n =12)

−66.3 CL for participants administered 1500 mg IV Q12W remternetug (n =7), and

−53.4 CL for participants administered 800 mg IV Q8W remternetug (n =14)

Florbetapir F18 PET scans were performed before and 8 weeks after initiation of open-label SC administration of remternetug. As of 22 September 2023, following raw mean change from baseline at Week 8 were observed:

−26.5 CL for participants administered 400 mg SC QW remternetug (n = 25), and

−22.3 CL for participants administered 800 mg SC Q4W remternetug (n =23)

Example 6: Assessment of Safety and Efficacy of Subcutaneous Remternetug in Early Symptomatic Alzheimer's Disease.

[00168] Study LAKD (EU trial number: 2022-501473-38-00) is an upcoming multicenter, randomized, double-blind, placebo-controlled, Phase 3 study to evaluate the safety and efficacy of remternetug in participants with early symptomatic AD with evidence of brain amyloid and tau pathology. The primary objective of Study LAKD will assess whether treatment with remternetug SC administration can slow the progression of the disease as assessed by clinical outcomes for cognition and function over 76 weeks of double-blinded observation.

[00169] Study LAKD Trial Design Synopsis: Study LAKD is a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study of remternetug in participants with early symptomatic AD. The study schema is depicted in Figure 8. Participants who meet entry criteria will be randomly assigned 1:1, respectively, to remternetug 400 mg SC weekly for 36 doses, or placebo SC.

[00170] The primary objective of this study is to test the hypothesis that treatment with remternetug SC will slow the progression of AD as measured by change from baseline on iADRS score through week 76 compared with placebo, which is the primary endpoint. It is anticipated based on prior studies that approximately two-thirds of the randomized participants are in the intermediate tau population. It is conceivable that some aspects of the trial design such as the primary analysis population (intermediate tau vs. intermediate and high tau, APOE ε4 carriers only vs. carriers and non-carriers), sample size, and other aspects of design such as randomization ratio may be changed.

[00171] Study LAKD (Main Protocol) Study Objectives: The primary objective of the study is to test the hypothesis that remternetug SC is superior to placebo in slowing clinical progression (as measured with iADRS) in participants with early symptomatic AD. Key secondary objectives of the study are to test the hypothesis that remternetug SC

is superior to placebo on slowing clinical progression as measured using: CDR-SB (Clinical Dementia Rating-Sum of Boxes); ADAS-Cog13 (13-Point Alzheimer's Disease Assessment Scale-Cognitive Subscale); ADCS-iADL (Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale); and/or MMSE (Mini-mental State Examination). Another secondary objective is to describe the safety of remternetug.

[00172] Study LAKD (Main Protocol) Patient Population: In general, an individual may take part in the Study LAKD if they: are 60 to 85 years of age, inclusive; have gradual and progressive change in cognitive function; have an MMSE score of 20 to 28, inclusive; have a biomarker consistent with the presence of brain amyloid pathology, if available; and have a tau positron emission tomography scan result consistent with the presence of tau pathology.

[00173] In general, an individual may not take part in the study if they: have a significant neurological disease or psychiatric diagnosis other than AD that may affect cognition, interfere with the analysis of the study or ability to complete the study; have any clinically important abnormality at screening that could be detrimental to the participant, could compromise the study, or show evidence of other etiologies for dementia; have current serious or unstable illness or condition that could interfere with the analysis of the study; and/or are a woman of childbearing potential.

[00174] Study LAKD Amyloid and Tau Substudy: The purpose of this substudy is to collect additional amyloid and tau PET scans in participants enrolled in Study LAKD. These additional PET scans will provide data on the effects of remternetug on brain amyloid plaque and tau pathology over time to inform the PD effects of remternetug. It is planned that approximately 250 participants across the study will participate.

[00175] Study LAKD Dose Justification: A dose of 400 mg administered SC once weekly for 36 doses was selected in consideration of the following factors:

Safety and tolerability data from Phase 1 development in participants with early symptomatic AD.

Observed bioavailability of SC drug product in healthy volunteers.

PK/PD (amyloid plaque) analysis of all available data across a wide dose range.

The inventors of the present disclosure provided herein, submit: the SC dosing regimen administered weekly for 36 doses is anticipated to result in approximately 90% of participants reaching amyloid plaque clearance while allowing a slower

increase in serum concentrations with a lower C_{max} compared to those achieved after IV administration. C_{max} at steady state following SC administration will be achieved after approximately 4 months of weekly dosing, providing a slower increase in serum concentration similar to that of a titration scheme. It is hypothesized that a lower C_{max} and a slower increase in serum concentration may reduce ARIA risk. (Hayato et al., "OC14: BAN2401 and ARIA-E in Early Alzheimer's Disease: Pharmacokinetic/pharmacodynamic Time-to-event Analysis from the Phase 2 Study in Early Alzheimer's Disease," *J. Prev. Alzheimer's Dis.* 7(Suppl. 1): 2–54 (2020); Salloway et al., "Amyloid-related Imaging Abnormalities in 2 Phase 3 Studies Evaluating Aducanumab in Patients with Early Alzheimer's Disease," *JAMA Neurol.* 79(1):13-21(2022); which are hereby incorporated by reference in their entireties).

Remternetug weekly SC dosing is projected to achieve monthly serum exposures within the range of observed steady-state exposures following 700 and 1400 mg IV Q4W from Phase 1 Study.

Additionally, remternetug may be administered at a dose of 800 mg SC every 4 weeks for 13 doses, administered at weeks, 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48. The subcutaneous dosing regimen of 800 mg administered once every 4 weeks for 13 doses is anticipated to result in approximately 90% of participants reaching amyloid plaque clearance at week 52 from the start of dosing.

Titration-based SC dosing regimens with built-in pauses are being evaluated in Study LAKC if C_{max} is not a predominant factor in ARIA development. A titration scheme may reduce the severity of observed ARIA while the initial 8- to 12- week dosing pauses serve to minimize ARIA risk associated with dose escalation. Therefore, based on the ongoing results from LAKC, one of the following alternative dosing regimens may be evaluated:

a titration dose of remternetug of 400 mg SC every 8 weeks for 2 doses, administered at weeks 0 and 8, with titration up to 800 mg of remternetug SC for 1 dose, administered at week 16, and administration of 800 mg remternetug SC every 4 weeks for 13 doses, administered at weeks 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72.

remternetug of 400 mg SC every 12 weeks for 2 doses, administered at weeks 0 and 12, with titration up to 800 mg of remternetug SC for 1 dose, administered at week 24, and administration of 800 mg remternetug SC every 4 weeks for 11 doses, administered at weeks 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72.

remternetug of 200 mg SC for 1 dose, administered at week 0, with titration up to 400 mg of remternetug SC every 8 weeks for 2 doses, administered at weeks 8 and 16, with titration up to 800 mg SC of remternetug for 1 dose, administered at week 24, and administration of 800 mg SC of remternetug every 4 weeks for 11 doses, administered at weeks 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, and 72.

a titration dose of remternetug of 100 mg SC administered every 8 weeks for 2 doses, administered at weeks 0, and 8, with titration up to 400 mg of remternetug SC every 8 weeks administered for 2 doses, administered at weeks 16 and 24, with titration up to 800 mg SC of remternetug administered for 2 doses every 8 weeks, administered at weeks 32 and 40, and administration of 800 mg SC of remternetug every 4 weeks for 7 doses, administered at weeks 48, 52, 56, 60, 64, 68, and 72.

Example 7: A Study to Investigate the Safety, Tolerability, and Pharmacokinetics of a Single Dose of Remternetug in Healthy Chinese Participants.

[00176] Study LAKE is an upcoming single site, randomized, participant- and investigator-blinded, placebo-controlled, parallel-group, single dose Phase 1 study. Study LAKE will investigate the safety, tolerability, and PK of single dose intravenous IV or SC administration of remternetug in healthy Chinese participants. To date, remternetug has not been evaluated in the native Chinese population. This study will support the future clinical development and registration of remternetug in China.

[00177] Study LAKE Trial Design Synopsis: The purpose of this study is to evaluate safety, tolerability, and PK with remternetug compared with placebo after a single IV or SC dose in healthy Chinese participants. The study will include 3 cohorts, with participants randomized in a 5:1 ratio to remternetug and placebo. The study schema is provided in Figure 9.

[00178] Approximately 36 participants will be enrolled in the study. The primary objective of this study is to evaluate the safety and tolerability of remternetug in healthy Chinese participants following single dose IV or SC administration.

[00179] Study LAKE Study Objectives: The primary objective of the Study LAKE study is to evaluate the safety and tolerability of remternetug in healthy Chinese participants following single dose IV or SC administration. Secondary objective assesses the serum PK of remternetug in healthy Chinese participants after a single dose IV infusion or a single dose SC administration.

[00180] Study LAKE Patient Population: The Study includes healthy males and females who are native Chinese, between 18 and 28 years old, inclusive, with a body mass index (BMI) between 18.0 and 32.0 kg/m2, inclusive. Participants who have evidence of cognitive impairment, a brain magnetic resonance imaging scan that demonstrated clinically significant findings, or a family history of early onset AD will be excluded.

Example 8: Assessment of Safety and Efficacy of Intravenous Remternetug in Early Symptomatic Alzheimer's Disease.

[00181] Study LAKF (EU trial number: 2022-501886-38-00) is an upcoming multicenter, randomized, double-blind, placebo-controlled, Phase 3 study to evaluate the safety and efficacy of remternetug in participants with early symptomatic AD with evidence of brain amyloid and tau pathology. The primary objective of Study LAKF will assess whether treatment with remternetug IV administration can slow the progression of the disease as assessed by clinical outcomes for cognition and function over 76 weeks of double-blinded observation.

[00182] Study LAKF Trial Design Synopsis: Study LAKF is a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study of remternetug in participants with early symptomatic AD. The study schema is provided in Figure 10. Participants who meet entry criteria will be randomly assigned 1:1, respectively, to remternetug 2300 mg IV Q12W for 3 doses (~N=1300), or placebo IV (~N=1300).

[00183] The primary objective of this study is to test the hypothesis that treatment with remternetug IV will slow the progression of AD as measured by change from baseline on iADRS score through week 76 compared with placebo, which is the primary endpoint. It

is anticipated that approximately two-thirds of the randomized participants are in the intermediate tau population.

[00184] It is conceivable that some aspects of the trial design such as the primary analysis population (intermediate tau vs. intermediate and high tau, APOE ε4 carriers only vs. carriers and non-carriers), sample size, and other aspects of design such as randomization ratio may be changed.

[00185] Study LAKF (Main Protocol) Study Objectives: The primary objective of this study is to test the hypothesis that remternetug IV is superior to placebo on slowing clinical progression (as measured with iADRS) in participants with early symptomatic AD. Key secondary objectives of this study are to test the hypothesis that remternetug IV is superior to placebo on slowing clinical progression as measured using assessment scales as define above: CDR-SB, ADAS-Cog13, ADCS-iADL, and/or MMSE.

[00186] Other secondary of the study is to describe the safety of remternetug.

[00187] Study LAKF (Main Protocol) Patient Population: In general, an individual may take part in the Study LAKF if they: are 60 to 85 years of age, inclusive; have gradual and progressive change in cognitive function; have an MMSE score of 20 to 28, inclusive; have a biomarker consistent with the presence of brain amyloid pathology, if available, or have a tau positron emission tomography scan result consistent with the presence of tau pathology.

[00188] In general, an individual may not take part in the study if they: have a significant neurological disease or psychiatric diagnosis other than AD that may affect cognition, interfere with the analysis of the study or ability to complete the study; have any clinically important abnormality at screening that could be detrimental to the participant, could compromise the study, or show evidence of other etiologies for dementia; have current serious or unstable illness or condition that could interfere with the analysis of the study; and/or are a woman of childbearing potential.

[00189] Study LAKF Amyloid and Tau Substudy: The purpose of this substudy is to collect additional amyloid and tau PET scans in participants enrolled in Study LAKF. These additional PET scans will provide data on the effects of remternetug on brain amyloid plaque and tau pathology over time to inform the PD effects of remternetug.

[00190] Study LAKF Dose Justification: A dose of 2300 mg administered IV once every 12 weeks for 3 doses was selected in consideration of the following factors:

Safety and tolerability data from Phase 1 development in participants with early symptomatic AD;

Observed bioavailability of SC drug product in healthy volunteers;

PK exposure-amyloid plaque analysis of all available data across a wide dose range;

The inventors of the present disclosure provided herein, submit: The 2300 mg remternetug administered once every 12 weeks given over three infusions (on weeks 0, 12, and 24) is anticipated to result in approximately 90% of participants reaching amyloid plaque clearance at week 52 from the start of dosing; and/or

The IV dosing regimen includes built-in dosing pauses (3 months between infusions). This IV dosing regimen is also anticipated to result in robust plaque clearance with the pause between doses serving to minimize ARIA risk. Anticipated exposure range will be within that previously explored in Phase 1. It is hypothesized that a 12-week dosing interval will allow time for potential asymptomatic ARIA to resolve and may decrease the risk of ARIA exacerbation (Salloway et al., "Amyloid-related Imaging Abnormalities in 2 Phase 3 Studies Evaluating Aducanumab in Patients with Early Alzheimer's Disease," *JAMA Neurol.* 79(1):13-21 (2022), which is hereby incorporate by reference in its entirety).

[00191] One or more of the following alternative dosing schedules and titrated dosing schedules with built-in pauses may be performed as protocol addenda to minimize ARIA risk while anticipating ≥80% of participants reach amyloid plaque clearance upon completion of the full dosing regimen:

800 mg IV every 8 weeks for 7 doses, administered at weeks 0, 8, 16, 24, 32, 40, and 48.

400 mg IV every 4 weeks for 13 doses, administered at weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48.

400 mg IV every 4 weeks for 3 doses, administered at weeks 0, 4, and 8; and 800 mg IV every 8 weeks for 5 doses, administered at weeks 16, 24, 32, 40, and 48.

400 mg IV every 4 weeks for 3 doses, administered at weeks 0, 4, and 8; and 800 mg IV every 8 weeks for 5 doses, administered at weeks 12, 20, 28, 36, and 44.

400 mg IV every 8 weeks for 2 doses, administered at weeks 0 and 8, and 800 mg IV every 8 weeks for 5 doses, administered at weeks 16, 24, 32, 40, and 48.

200 mg IV every 8 weeks for 2 doses, administered at week 0 and 8, with titration up to 400 mg IV every 8 weeks for 2 doses, administered at weeks 16 and 24, and titration up to 800 mg IV every 8 weeks for 6 doses, administered at weeks 32, 40, 48, 56, 64, and 72.

Example 9: Utilization of Baseline Tau in Participant Screening.

[00192] Tau baseline of participants may be screened substantially as described herein. For stratification in Studies LAKD and LAKF, tau levels may be determined based on an initial visual assessment of a flortaucipir scan, followed by a quantitative analysis. An example is reflected in Figure 11. As exemplified in Figure 11, visual assessments may be tiered according to (AD-, AD+, AD++) based on the presence of tracer uptake in specific regions of the neocortex. Quantitative analysis may be determined based on calculation of SUVr, which represents counts within a specific target region of interest in the brain (e.g., multiblock barycentric discriminant analysis or MUBADA) when compared with a reference region (parametric estimate of reference signal intensity or PERSI). Participants may be stratified based on the screens, substantially as described herein, and as exemplified, for example, in Figure 11.

Example 10: Management of ARIA.

[00193] The development of ARIA-E (cerebral edema/effusion) and/or ARIA-H (cerebral microhemorrhage [MCH], cortical superficial siderosis [cSS], or cerebral macrohemorrhages) are expected events that have occurred with amyloid plaque-clearing antibodies such as remternetug.

[00194] MCHs are known to occur during aging and in individuals with AD, and the presence of MCHs may or may not be an ARIA-H finding related to remternetug (Goos et al., 2010, Carlson et al. 2016, Sperling et al 2012, Poels et al., 2011). Risk factors for heighted risk of ARIA during treatment with amyloid plaque-clearing antibodies include APOE ε4 status and MCH/cSS/white matter disease (WMD) observed at baseline (Arrighi et al., 2016).

[00195] MRI-identified ARIA-E and ARIA-H have been associated with administration of remternetug. The incidence of ARIA-E was higher in participants who are APOE ε4/ε4 compared to heterozygous or noncarriers of the APOE ε4 allele. The incidence of SAEs

associated with ARIA was higher in participants with pre-existing superficial siderosis. Ongoing studies have excluded further participants with baseline superficial siderosis to enroll at the currently studied dosing regimens.

[00196] ARIA was observed in both fixed-dose and titration cohorts, was generally asymptomatic, and resolved with treatment pauses. ARIA was generally observed in initial doses of remternetug (e.g., the first three months of treatment).

[00197] The IV dosing regimens of remternetug includes built-in dosing pauses (2 or 3 months between infusions). Due to the relatively long half-life of remternetug, these IV dosing regimens are anticipated to not only result in robust plaque clearance but also the pauses between doses serve to minimize ARIA risk. The pauses may also allow observed MRI-identified ARIA between doses to resolve and/or stabilize prior to the next dose. The incidence of ARIA-E was generally higher in cohorts testing higher doses of remternetug administered intravenously; therefore, dosing regimens with a titration scheme may reduce the incidence and severity of observed ARIA with lower starting doses and lead to robust amyloid plaque clearance with higher dosages later in the titration scheme.

[00198] The fixed-dosed SC dosing regimens are anticipated to reach Cmax at steady state after approximately 4 months of dosing. The SC dosing regimens provide a slower increase in serum concentration relative to the IV dosing regimens and is like that of a titration scheme. It has been hypothesized that a lower Cmax and a slower increase in serum concentration may reduce ARIA risk. (Hayato et al. 2020; Salloway et al. 2022); however, ARIA-E incidence was lower in participants receiving less frequent dosing administered subcutaneously (800 mg Q4W compared to 400 mg QW) even though the initial dose was higher in the Q4W dosing regimen. Therefore, titration based dosing schemes with subcutaneous dosing are also being investigated; it is hypothesized that dosing regimens with a titration scheme may reduce the incidence and severity of observed ARIA with lower starting doses and less frequent dosing initially and lead to robust amyloid plaque clearance with higher dosages and more frequent dosing later in the titration scheme.

Example 11: MRI Schedules for Phase 3 Clinical Trials of Early Symptomatic AD Participants.

[00199] In all clinical trials investigating remternetug, scheduled MRI brain scans are conducted to routinely monitor ARIA. In addition, unscheduled MRIs are to be performed upon suspicion of ARIA by the investigator.

[00200] All participants must have an MRI during screening to become eligible for enrollment. Considering potential risk factors for ARIA, participants with a centrally read MRI demonstrating presence of ARIA-E, macrohemorrhage, greater than 4 MCHs, cortical superficial siderosis, or severe white matter disease (WMD) at screening are excluded.

[00201] MRI scans are read locally and are sent for analysis to a centralized MRI vendor. Specific analyses of the scans are interpreted by the centralized MRI vendor for data analysis and reporting. Results of the centrally read MRIs regarding participant care and safety are reported back to the investigator.

[00202] Study LAKC Open-Label Addenda: The MRI schedules for Study LAKC (Addendum 1), Study LAKC (Addendum 3), Study LAKC (Addendum 4), and Study LAKC (Addendum 5) are listed below (Tables 9, 10, 11, and 12).

Table 9: Study LAKC (Addendum 1) – Scheduled MRIs.

Visit	1	2	5	6	7	8	9	10	11	ED	801
Week Post Randomization	Screening	0	4	8	12	16	24	36	52		
Scheduled MRI	X		X		X	X	X				

ED=early discontinuation; V801 is the followup visit

Scheduled MRIs at dosing visits must be performed and analyzed prior to dosing.

Table 10: Study LAKC (Addendum 3) – Scheduled MRIs

Visit	1	2	5	6	7	8	9	10	11	12	13	ED	801
Week Post Randomization	Screening	0	4	8	12	16	24	32	40	48	52		
800 mg Q8W	X		X	X		X	X				X	X	
IV Titration #1	X		X	X		X	X				X	X	
IV Titration #2	X		X	X		X	X				X	X	
IV Titration #3	X		X	X		X	X	X	X		X	X	

ED=early discontinuation; V801 is the followup visit.
IV Titration 1 = 400 mg Q4Wx2; 400 mg Q8Wx1; 800 mg Q8Wx5
IV Titration 2 = 400 mg Q8Wx2; 800 mg Q8Wx5
IV Titration 3 = 200 mg Q8Wx2; 400 mg Q8Wx2; 800 mg Q8Wx3
Scheduled MRIs at dosing visits must be performed and analyzed prior to dosing.

Table 11: Study LAKC (Addendum 4) – Scheduled MRIs.

Visit	1	2	3	4	5	6	7	9	10	11	ED	801
Week Post Randomization	Screening	0	1	2	4	8	12	24	36	52		
Scheduled MRI	X				X	X	X	X			X	

ED=early discontinuation; V801 is the followup visit; Scheduled MRIs at visits with scheduled onsite dosing must be performed and analyzed prior to dosing.

Table 12: Study LAKC (Addendum 5) –SC Titration Dosing Regimens and Scheduled MRIs

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	ED	801
Week Post Random-ization	Screening	0	4	8	12	16	24	32	40	48	56	64	76		
Scheduled MRI	X			X		X	X	X	X		x		X	X	

ED=early discontinuation; V801 is the followup visit; Scheduled MRIs at visits with onsite dosing must be performed and analyzed prior to dosing.

[00203] The Study LAKC Open-Label Addenda MRI schedules are designed to monitor potential ARIA for participant safety and provide information on dose selection for IV and SC dosing. MRIs conducted at visits in the first 12 weeks of dosing provide information on the potential development of ARIA shortly after study drug administration and the impact on the starting dosage. These early analyses will also provide information if built-dosing pauses will give time for asymptomatic ARIA to resolve and/or stabilize prior to subsequent doses in the schedule.

[00204] For titration-based dosing regimens, MRIs are performed at Visits prior to and after dosage escalation or increased frequency in dosing. These MRIs serve dual purposes: (1) monitor potential ARIA prior to dosing and inform on the decision to ultimately dose as described in the ARIA Management Plan (next section) and (2) examine the impact of dosage escalation or increased frequency in the titration-based dosing schedule. Investigators are permitted to conduct unscheduled MRIs under suspicion of ARIA.

[00205] Study LAKC (Main Protocol): The MRI schedules for Study LAKC (main protocol) are listed below (Table 13a and Table 13b).

Table 13a: MRI Schedule for Study LAKC (Main Protocol; SC cohorts).

Visit	601	1	2	3	4	5	6	7	8	9	10	11
Week Post Randomization	Screening		0	1	2	4	8	12	16	24	36	52
Scheduled MRI		X				X	X	X		X		X
Visit	12	13	14	15	16	17	18	19	20	ED	801	
Week Post Randomization	54	55	56	58	62	66	78	90	106			
Scheduled MRI				X	X	X	X			X		

Scheduled MRIs at dosing visits must be performed and analyzed prior to dosing.

Table 13b: MRI Schedule for Study LAKC (Main Protocol; IV cohorts).

Visit	601	1	5	6	7	8	9	10	11	12	13		
Week Post Random-ization	Screening		4	8	12	16	24	32	40	48	52		
Schedule d MRI		X		X		X	X				X		
Visit	14	15	16	17	18	19	20	21	22	23	24	E D	801
Week Post Random-ization	54	58	62	66	70	78	86	90	94	102	106	--	--
Schedule d MRI			X		X	X						X	

Scheduled MRIs at dosing visits must be performed and analyzed prior to dosing.

[00206] The Study LAKC MRI schedule is designed to monitor potential ARIA for participant safety for both the IV and SC dosing regimens; the impact of dosage and dosing frequency on ARIA development is noted previously in relation to the open label safety addenda.

[00207] MRIs after initial dosing visits monitor potential ARIA prior to dosing and inform on the decision to ultimately dose as described in the ARIA Management Plan (next section). These MRIs also serve to continue to monitor those on the SC dosing regimen. MRI at week 52 informs on current ARIA status prior to crossover dosing in the second 52 weeks of the study.

[00208] There are no scheduled MRIs after Visit 18 (week 78, 24 weeks after crossover). As demonstrated in Studies LAKB and LAKC, described herein, the potential ARIA risk is primarily in the first few months of dosing. Investigators are still permitted to conduct unscheduled MRIs under suspicion of ARIA.

[00209] Study LAKD (Subcutaneous Dosing): The MRI schedule for Study LAKD is listed below (Table 14).

Table 14: MRI Schedule for Study LAKD (SC dosing).

Visit	601	1	2	3	4	5	6	7	8	9	10	11	12
Week Post Randomization	Screening		0	1	2	4	8	12	24	36	52	64	76
Scheduled MRI		X				X		X	X				X
Visit	13	14	15	16	17	18	19	20	21	ED	801		
Week Post Randomization	78	79	80	82	86	90	102	114	130				
Scheduled MRI				X		X	X						

[00210] The Study LAKD MRI schedule is designed to monitor potential ARIA for participant safety for the SC dosing regimen. MRI at week 76 informs on current ARIA status prior to crossover dosing in the second 52 weeks of the study.

[00211] There are no scheduled MRIs after Visit 19 (week 102, 24 weeks after crossover). As described in Studies LAKB and LAKC, ARIA risk is primarily in the first few months of dosing. Investigators are still permitted to conduct unscheduled MRIs under suspicion of ARIA.

[00212] Study LAKF (Intravenous Dosing): The MRI schedule for Study LAKF is listed below (Table 15).

Table 15: MRI Schedule for Study LAKF (IV Dosing).

Visit	601	1	2	3	4	5	7	9	12	13	14
Week Post Randomization	Screening		0	4	8	12	24	36	52	64	76
Scheduled MRI		X				X	X				X
Visit	15	16	17	18	20	22	25	ED	V801		
Week Post Randomization	78	82	86	90	102	114	130				
Scheduled MRI				X	X			X			

MRIs at Visits 5, 7, 18, and 20 must be performed and analyzed prior to dosing.

[00213] The Study LAKF MRI schedule is designed to monitor potential ARIA for participant safety for the IV dosing regimen. MRIs are to be performed prior to the participant's 2nd and 3rd dose. These MRIs monitor potential ARIA prior to dosing and inform on the decision to ultimately dose as described in the ARIA Management Plan

(next section). MRI at week 76 informs on current ARIA status prior to crossover dosing in the second 52 weeks of the study.

[00214] There are no scheduled MRIs after Visit 20 (week 102, 24 weeks after crossover). As demonstrated in Studies LAKB and LAKC, the potential ARIA risk is primarily in the first few months of dosing. Investigators are still permitted to conduct unscheduled MRIs under suspicion of ARIA.

Example 12: ARIA Management Plan for Studies LAKD and LAKF.

[00215] The development of ARIA-E and/or ARIA-H are expected events and have occurred in some participants treated with remternetug (as observed in Studies LAKB and LAKC). Monitoring of ARIA (as detailed in previous section) is, in part, determined by scheduled MRIs. A single symptom suggestive of ARIA may warrant an unscheduled MRI per the investigator's discretion. If a participant simultaneously develops more than 1 of the symptoms suggestive of ARIA, unscheduled MRIs are to be performed.

[00216] Treatment must be permanently discontinued in participants with SAEs associated with treatment-emergent ARIA-E and/or ARIA-H, and in participants who develop 1 or more macrohemorrhages.

[00217] Treatment with study intervention may be permanently discontinued in participants with treatment-emergent ARIA-E and/or ARIA-H at the discretion of the investigator and based on severity of clinical and radiologic findings.

[00218] Management of ARIA is fully detailed in the manual of operations for each clinical trial. Management of ARIA may be modified considering additional clinical trial data and/or changes in standard of care; changes would be reflected in updates to the manual of operations and/or amendments to clinical trial protocols. The ARIA management plan for ARIA-E is detailed in Table 16 below.

Table 16: Management Plan for ARIA-E.

Finding	Symptoms	MRI Severity	Actions
ARIA-E	Asymptomatic	Any Severity	Withhold study intervention Upon complete resolution, may restart study intervention at investigator's discretion If no resolution by the end of the primary study period, permanently discontinue study intervention
	Symptomatic	Any Severity	Withhold study intervention Upon complete resolution of ARIA-E and associated clinical symptoms, may restart study intervention at investigator's discretion If ARIA-E or associated symptoms do not resolve by the end of the primary study period, permanently discontinue study intervention If the ARIA-E or associated symptoms are reported as a Serious Adverse Event (SAE), permanently discontinue study intervention

[00219] Complete resolution of ARIA-E (Table 14) is determined by the first MRI scan noting absence of ARIA-E. In participants who are on a SC dosing regimen, injection should be resumed and continue through the end of the study period upon ARIA-E resolution. In participants who are on an IV dosing regimen, investigators should consult with Lilly personnel on timing to resume IV dosing. Infusions should not occur less than 4-12 weeks apart depending on dosing regimen, and all infusions must be completed by end of study period. Unscheduled visits may be necessary to administer missed infusions. The ARIA management plan for ARIA-H is detailed in Table 17 below.

Table 17: Management plan for ARIA-H and Macrohemorrhages.

Finding	Symptoms	MRI Severity	Actions
ARIA-H MCH, superficial siderosis	Asymptomatic	≤4 new MCH from baseline and/or 1 superficial siderosis	If within 16 weeks of the start of dosing, withhold study intervention Upon stabilization of ARIA-H on imaging, may restart study intervention at investigator's discretion
			If at or beyond 16 weeks of the start of dosing, may proceed with dosing at investigator's discretion
		>4 new MCH from baseline and/or ≥2 superficial sideroses	Withhold study intervention Upon stabilization of ARIA-H on imaging, may restart study intervention at investigator's discretion If not stable by the end of the primary study period permanently discontinue study intervention NOTE: Participants who develop any treatment-emergent superficial siderosis during the primary study period are excluded from participation in the extension period
	Symptomatic	Any Severity	Withhold study intervention Upon stabilization of ARIA-H and resolution of associated clinical symptoms, may restart study intervention at investigator's discretion If ARIA-H does not stabilize or associated symptoms do not resolve by the end of the primary study period, permanently discontinue study intervention If ARIA-H or associated symptoms are reported as an SAE, permanently discontinue SI
Macro-hemorrhage	Asymptomatic or Symptomatic	Any Severity	Permanently discontinue study intervention

NOTE: Participants who develop any treatment-emergent superficial siderosis during the primary study period are excluded from participation in the extension period

[00220] Stabilization of ARIA-H and/or macrohemorrhage (Table 15) is defined as the first MRI scan noting: No new or increase in the size of cSS; Not more than one new MCH; and/or No increase in the size of macrohemorrhage

[00221] For mild to moderate symptoms associated with ARIA-E, the use of oral or IV steroids on an outpatient basis can be considered. In the case of severe symptoms associated with ARIA-E, it is recommended to hospitalize the participant for close observation and consider the use of IV steroids such as high-dose dexamethasone, methylprednisolone or a similar agent (can be switched to oral as an outpatient). Choice of steroid below is based on high anti-inflammatory action and no mineralocorticoid action. Final treatment decisions are ultimately at the discretion of the investigator or treating physician.

Example 13: Assessment of Safety, Efficacy, and Tolerability of Remternetug in Preclinical Alzheimer's Disease.

[00222] Remternetug will be investigated in participants with preclinical Alzheimer's disease, either as an addendum to Study AACM or as a standalone Phase 3 clinical trial. Study AACM (NCT05026866, clinicaltrials.gov, TRAILBLAZER-3) is an ongoing multicenter, randomized, double-blind, placebo-controlled, Phase 3 study evaluating the safety, tolerability, and efficacy of donanemab in participants with preclinical AD.

[00223] The primary objective will be to assess whether treatment with remternetug administration can slow clinical progression in participants with preclinical AD. Clinical progression will be assessed by the slowing of progression from normal cognition to mild cognitive impairment (MCI)/dementia as measured by the Clinical Dementia Rating Global Score (CDR-GS) and using a time-to-event analysis. The primary outcome event will be the time to clinical progression as measured by an increase in CDR-GS from baseline at 2 consecutive visits (conversion). Participants may be followed until a pre-specified number of participants experience a primary outcome event of clinical progression, so the total duration of study participation will vary for each participant and be dependent on the overall conversion rate.

[00224] Trial Design Synopsis: The clinical trial will be a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study of remternetug in participants with preclinical AD. Participants who meet entry criteria will be randomly assigned 1:1, respectively, to remternetug, or placebo.

[00225] Participants will be dosed in a double-blind treatment period until dosing has been completed. Participants will then enter a double-blind observation phase with visits every 26 weeks not exceeding 150 weeks in total.

[00226] Study Objectives: The primary objective of this study will be to test the hypothesis that remternetug is superior to placebo in slowing time to clinical progression (as measured with CDR-GS) in participants with pre-clinical AD. Key secondary objectives include describing the safety of remternetug and to test the hypothesis that remternetug is superior to placebo on slowing clinical progression as measured using the following scales:

SAP (statistical analysis plan),
ISLT (International Shopping List Test),
CPAL (Continuous Paired Associate Learning),
iDSSTm (International Daily Symbol Substitution Test-Medicines),
Category Fluency,
FNAME (Face Name Association Test),
BPS-O (Behavioral Pattern Separation-Object test),
CBB (Cogstate Brief Battery),
CDR-SB (Clinical Dementia Rating-Sum of Boxes),
CFI (Cognitive Function Index), and/or
MoCA score (Montreal Cognitive Assessment).

[00227] Patient Population: In general, an individual may take part in the study if they
are 55 to 80 years of age, inclusive,
a TICS-M score reflective of intact cognitive functioning,
have a biomarker consistent with the presence of brain amyloid pathology, and/or
have a reliable study partner.

[00228] In general, an individual may not take part in the study if they
have mild impairment, dementia, or other CNS disease affecting cognition,

have any clinically important abnormality at screening that could be detrimental to the participant or could compromise the study, and/or

have current serious or unstable illness or condition that could interfere with the analysis of the study.

[00229] Dose Justification: The dosing regimen of remternetug will be selected in consideration of the following factors:

Safety and tolerability data from Phase 1 and Phase 3 development,

PK exposure-amyloid plaque analysis of all available data across a wide dose range, and/or

A fixed dosing or titrated dosing regimen anticipated to result in approximately 80-90% of participants reaching amyloid plaque clearance during the duration of treatment.

[00230] One of the following dosing regimens for remternetug may be performed as part of the clinical trial:

2300 mg IV every 12 weeks for 2 doses, administered at weeks 0 and 12.

1500 mg IV every 12 weeks for 3 doses, administered at weeks 0, 12, and 24.

800 mg IV every 8 weeks for 5 doses, administered at weeks 0, 8, 16, 24, and 32.

400 mg IV every 4 weeks for 3 doses, administered at weeks 0, 4, and 8, with titration up to 800 mg IV every 8 weeks for 3 or 4 doses, administered at weeks 16, 24, 32 and/or 40.

400 mg IV every 8 weeks for 2 doses, administered at weeks 0 and 8, with titration up to 800 mg IV every 8 weeks for 3 or 4 doses, administered at weeks 16, 24, 32, and/or 40.

400 mg IV every 4 weeks for 10 doses, administered at weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, and 36.

200 mg IV every 8 weeks for 2 doses, administered at weeks 0 and 8, with titration up to 400 mg IV every 8 weeks for 2 doses, administered at weeks 16 and 24, with titration up to 800 mg IV every 8 weeks for 3 or 4 doses, administered at weeks 32, 40, 48 and/or 56.

100 mg SC every 8 weeks for 2 doses, administered at weeks 0 and 8, then 400 mg SC every 8 weeks for 2 doses administered at weeks 16 and 24, then 800 mg SC every 8 weeks for 2 doses, administered at weeks 32 and 40, then 800 mg

SC every 4 weeks for up to 7 doses (e.g., a dose administered at weeks 44, 48, 52, 56, 60, 64, 68 and 72).

200 mg SC every 8 weeks for 1 dose, administered at week 0, then 400 mg SC every 8 weeks for 2 doses administered at weeks 8 and 16, then 800 mg SC every 8 weeks for 1 dose administered at week 24, then 800 mg SC every 4 weeks for between 9 and 11 doses (e.g., a dose administered at weeks 28, 31, 36, 40 and so on up to at least week 64 or as long as week 72).

400 SC mg every 8 weeks for 2 doses, administered at weeks 0 and 8, then 800 mg SC every 8 weeks for 1 dose administered at week 16, then 800 mg SC administered every 4 weeks for between 8 and 13 doses (e.g., a dose administered at weeks 20, 24, 28, 32, 36, 40 and so on up to at least week 48 or as long as week 72).

400 mg SC every 12 weeks for 21 doses, administered at weeks 0 and 12, then 800 mg SC every 8 weeks for 1 dose administered at week 20, then 800 mg SC administered every 4 weeks for between 9 and 11 doses (e.g., a dose administered at weeks 24, 28, 32, 36, 40 and so on up to at least week 64 or as long as week 72).

400 mg SC every week for 25 doses, administered at weeks 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 24.

800 mg SC every 4 weeks for 10 doses, administered at weeks, 0, 4, 8, 12, 16, 20, 24, 28, 32, and 36.

400 mg SC every 4 weeks for 3 doses, administered at weeks 0, 4, and 8, with titration up to 800 mg SC every 4 weeks for 8 doses, administered at weeks 12, 16, 20, 24, 28, 32, 36, and 40.

[00231] In the trial design for remternetug in preclinical AD, a MRI schedule may be designed to monitor potential ARIA for participant safety for either IV or SC dosing regimen(s). Investigators will be able conduct unscheduled MRIs to test for ARIA at any time throughout the study or upon suspicion of ARIA.

Example 14. Use of remternetug to prevent or delay onset of Alzheimer's Disease.

[00232] Remternetug may be used to prevent or delay the onset or progression of Alzheimer's Disease substantially as set forth herein. According to some embodiments,

such patients may be at risk of AD. For example, patients may have a family history of AD and / or be at risk as identified by biomarkers of AD pathology. Additionally, remternetug may be used to prevent or delay the onset or progression of Alzheimer's Disease, substantially as described herein, in patients being homozygous or heterozygous APOE ε4 and / or in patients having dominantly-inherited (also known as autosomal dominant) genetic profile for AD. Additionally, remternetug may be used as maintenance therapy to prevent or delay the progression of AD after treatment with an Aβ-lowering/ Aβ-clearing disease modifying therapy, such as after treatment with donanemab, remternetug, Leqembi® (lecanemab), or Aduhelm® (aducanemab). For example, embodiments in patients with dominantly-inherited AD, a family history of AD, other at risk populations with identified biomarkers of AD pathology, after treatment with any Aβ -lowering / Aβ-clearing disease modifying therapy, and / or where a patient has been previously treated with an Aβ -lowering / Aβ-clearing disease modifying therapy and cleared Aβ plaques below a specific level (for example, 24 centiloids), remternetug may be administered as follows:

about 200mg or about 400 mg via subcutaneous injection every 12 weeks with chronic administration (for example, up to 72 or 76 weeks);

about 200mg or about 400 mg via subcutaneous injection every 12 weeks for 5 doses, followed by about 400 mg via subcutaneous injections every 8 weeks with chronic administration (for example, up to 72 or 76 weeks);

about 200mg or about 400 mg via subcutaneous injection every 12 weeks for 5 doses, followed by about 400mg and/or about 800 mg via subcutaneous injections every 8 or 12 weeks with chronic administration (for example, up to 72 or 76 weeks).

[00233] Additional embodiment may comprise use for primary prevention of AD in subject populations with known homozygous or heterozygous APOE ε4 genetic profile, and/or other at risk populations with identified biomarkers of AD pathology, wherein remternetug may be administered as follows:

about 200 mg via subcutaneous injection every 26 weeks with chronic administration (for example, up to 72 or 76 weeks);

about 200 mg via subcutaneous injection every 52 weeks with chronic administration (for example, up to 72 or 76 weeks);

about 400 mg via subcutaneous injection every 26 weeks with chronic administration (for example, up to 72 or 76 weeks);

about 400 mg via subcutaneous injection every 52 weeks with chronic administration (for example, up to 72 or 76 weeks);

about 600 mg via subcutaneous injection every 26 weeks with chronic administration (for example, up to 72 or 76 weeks); or

about 600 mg via subcutaneous injection every 52 weeks with chronic administration (for example, up to 72 or 76 weeks).

[00234] Additional embodiment may comprise use as a maintenance therapy after treatment with an Aβ-lowering / Aβ-clearing disease modifying therapy, whereby progression of Aβ pathology is prevented. According to such embodiments, remternetug may be administered according to a dose regimen as set forth in Example 14 provided herein.

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A Study of Remternetug (LY3372993) in Participants With Alzheimer's Disease (TRAILRUNNER-ALZ 1) (Clinical Trial No.: NCT05463731) https://clinicaltrials.gov/ct2/show/NCT05463731?term=LY3372993&draw=2&rank=3

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US Patent No. 11,078,261

US Patent Application No. 17/711,099

International Patent Application No. PCT/US2022/011894

US Patent Application No. 17/391,821

EXEMPLARY EMBODIMENTS

1. A method of treating or preventing a disease characterized by deposition of amyloid beta (Aβ) plaques in the brain of a human subject in need thereof comprising:

administering to the subject one or more intravenous (IV) doses from about 20 mg to about 3000 mg of an anti-N3pG Aβ antibody at a frequency of:

i) about once every twelve weeks (Q12W);

ii) about once every eight weeks (Q8W); or

iii) about once every four weeks (Q4W);

wherein the anti-N3pGlu Aβ antibody comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 8 and a heavy chain variable region (HCVR), comprising the amino acid sequence of SEQ ID NO: 7.

2. The method of embodiment 1, wherein the subject is administered one or more doses of the antibody for a duration sufficient to treat or prevent the disease.

3. The method of embodiment 1 or 2, wherein the antibody is administered until the Aβ plaques in the brain of the human subject are cleared.

4. The method of embodiment 1, wherein the antibody is administered until at least one of the following occurs:

i) the Aβ plaques in the brain of the human subject are 24.1 centiloids or lower as measured by two consecutive amyloid PET imaging scans, wherein the two consecutive amyloid PET imaging scans are at least 6 months apart; or

ii) the Aβ plaques in the brain of the human subject are 11 centiloids or lower as measured by a single amyloid PET imaging scan.

5. The method of embodiment 1 or 2, wherein the antibody is administered until the subject is amyloid negative.

6. The method of embodiment 1 or 2, wherein the antibody is administered until an Aβ plaque level of ≤24.1 centiloids is reached as measured by amyloid PET imaging scan.

7. The method of embodiment 1, wherein the subject is administered from about one dose to about 20 doses of the antibody or from about one dose to about 10 doses of the antibody.

8. The method of embodiment 1, wherein the subject is administered from about 3 doses to about 7 doses.

9. The method of embodiment 1, wherein the subject is administered the antibody at a dose of from about 250 mg to about 2800 mg.

10. The method of embodiment 1, wherein the subject is administered at least two doses of about 2300 mg of the antibody at a frequency of about once every twelve weeks (Q12W).

11. The method of embodiment 10, wherein the subject is administered two doses of about 2300 mg of the antibody at a frequency of about once every twelve weeks.

12. The method of embodiment 11, wherein the subject has preclinical AD.

13. The method of embodiment 11, wherein the subject is administered three doses of about 2300 mg of the antibody at a frequency of about once every twelve weeks.

14. The method of embodiment 13, wherein the subject has early symptomatic AD.

15. The method of embodiment 1, wherein the subject is administered at least two doses of about 1500 mg of the antibody at a frequency of about once every twelve weeks (Q12W).

16. The method of embodiment 15, wherein the subject is administered three doses of about 1500 mg of the antibody at a frequency of about once every twelve weeks.

17. The method of embodiment 16, wherein the subject has preclinical AD.

18. The method of embodiment 15, wherein the subject is administered four doses of about 1500 mg of the antibody at a frequency of about once every twelve weeks.

19. The method of embodiment 18, wherein the subject has early symptomatic AD.

20. The method of embodiment 1, wherein the subject is administered at least two doses of about 800 mg of the antibody at a frequency of about once every 8 weeks (Q8W).

21. The method of embodiment 20, wherein the subject is administered from about 5 to about 7 doses of about 800 mg of the antibody at a frequency of about once every 8 weeks.

22. The method of embodiment 21, wherein the subject is administered about 5 doses, about 6 doses, or about 7 doses of the antibody.

23. The method of embodiment 1, wherein the subject is administered at least two doses of about 800 mg of the antibody at a frequency of about once every 4 weeks (Q4W).

24. The method of embodiment 23, wherein the subject is administered from about 5 to about 7 doses of about 800 mg of the antibody at a frequency of about once every 4 weeks.

25. The method of embodiment 24, wherein the subject is administered about 5 doses, about 6 doses, or about 7 doses.

26. The method of any one of embodiments 1-25, wherein the disease characterized by Aβ plaques in the brain of the human subject is selected from preclinical Alzheimer's disease (AD), clinical AD, prodromal AD, mild AD, moderate AD, severe AD, Down's syndrome, clinical cerebral amyloid angiopathy, and pre-clinical cerebral amyloid angiopathy.

27. The method of embodiment 1, wherein the disease is preclinical AD.

28. The method of embodiment 1, wherein the disease is early symptomatic AD, prodromal AD, or mild dementia due to AD.

29. The method of any one of embodiments above, wherein the treatment or prevention of the disease causes i) reduction of Aβ plaques in the brain of the human subject; ii) slowing of cognitive decline in the human subject; or iii) slowing of functional decline in the human subject.

30. The method of embodiment 29, wherein the reduction of Aβ plaques in the brain of the human subject is determined by amyloid PET brain imaging or a diagnostic that detects Aβ or a biomarker for Aβ.

31. The method of any one of embodiments above, wherein the administration of the antibody does not result in amyloid-related imaging abnormality (ARIA) events in the subject.

32. The method of any one of embodiments above, wherein the administration of the antibody does not result in symptomatic ARIA events in the subject.

33. The method of embodiment 1, further comprising a step of evaluating magnetic resonance image (MRI) scan of the subject's brain for ARIA after the administration of at least one dose of the antibody and modifying the administration steps until ARIA has resolved.

34. The method of embodiment 33, wherein administration of the antibody is temporarily withheld or discontinued if symptoms consistent with ARIA occur.

35. The method of embodiment 33, wherein administration of the antibody is temporarily withheld if symptoms consistent with mild to moderate ARIA occur.

36. The method of embodiment 33, wherein administration of the anti-N3pGlu Aβ antibody is discontinued if symptoms consistent with severe or symptomatic ARIA occur.

37. The method of any one of embodiments above, wherein the anti-N3pGlu Aβ antibody comprises a LC and a HC, wherein the LC comprises the amino acid sequence of SEQ ID NO: 10 and the HC comprises the amino acid sequence of SEQ ID NO: 9.

38. The method of any one of embodiments above, wherein the anti-N3pGlu Aβ antibody comprises two light chains and two heavy chains, wherein the LC comprises the amino acid sequence of SEQ ID NO: 10 and the HC comprises the amino acid sequence of SEQ ID NO: 9.

39. The method of embodiment 1, wherein the subject has a brain tau level of less than 1.46 standardized uptake value ratio (SUVr) prior to administering the antibody, wherein the brain tau level is measured by tau PET imaging scan.

40. The method of embodiment 1, wherein the subject has a brain tau level of greater than 1.10 SUVr and less than 1.46 SUVr prior to administering the antibody, wherein the brain tau level is measured by tau PET imaging scan.

41. The method of embodiment 39 or embodiment 40, wherein brain tau level is measured by ^{18}F-flortaucipir PET imaging.

42. The method of embodiment 1, wherein the subject has at least one *APOE4* allele.

43. The method of any one of embodiments above, wherein the dose of antibody is administered to the human subject until the Aβ plaques in the brain of the human subject are reduced by i) about an average of about 25 centiloids to about 100 centiloids, ii) about an average of about 50 centiloids to about 100 centiloids, or iii) about 100 centiloids, or iv) about 84 centiloids.

44. The method of any one of embodiments above, wherein the dose of antibody is administered to the human subject until the Aβ plaques in the brain of the

human subject are reduced by i) about 25 centiloids to about 100 centiloids or ii) about 50 centiloids to about 100 centiloids.

45. A method of treating or preventing a disease characterized by deposition of amyloid beta plaques in the brain of a human subject in need thereof comprising:

administering to the subject one or more subcutaneous doses from about 20 mg to about 1000 mg of an anti-N3pG Aβ antibody at a frequency of:

i) about once every week (Q1W);

ii) about once every 2 weeks (Q2W); or

iii) about once every four weeks (Q4W);

wherein the anti-N3pGlu Aβ antibody comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 8 and a heavy chain variable region (HCVR), comprising the amino acid sequence of SEQ ID NO: 7.

46. The method of embodiment 45, wherein the subject is administered one or more doses of the antibody for a duration sufficient to treat or prevent the disease.

47. The method of embodiment 45 or 46, wherein the antibody is administered until the Aβ plaques in the brain of the human subject are cleared.

48. The method of embodiment 45, wherein the antibody is administered until at least one of the following occurs:

i) the Aβ plaques in the brain of the human subject are 24.1 centiloids or lower as measured by two consecutive amyloid PET imaging scans, wherein the two consecutive amyloid PET imaging scans are at least 6 months apart, or

ii) the Aβ plaques in the brain of the human subject are 11 centiloids or lower as measured by a single amyloid PET imaging scan.

49. The method of embodiment 45 or 46, wherein the antibody is administered until the subject is amyloid negative.

50. The method of embodiment 45 or 46, wherein the antibody is administered until the Aβ plaque level of ≤24.1 centiloids is reached as measured by amyloid PET imaging scan.

51. The method of embodiment 45, wherein the subject is administered from about one dose to about 100 doses of the antibody.

52. The method of embodiment 45, wherein the subject is administered 24 doses.

53. The method of embodiment 45, wherein the subject is administered 36 doses.

54. The method of embodiment 45, wherein the subject is administered 52 doses.

55. The method of embodiment 45, wherein the subject is administered 76 doses.

56. The method of embodiment 45, wherein the subject is administered the antibody at a dose of from about 250 mg to about 500 mg.

57. The method of embodiment 45, wherein 400 mg of the antibody is administered to the subject at a frequency of about once every week (Q1W) for 24 weeks or once every week for 36 weeks.

58. The method of embodiment 45, wherein 400 mg of the antibody is administered to the subject at a frequency of about once every two weeks (Q2W) for 36 weeks, 52 weeks, or 76 weeks.

59. The method of any one of embodiments 45-58, wherein the disease characterized by Aβ plaques in the brain of the human subject is selected from preclinical AD, clinical AD, prodromal AD, mild AD, moderate AD, severe AD, Down's syndrome, clinical cerebral amyloid angiopathy, and pre-clinical cerebral amyloid angiopathy.

60. The method of embodiment 45, wherein the disease is preclinical AD.

61. The method of embodiment 60, wherein the subject is administered from about 1 dose to about 24 doses of 400 mg of the antibody at a frequency of once every week.

62. The method of embodiment 60, wherein the subject is administered from about 1 dose to about 26 doses of 400 mg of the antibody at a frequency of once every two weeks.

63. The method of embodiment 62, wherein the subject is administered 18 doses or 26 doses of the antibody.

64. The method of embodiment 45, wherein the disease is early symptomatic AD, prodromal AD, or mild dementia due to AD.

65. The method of embodiment 45, wherein the disease is early symptomatic AD.

66. The method of embodiment 65, wherein the subject is administered from about 1 dose to about 36 doses of 400 mg of the antibody at a frequency of once every week.

67. The method of embodiment 65, wherein the subject is administered from about 1 dose to about 38 doses of 400 mg of the antibody at a frequency of once every two weeks.

68. The method of embodiment 67, wherein the subject is administered 26 doses or 38 doses of the antibody.

69. The method of any one of embodiments above, wherein the administration of the antibody does not result in amyloid-related imaging abnormality (ARIA) events in the subject.

70. The method of any one of embodiments above, wherein the administration of the antibody does not result in symptomatic ARIA events in the subject.

71. The method of embodiment 45, further comprising a step of evaluating magnetic resonance image (MRI) scan of the subject's brain for ARIA after the administration of at least one dose of the antibody and modifying the administration steps until ARIA has resolved.

72. The method of embodiment 71, wherein administration of the antibody is temporarily withheld or discontinued if symptoms consistent with ARIA occur.

73. The method of embodiment 72, wherein administration of the antibody is temporarily withheld if symptoms consistent with mild to moderate ARIA occur.

74. The method of embodiment 72, wherein administration of the anti-N3pGlu Aβ antibody is discontinued if symptoms consistent with severe or symptomatic ARIA occur.

75. The method of any one of embodiments above, wherein the anti-N3pGlu Aβ antibody comprises a LC and a HC, wherein the LC comprises the amino acid sequence of SEQ ID NO: 10 and the HC comprises the amino acid sequence of SEQ ID NO: 9.

76. The method of any one of embodiments above, wherein the anti-N3pGlu Aβ antibody comprises two light chains and two heavy chains, wherein the LC comprises the amino acid sequence of SEQ ID NO: 10 and the HC comprises the amino acid sequence of SEQ ID NO: 9.

77. The method of any one of embodiments above, wherein the treatment or prevention of the disease causes i) reduction of Aβ plaques in the brain of the human subject; ii) slowing of cognitive decline in the human subject; or iii) slowing of functional decline in the human subject.

78. The method of embodiment 77, wherein the reduction of Aβ plaques in the brain of the human subject is determined by amyloid PET brain imaging or a diagnostic that detects Aβ or a biomarker for Aβ.

79. The method of embodiment 45, wherein the subject has a brain tau level of less than 1.46 standardized uptake value ratio (SUVr) prior to administering the antibody, wherein the brain tau level is measured by tau PET imaging scan.

80. The method of embodiment 45, wherein the subject has a brain tau level of greater than 1.10 SUVr and less than 1.46 SUVr prior to administering the antibody, wherein the brain tau level is measured by tau PET imaging scan.

81. The method of embodiment 79 or embodiment 80, wherein brain tau level is measured by ^{18}F-flortaucipir PET imaging.

82. The method of embodiment 45, wherein the subject has at least one *APOE4* allele.

83. The method of any one of embodiments above, wherein the dose of antibody is administered to the human subject until the Aβ plaques in the brain of the human subject are reduced by i) about an average of about 25 centiloids to about 100 centiloids, ii) about an average of about 50 centiloids to about 100 centiloids, or iii) about 100 centiloids, or iv) about 84 centiloids.

84. The method of any one of embodiments above, wherein the dose of antibody is administered to the human subject until the Aβ plaques in the brain of the human subject are reduced by i) about 25 centiloids to about 100 centiloids or ii) about 50 centiloids to about 100 centiloids.

85. A method of reducing of amyloid beta plaques in the brain of a human subject in need thereof comprising:

administering to the subject one or more intravenous doses from about 20 mg to about 3000 mg of an anti-N3pG Aβ antibody at a frequency of:

i) about once every twelve weeks;

ii) about once every eight weeks; or

iii) about once every four weeks;

wherein the anti-N3pGlu Aβ antibody comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 8 and a heavy chain variable region (HCVR), comprising the amino acid sequence of SEQ ID NO: 7.

86. A method of reducing amyloid beta in the brain of a human subject in need thereof comprising:

administering to the subject one or more subcutaneous doses from about 20 mg to about 1000 mg of an anti-N3pG Aβ antibody at a frequency of:

i) about once every week;

ii) about once every 2 weeks; or

iii) about once every four weeks;

wherein the anti-N3pGlu Aβ antibody comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 8 and a heavy chain variable region (HCVR), comprising the amino acid sequence of SEQ ID NO: 7.

87. A method of slowing disease progression of Alzheimer's Disease (AD) in a human subject in need thereof comprising:

administering to the subject one or more intravenous doses from about 20 mg to about 3000 mg of an anti-N3pG Aβ antibody at a frequency of:

i) about once every twelve weeks;

ii) about once every eight weeks; or

iii) about once every four weeks;

wherein the anti-N3pGlu Aβ antibody comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 8 and a heavy chain variable region (HCVR), comprising the amino acid sequence of SEQ ID NO: 7.

88. A method of slowing disease progression of Alzheimer's Disease (AD) in a human subject in need thereof comprising:

administering to the subject one or more subcutaneous doses from about 20 mg to about 1000 mg of an anti-N3pG Aβ antibody at a frequency of:

i) about once every week;

ii) about once every 2 weeks; or

iii) about once every four weeks;

wherein the anti-N3pGlu Aβ antibody comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 8 and a heavy chain variable region (HCVR), comprising the amino acid sequence of SEQ ID NO: 7.

89. An improved method of reducing amyloid beta in the brain of a human subject in need thereof comprising:

i) administering to the subject one to three IV doses of 2300 mg of an anti-N3pGlu Aβ antibody at a frequency of once every 12 weeks (Q12W);

ii) administering to the subject one to four IV doses of 1500 mg of the anti-N3pGlu Aβ antibody at a frequency of once every 12 weeks (Q12W); or

iii) administering to the subject one to seven IV doses of 800 mg of the anti-N3pGlu Aβ antibody at a frequency of once every 8 weeks (Q8W);

wherein the anti-N3pGlu Aβ antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR consists of the amino acid sequence of SEQ ID NO: 8 and the HCVR consists of the amino acid sequence of SEQ ID NO: 7.

90. An improved method of reducing amyloid beta in the brain of a human AD subject in need thereof comprising:

i) administering to the subject one to 36 SC doses of 400 mg of an anti-N3pGlu Aβ antibody at a frequency of once every week (Q1W);

ii) administering to the subject one to 26 SC doses of 400 mg of the anti-N3pGlu Aβ antibody at a frequency of once every 2 weeks (Q2W); or

iii) administering to the subject one to 38 SC doses of 400 mg of the anti-N3pGlu Aβ antibody at a frequency of once every 2 weeks (Q2W);

wherein the anti-N3pGlu Aβ antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR consists of the amino acid sequence of SEQ ID NO: XX and the HCVR consists of the amino acid sequence of SEQ ID NO: XX.

91. The method of any one of embodiments 85-90, further comprising a step of evaluating magnetic resonance image (MRI) scan of the subject's brain for amyloid-related imaging abnormality (ARIA) after the administration of a dose of the anti-N3pGlu Aβ antibody wherein further administration of doses is temporarily withheld if symptoms consistent with ARIA occur.

92. The method of embodiment 91, wherein the administration of further doses is re-initiated after resolution of ARIA symptoms or radiographic stabilization on MRI.

93. The method of embodiment 91, wherein further doses are withheld, and corticosteroids are administered to the subject.

94. The method of any one of embodiments 85-90, further comprising a step of evaluating magnetic resonance image (MRI) scan of the subject's brain for amyloid-related imaging abnormality (ARIA), after the administration of a dose wherein further administration of doses is discontinued if symptoms consistent with severe or symptomatic ARIA occur.

95. The method of embodiment 94, wherein the administration of further doses is re-initiated after resolution of ARIA symptoms or radiographic stabilization on MRI.

96. The method of embodiment 94, wherein further doses are withheld, and, optionally, corticosteroids are administered to the subject.

97. The method of embodiment 94, wherein further administration of doses is discontinued, and, optionally, corticosteroids are administered to the subject.

98. A method of treating Alzheimer's Disease in a subject in need thereof until symptoms consistent with ARIA-E occur comprising:

i) administering to the subject one or more intravenous doses from about 20 mg to about 3000 mg of an anti-N3pG Aβ antibody at a frequency of about once every twelve weeks, about once every eight weeks, or about once every four weeks; or

ii) administering to the subject one or more subcutaneous doses from about 20 mg to about 1000 mg of an anti-N3pG Aβ antibody at a frequency of about once every week, about once every 2 weeks, or about once every four weeks;

wherein the anti-N3pGlu Aβ antibody comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 8 and a heavy chain variable region (HCVR), comprising the amino acid sequence of SEQ ID NO: 7.

99. The method of embodiment 98, wherein the symptoms of ARIA are detected by MRI or are presented in the subject.

100. A method for treating a patient with remternetug, wherein the patient is suffering from Alzheimer's disease, the method comprising the steps of:

a) administering [or having administered] to the subject i) one or more intravenous doses from about 20 mg to about 3000 mg of an anti-N3pG Aβ antibody at a frequency of about once every twelve weeks, about once every eight weeks, or about once every four weeks; or ii) one or more subcutaneous doses from about 20 mg to about 1000 mg of an anti-N3pG Aβ antibody at a frequency of about once every week, about once every 2 weeks, or about once every four weeks;

b) determining whether the patient has symptoms of ARIA-E i) by performing or having performed an MRI after administration of the antibody or ii) if clinical symptoms consistent with ARIA-E occur; and

c) if the patient has moderate symptoms of ARIA-E, temporarily discontinuing treatment with remternetug; and

d) if the patient does not have symptomatic ARIA-E, administering remternetug to the patient until brain amyloid is cleared, is amyloid negative, or is <24.1 centiloids.

101. An improved method for treating a patient with remternetug, wherein the patient is suffering from Alzheimer's disease, wherein the improvement comprises:

a) administering [or having administered] to the subject i) one or more intravenous doses from about 20 mg to about 3000 mg of an anti-N3pG Aβ antibody at a frequency of about once every twelve weeks, about once every eight weeks, or about once every four weeks; or ii) one or more subcutaneous doses from about 20 mg to about 1000 mg of an anti-N3pG Aβ antibody at a frequency of about once every week, about once every 2 weeks, or about once every four weeks;

b) determining whether the patient has symptoms of ARIA-E i) by performing or having performed an MRI after administration of the antibody or ii) if clinical symptoms consistent with ARIA-E occur; and

c) if the patient has moderate symptoms of ARIA-E, temporarily discontinuing treatment with remternetug; and

d) if the patient does not have symptomatic ARIA-E, administering remternetug to the patient until brain amyloid is cleared, is amyloid negative, or is <24.1 centiloids.

102. A method for treating a patient with remternetug, wherein the patient is suffering from Alzheimer's disease, the method comprising the steps of:

a) administering [or having administered] to the subject i) one or more intravenous doses from about 20 mg to about 3000 mg of an anti-N3pG Aβ antibody at a frequency of about once every twelve weeks, about once every eight weeks, or about once every four weeks; or ii) one or more subcutaneous doses from about 20 mg to about 1000 mg of an anti-N3pG Aβ antibody at a frequency of about once every week, about once every 2 weeks, or about once every four weeks;

b) discontinuing treatment if the patient has moderate symptoms of ARIA-E; and

c) continuing treatment once ARIA-E resolves by administering remternetug to the patient until brain amyloid is cleared, is negative, is <24.1 CL, or ARIA-E symptoms reappear.

103. The method of embodiment 102, wherein the symptoms or ARIA-E are confirmed or are determined by an MRI scan.

104. A method for treating a patient with remternetug, wherein the patient is suffering from Alzheimer's disease, the method comprising the steps of:

a) administering [or having administered] to the subject i) one or more intravenous doses from about 20 mg to about 3000 mg of an anti-N3pG Aβ antibody at a frequency of about once every twelve weeks, about once every eight weeks, or about once every four weeks; or ii) one or more subcutaneous doses from about 20 mg to about 1000 mg of an anti-N3pG Aβ antibody at a frequency of about once every week, about once every 2 weeks, or about once every four weeks;

b) continuing treatment with remternetug until brain amyloid is cleared, is negative, or is <24.1 CL so long as the patient does not have symptomatic ARIA-E.

105. The method of embodiment 104, wherein the symptoms or ARIA-E are confirmed or are determined by an MRI scan.

106. A method of treating or preventing early symptomatic Alzheimer's disease in a human subject in need thereof comprising:

a. administering to the subject three doses of 2300 mg of an anti-N3pGlu Aβ antibody at a frequency of one dose every 12 weeks (Q12W);

b. administering to the subject four doses of 1500 mg of the antibody at a frequency of one dose every 12 weeks (Q12W);

c. administering to the subject seven doses of 800 mg of the antibody at a frequency of one dose every 8 weeks (Q8W);

d. administering to the subject three doses of 400 mg of the antibody at a frequency of one dose every 4 weeks (Q4W) followed by five doses of 800 mg of the antibody at a frequency of one dose every 8 weeks (Q8W); or

e. administering to the subject thirteen doses of 400 mg of the antibody at a frequency of one dose every 8 weeks (Q8W);

wherein the anti-N3pGlu Aβ antibody comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 8 and a heavy chain variable region (HCVR), comprising the amino acid sequence of SEQ ID NO: 7 and each dose is administered intravenously.

107. A method of treating or preventing early symptomatic Alzheimer's disease in a human subject in need thereof comprising:

a. administering to the subject thirty-six doses of 400 mg of an anti-N3pGlu Aβ antibody at a frequency of one dose every week (Q1W);

b. administering to the subject thirteen doses of 800 mg of the antibody at a frequency of one dose every 4 weeks (Q4W); or

c. administering to the subject three doses of 400 mg of the antibody at a frequency of one dose every 4 weeks (Q4W) followed by ten doses of 800 mg of the antibody at a frequency of one dose every 4 weeks (Q4W);

wherein the anti-N3pGlu Aβ antibody comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 8 and a heavy chain variable region (HCVR), comprising the amino acid sequence of SEQ ID NO: 7 and each dose is administered subcutaneously.

108. A method of treating or preventing preclinical Alzheimer's disease in a human subject in need thereof comprising:

a. administering to the subject two doses of 2300 mg of an anti-N3pGlu Aβ antibody at a frequency of one dose every 12 weeks (Q12W);

b. administering to the subject three doses of 1500 mg of the antibody at a frequency of one dose every 12 weeks (Q12W);

c. administering to the subject five doses of 800 mg of the antibody at a frequency of one dose every 8 weeks (Q8W);

d. administering to the subject three doses of 400 mg of the antibody at a frequency of one dose every 4 weeks (Q4W) followed by three doses of 800 mg of the antibody at a frequency of one dose every 8 weeks (Q8W);

e. administering to the subject three doses of 400 mg of the antibody at a frequency of one dose every 4 weeks (Q4W) followed by four doses of 800 mg of the antibody at a frequency of one dose every 8 weeks (Q8W); or

f. administering to the subject ten doses of 400 mg of the antibody at a frequency of one dose every 8 weeks (Q8W);

wherein the anti-N3pGlu Aβ antibody comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 8 and a heavy chain variable region (HCVR), comprising the amino acid sequence of SEQ ID NO: 7 and wherein each dose is administered intravenously.

109. A method of treating or preventing preclinical Alzheimer's disease in a human subject in need thereof comprising:

a. administering to the subject twenty-five doses of 400 mg of an anti-N3pGlu Aβ antibody at a frequency of one dose every week (Q1W);

b. administering to the subject ten doses of 800 mg of the antibody at a frequency of one dose every 4 weeks (Q4W); or

c. administering to the subject three doses of 400 mg of the antibody at a frequency of one dose every 4 weeks (Q4W) followed by eight doses of 800 mg of the antibody at a frequency of one dose every 4 weeks (Q4W);

wherein the anti-N3pGlu Aβ antibody comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 8 and a heavy chain variable region (HCVR), comprising the amino acid sequence of SEQ ID NO: 7 and each dose is administered subcutaneously.

110. The method of any one of embodiments 106-109, wherein the at least one of the following occurs upon completion of the administration:

a. the Aβ plaques in the brain of the human subject are 24.1 centiloids or lower as measured by two consecutive amyloid PET imaging scans, wherein the two consecutive amyloid PET imaging scans are at least 6 months apart;

b. the subject is amyloid negative;

c. the Aβ plaques in the brain of the human subject are 11 centiloids or lower as measured by a single amyloid PET imaging scan.

111. The method of any one of embodiments 106-110, wherein the treatment or prevention of the disease causes i) reduction of Aβ plaques in the brain of the human subject; ii) slowing of cognitive decline in the human subject; or iii) slowing of functional decline in the human subject.

112. The method of embodiment 111, wherein the reduction of Aβ plaques in the brain of the human subject is determined by amyloid PET brain imaging or a diagnostic that detects Aβ or a biomarker for Aβ.

113. The method of any one of embodiments 106-112, wherein the administration of the antibody does not result in amyloid-related imaging abnormality (ARIA) events in the subject.

114. The method of any one of embodiments 106-113, wherein the administration of the antibody does not result in symptomatic ARIA events in the subject.

115. The method of any one of embodiments 106-109, further comprising a step of evaluating magnetic resonance image (MRI) scan of the subject's brain for ARIA after the administration of at least one dose of the antibody and modifying the administration steps until ARIA has resolved.

116. The method of embodiment 115, wherein administration of the antibody is temporarily withheld or discontinued if symptoms consistent with ARIA occur.

117. The method of embodiment 115, wherein administration of the antibody is temporarily withheld if symptoms consistent with mild to moderate ARIA occur.

118. The method of embodiment 115, wherein administration of the anti-N3pGlu Aβ antibody is discontinued if symptoms consistent with severe or symptomatic ARIA occur.

119. The method of any one of embodiments 106-118, wherein the anti-N3pGlu Aβ antibody comprises a LC and a HC, wherein the LC comprises the amino acid sequence of SEQ ID NO: 10 and the HC comprises the amino acid sequence of SEQ ID NO: 9.

120. The method of any one of embodiments 106-119, wherein the anti-N3pGlu Aβ antibody comprises two light chains and two heavy chains, wherein the LC comprises the amino acid sequence of SEQ ID NO: 10 and the HC comprises the amino acid sequence of SEQ ID NO: 9.

121. The method of any one of embodiments 106-109, wherein the subject has a brain tau level of less than 1.46 standardized uptake value ratio (SUVr) prior to administering the antibody, wherein the brain tau level is measured by tau PET imaging scan.

122. The method of any one of embodiments 106-109, wherein the subject has a brain tau level of greater than 1.10 SUVr and less than 1.46 SUVr prior to administering the antibody, wherein the brain tau level is measured by tau PET imaging scan.

123. The method of embodiment 121 or embodiment 122, wherein brain tau level is measured by ^{18}F-flortaucipir PET imaging.

124. The method of any one of embodiments 106-109, wherein the subject has at least one *APOE4* allele.

125. The method of any one of embodiments 106-124, wherein the patient has no baseline superficial siderosis.

SEQUENCES

Antibody 1 (Remternetug), HCDR1 (SEQ ID NO: 1)
AASGFTFSSYPMS

Antibody 1, HCDR2 (SEQ ID NO: 2)
AISGSGGSTYYADSVKG

Antibody 1, HCDR3 (SEQ ID NO: 3)
AREGGSGSYYNGFDY

Antibody 1, LCDR1 (SEQ ID NO: 4)
RASQSLGNWLA

Antibody 1, LCDR2 (SEQ ID NO: 5)
YQASTLES

Antibody 1, LCDR3 (SEQ ID NO: 6)
QHYKGSFWT

Antibody 1, HCVR (SEQ ID NO: 7)
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYPMSWVRQAPGKGLEWVSAISGS
GGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREGGSGSYYN
GFDYWGQGTLVTVSS

Antibody 1, LCVR (SEQ ID NO: 8)
DIQMTQSPSTLSASVGDRVTITCRASQSLGNWLAWYQQKPGKAPKLLIYQASTLE
SGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQHYKGSFWTFGQGTKVEIK

Antibody 1, Heavy Chain (SEQ ID NO: 9)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYPMSWVRQAPGKGLEWVSAISGS
GGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREGGSGSYYN
GFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD
KKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH
EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK
CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPG

Antibody 1, Light Chain (SEQ ID NO: 10)

DIQMTQSPSTLSASVGDRVTITCRASQSLGNWLAWYQQKPGKAPKLLIYQASTLE
SGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCQHYKGSFWTFGQGTKVEIKRTVA
APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ
DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Exemplified DNA for Expressing Antibody 1 Heavy Chain (SEQ ID NO: 11)

gaggtgcagctgttggagtctgggggaggcttggtacagcctgggggtccctgagactctcctgtgcagcctctggattcacct
ttagcagctatcctatgagctgggtccgccaggctccagggaaggggctggagtgggtctcagctattagtggtagtggtggtag
cacatactacgcagactccgtgaagggccggttcaccatctccagagacaattccaagaacacgctgtatctgcaaatgaacag
cctgagagccgaggacacggccgtatattactgtgcgagagaggggggctcagggagttattataacggctttgattattgggg
ccagggaaccctggtcaccgtctcctcagcctccaccaagggcccatcggtcttcccgctagcaccctcctccaagagcacctc
tgggggcacagcggccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctg
accagcggcgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctccagc

agcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaacaccaaggtggacaagaaagttgagcccaaatc
ttgtgacaaaactcacacatgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttcctcttcccccaaaaccc
aaggacaccctcatgatctcccggacccctgaggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagtt
caactggtacgtggacggcgtggaggtgcataatgccaagacaaagccgcgggaggagcagtacaacagcacgtaccgtgt
ggtcagcgtcctcaccgtcctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctccaacaaagccctcccag
cccccatcgagaaaaccatctccaaagccaaagggcagccccgagaaccacaggtgtacaccctgcccccatcccgggacg
agctgaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatcccagcgacatcgccgtggagtgggagagcaat
gggcagccggagaacaactacaagaccacgcccccgtgctggactccgacggctccttcttcctctatagcaagctcaccgtg

gacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacgcagaagag
cctctccctgtctccgggt

Exemplified DNA for Expressing Antibody 1 Light Chain (SEQ ID NO: 12)

gacatccagatgacccagtctccttccaccctgtctgcatctgtaggagacagagtcaccatcacttgccgggccagtcagagtct
tggtaactggttggcctggtatcagcagaaaccagggaaagcccctaaactcctgatctatcaggcgtctactttagaatctgggg
tcccatcaagattcagcggcagtggatctgggacagagttcactctcaccatcagcagcctgcagcctgatgattttgcaacttatt
actgccaacattataaaggttctttttggacgttcggccaagggaccaaggtggaaatcaaacggaccgtggctgcaccatctgtc
ttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagagaggcca
aagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagca
cctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatca
gggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgc

N3pGlu Aβ (SEQ ID NO: 13)

[pE]FRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA

CLAIMS

1. A method of reducing amyloid beta (Aβ) plaques in the brain of a human subject in need thereof, treating a disease characterized by deposition of Aβ plaques in the brain of a human subject in need thereof, preventing a disease characterized by deposition of Aβ plaques in the brain of a human subject in need thereof, or delaying onset of a disease characterized by deposition of Aβ plaques in the brain of a human subject in need thereof comprising:

administering to the subject one or more intravenous (IV) doses from about 20 mg to about 3000 mg of an anti-N3pG Aβ antibody at a frequency of about once every twelve weeks (Q12W), about once every eight weeks (Q8W), about once every four weeks (Q4W), or a combination thereof,

wherein the anti-N3pGlu Aβ antibody comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 8 and a heavy chain variable region (HCVR), comprising the amino acid sequence of SEQ ID NO: 7.

2. The method of claim 1, wherein the one or more IV doses is selected from one of: about 200 mg; about 400 mg; about 700 mg; about 800 mg; about 1400 mg; about 1500 mg; about 2300 mg; about 2800 mg, or a combination thereof.

3. The method of claim 1 or 2, wherein the one or more IV doses is selected from one of:

i. about 200 mg administered at a frequency of about once every 4 weeks (Q4W);
ii. about 400 mg administered at a frequency of about once every 4 weeks (Q4W);
iii. about 700 mg administered at a frequency of about once every 4 weeks (Q4W);
iv. about 800 mg administered at a frequency of about once every 4 weeks (Q4W);
v. about 200 mg administered at a frequency of about once every 8 weeks (Q8W);

vi. about 400 mg administered at a frequency of about once every 8 weeks (Q8W);

vii. about 800 mg administered at a frequency of about once every 8 weeks (Q8W);

viii. about 1500 mg administered at a frequency of about once every twelve weeks (Q12W); or

ix. about 2300 mg administered at a frequency of about once every twelve weeks (Q12W).

4. The method of any one of claims 1-3, wherein said step of administering comprises one of:

administering to the subject an intravenous dose of about 2300 mg of the anti-N3pG Aβ antibody at a frequency of about once every 12 weeks (Q12W) for a period of at least 24 weeks;

administering to the subject an intravenous dose of about 1500 mg of the anti-N3pG Aβ antibody at a frequency of about once every 12 weeks (Q12W) for a period of at least 36 weeks;

administering to the subject an intravenous dose of about 800 mg of the anti-N3pG Aβ antibody at a frequency of about once every 8 weeks (Q8W) for a period of at least 48 weeks;

administering to the subject an intravenous dose of about 400 mg of the anti-N3pG Aβ antibody at a frequency of about once every 4 weeks (Q4W) for a period of 8 weeks, followed by administering to the subject an intravenous dose of about 800 mg of the anti-N3pG Aβ antibody at a frequency of about once every 8 weeks (Q8W) for a period of at least 32 weeks; or

administering to the subject an intravenous dose of about 400 mg of the anti-N3pG Aβ antibody at a frequency of about once every 8 weeks (Q8W) for a period of 8 weeks, followed by administering to the subject an intravenous dose of about 800 mg of the anti-N3pG Aβ antibody at a frequency of about once every 8 weeks (Q8W) for a period of at least 32 weeks.

5. A method of reducing amyloid beta (Aβ) plaques in the brain of a human subject in need thereof, treating a disease characterized by deposition of Aβ plaques in the brain

of a human subject in need thereof, preventing a disease characterized by deposition of Aβ plaques in the brain of a human subject in need thereof, or delaying onset of a disease characterized by deposition of Aβ plaques in the brain of a human subject in need thereof comprising:

administering to the subject an intravenous dose of about 200 mg of an anti-N3pG Aβ antibody at a frequency of about once every 8 weeks (Q8W), wherein a dose of about 200 mg is administered at week 0 and week 8;

thereafter, administering to the subject an intravenous dose of about 400mg of the anti-N3pG Aβ antibody at a frequency of about once every 8 weeks (Q8W), wherein a dose of about 400 mg is administered at week 16 and week 24; and

thereafter, administering to the subject an intravenous dose of about 800 mg of the anti-N3pG Aβ antibody at a frequency of about once every 8 weeks (Q8W), wherein a dose of about 800 mg is administered at weeks 32, 40, 48, 56, 64 and 72,
wherein the anti-N3pGlu Aβ antibody comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 8 and a heavy chain variable region (HCVR), comprising the amino acid sequence of SEQ ID NO: 7.

6. A method of reducing amyloid beta (Aβ) plaques in the brain of a human subject in need thereof, treating a disease characterized by deposition of Aβ plaques in the brain of a human subject in need thereof, or preventing a disease characterized by deposition of Aβ plaques in the brain of a human subject in need thereof comprising:

administering to the subject one or more subcutaneous doses from about 100 mg to about 1000 mg of an anti-N3pG Aβ antibody at a frequency of about once every 2 weeks (Q2W), about once every four weeks (Q4W), about once every eight weeks (Q8W), about once every twelve weeks (Q12W), or a combination thereof,
wherein the anti-N3pGlu Aβ antibody comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 8 and a heavy chain variable region (HCVR), comprising the amino acid sequence of SEQ ID NO: 7.

7. The method of claim 6, wherein the one or more subcutaneous doses is selected from one of: about 100mg; about 200mg; about 400 mg; about 800 mg; or about 1000 mg.

8. The method of claim 5 or 6, wherein the one or more subcutaneous doses is selected from one of:

i. about 100 mg administered at a frequency of about once every 8 weeks (Q8W);
ii. about 100 mg administered at a frequency of about once every 12 weeks (Q12W);
iii. about 200 mg administered at a frequency of about once every 8 weeks (Q8W);
iv. about 200 mg administered at a frequency of about once every 12 weeks (Q12W);
v. about 200 mg administered at a frequency of about once every 16 weeks (Q16W);
vi. about 400 mg administered at a frequency of about once every week (Q1W);
vii. about 400 mg administered at a frequency of about once every 2 weeks (Q2W);
viii. about 400 mg administered at a frequency of about once every 4 weeks (Q4W);
ix. about 400 mg administered at a frequency of about once every 8 weeks (Q8W);
x. about 400 mg administered at a frequency of about once every 12 weeks (Q12W);
xi. about 400 mg administered at a frequency of about once every 16 weeks (Q16W);
xii. about 600 mg administered at a frequency of about once every 8 weeks (Q8W);
xiii. about 600 mg administered at a frequency of about once every 12 weeks (Q12W);
xiv. about 600 mg administered at a frequency of about once every 16 weeks (Q16W);
xv. about 800 mg administered at a frequency of about once every 2 weeks (Q2W);

xvi. about 800 mg administered at a frequency of about once every 4 weeks (Q4W);

xvii. about 800 mg administered at a frequency of about once every 8 weeks (Q8W); or

xviii. about 800 mg administered at a frequency of about once every 12 weeks (Q12W).

9. The method of any of claims 6-8, wherein said step of administering comprises one of:

administering to the subject a subcutaneous dose of about 400 mg of the anti-N3pG Aβ antibody at a frequency of about once every week (Q1W) for a period of at least 35 weeks;

administering to the subject a subcutaneous dose of about 800 mg of the anti-N3pG Aβ antibody at a frequency of about once every 4 weeks (Q4W) for a period of at least 48 weeks;

administering to the subject a subcutaneous dose of about 400 mg of the anti-N3pG Aβ antibody at a frequency of about once every 8 weeks (Q8W) for a period of at least 8 weeks, followed by administering to the subject a subcutaneous dose of about 800 mg of the anti-N3pG Aβ antibody, followed 8 weeks later by administering to the subject a subcutaneous dose of about 800 mg of the anti-N3pG Aβ antibody at a frequency of about once every 4 weeks (Q4W) for a period of at least weeks for a period of at least 24 weeks to about 48 weeks;

administering to the subject a subcutaneous dose of about 200 mg of the anti-N3pG Aβ antibody, followed 8 weeks later by administering to the subject a subcutaneous dose of about 400 mg of the anti-N3pG Aβ antibody at a frequency of about once every 8 weeks (Q8W) for a period of 8 weeks, followed by administering to the subject a subcutaneous dose of about 800 mg of the anti-N3pG Aβ antibody, followed 8 weeks later by administering to the subject a subcutaneous does of about 800 mg at a frequency of about once every 4 weeks (Q4W) for a period of at least 32 weeks to about 40 weeks; or

administering to the subject a subcutaneous dose of about 100 mg of the anti-N3pG Aβ antibody at a frequency of about once every 8 weeks (Q8W) for a period of 8

weeks, followed by administering to the subject a subcutaneous dose of about 400 mg of the anti-N3pG Aβ antibody at a frequency of about once every 8 weeks (Q8W) for a period of 8 weeks, followed by administering to the subject a subcutaneous dose of about 800 mg of the anti-N3pG Aβ antibody at a frequency of about once every 8 weeks (Q8W) for a period of 8 weeks, followed by administering to the subject a subcutaneous does of about 800 mg at a frequency of about once every 4 weeks (Q4W) for a period of at least 24 weeks to at about 28 weeks; or

administering to the subject a subcutaneous dose of about 400 mg of the anti-N3pG Aβ antibody at a frequency of about once every 12 weeks (Q12W) for a period of 12 weeks, followed by administering to the subject a subcutaneous dose of about 800 mg of the anti-N3pG Aβ antibody, followed 8 weeks later by administering to the subject a subcutaneous dose of about 800 mg of the anti-N3pG Aβ antibody at a frequency of about once every 4 weeks (Q4W) for a period of at least 32 weeks to about 40 weeks.

10. The method of any one of claims 1-9, wherein the human subject has one of MCI, preclinical AD, or early symptomatic Alzheimer's Disease.

11. The method of any one of claims 1-10, wherein the antibody is administered until the Aβ plaques in the brain of the human subject are 24.1 centiloids or lower as measured by an amyloid PET imaging scan.

12. The method of any one of claims 1-11, wherein the step of administration results in at least one of: (i.) reduction of Aβ plaques in the brain as determined by an amyloid PET imaging scan; (ii.) slowing of cognitive decline; or (iii.) slowing of functional decline.

13. The method of any one of claims 1-12, wherein the subject has at least one *APOE4* allele.

14. A method of preventing the progression of AD, delaying the onset of AD, or preventing the progression of Aβ pathology in a human subject in need thereof, comprising administering to the subject a subcutaneous dose of about 100 mg to about

800 mg of an anti-N3pG Aβ antibody at a frequency of about once every eight weeks (Q8W), about once every twelve weeks (Q12W), about once every twenty-six weeks (Q26W), or about once every fifty-two weeks (Q52W),
wherein the anti-N3pGlu Aβ antibody comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 8 and a heavy chain variable region (HCVR), comprising the amino acid sequence of SEQ ID NO: 7.

15. A method of preventing the progression of AD, delaying the onset of AD, or preventing the progression of Aβ pathology in a human subject in need thereof, comprising administering a subcutaneous dose of an anti-N3pG Aβ antibody to the subject at a dose and frequency of:

i. about 200 mg about once every twenty-six weeks (Q26W) over a period of up to 52 weeks;
ii. about 200 mg about once every fifty-two weeks (Q52W) over a period of up to 52 weeks;
iii. about 400 mg about once every twelve weeks (Q12W) over a period of up to a 72 weeks;
iv. about 400 mg about once every twenty-six weeks (Q26W) over a period of up to 52 weeks;
v. about 400 mg about once every fifty-two weeks (Q52W) over a period of up to 52 weeks;
vi. about 600 mg about once every twenty-six weeks (Q26W) over a period of up to 52 weeks;
vii. about 600 mg about once every fifty-two weeks (Q52W) over a period of up to 52 weeks;
viii. about 400 mg about once every twelve weeks (Q12W) for about 48 weeks, thereafter about 400 mg about once every eight weeks (Q8W);
ix. about 400 mg about once every twelve weeks (Q12W) for about 48 weeks, thereafter about 800 mg about once every twelve weeks (Q12W); or
x. about 400 mg about once every eight weeks (Q8W) for about 16 weeks, thereafter about 800 mg about once every eight weeks (Q8W) for about 16 weeks, thereafter about 800 mg about once every four weeks (Q4W),

wherein the anti-N3pGlu Aβ antibody comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 8 and a heavy chain variable region (HCVR), comprising the amino acid sequence of SEQ ID NO: 7.

16. The method of claim 14 or 15, wherein the human subject has a family history of AD, has a biomarker of AD pathology, has an APOe4 allele, is homozygous for APOe4, has a dominantly-inherited genetic profile for AD, or has been previously treated for AD with an anti-N3pG Aβ antibody.

17. The method of any one of claims 1-16, wherein the anti-N3pGlu Aβ antibody comprises a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 10 and a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 9.

18. The method of any one of claims 1-17, wherein the step of administration does not result in symptomatic amyloid-related imaging abnormality (ARIA) in the human subject.

19. The method of any one of claims 1-18, wherein following administration of one or more doses of the anti-N3pGlu Aβ antibody, the human subject experiences symptoms consistent with mild to moderate ARIA.

20. The method of claim 19 further comprising the step of administering a corticosteroid to the human subject.

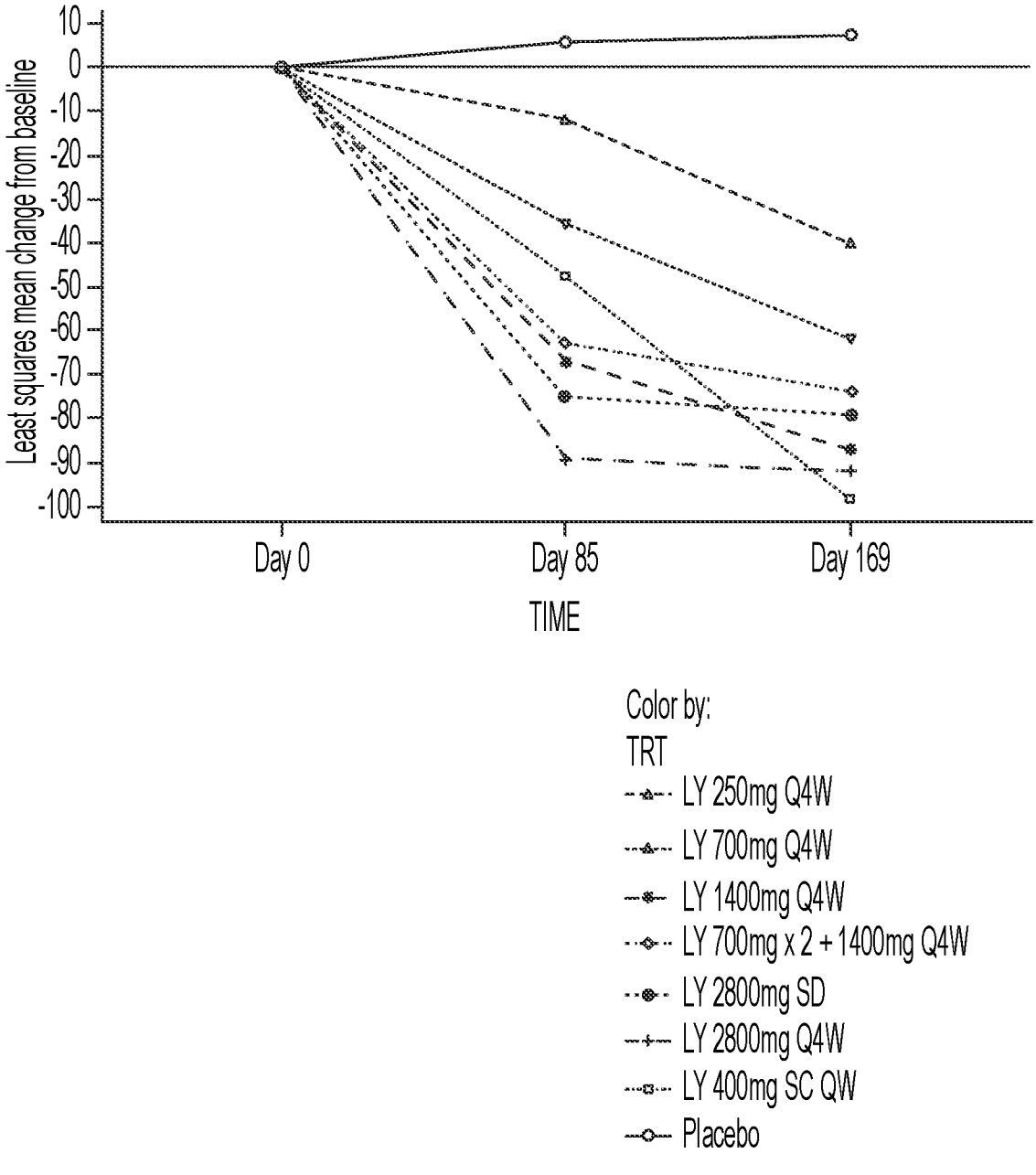
Least squares mean change from baseline
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
Day 0
Day 85
Day 169
TIME
Color by:
TRT
LY 250mg Q4W
LY 700mg Q4W
LY 1400mg Q4W
LY 700mg x 2 + 1400mg Q4W
LY 2800mg SD
LY 2800mg Q4W
LY 400mg SC QW
Placebo

FIG. 1

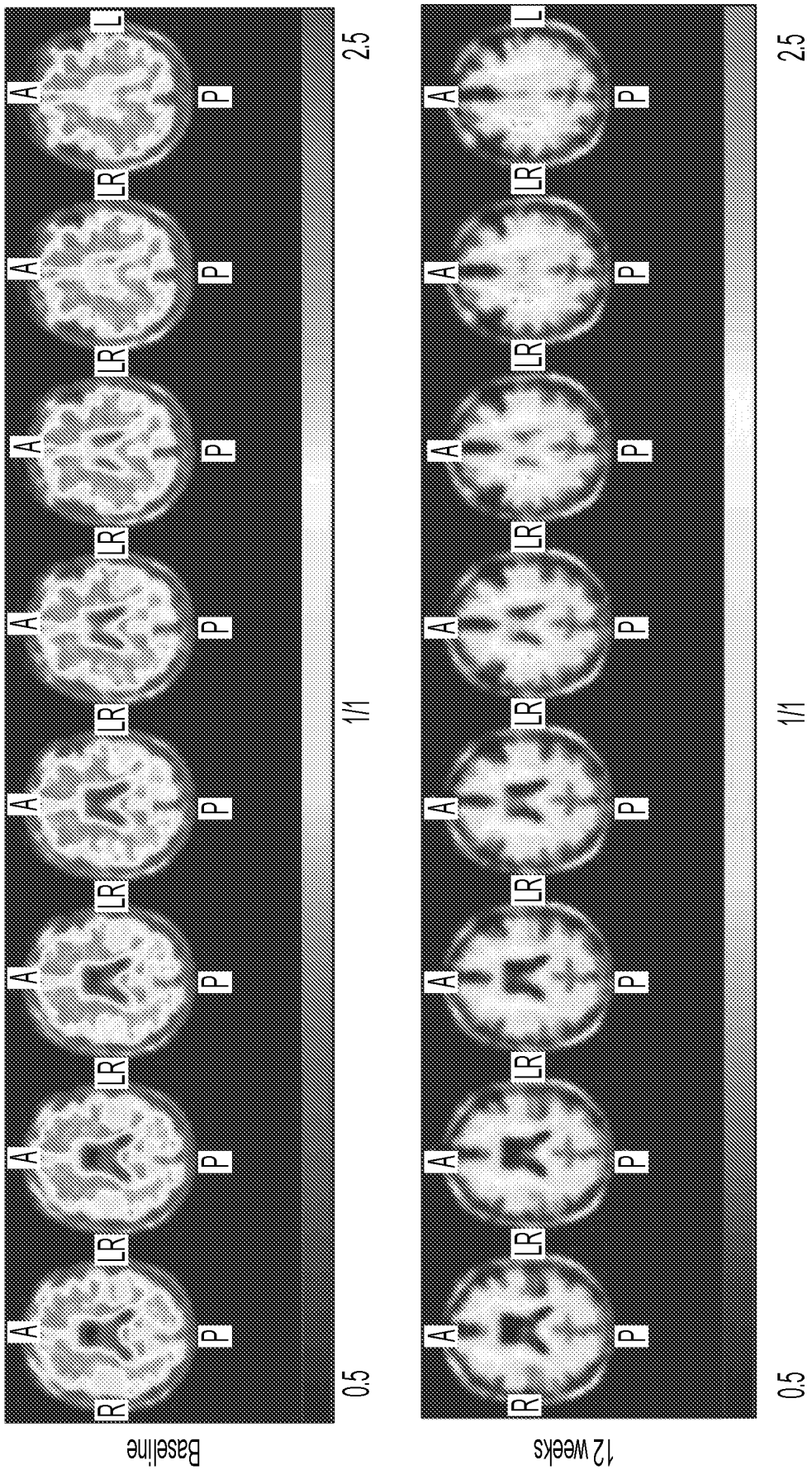

FIG. 2

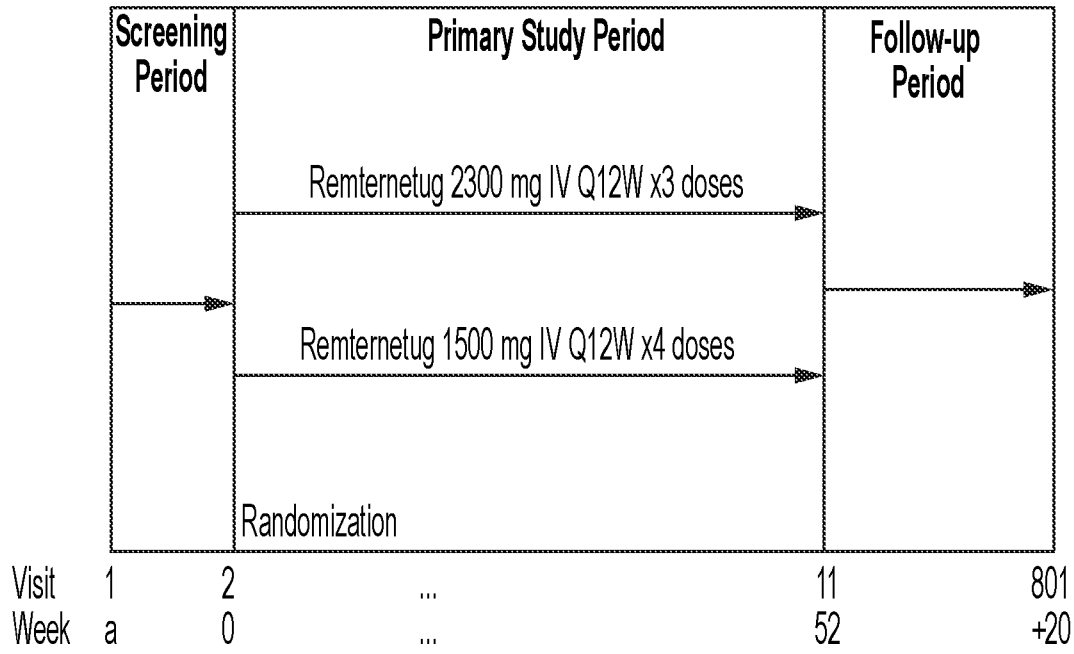
Screening Period
Primary Study Period
Follow-up Period
Remternetug 2300 mg IV Q12W x3 doses
Remternetug 1500 mg IV Q12W x4 doses
Randomization
Visit 1 2 ... 11 801
Week a 0 ... 52 +20

FIG. 3

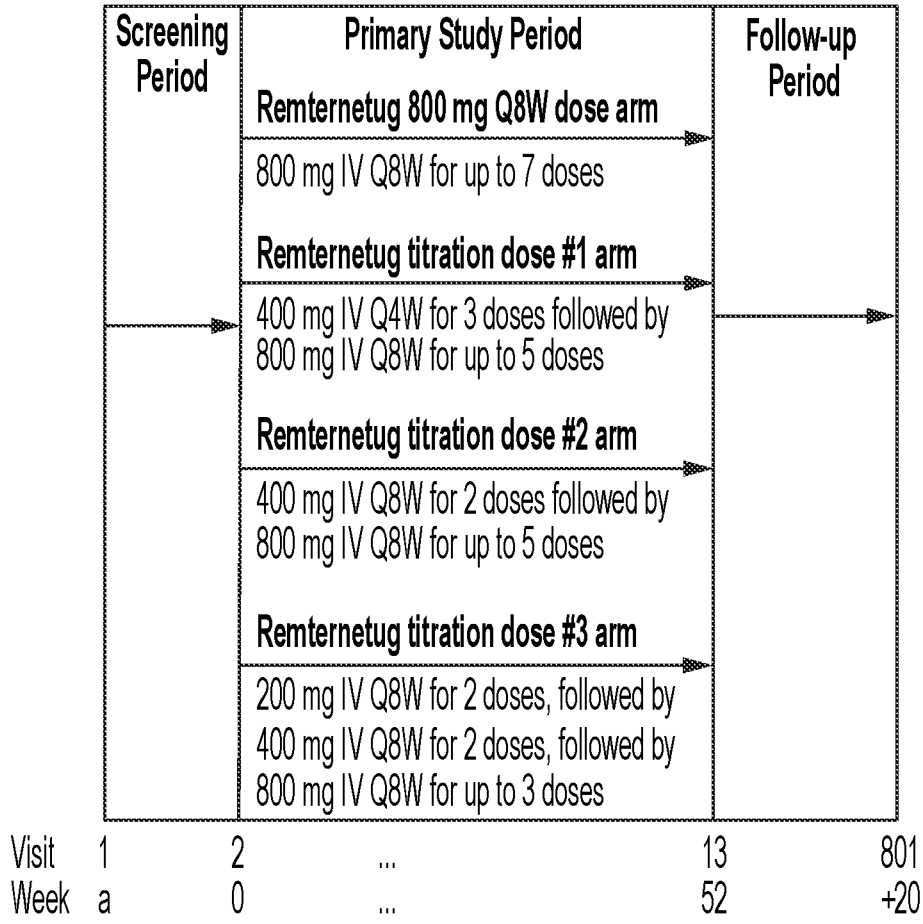
Screening Period
Primary Study Period
Remternetug 800 mg Q8W dose arm
800 mg IV Q8W for up to 7 doses
Remternetug titration dose #1 arm
400 mg IV Q4W for 3 doses followed by
800 mg IV Q8W for up to 5 doses
Remternetug titration dose #2 arm
400 mg IV Q8W for 2 doses followed by
800 mg IV Q8W for up to 5 doses
Remternetug titration dose #3 arm
200 mg IV Q8W for 2 doses, followed by
400 mg IV Q8W for 2 doses, followed by
800 mg IV Q8W for up to 3 doses
Follow-up Period
Visit 1 2 ... 13 801
Week a 0 ... 52 +20

FIG. 4

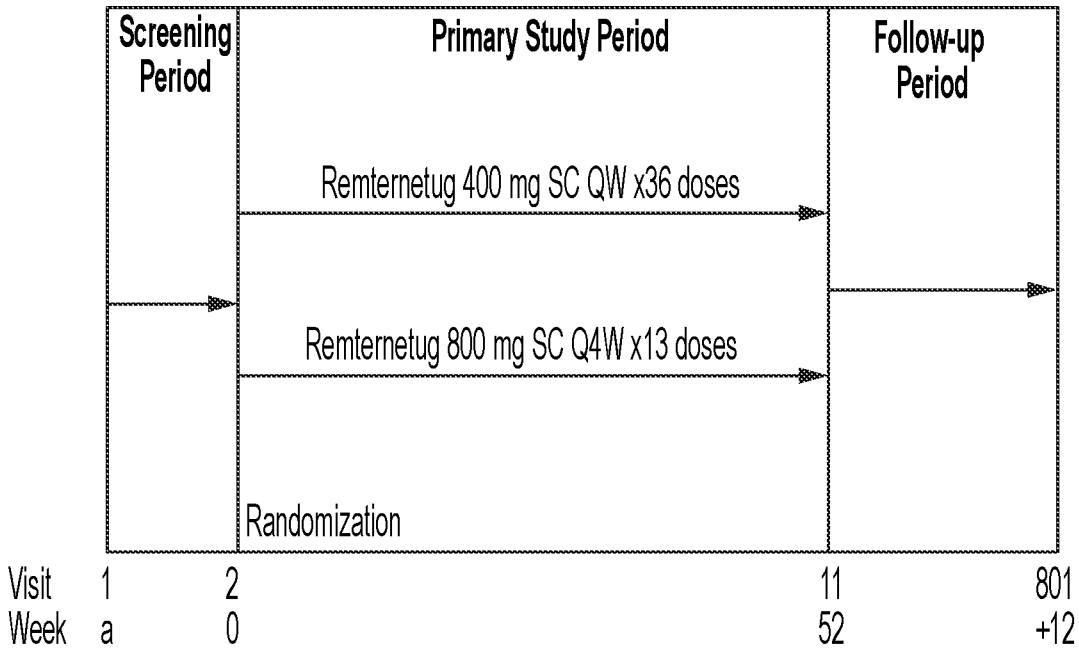
Screening Period
Primary Study Period
Follow-up Period
Remternetug 400 mg SC QW x36 doses
Remternetug 800 mg SC Q4W x13 doses
Randomization
Visit 1 2 11 801
Week a 0 52 +12

FIG. 5

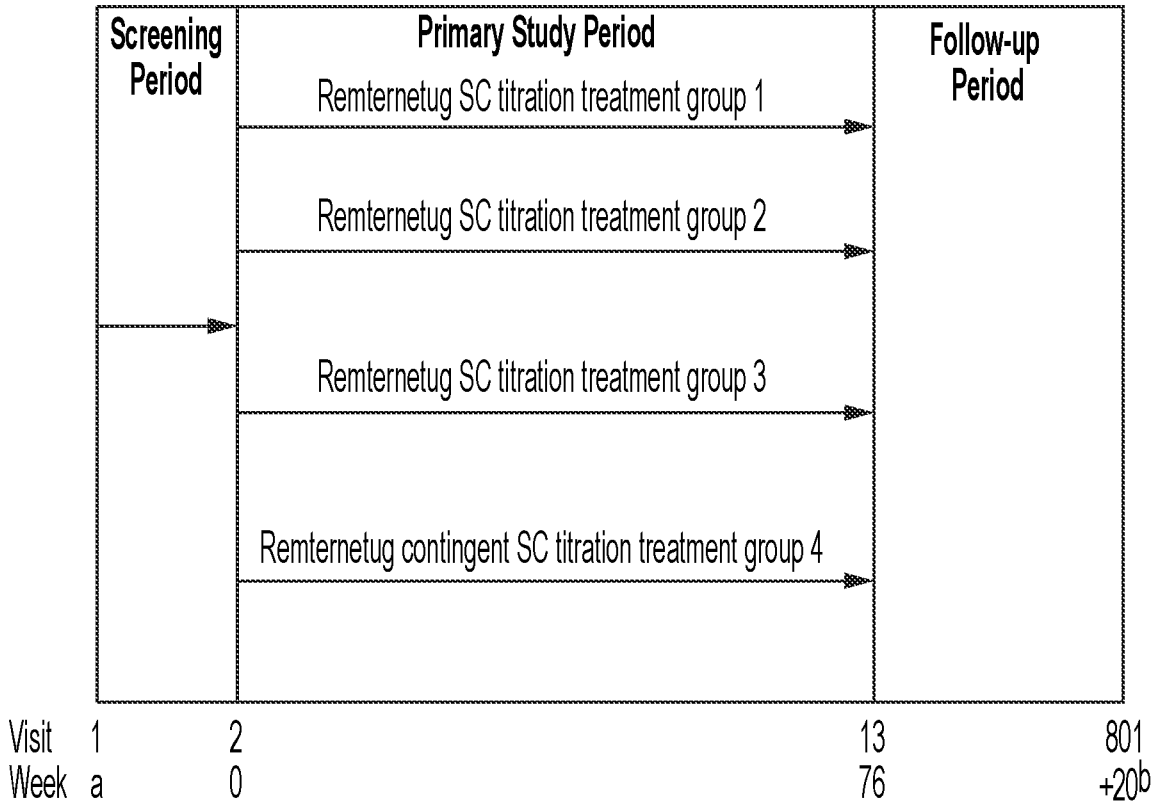
Screening Period
Primary Study Period
Follow-up Period
Remternetug SC titration treatment group 1
Remternetug SC titration treatment group 2
Remternetug SC titration treatment group 3
Remternetug contingent SC titration treatment group 4
Visit 1 2 13 801
Week a 0 76 +20b

FIG. 6

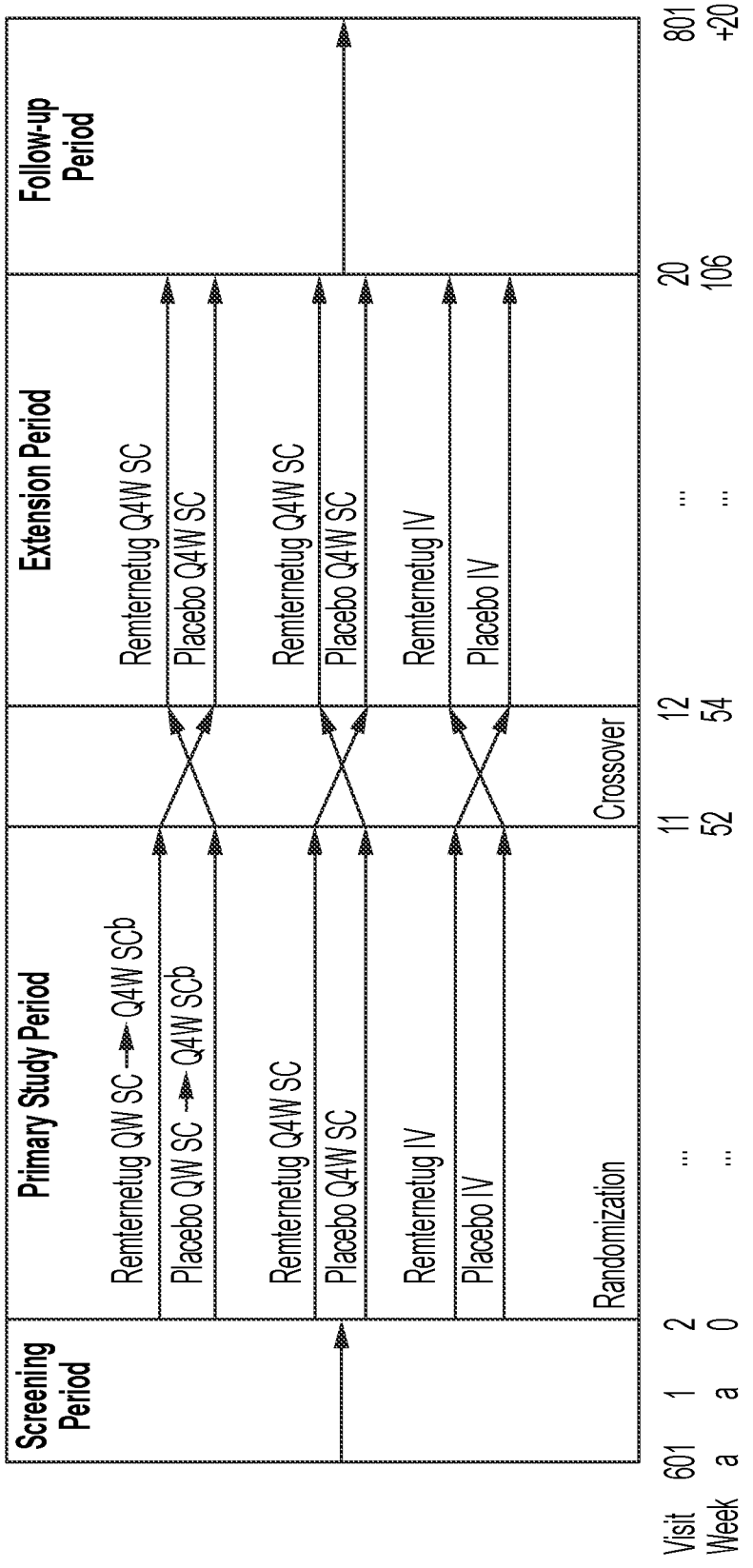
Screening Period
Primary Study Period
Extension Period
Follow-up Period
Remternetug QW SC → Q4W SCb
Placebo QW SC → Q4W SCb
Remternetug Q4W SC
Placebo Q4W SC
Remternetug IV
Placebo IV
Randomization
Crossover
Remternetug Q4W SC
Placebo Q4W SC
Remternetug Q4W SC
Placebo Q4W SC
Remternetug IV
Placebo IV
Visit 601 1 2 ... 11 12 ... 20 801
Week a a 0 ... 52 54 ... 106 +20

FIG. 7

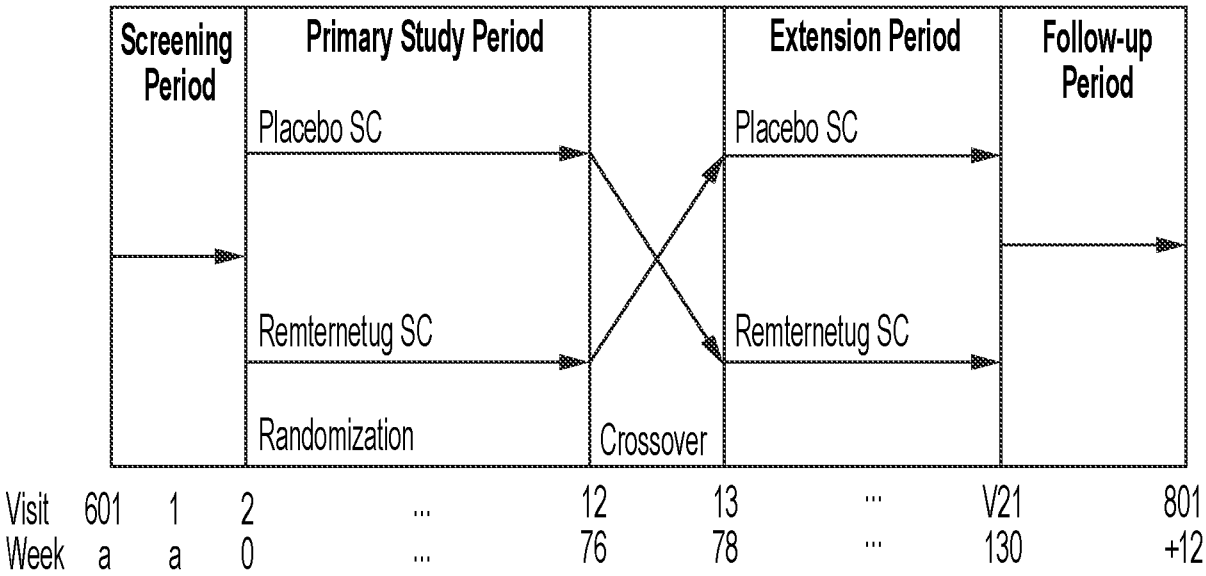
Screening Period
Primary Study Period
Placebo SC
Remternetug SC
Randomization
Crossover
Extension Period
Placebo SC
Remternetug SC
Follow-up Period
Visit 601 1 2 ... 12 13 ... V21 801
Week a a 0 ... 76 78 ... 130 +12

FIG. 8

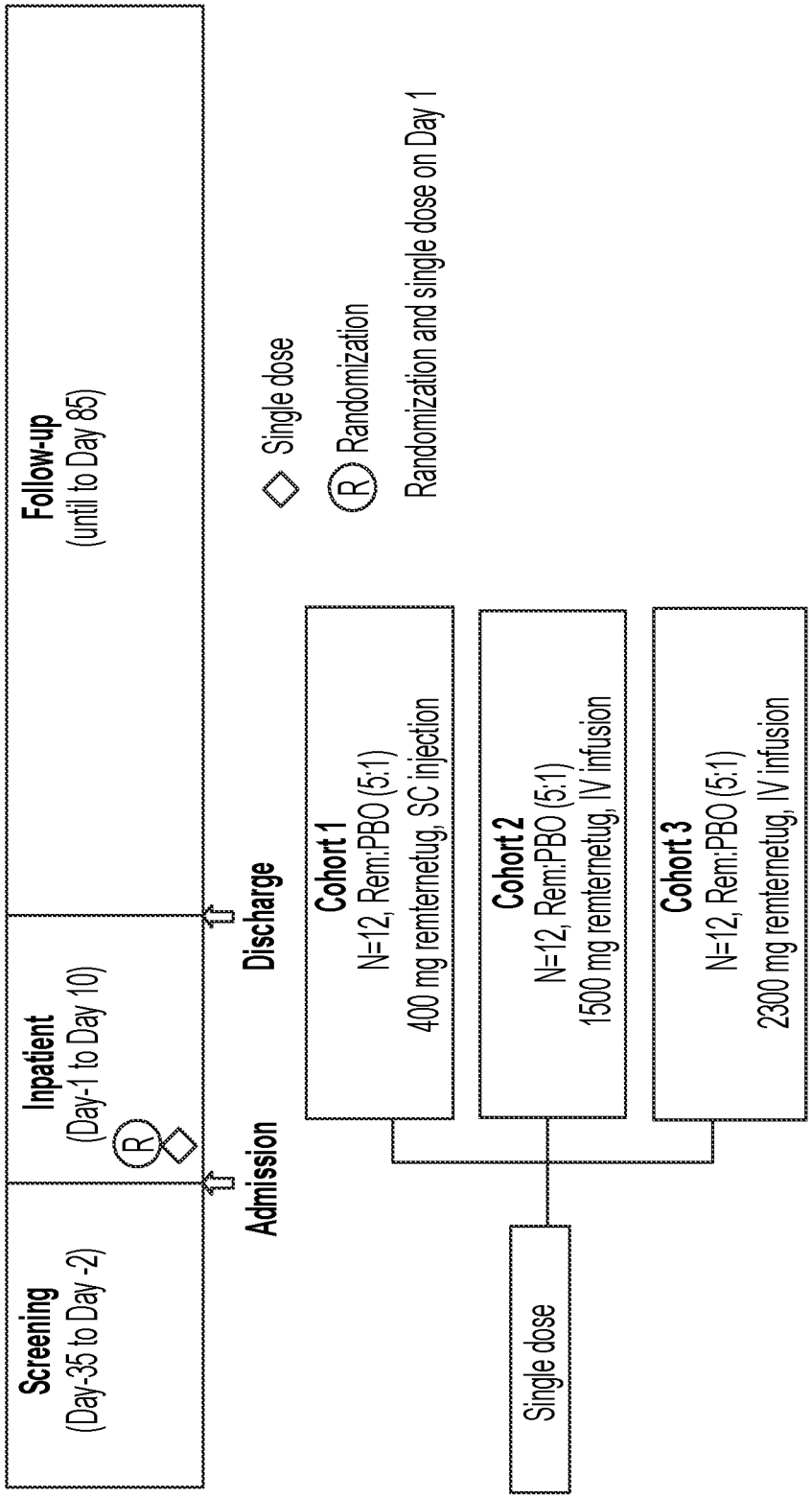
Screening
(Day-35 to Day -2)
Inpatient
(Day-1 to Day 10)
Follow-up
(until to Day 85)
Admission
Discharge
Single dose
Randomization
Randomization and single dose on Day 1
Cohort 1
N=12, Rem:PBO (5:1)
400 mg remternetug, SC injection
Cohort 2
N=12, Rem:PBO (5:1)
1500 mg remternetug, IV infusion
Cohort 3
N=12, Rem:PBO (5:1)
2300 mg remternetug, IV infusion
Single dose

FIG. 9

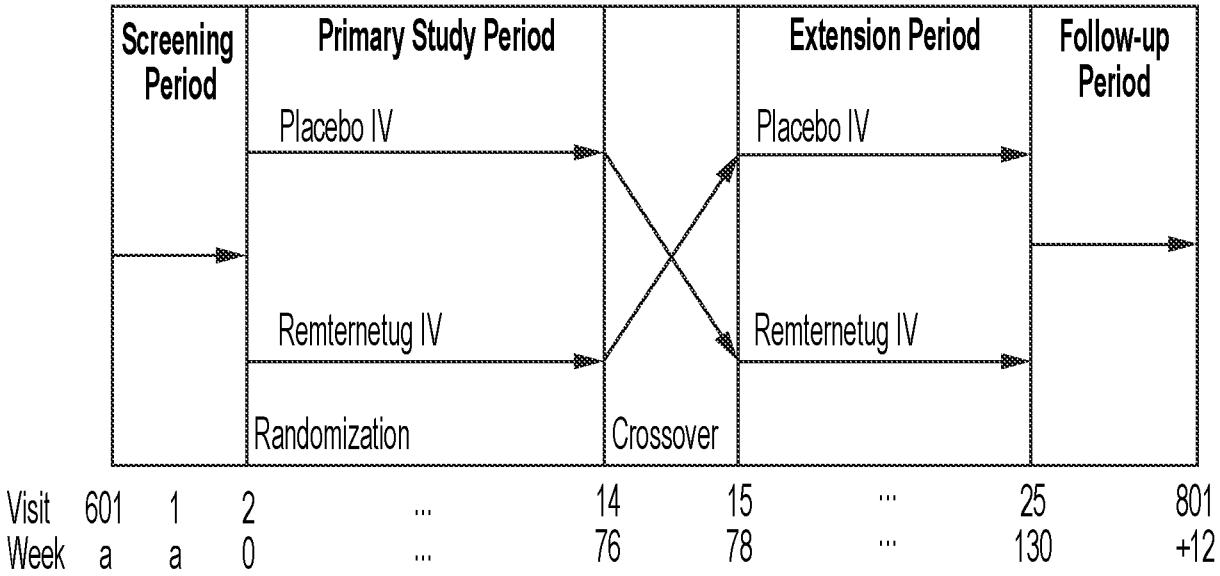
Screening Period
Primary Study Period
Extension Period
Follow-up Period
Placebo IV
Placebo IV
Remternetug IV
Remternetug IV
Randomization
Crossover
Visit 601 1 2 ... 14 15 ... 25 801
Week a a 0 ... 76 78 ... 130 +12

FIG. 10

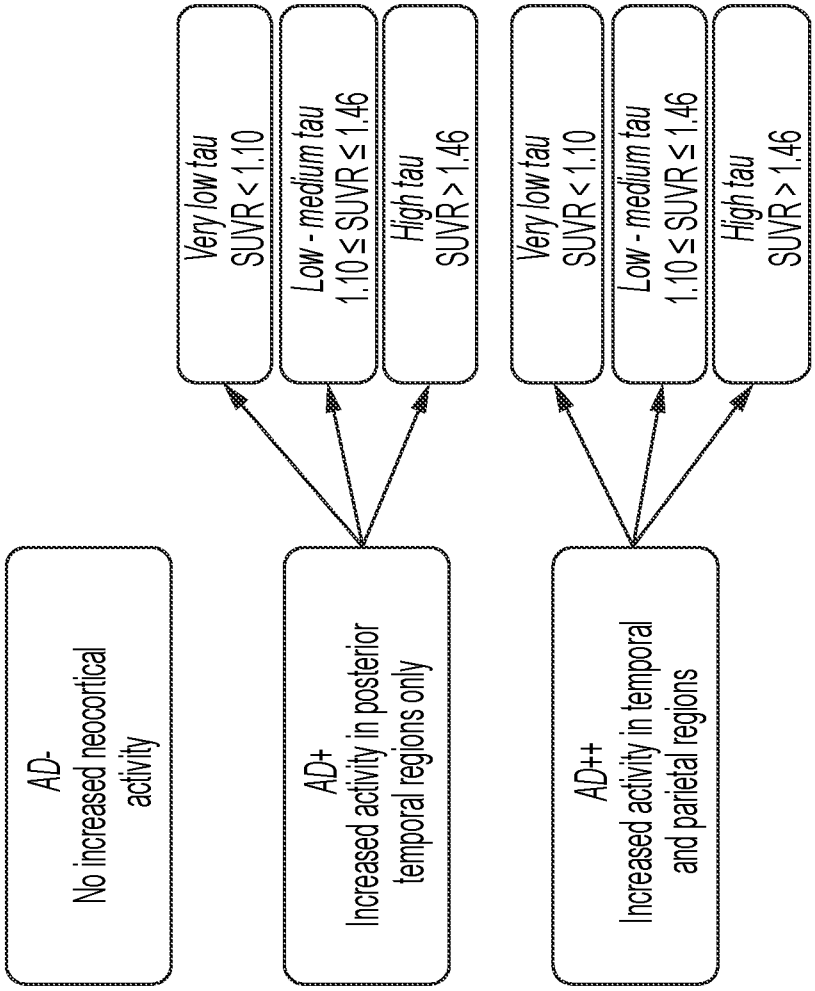
AD-
No increased neocortical activity
AD+
Increased activity in posterior temporal regions only
AD++
Increased activity in temporal and parietal regions
Very low tau
SUVR < 1.10
Low - medium tau
1.10 ≤ SUVR ≤ 1.46
High tau
SUVR > 1.46
Very low tau
SUVR < 1.10
Low - medium tau
1.10 ≤ SUVR ≤ 1.46
High tau
SUVR > 1.46

FIG. 11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/079578

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***A61P 25/28*** (2024.01); *A61K 39/395* (2024.01); *C07K 16/18* (2024.01); *C07K 16/46* (2024.01); *C12N 15/13* (2024.01)

CPC: ***A61P 25/28; C07K 16/18;*** *C07K 2317/56; A61K 2039/545*

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2022/150735 A1 (ELI LILLY AND COMPANY) 14 July 2022 (14.07.2022) entire document	1-3, 6-8, 14-16
Y	US 2018/0305444 A1 (ELI LILLY AND COMPANY) 25 October 2018 (25.10.2018) entire document	1-3, 6-8, 14-16
A	US 2021/0032315 A1 (VIVORYON THERAPEUTICS AG) 04 February 2021 (04.02.2021) entire document	1-3, 5-8, 14-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 January 2024 (31.01.2024)	**13 February 2024 (13.02.2024)**

Name and mailing address of the ISA/US	Authorized officer
Mail Stop PCT, Attn: ISA/US **Commissioner for Patents** **P.O. Box 1450, Alexandria, VA 22313-1450**	**MATOS** **TAINA**
Facsimile No. **571-273-8300**	Telephone No. **571-272-4300**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/079578

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
   a. ☑ forming part of the international application as filed.
   b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)),
      ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/079578

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☑ Claims Nos.: **4, 9-13, 17-20**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).