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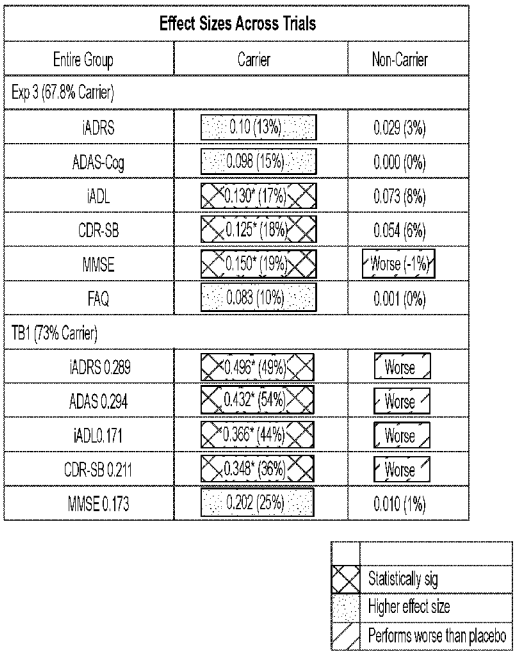

FIG. 1

(57) Abstract: The present disclosure is directed to treatment or prevention of a disease characterized by deposition of Aβ in the brain using anti-Aβ antibodies. The diseases that can be treated or prevented include, e.g., Alzheimer's disease, Down's syndrome, and cerebral amyloid angiopathy. The invention, in some aspects, is related to doses and dosing regimens useful for such treatments. The invention is also related to, in some aspects, human subjects who are responsive to treatment or prevention of a disease characterized by Aβ in the brain using anti-Aβ antibodies. The invention is also related to patients who have one or more alleles of APOE e4.

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ANTI-AMYLOID BETA ANTIBODIES AND USES THEREOF

The present disclosure is related to methods of preventing or treating a disease with anti-amyloid beta antibodies, wherein the disease is characterized by deposition of amyloid beta (Aβ) in a human subject. The present disclosure is also related to doses and dosing regimens of the anti-Aβ antibodies useful for treating or preventing a disease characterized by deposition of Aβ. Some aspects of the present disclosure are related to treating or preventing a disease characterized by deposition of Aβ in human subjects, wherein the human subjects are selected, and/or treated with the antibodies of the present disclosure, based on the presence of one or two alleles of APOE ε4 in the subject's genome. 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). In some embodiments, the present disclosure is related to slowing cognitive decline, functional decline, and/or memory loss in the subject. In some embodiments, the present disclosure is related to reducing amyloid load in the brain of the human subject.

BACKGROUND

A cure for AD is one of the most significant unmet needs of society. Accumulation of amyloid-β (Aβ) peptide in the form of brain amyloid deposits/plaques is an early and essential event in Alzheimer's disease (AD) leading to neurodegeneration and consequently the onset of clinical symptoms, such as, cognitive and functional impairment (Selkoe, "The Origins of Alzheimer Disease: A is for Amyloid," *JAMA* 283:1615-7 (2000); Hardy *et al.*, "The Amyloid Hypothesis of Alzheimer's Disease: Progress and Problems on the Road to Therapeutics," *Science* 297:353-6 (2002); Masters *et al.*, "Alzheimer's Disease," *Nat. Rev. Dis. Primers* 1:15056 (2015); and Selkoe *et al.*, "The Amyloid Hypothesis of Alzheimer's Disease at 25 years," *EMBO Mol. Med.* 8:595-608 (2016)).

Amyloid beta (Aβ) 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 several 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, insoluble, and can further aggregate to form amyloid deposits or plaques. The amyloid deposits 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).

The role for amyloid deposits 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, the presence of amyloid deposits 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)). Interventions or therapies aiming at removal of Aβ deposits (including amyloid plaques) are hypothesized to slow the clinical progression of AD.

Antibodies targeting amyloid are known, including, e.g., bapineuzumab, gantenerumab, aducanumab, GSK933776, solanezumab, crenezumab, ponezumab, and lecanemab (BAN2401). Some antibodies targeting amyloid have shown promise as a therapeutic for Alzheimer's disease in preclinical studies. Despite this promise, most antibodies targeting amyloid have failed to meet therapeutic endpoints in multiple clinical trials. For example, solanezumab, an anti-Aβ, has been studied in multiple Phase 3 clinical trials but did not meet its clinical endpoint. *See* Honig, *et al.*, "Trial of Solanezumab for Mild Dementia Due to Alzheimer's Disease," *New England Journal of Medicine*, vol 78, No. 4, pp. 321-300 (2018) (which is hereby incorporated by reference in its entirety). This article cites other Phase 3 trials of solanezumab that also failed to meet their clinical endpoints. Additional information about trials of solanezumab are published as Doody, *et al.*, "Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease", *New England Journal of Medicine*, 370; 4, pp. 311-321 (2014) (which is hereby incorporated by reference in its entirety). 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.*, *The Journal of Prevention of Alzheimer's Disease* 4.4:255 (2017) and Klein, *et al.*, *Alzheimer's Research & Therapy* 11.1:101 (2019)).

Additionally, significant problems exist with long term chronic administration of Aβ antibodies. 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 hemosiderin 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).

Although the exact cause of such adverse events is not known, it is believed that antibody treatment disrupts blood-brain barrier through interaction with the cerebral vascular amyloid and that this disruption leads to leaky barrier and the manifestation of edema in patients. Several mechanisms of action have been postulated, *e.g.*, that removal of amyloid from the vessel wall destabilizes the neurovascular unit, localized inflammation/infiltrates in the neurovascular unit, increased levels of cerebral vascular amyloid due to higher levels of interstitial soluble Aβ in response to parenchymal plaque clearance or altered localization of AQP-4 in astrocytic end feet projections in the neurovascular unit. Additionally, several therapeutic amyloid targeting 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 APOE ε4).

To decrease the rate of ARIA-E adverse event while maintaining plaque clearance, some antibody treatment programs implement dose-titration schemes that include multiple dose escalations (3-4 steps) over a period of about 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.

Furthermore, one of the challenges in treating Alzheimer's disease is that it is still principally diagnosed and treated based on symptoms, *e.g.*, like a psychiatric illness, rather than based on brain pathology. This causes clinical trials to include heterogenous populations (*e.g.*, with wide variation in levels of underlying pathology and/or different underlying diseases) which makes replicating clinical trial data very challenging. As such, determining whether subjects having Aβ deposits may respond to an anti-Aβ antibody treatment is uniquely challenging and the task of properly identifying whether a patient may respond to anti-Aβ antibody treatments is of utmost importance for, *e.g.*, a timely referral to a memory clinic, a correct and early AD diagnosis, initiation of symptomatic treatment, future planning, and initiating disease-modifying treatments.

Thus, a need exists for improved doses, dosing regimens, or methods that effectively treat/prevent AD and other forms of dementia, CAA and/or Down's syndrome patients with anti-amyloid beta antibodies without causing or increasing problematic adverse events such as ARIA and ARIA-E. Additionally, a need exists for improved methods that properly identify whether a subject is going to respond to amyloid targeting therapeutics.

BRIEF DESCRIPTION OF DRAWINGS

"Fig." denotes Figure.

Fig. 1 shows a table describing the effect size for APOE ε4 carrier vs. non-carrier across Expedition-3 and Trailblazer-1 Clinical Trials. Abbreviations: Statistically sig = Statistically significant ($p<0.05$) Worse = performed worse than placebo; iADRS =

Integrated Alzheimer's Disease (AD) Rating Scale; ADAS-Cog = Alzheimer's Disease Assessment Scale cognitive subscale; iADL = instrumental Activities of Daily Living; CDR-SB = Clinical Dementia Rating scale - sum of boxes; MMSE = Mini-Mental State Exam; ADAS = Alzheimer's Disease Assessment Scale; FAQ = Function Activities Questions.

Fig. 2 shows the effect size for APOE ε4 carrier vs. non-carrier. Effect sizes of Mild AD in Sola (not amyloid selected). Abbreviations: Statistically sig = Statistically significant; Worse = performed worse than placebo; NA = Not available; ADAS-Cog-14 = 14-item Alzheimer's Disease Assessment Scale – Cognitive subscale; MMSE = Mini-Mental State Exam; CDR-SB = Clinical Dementia Rating scale - sum of boxes; ADL = Activities of Daily Living.

Fig. 3 shows change in cognition ADAS-Cog14 (primary endpoint) from the Expedition-3 clinical trial of solanezumab initiated in patients with mild AD dementia. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; ADAS-Cog14=AD Assessment Scale-Cognitive 14-item Subscale; LS=least squares; n=number; SE=Standard Error.

Fig. 4A shows change in cognition ADAS-Cog14 by APOE ε4 status from the Expedition-3 clinical trial of solanezumab initiated in patients with mild AD dementia, patients that are carriers of APOE ε4. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. The APOE ε4 carrier status-by-treatment interaction showed a p-value = 0.157. Abbreviations: AD=Alzheimer's disease; ADAS-Cog14=AD Assessment Scale-Cognitive 14-item Subscale; LS=least squares; n=number; SE=Standard Error; APOE = Apolipoprotein E.

Fig. 4B shows change in cognition ADAS-Cog14 by APOE ε4 status from Expedition-3 Clinical Trial of Solanezumab initiated in patients with mild AD dementia, patients that are not carriers of APOE ε4. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. The APOE ε4 carrier status-by-treatment interaction showed a p-value = 0.157. Abbreviations: AD=Alzheimer's disease; ADAS-Cog14=AD Assessment Scale-Cognitive 14-item Subscale; LS=least squares; n=number; SE=Standard Error; APOE = Apolipoprotein E.

Fig. 5A shows change in cognition ADAS-Cog14 by APOE ε4 Status. Pooled Expedition-1 and Expedition-2 Clinical Trial patients with Solanezumab in Mild AD Dementia, APOE ε4 carriers. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; ADAS-Cog14=AD Assessment Scale-Cognitive 14-item Subscale; LS=least squares; n=number; SE=Standard Error; APOE = apolipoprotein E.

Fig. 5B shows change in cognition ADAS-Cog14 by APOE ε4 status. This data related to pooled Expedition-1 and Expedition-2 clinical trial patients with solanezumab in mild AD dementia, APOE ε4 non-carriers. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; ADAS-Cog14=AD Assessment Scale-Cognitive 14-item Subscale; LS=least squares; n=number; SE=Standard Error; APOE = apolipoprotein E.

Fig. 6 shows change in complex ADLs - ADCS-iADL in Expedition-3 clinical trial of solanezumab initiated in patients with mild AD dementia. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; ADL=Activities of Daily Living; ADCS-iADL=AD Cooperative Study-Instrumental Activities of Daily Living; LS=least squares; n=number; SE=Standard Error.

Fig. 7A shows change in ADLs - ADCS-iADL by APOE ε4 status in Expedition-3 clinical trial of solanezumab initiated in patients with mild AD dementia, APOE ε4 carriers. The APOE ε4 carrier status-by-treatment interaction displayed a p-value = 0.878. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; ADCS-iADL=AD Cooperative Study-Instrumental Activities of Daily Living; LS=least squares; n=number; APOE=apolipoprotein E; SE=Standard Error.

Fig. 7B shows change in ADLs - ADCS-iADL by APOE ε4 status in Expedition-3 clinical trial of solanezumab initiated in patients with mild AD dementia, APOE ε4 non-carriers. The APOE ε4 carrier status-by-treatment interaction displayed a p-value = 0.878. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; ADCS-

iADL=AD Cooperative Study-Instrumental Activities of Daily Living; LS=least squares; n=number; APOE=apolipoprotein E; SE=Standard Error.

Fig. 8A shows change in ADCS-iADLs by APOE ε4 status in pooled Expedition-1 and Expedition-2 clinical trial patients with solanezumab in mild AD dementia, APOE ε4 carriers. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; ADCS-iADL=AD Cooperative Study-Instrumental Activities of Daily Living; LS=least squares; SE=Standard Error; n=number.

Fig. 8B shows change in ADCS-iADLs by APOE ε4 status in pooled Expedition-1 and Expedition-2 clinical trial patients with solanezumab in mild AD dementia, APOE ε4 non-carriers. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; ADCS-iADL=AD Cooperative Study-Instrumental Activities of Daily Living; LS=least squares; SE=Standard Error; n=number.

Fig. 9 shows change in cognition-MMSE in Expedition-3 clinical trial of solanezumab initiated in patients with mild AD dementia. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; LS=least squares; MMSE=Mini–Mental State Examination; n=number; SE=Standard Error.

Fig. 10A shows change in cognition-MMSE by APOE ε4 status in Expedition-3 clinical trial of solanezumab initiated in patients with mild AD dementia, APOE ε4 carriers. The APOE ε4 carrier status-by- treatment interaction displayed a p-value of 0.201. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; MMSE=Mini–Mental State Examination; LS=least squares; n=number; APOE=apolipoprotein E; SE=Standard Error.

Fig. 10B shows change in cognition-MMSE by APOE ε4 status in Expedition-3 clinical trial of solanezumab initiated in patients with mild AD dementia, APOE ε4 non-carriers. The APOE ε4 carrier status-by-treatment interaction displayed a p-value of 0.201. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; MMSE=Mini–Mental

State Examination; LS=least squares; n=number; APOE=apolipoprotein E; SE=Standard Error.

Fig. 11 shows change in composite scale CDR-SB in Expedition-3 clinical trial of solanezumab initiated in patients with mild AD dementia. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; CDR-SB=Clinical Dementia Rating Sum of Boxes; LS=least squares; n=number; SE=Standard Error.

Fig. 12A shows change in composite scale CDR-SB by APOE ε4 status in Expedition-3 clinical trial of solanezumab initiated in patients with mild AD dementia, APOE ε4 carriers. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; CDR-SB=Clinical Dementia Rating Sum of Boxes; LS=least squares; n=number; SE=Standard Error; APOE/Apoe = apolipoprotein.

Fig. 12B shows change in composite scale CDR-SB by APOE ε4 status in Expedition-3 clinical trial of solanezumab initiated in patients with mild AD dementia, APOE ε4 non-carriers. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; CDR-SB=Clinical Dementia Rating Sum of Boxes; LS=least squares; n=number; SE=Standard Error; APOE/Apoe = apolipoprotein.

Fig. 13 shows change in ADCS-ADL in Expedition-3 clinical trial of solanezumab initiated in patients with mild AD dementia. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; ADL=Activities of Daily Living; ADCS-ADL=AD Cooperative Study-Activities of Daily Living; LS=least squares; n=number; SE=Standard Error.

Fig. 14A shows change in ADCS-ADL by APOE ε4 status in Expedition-3 clinical trial of solanezumab initiated in patients with mild AD dementia, APOE ε4 carriers. The APOE ε4 carrier status-by-treatment interaction displayed a p-value of 0.714. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; ADCS-iADL=AD Cooperative Study-Instrumental Activities of Daily Living; LS=least squares; n=number; APOE=apolipoprotein E; SE=Standard Error.

Fig. 14B shows change in ADCS-ADL by APOE ε4 status in Expedition-3 clinical trial of solanezumab initiated in patients with mild AD dementia, APOE ε4 non-carriers. The APOE ε4 carrier status-by-treatment interaction displayed a p-value of 0.714. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; ADCS-iADL=AD Cooperative Study-Instrumental Activities of Daily Living; LS=least squares; n=number; APOE=apolipoprotein E; SE=Standard Error.

Fig. 15 shows change in composite scale: iADRS in Expedition-3 clinical trial of solanezumab initiated in patients with mild AD dementia. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; iADRS=Integrated AD Rating Scale; LS=least squares; n=number; SE=Standard Error.

Fig. 16 shows change in cognition and ADLs at 80 weeks in Expedition-3 clinical trial of Solanezumab initiated in patients with mild AD dementia. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; ADL=Activities of Daily Living; ADAS-Cog14=AD Assessment Scale-Cognitive 14-item Subscale; ADCS-ADL=AD Cooperative Study-Activities of Daily Living; CDR-SB=Clinical Dementia Rating Sum of Boxes; FAQ= Function Activities Questionnaire; iADRS=Integrated AD Rating Scale; LS=least squares; n=number of patients with evaluable 80-Week scale data; N/A=not applicable; MMSE=Mini–Mental State Examination; SE=standard error.

Fig. 17 shows baseline demographics pooled from Expedition-1 and Expedition-2 clinical trials of Solanezumab in mild AD dementia. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: * = Based on number of patients with available APOE status (placebo N=614; solanezumab N=595); AD=Alzheimer's disease; n=number; SD=standard deviation; APOE=Apolipoprotein E.

Fig. 18 shows baseline clinical characteristics of Expedition-3 clinical trial of solanezumab initiated in mild AD dementia. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AChEI=acetylcholinesterase inhibitor; ADCS-ADL=AD Cooperative Study-Activities of Daily Living; ADAS-Cog14=AD Assessment Scale-Cognitive 14-item Subscale; CDR-

SB=Clinical Dementia Rating Sum of Boxes; FAQ= Function Activities Questionnaire; MMSE=Mini–Mental State Examination; n=number; NA=not available from topline results.

Fig. 19 shows baseline clinical characteristics pooled from Expedition-1 and Expedition-2 clinical trials of solanezumab in mild AD dementia. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; AChEI=acetylcholinesterase inhibitor; ADCS-ADL=AD Cooperative Study-Activities of Daily Living; ADAS-Cog14=AD Assessment Scale-Cognitive 14-item Subscale; CDR-SB=Clinical Dementia Rating Sum of Boxes; FAQ= Function Activities Questionnaire; n=number; MMSE=Mini–Mental State Examination; N/A=not applicable; SD=standard deviation.

Fig. 20A shows change in complex ADLs: ADCS-iADL from Expedition-1 clinical Trial. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; ADL=Activities of Daily Living; ADCS-iADL=AD Cooperative Study-Instrumental Activities of Daily Living; LS=least squares; n=number; SE=Standard Error.

Fig. 20B shows change in complex ADLs: ADCS-iADL from Expedition-2 clinical trial. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; ADL=Activities of Daily Living; ADCS-iADL=AD Cooperative Study-Instrumental Activities of Daily Living; LS=least squares; n=number; SE=Standard Error.

Fig. 20C shows change in complex ADLs: ADCS-iADL pooled from Expedition-1 and Expedition-2 clinical trials. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; ADL=Activities of Daily Living; ADCS-iADL=AD Cooperative Study-Instrumental Activities of Daily Living; LS=least squares; n=number; SE=Standard Error.

Fig. 20D shows change in complex ADLs: ADCS-iADL from Expedition-3 clinical trial. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; ADL=Activities of Daily Living; ADCS-iADL=AD Cooperative Study-Instrumental Activities of Daily Living; LS=least squares; n=number; SE=Standard Error.

Fig. 21A shows change in cognition: ADAS-Cog14 from Expedition-1 clinical trial. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; ADAS-Cog14=AD Assessment Scale-Cognitive 14-item Subscale; LS=least squares; n=number; SE=Standard Error.

Fig. 21B shows change in cognition: ADAS-Cog14 from Expedition-2 clinical trial. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; ADAS-Cog14=AD Assessment Scale-Cognitive 14-item Subscale; LS=least squares; n=number; SE=Standard Error.

Fig. 21C shows change in cognition: ADAS-Cog14 pooled from Expedition-1 and -2 clinical trials. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; ADAS-Cog14=AD Assessment Scale-Cognitive 14-item Subscale; LS=least squares; n=number; SE=Standard Error.

Fig. 21D shows change in cognition: ADAS-Cog14 pooled from Expedition-3 clinical trials. Patients could continue stable standard of care for AD, including drug and non-drug treatments, throughout the study. Abbreviations: AD=Alzheimer's disease; ADAS-Cog14=AD Assessment Scale-Cognitive 14-item Subscale; LS=least squares; n=number; SE=Standard Error.

DETAILED DESCRIPTION

One aspect of the present disclosure provides for doses and dosing regimens of solanezumab circumventing problematic adverse events, such as ARIA with vasogenic edema, which have been observed in patients receiving therapeutic antibodies that bind to deposited amyloid and has been dose limiting for clinical development programs. Additionally, aspects of the present disclosure provide improved methods for identifying patients for treatment of AD and other forms of dementia, CAA and/or Down's syndrome patients with anti-amyloid beta antibodies.

Doody et al., *New England Journal of Medicine*, 370; 4, pp. 311-321 (2014) (which is hereby incorporated by reference in its entirety) indicates that "[n]o clear differential treatment effects on efficacy measures were observed between APOE ε4 carriers and

noncarriers" in the Expedition-1 study. However surprisingly, it has now been found that administering solanezumab to a human subject that has one or two alleles of APOE ε4 (*e.g.*, a carrier of APOE ε4) provides unexpected and surprising efficacy when compared to non-carriers of one or more of those alleles. Thus, the present disclosure involves administering doses of solanezumab or other anti-Aβ antibodies to patients who have one or two alleles of APOE ε4 as a means of treating patients with AD, preventing AD, and/or slowing cognitive/functional decline in patients.

Specifically, it has been found that there is a greater effect in carriers of APOE ε4 than in non-carriers when the patients are administered anti-Aβ antibodies. This means that the patients that have APOE ε4 have less cognitive decline than non-carriers, when measured using various clinical measurements and at various endpoints. In fact, as shown herein, the data from Expedition-1 and Expedition-2 trials, when combined, show that there is a surprising difference in cognitive outcomes for carriers vs. non-carriers of APOE ε4.

Another aspect of the present disclosure is based on the discovery that Alzheimer's patients having one or two alleles of APOE ε4 are more responsive to treatment with anti-N3pGlu Aβ antibodies as compared to non-carriers of APOE ε4. Yet another aspect of the present disclosure is based on the discovery that Alzheimer's patients having one or two alleles of APOE ε4 and low or moderate tau, very low to moderate tau, or not having high tau are responsive to treatment with anti-N3pGlu Aβ antibodies.

In some embodiments, the patients can be stratified/identified/selected/treated based on the amount of tau present in the subject's brain (*e.g.*, in the whole brain or in portions of the brain) and the presence of one or two alleles of APOE ε4. In some embodiments, the patients can be stratified/identified/selected/treated based on the stages of AD progression (*e.g.*, based on the spread of tau in the brain) and the presence of one or two alleles of APOE ε4.

Some aspects of the present disclosure provide for a dosing regimen where a human subject, suffering from a disease characterized by Aβ deposits in their brain, is administered solanezumab in one step or two steps. In some embodiments, the human subject is administered one or more doses of the antibodies of the present disclosure, optionally, once about every 4 weeks. In some embodiments, the human subject is administered one or more doses of solanezumab in a first step, wherein each dose is administered once about every 4

weeks. About four weeks after administering the one or more first doses, the human subject is administered one or more second doses in a second step.

Some aspects of the present disclosure are related to identifying the stage/progression of AD in a patient based on i) the global or overall tau burden in the brain of a human subject or ii) the spread of tau in the subject's brain or portions thereof. See, *e.g.*, International Patent Application No. PCT/US2022/011894, which is hereby incorporated by reference in its entirety. The stratification of patients based on amount of tau in the brain or AD progression in portions of brain can be used to determine, *e.g.*, whether a patient will respond to treatments. Stratification/selection of patient population based on amount of tau in the brain or AD progression in portions of brain is also helpful in solving the patient heterogeneity and replicability problems faced during design and performance of clinical trials. See, *e.g.*, International Patent Application No. PCT/US2022/011894, which is hereby incorporated by reference in its entirety.

In some embodiments, the patients can be stratified/identified/selected/treated based on the amount of tau present in the subject's brain (*e.g.*, in the whole brain or in portions of the brain). See, *e.g.*, International Patent Application No. PCT/US2022/011894, which is hereby incorporated by reference in its entirety. In other embodiments, the patients are stratified/identified/selected/treated based on stages of AD progression (*e.g.*, based on the spread of tau in the brain). For example, during some stages, tau burden in an AD patient is isolated to frontal lobe or regions of the temporal lobe that do not include the posterolateral temporal region (PLT). Another stage of AD is where tau burden in an AD patient is limited to the posterolateral temporal (PLT) or occipital regions. Yet another stage of AD is when the tau burden in an AD patient is present in the parietal or precuneus region or in the frontal region along with tau burden in PLT or occipital regions. See, *e.g.*, International Patent Application No. PCT/US2022/011894, which is hereby incorporated by reference in its entirety.

Other aspects of the present disclosure provide for human subjects that are responsive to treatment or prevention of a disease characterized by amyloid beta (Aβ) deposits in the brain of a human subject. In some embodiments, of this aspect of the present disclosure, the responsive human subjects include human subjects having low to moderate tau burden or very low to moderate tau burden, optionally having one or more alleles of APOE ε4. In some embodiments, of this aspect of the present disclosure, the responsive human subjects

exclude human subjects with high tau burden, optionally having one or more alleles of APOE ε4. In some embodiments, solanezumab is administered to the responsive human subjects for treatment or prevention of a disease characterized by amyloid beta (Aβ) deposits in the brain of a human subject. See, *e.g.*, International Patent Application No. PCT/US2022/011894, which is hereby incorporated by reference in its entirety.

Some aspects of the present disclosure are related to a method of treating or preventing a disease characterized by Aβ deposits in the brain of a human subject wherein the human subject is clinically asymptomatic. This method includes administering to an APOE ε4 carrier (*e.g.*, one who has one or more of the APOE ε4 alleles) a dose of solanezumab. In terms of solanezumab the dose may be 400 mg every 4 weeks, 800 mg every 4 weeks, 1200 mg every 4 weeks, or 1600 mg every 4 weeks. Of course, other doses may be used. This may be giving an initial dose of 400 mg, and either maintaining the patient at 400 mg or titrating up to 800 mg every 4 weeks, or titrating up 1200 mg every 4 weeks, or titrating up 1600 mg over time. Other embodiments may involve giving an initial dose of 1600 mg and then maintaining at that dose or titrating down to 400 mg, 800 mg, or 1200 mg. Those skilled in the art will appreciate how to titrate up or down the solanezumab dose, or to maintain the patient on a particular dose (and the timing associated with making a dosing change).

Those skilled in the art will appreciate that changing the dose of solanezumab may be based upon numerous factors, including PET scans, clinical observations, performance by the patient on various “tests,” etc.

In some embodiments, the clinically asymptomatic subjects are known to have an Alzheimer's disease-causing genetic mutation. In the present disclosure, “clinically asymptomatic subjects known to have an Alzheimer's disease-causing genetic mutation” include patients known to have a PSEN1 E280A Alzheimer's disease-causing genetic mutation (Paisa mutation), a genetic mutation that causes autosomal-dominant Alzheimer's disease or are at higher risk for developing AD by virtue of carrying one or two APOE ε4 alleles.

As used herein, “anti-Aβ antibody" refers to an antibody that binds to an epitope present on Aβ. In some embodiments, the anti-Aβ antibody binds to a soluble form of Aβ. In other embodiments, the anti-Aβ antibody binds to an insoluble form of Aβ, such as Aβ plaques.

In some embodiments, the anti-Aβ antibody binds an epitope present in Aβ1-40 or Aβ1-42. In other embodiments, the anti-Aβ antibody binds an epitope present in a truncated form of Aβ1-40 or Aβ1-42, for example, a truncated form lacking 1-20 N terminal amino acids and/or lacking 1-20 C-terminal amino acids. In other embodiments, the anti-Aβ antibody binds an epitope present in a fragment of Aβ1-40 or Aβ1-42 and having a length of about 5-20 amino acids. Anti-Aβ antibodies have been disclosed in the art. (*See, e.g.,* U.S. Patent Nos. 10,851,156; 10,738,109; 10,662,239; 10,654,917; 10,647,759; 10,603,367; 10,519,223; 10,494,425; 10,464,976; 10,112,991; 10,112,987; 10,035,847; 9,944,696; 9,939,452; 9,895,429; 9,834,598; 9,738,712; 9,585,956; 9,573,994; 9,382,312; 9,329,189; 9,309,309; 9,309,307; 9,272,031; 9,181,332; 9,176,150; 9,175,094;9,146,244; 9,133,267; 9,125,846; 9,062,102; 9,051,364; 9,051,363; 8,916,165; 8,906,370; 8,906,367; 8,889,138; 8,796,439; 8,795,664; 8,710,193; 8,636,981; 8,614,299; 8,591,894; 8,507,206; 8,491,903; 8,470,321; 8,425,905; 8,420,093; 8,414,893; 8,398,978; 8,383,113; 8,337,848; 8,333,967; 8,323,654; 8,303,954; 8,268,973; 8,268,593; 8,246,954; 8,227,576; 8,222,002; 8,221,750; 8,173,127; 8,128,930; 8,128,928; 8,124,353; 8,124,076; 8,106,164; 8,105,594; 8,105,593; 8,025,878; 7,955,812; 7,939,075; 7,932,048; 7,927,594; 7,906,625; 7,902,328; 7,893,214; 7,892,545; 7,892,544; 7,871,615; 7,811,563; 7,807,165; 7,807,157; 7,790,856; 7,780,963; 7,772,375; 7,763,250; 7,763,249; 7,741,448; 7,731,962; 7,700,751; 7,625,560; 7,582,733; 7,575,880; 7,339,035; 7,320,790; 7,318,923; 7,256,273; 7,195,761; 7,189,819; 7,179,892; 7,122,374; 7,060,270; 6,815,175; 6,787,637; and 6,750,324; which are hereby incorporated by reference in their entireties).

One aspect of the present disclosure is related to a method of treating or preventing a disease characterized by amyloid beta (Aβ) deposits in the brain of a human subject having an APOE ε4 allele comprising: i) administering a therapeutically effective amount of an antibody comprising SEQ ID NO: 1 and SEQ ID NO: 2, or pharmaceutical composition thereof, to the human subject that has one or two alleles of APOE ε4. In some embodiments, the antibody administered to the human subject is an anti-Aβ antibody.

Another aspect of the present disclosure is related to a method of treating or preventing a disease characterized by amyloid beta (Aβ) deposits in the brain of a human subject having been identified as having an APOE ε4 allele, comprising: i) administering a therapeutically effective amount of an antibody comprising SEQ ID NO: 1 and SEQ ID

NO: 2 to the human subject. In some embodiments, the antibody administered to the human subject is an anti-Aβ antibody.

Yet another aspect of the present disclosure is related to method of treating or preventing a disease characterized by amyloid beta (Aβ) deposits in the brain of a human subject, comprising: i) identifying or having identified the human subject as having an APOE ε4 allele; and ii) if the human subject is identified as having an APOE ε4 allele, administering or having administered a therapeutically effective amount of an antibody comprising SEQ ID NO: 1 and SEQ ID NO: 2 to the human subject. In some embodiments, the antibody administered to the human subject is an anti-Aβ antibody.

In one aspect the present disclosure is related to a method of treating or preventing a disease characterized by amyloid beta (Aβ) deposits in the brain of a human subject, comprising: i) administering a therapeutically effective amount of an antibody comprising SEQ ID NO: 1 and SEQ ID NO: 2 to the human subject, wherein the human subject has an APOE ε4 allele. In some embodiments, the antibody administered to the human subject is an anti-Aβ antibody.

One aspect of the present disclosure is related to a method of reducing amyloid load in the brain of a human subject having an APOE ε4 allele comprising: i) administering a therapeutically effective amount of an antibody comprising SEQ ID NO: 1 and SEQ ID NO: 2, or pharmaceutical composition thereof, to the human subject that has one or two alleles of APOE ε4.

Another aspect of the present disclosure is related to a method of reducing amyloid load in the brain of a human subject having been identified as having an APOE ε4 allele, comprising: i) administering an antibody comprising SEQ ID NO: 1 and SEQ ID NO: 2 to the human subject.

An aspect of the present disclosure is related to a method of reducing amyloid load in the brain of a human subject, comprising: i) identifying or having identified the human subject as having an APOE ε4 allele; and ii) if the human subject is identified as having an APOE ε4 allele, administering or having administered an antibody comprising SEQ ID NO: 1 and SEQ ID NO: 2 to the human subject.

Another aspect of the present disclosure is related to a method of reducing amyloid load in the brain of a human subject, comprising: i) administering an antibody comprising SEQ

ID NO: 1 and SEQ ID NO: 2 to the human subject, wherein the human subject has an APOE ε4 allele.

Another aspect of the present disclosure is related to a method of treating or preventing a disease characterized by amyloid beta (Aβ) deposits in the brain of a human subject comprising administering to the human subject an effective amount of solanezumab, wherein the human subject has been determined as having a very low to moderate tau burden or low to moderate tau burden. In some embodiments of this aspect of the present disclosure, the human subject has one or two alleles of APOE ε4.

Another aspect of the present disclosure is related to a method of treating or preventing a disease characterized by amyloid beta (Aβ) deposits in the brain of a human subject who has been determined to have one or two alleles of APOE ε4 and very low to moderate tau burden or low to moderate tau burden comprising: administering to the human subject an effective amount of solanezumab. In some embodiments of this aspect of the present disclosure, the human subject has one or two alleles of APOE ε4.

In one aspect, the present disclosure is related to a method of treating or preventing a disease characterized by amyloid beta (Aβ) deposits in the brain of a human subject who has been determined as not having a high tau burden comprising: administering to the human subject an effective amount of solanezumab. In some embodiments of this aspect of the present disclosure, the human subject has one or two alleles of APOE ε4.

Another aspect of the present disclosure is related to a method of treating or preventing a disease characterized by amyloid beta (Aβ) deposits in the brain of a human subject comprising determining whether the human subject has low to moderate tau burden or a very low to moderate tau burden; and if the human subject has low to moderate tau burden or a very low to moderate tau burden, then: administering to the human subject an effective amount of solanezumab. In some embodiments of this aspect of the present disclosure, the human subject has one or two alleles of APOE ε4.

Another aspect of the present disclosure is related to a method of treating or preventing a disease characterized by amyloid beta (Aβ) deposits in the brain of a human subject comprising administering to the human subject an effective amount of solanezumab, wherein the human subject has been determined as not having a high tau burden. In some

embodiments of this aspect of the present disclosure, the human subject has one or two alleles of APOE ε4.

Another aspect of the present disclosure is related to a method of treating or preventing a disease characterized by amyloid beta (Aβ) deposits in the brain of a human subject comprising determining whether the human subject has high tau burden; and if the human subject does not have high tau burden, then: administering to the human subject an effective amount of solanezumab. In some embodiments of this aspect of the present disclosure, the human subject has one or two alleles of APOE ε4.

In some aspects, an anti-Aβ antibody may be used to decrease, prevent further increase of tau burden, or slow the rate of tau accumulation in different portions of a human brain, *e.g.*, in different lobes of the brain of a human subject. In some embodiments, solanezumab is used to decrease, prevent further increase, or slow the rate of tau burden/accumulation in the frontal lobe of the human brain. In some embodiments, solanezumab is used to decrease, prevent further increase, or slow the rate of tau burden/accumulation in the parietal lobe of the human brain. In some embodiments, solanezumab is used to decrease, prevent further increase, or slow the rate of tau burden/accumulation in the occipital lobe of the human brain. In some embodiments, solanezumab is used to decrease, prevent further increase, or slow the rate of tau burden/accumulation in the temporal lobe of the human brain. In some embodiments, solanezumab is used to decrease, prevent further increase, or slow the rate of tau burden/accumulation in the posterolateral temporal lobe.

An aspect of the present disclosure is related to a method of treating or preventing a disease characterized by amyloid beta (Aβ) deposits in the brain of a human subject who has been determined to have tau burden in the temporal lobe of the brain wherein the method comprises administering an anti-Aβ to the human subject. Another aspect of the invention is related to a method of treating or preventing a disease characterized by amyloid beta deposits in the brain of a human subject comprising determining whether the human subject has tau burden in the temporal lobe of the brain and administering an anti-Aβ to the human subject. In some embodiments, the human subject has tau burden in the posterolateral temporal lobe.

Another aspect of the present disclosure is related to a method of treating or preventing a disease characterized by amyloid beta (Aβ) deposits in the brain of a human subject who has been determined to have tau burden in the occipital lobe of the brain wherein the method

comprises administering an anti-Aβ to the human subject. Another aspect of the invention is related to a method of treating or preventing a disease characterized by amyloid beta (Aβ) deposits in the brain of a human subject comprising determining whether the human subject has tau burden in the occipital lobe of the brain and administering an anti-Aβ to the human subject.

Another aspect of the present disclosure is related to a method of treating or preventing a disease characterized by amyloid beta (Aβ) deposits in the brain of a human subject who has been determined to have tau burden in the parietal lobe of the brain wherein the method comprises administering an anti-Aβ to the human subject. Another aspect of the invention is related to a method of treating or preventing a disease characterized by amyloid beta (Aβ) deposits in the brain of a human subject comprising determining whether the human subject has tau burden in the parietal lobe of the brain and administering an anti-Aβ to the human subject.

Another aspect of the present disclosure is related to a method of treating or preventing a disease characterized by amyloid beta deposits in the brain of a human subject who has been determined to have tau burden in the frontal lobe of the brain wherein the method comprises administering an anti-Aβ to the human subject. Another aspect of the invention is related to a method of treating or preventing a disease characterized by amyloid beta deposits in the brain of a human subject comprising determining whether the human subject has tau burden in the frontal lobe of the brain and administering an anti-Aβ to the human subject. Another aspect of the present disclosure is related to a method of treating or preventing a disease characterized by amyloid beta deposits in the brain of a human subject who has been determined to have tau burden in the posterolateral temporal (PLT) and/or occipital lobe of the brain wherein the method comprises administering an anti-Aβ to the human subject. Another aspect of the invention is related to a method of treating or preventing a disease characterized by amyloid beta deposits in the brain of a human subject comprising determining whether the human subject has tau burden in the posterolateral temporal (PLT) and/or occipital lobe of the brain and administering an anti-Aβ to the human subject.

Another aspect of the present disclosure is related to a method of treating or preventing a disease characterized by amyloid beta deposits in the brain of a human subject who has been determined to have tau burden in i) parietal or precuneus region or ii) in frontal region

along with tau burden in PLT or occipital regions of the brain wherein the method comprises administering an anti-Aβ to the human subject. Another aspect of the invention is related to a method of treating or preventing a disease characterized by amyloid beta deposits comprising determining whether the human subject has tau burden in i) parietal or precuneus region or ii) in the frontal region along with tau burden in PLT or occipital regions of the brain and administering an anti-Aβ to the human subject.

Another aspect of the present disclosure is related to a method of treating or preventing a disease characterized by amyloid beta deposits in the brain of a human subject who has been determined to have tau burden i) isolated to frontal lobe or ii) in regions of the temporal lobe that do not include the posterolateral temporal region (PLT) of the brain wherein the method comprises administering an anti-Aβ to the human subject. Another aspect of the invention is related to a method of treating or preventing a disease characterized by amyloid beta deposits comprising determining whether the human subject has tau burden i) isolated to frontal lobe or ii) in regions of the temporal lobe that do not include the posterolateral temporal region (PLT) of the brain and administering an anti-Aβ to the human subject.

In some aspects, the present disclosure is related to a method of selecting a human subject for treatment or prevention of a disease characterized by amyloid beta deposits in the brain of a human subject. In some embodiments, the human subject is selected based on the amount of global (overall) tau in the brain of the human subject. For example, the human subject is selected for treatment or prevention of a disease characterized by amyloid beta deposits in the brain because the patient has very low to moderate tau in the brain. In another embodiment, the human subject is selected for treatment or prevention of a disease characterized by amyloid beta deposits in the brain because the patient has low to moderate tau (or intermediate tau) in the brain. In another embodiment, the human subject is excluded from treatment or prevention of a disease characterized by amyloid beta deposits in the brain because the patient has high tau in the brain. In some embodiments, the human subject is selected based on progression of AD in the brain of the human subject. For example, the human subject is selected for treatment or prevention of a disease characterized by amyloid beta deposits in the brain because the patient has tau burden present in the frontal lobe of the brain. In another embodiment, the human subject is selected for treatment or prevention of a disease characterized by amyloid beta deposits in the brain because the patient has tau

burden present in the parietal lobe of the brain. In another embodiment, the human subject is selected for treatment or prevention of a disease characterized by amyloid beta deposits in the brain because the patient has tau burden present in the occipital lobe of the brain. In another embodiment, the human subject is selected for treatment or prevention of a disease characterized by amyloid beta deposits in the brain because the patient has tau burden present in the temporal lobe of the brain. In some embodiments, the human subject is selected for treatment or prevention of a disease characterized by amyloid beta deposits in the brain because the patient has tau burden present in the posterolateral temporal (PLT) and/or occipital lobe of the brain. In some embodiments, the human subject is selected for treatment or prevention of a disease characterized by amyloid beta deposits in the brain because the patient has tau burden present in i) parietal or precuneus region or ii) in frontal region along with tau burden in PLT or occipital regions of the brain. In some embodiments, the human subject is selected for treatment or prevention of a disease characterized by amyloid beta deposits in the brain because the patient has tau burden i) isolated to frontal lobe or ii) in regions of the temporal lobe that do not include the posterolateral temporal region (PLT) of the brain.

In some embodiments, the subject described in the various aspects of the present disclosure has been determined to have a posterior-lateral temporal lobe tau burden. In some embodiments, the subject described in the various aspects of the present disclosure has been determined to have posterior-lateral temporal lobe and occipital lobe tau burden. In some embodiments, the subject described in the various aspects of the present disclosure has been determined to have posterior-lateral temporal lobe, occipital lobe, and parietal lobe tau burden. In some embodiments, the subject described in the various aspects of the present disclosure has been determined to have posterior-lateral temporal lobe, occipital lobe, parietal lobe, and frontal lobe tau burden. In some embodiments, the subject described in the various aspects of the present disclosure has been determined to have posterior-lateral temporal lobe, occipital lobe, parietal lobe and / or frontal lobe tau burden. In some embodiments, the subject described in the various aspects of the present disclosure has been determined to have posterior-lateral temporal lobe, occipital lobe, parietal lobe and / or frontal lobe tau burden corresponds a neurological tau burden of greater than 1.46 SUVr based on PET imaging.

In some embodiments, tau burden in a portion of the human brain (*e.g.*, in a lobe of the brain) can be used to determine whether administration of the anti-Aβ should be discontinued. For instance, decrease, prevention of further increase, or slowing in the rate of tau burden/accumulation in a portion of the brain can be used as metric to determine the duration of administration of solanezumab. In some embodiments, solanezumab is administered to the subject until there is a decrease, prevention of further increase, or slowing in the rate of tau burden/accumulation in the temporal lobe, the occipital lobe, the parietal lobe, or the frontal lobe.

In some embodiments, the tau burden present in a portion of the brain of a human subject can be used for selection of optimal treatment regimens or for administration of therapeutic modalities in combination with solanezumab. For example, the presence of tau burden in the frontal lobe of the brain of an amyloid positive human subject can be used as a metric to determine whether the human subject will benefit from administration of an anti-Aβ antibody alone or its combination with an anti-tau antibody. In some embodiments, solanezumab in combination with an anti-tau antibody may be used to decrease, prevent further increase, or slow the rate of tau burden/accumulation in different portions of a human brain, *e.g.*, in different lobes of the brain of a human subject. In some embodiments, the tau burden in different portions of a human brain, *e.g.*, in different lobes of the brain of a human subject can be used for i) tracking patient's response to treatment, or ii) when a therapy may need to be reinitiated.

In some embodiments, the antibodies, methods, or dosing regimens described in various aspects of the present disclosure cause: i) reduction in Aβ deposits in the brain of the human subject and/or ii) slow cognitive decline or functional decline in the human subject. In some embodiments, the antibodies, methods, or dosing regimens described herein results in reduction of amyloid plaques.

Table 1 below shows how administration of solanezumab affects the amount of tau in various lobes of the brain, and how that amount differs based upon whether the patient is an APOE ε4 carrier or non-carrier.

Table 1:

Brain Region	APOE ε4 Status	Solanezumab	Placebo	p-value
	Carriers	0.02213	0.05428	0.1599

Brain Region	APOE ε4 Status	Solanezumab	Placebo	p-value
TAU PET FRONTAL (CC) SUVR	Non-carrier	0.02703	0.04672	0.6093
TAU PET LAT. TEMPORAL (CC) SUVR	Carriers	0.03071	0.07924	0.07591
	Non-carrier	0.02310	0.06418	0.3645
TAU PET MUBADA (CC) SUVR	Carriers	0.05636	0.08154	0.2586
	Non-carrier	0.03472	0.1029	0.06806
TAU PET OCCIPITAL (CC) SUVR	Carriers	0.04305	0.05725	0.4372
	Non-carrier	0.04089	0.07102	0.3278
TAU PET PARIETAL (CC) SUVR	Carriers	0.02299	0.06676	0.05990
	Non-carrier	0.03192	0.07434	0.2775

In some embodiments, solanezumab is administered to the subject for a duration sufficient to treat or prevent the disease. In some embodiments, solanezumab (including the first doses of the antibody and the second doses of the antibody) is administered to the subject for a duration of up to about 54 weeks, about 72 weeks, or about 80 weeks, optionally, about once every 4 weeks or about once every month.

In some embodiments, the antibody of the present disclosure is administered to the patient till amyloid levels in the brain of the patient reach a normal range. In some embodiments, the antibody of the present disclosure is administered to the subject till amyloid deposits or plaques are cleared from the subject's brain. In some embodiments, the antibody is administered to the subject till the subject reaches amyloid negative status (defined as <24.1 CL amyloid plaque). In the present disclosure, the term "normal range" of amyloid plaque in brain is used interchangeably with brain amyloid plaque is "cleared." The normal range of amyloid plaque is defined as demonstrating an amyloid plaque level of 25 centiloids or lower for two consecutive PET scans at least 6 months apart or a single PET scan demonstrating a plaque level of less than 11 centiloids.

In some embodiments, the dose of solanezumab is every 4 weeks (possibly modifying the dose every 4 weeks, as outlined herein) for up to about 54 weeks, about 72 weeks, or about 80 weeks. In some embodiments, solanezumab slows disease progression in patients with early symptomatic Alzheimer's disease (AD) and with the presence of intermediate brain tau burden.

In some embodiments, the antibody of the present disclosure is administered to the subject as one dose or more than one doses. In some embodiments, the patients receive solanezumab at a dose of 400 mg given intravenously every 4 weeks for 76 weeks or 80 weeks or some other time period. In some embodiments, the dose of solanezumab may be increased to 800 mg, 1200 mg, or 1600 mg given every 4 weeks. In some embodiments, the antibody of the present disclosure is administered at a dose of 400 mg every 4 weeks, 800 mg every 4 weeks, 1200 mg every 4 weeks, 1600 mg every 4 weeks, 2000 mg every 4 weeks, 2400 mg every 4 weeks, 2800 mg every 4 weeks, 3200 mg every 4 weeks, 3600 mg every 4 weeks, 4000 mg every 4 weeks, 4400 mg every 4 weeks, 4800 mg every 4 weeks, 5200 mg every 4 weeks, or 5600 mg every 4 weeks.

A brain MRI scan may be administered to the human subject to monitor/evaluate a human subject (*e.g.*, for ARIA-E or ARIA-H). In some embodiments, a brain MRI scan can be administered to the human subject to diagnose/evaluate/monitor adverse event(s) caused by administration of the antibody of the present disclosure. In some embodiments, the human subject is administered an MRI scan in between the administration of doses. In some embodiments, the human subject is administered an MRI scan before an increase in the dose of solanezumab. In some embodiments, the human subject is administered an MRI scan before administering a higher mg dose. In some embodiments, the human subject is administered an MRI scan before administering a dose of solanezumab.

Those skilled in the art will appreciate how to measure centiloids reduction associated with amyloid plaques. *See*, *e.g.*, Klunk *et al.*, "The Centiloid Project: Standardizing Quantitative Amyloid Plaque Estimation by PET," *Alzheimer's & Dementia* 11.1: 1-15 (2015) and Navitsky *et al.*, "Standardization of Amyloid Quantitation with Florbetapir Standardized Uptake Value Ratios to the Centiloid Scale," *Alzheimer's & Dementia* 14.12: 1565-1571 (2018), which are hereby incorporated by reference in their entireties.

In some embodiments, the administration of solanezumab causes a reduction in the soluble Aβ that is available in the brain. This reduction may be measured at about 4 weeks, about 8 weeks, about 12 weeks, about 16 weeks, about 20 weeks, about 24 weeks, about 28 weeks, about 32 weeks, about 36 weeks, about 40 weeks, about 44 weeks, about 48 weeks, about 52 weeks, about 56 weeks, about 60 weeks, about 64 weeks, about 68 weeks, or about 72 weeks or about 80 weeks.

In some embodiments, the administration of solanezumab results in a 5% lowering of the soluble Aβ concentration. In other embodiments, administration of solanezumab results in a 10% lowering of the soluble Aβ concentration. In other embodiments, administration of solanezumab results in a 15% lowering of the soluble Aβ concentration. In other embodiments, administration of solanezumab results in a 20% lowering of the soluble Aβ concentration. In other embodiments, administration of solanezumab results in a 25% lowering of the soluble Aβ concentration. In other embodiments, administration of solanezumab results in a 30% lowering of the soluble Aβ concentration. In other embodiments, administration of solanezumab results in a 35% lowering of the soluble Aβ concentration. In other embodiments, administration of solanezumab results in a 40% lowering of the soluble Aβ concentration. In other embodiments, administration of solanezumab results in a 45% lowering of the soluble Aβ concentration. In other embodiments, administration of solanezumab results in a 50% lowering of the soluble Aβ concentration. In other embodiments, administration of solanezumab results in a greater than 50% lowering of the soluble Aβ concentration. In other embodiments, administration of solanezumab results in a 55% lowering of the soluble Aβ concentration. In other embodiments, administration of solanezumab results in a 60% lowering of the soluble Aβ concentration. In other embodiments, administration of solanezumab results in a 65% lowering of the soluble Aβ concentration. In other embodiments, administration of solanezumab results in a 70% lowering of the soluble Aβ concentration. In other embodiments, administration of solanezumab results in a 75% lowering of the soluble Aβ concentration. In other embodiments, administration of solanezumab results in an 80% lowering of the soluble Aβ concentration. In other embodiments, administration of solanezumab results in an 85% lowering of the soluble Aβ concentration. In other embodiments, administration of solanezumab results in a 90% lowering of the soluble Aβ concentration.

Those skilled in the art will appreciate how to measure the concentration of the soluble Aβ concentration. *See , e.g.,* Siemers ER, Friedrich S, Dean RA, *et al.*, "Safety and changes in plasma and cerebrospinal fluid amyloid β after a single administration of an amyloid β monoclonal antibody in subjects with Alzheimer disease," *Clin. Neuropharmacol.* 2010; 33:67-73; and Farlow M, Arnold SE, van Dyck CH, *et al.*, "Safety and biomarker effects

of solanezumab in patients with Alzheimer's disease," *Alzheimer's Dement* 2012; 8:261-71 (both of which are expressly incorporated herein by reference in their entirety).

In some embodiments, the present disclosure results in about 15 to about 45 percent slowing of decline in the cognitive-functional composite endpoints from baseline. In some embodiments, the present disclosure results in about 15 to about 45 percent slowing of decline in the cognitive-functional composite endpoints from baseline over a duration of about 4 weeks, about 8 weeks, about 12 weeks, about 16 weeks, about 20 weeks, about 24 weeks, about 28 weeks, about 32 weeks, about 36 weeks, about 40 weeks, about 44 weeks, about 48 weeks, about 52 weeks, about 56 weeks, about 60 weeks, about 64 weeks, about 68 weeks, about 72 weeks, or 76 weeks or about 80 weeks.

In some embodiments, solanezumab is administered to the patient about every 4 weeks, about 8 weeks, about 12 weeks, about 16 weeks, about 20 weeks, about 24 weeks, about 28 weeks, about 32 weeks, about 36 weeks, about 40 weeks, about 44 weeks, about 48 weeks, about 52 weeks, about 56 weeks, about 60 weeks, about 64 weeks, about 68 weeks, about 72 weeks, about 76 weeks, or about 80 weeks.

In some embodiments, the present disclosure results in about 15 to about 45 percent slowing of decline in the cognitive-functional composite endpoints from baseline over a duration of 80 weeks. In some embodiments, the slowing of decline in the cognitive-functional composite endpoints from baseline is provided from the MMRM model or the Bayesian Disease Progression Model (DPM). In some embodiments, the antibody of the present disclosure is administered to the subject till it reaches about 15 to about 45 percent slowing of decline in the cognitive-functional composite endpoints from baseline. In some embodiments, the first or the second dose of the present disclosure is administered to the subject till it reaches about 15 to about 45 percent slowing of decline in the cognitive-functional composite endpoints from baseline.

In some embodiments, the present disclosure results in about 15 to about 45 percent slowing of decline on the Integrated Alzheimer's Disease Rating Scale (iADRS) from baseline. In some embodiments, the present disclosure results in about 15 to about 45 percent slowing of decline on the Integrated Alzheimer's Disease Rating Scale from baseline over a duration of about 4 weeks, about 8 weeks, about 12 weeks, about 16 weeks, about 20 weeks, about 24 weeks, about 28 weeks, about 32 weeks, about 36 weeks, about

40 weeks, about 44 weeks, about 48 weeks, about 52 weeks, about 56 weeks, about 60 weeks, about 64 weeks, about 68 weeks, about 72 weeks, or 76 weeks.

In some embodiments, the present disclosure results in about 20 percent, about 25 percent, about 30 percent, about 32 percent, about 35 percent, about 40 percent, or about 45 percent slowing of decline in the Integrated Alzheimer's Disease Rating Scale from baseline.

In some embodiments, the present disclosure results in about 15 to about 45 percent slowing of decline on the Integrated Alzheimer's Disease Rating Scale from baseline over a duration of 76 weeks. In a particular embodiment, the present disclosure results in about 32 percent slowing of decline on the Integrated Alzheimer's Disease Rating Scale from baseline over a duration of 76 weeks. In some embodiments, the antibody of the present disclosure is administered to the subject till it reaches about 15 to about 45 percent slowing of decline on the Integrated Alzheimer's Disease Rating Scale from baseline. In some embodiments, the first or the second dose of the present disclosure is administered to the subject till it reaches about 15 to about 45 percent slowing of decline on the Integrated Alzheimer's Disease Rating Scale (iADRS) from baseline.

In some embodiments, the cognitive functional composite endpoint, including iADRS, of the subject is measured at about 4 weeks, about 8 weeks, about 12 weeks, about 16 weeks, about 20 weeks, about 24 weeks, about 28 weeks, about 32 weeks, about 36 weeks, about 40 weeks, about 44 weeks, about 48 weeks, about 52 weeks, about 56 weeks, about 60 weeks, about 64 weeks, about 68 weeks, about 72 weeks, or about 80 weeks.

In some embodiments, solanezumab is administered to the patient who is a carrier of at least one allele of APOE ε4 and causes at least a 5% slowing of cognitive decline versus placebo on the MMSE scale. In other embodiments, solanezumab is administered to the patient who is a carrier of at least one allele of APOE ε4 and causes at least a 10% slowing of cognitive decline versus placebo on the MMSE scale. In other embodiments, solanezumab is administered to the patient who is a carrier of at least one allele of APOE ε4 and causes at least a 15% slowing of cognitive decline versus placebo on the MMSE scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 20% slowing of cognitive decline versus placebo on the MMSE scale. In other embodiments, solanezumab is administered to the patient who is a

carrier of APOE ε4 and causes at least a 25% slowing of cognitive decline versus placebo on the MMSE scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 30% slowing of cognitive decline versus placebo on the MMSE scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 35% slowing of cognitive decline versus placebo on the MMSE scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 40% slowing of cognitive decline versus placebo on the MMSE scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 45% slowing of cognitive decline versus placebo on the MMSE scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 50% slowing of cognitive decline versus placebo on the MMSE scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 55% slowing of cognitive decline versus placebo on the MMSE scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 60% slowing of cognitive decline versus placebo on the MMSE scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 65% slowing of cognitive decline versus placebo on the MMSE scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 70% slowing of cognitive decline versus placebo on the MMSE scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 75% slowing of cognitive decline versus placebo on the MMSE scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 80% slowing of cognitive decline versus placebo on the MMSE scale.

In some embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 5% slowing of cognitive decline versus placebo on the CDS-SB scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 10% slowing of cognitive decline versus placebo on the CDS-SB scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 15% slowing of cognitive decline versus placebo

on the CDS-SB scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 20% slowing of cognitive decline versus placebo on the CDS-SB scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 25% slowing of cognitive decline versus placebo on the CDS-SB scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 30% slowing of cognitive decline versus placebo on the CDS-SB scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 35% slowing of cognitive decline versus placebo on the CDS-SB scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 40% slowing of cognitive decline versus placebo on the CDS-SB scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 45% slowing of cognitive decline versus placebo on the CDS-SB scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 50% slowing of cognitive decline versus placebo on the CDS-SB scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 55% slowing of cognitive decline versus placebo on the CDS-SB scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 60% slowing of cognitive decline versus placebo on the CDS-SB scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 65% slowing of cognitive decline versus placebo on the CDS-SB scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 70% slowing of cognitive decline versus placebo on the CDS-SB scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 75% slowing of cognitive decline versus placebo on the CDS-SB scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 80% slowing of cognitive decline versus placebo on the CDS-SB scale.

In some embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 5% slowing of cognitive decline versus placebo on the ADCS-ADL scale In other embodiments, solanezumab is administered to the patient who

is a carrier of APOE ε4 and causes at least a 10% slowing of cognitive decline versus placebo on the ADCS-ADL scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 15% slowing of cognitive decline versus placebo on the ADCS-ADL scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 20% slowing of cognitive decline versus placebo on the ADCS-ADL scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 25% slowing of cognitive decline versus placebo on the ADCS-ADL scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 30% slowing of cognitive decline versus placebo on the ADCS-ADL scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 35% slowing of cognitive decline versus placebo on the ADCS-ADL scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 40% slowing of cognitive decline versus placebo on the ADCS-ADL scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 45% slowing of cognitive decline versus placebo on the ADCS-ADL scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 50% slowing of cognitive decline versus placebo on the ADCS-ADL scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 55% slowing of cognitive decline versus placebo on the ADCS-ADL scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 60% slowing of cognitive decline versus placebo on the ADCS-ADL scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 65% slowing of cognitive decline versus placebo on the ADCS-ADL scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 70% slowing of cognitive decline versus placebo on the ADCS-ADL scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 75% slowing of cognitive decline versus placebo on the ADCS-ADL scale. In other embodiments, solanezumab is administered to the patient

who is a carrier of APOE ε4 and causes at least a 80% slowing of cognitive decline versus placebo on the ADCS-ADL scale.

In some embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 5% slowing of cognitive decline versus placebo on the ADCS-iADL scale In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 10% slowing of cognitive decline versus placebo on the ADCS-iADLs scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 15% slowing of cognitive decline versus placebo on the ADCS-iADLs scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 20% slowing of cognitive decline versus placebo on the ADCS-iADLs scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 25% slowing of cognitive decline versus placebo on the ADCS-iADLs scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 30% slowing of cognitive decline versus placebo on the ADCS-iADLs scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 35% slowing of cognitive decline versus placebo on the ADCS-iADLs scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 40% slowing of cognitive decline versus placebo on the ADCS-iADLs scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 45% slowing of cognitive decline versus placebo on the ADCS-iADLs scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 50% slowing of cognitive decline versus placebo on the ADCS-iADLs scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 55% slowing of cognitive decline versus placebo on the ADCS-iADLs scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 60% slowing of cognitive decline versus placebo on the ADCS-iADLs scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 65% slowing of cognitive decline versus placebo on the ADCS-iADLs scale. In other embodiments, solanezumab is administered to the patient who

is a carrier of APOE ε4 and causes at least a 70% slowing of cognitive decline versus placebo on the ADCS-iADLs scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 75% slowing of cognitive decline versus placebo on the ADCS-iADLs scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 80% slowing of cognitive decline versus placebo on the ADCS-iADLs scale.

In some embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 5% slowing of cognitive decline versus placebo on the ADAS-Cog14 scale In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 10% slowing of cognitive decline versus placebo on the ADAS-Cog14 scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 15% slowing of cognitive decline versus placebo on the ADAS-Cog14 scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 20% slowing of cognitive decline versus placebo on the ADAS-Cog14 scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 25% slowing of cognitive decline versus placebo on the ADAS-Cog14 scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 30% slowing of cognitive decline versus placebo on the ADAS-Cog14 scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 35% slowing of cognitive decline versus placebo on the ADAS-Cog14 scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 40% slowing of cognitive decline versus placebo on the ADAS-Cog14 scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 45% slowing of cognitive decline versus placebo on the ADAS-Cog14 scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 50% slowing of cognitive decline versus placebo on the ADAS-Cog14 scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 55% slowing of cognitive decline versus placebo on the ADAS-Cog14 scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and

causes at least a 60% slowing of cognitive decline versus placebo on the ADAS-Cog14 scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 65% slowing of cognitive decline versus placebo on the ADAS-Cog14 scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 70% slowing of cognitive decline versus placebo on the ADAS-Cog14 scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 75% slowing of cognitive decline versus placebo on the ADAS-Cog14 scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 80% slowing of cognitive decline versus placebo on the ADAS-Cog14 scale.

In embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 5% slowing of cognitive decline versus placebo on the iADRS scale In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 10% slowing of cognitive decline versus placebo on the iADRS scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 15% slowing of cognitive decline versus placebo on the iADRS scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 20% slowing of cognitive decline versus placebo on the iADRS scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 25% slowing of cognitive decline versus placebo on the iADRS scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 30% slowing of cognitive decline versus placebo on the iADRS scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 35% slowing of cognitive decline versus placebo on the iADRS scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 40% slowing of cognitive decline versus placebo on the iADRS scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 45% slowing of cognitive decline versus placebo on the iADRS scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 50% slowing of cognitive decline versus placebo on the iADRS scale. In

other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 55% slowing of cognitive decline versus placebo on the iADRS scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 60% slowing of cognitive decline versus placebo on the iADRS scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 65% slowing of cognitive decline versus placebo on the iADRS scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 70% slowing of cognitive decline versus placebo on the iADRS scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 75% slowing of cognitive decline versus placebo on the iADRS scale. In other embodiments, solanezumab is administered to the patient who is a carrier of APOE ε4 and causes at least a 80% slowing of cognitive decline versus placebo on the iADRS scale.

In some embodiments, the antibody of the present disclosure can be administered in simultaneous, separate, or sequential combination with an effective amount of a symptomatic agent to treat Alzheimer's disease. Symptomatic agents can be selected from cholinesterase inhibitors (ChEIs) and/or a partial *N*-methyl-D-aspartate (NMDA) antagonists. 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 disease characterized by Aβ deposit in the brain of the subject is selected from preclinical Alzheimer's disease, clinical AD, prodromal AD, mild AD, moderate AD, severe AD, Down's syndrome, clinical cerebral amyloid angiopathy, or pre-clinical cerebral amyloid angiopathy. In some embodiments, the subject is an early symptomatic AD patient. In some embodiments, the subject has prodromal AD and mild dementia due to AD. In some embodiments, the human subject has preclinical AD. In embodiments, the human subject has evidence of elevated brain amyloid.

In some embodiments, the subject has a genetic mutation that causes autosomal-dominant Alzheimer's disease or at a higher risk for developing AD by virtue of carrying one or two APOE ε4 alleles. In particular embodiments, the subject carries one or two APOE ε4 alleles, *i.e.*, the patient is heterozygous or homozygous.

The present disclosure includes use of biomarkers of a disease characterized by Aβ deposits in the brain of a human subject, including Alzheimer's disease. Such biomarkers include, *e.g.*, amyloid deposits, amyloid plaque, Aβ in CSF, Aβ in the plasma, brain tau deposition, tau in plasma, or tau in cerebrospinal fluid and their use in screening, diagnosis, treatment, or prevention. Non-limiting potential uses of such biomarkers include: 1) identification of subjects destined to become affected or who are in the "preclinical" stages of a disease; 2) reduction in disease heterogeneity in clinical trials or epidemiologic studies; 3) reflection of the natural history of disease encompassing the phases of induction, latency, and detection; and 4) target subjects for a clinical trial or for treatment/prevention of a disease.

In some embodiments, the biomarkers may be used to assess whether a subject can be treated using the antibodies, the dosing regimen, or the methods described herein. In some embodiments, the biomarkers may be used to assess whether a disease (as described herein) can be prevented in the subject using the antibodies, the dosing regimen, or the methods described herein. In some embodiments, the biomarkers can be used to assess whether a subject is responsive to treatment or prevention of a disease (as described herein) using the antibodies, the dosing regimen, or the methods described herein. In some embodiments, the biomarkers can be used to stratify or classify subjects into groups and to identify which group of subjects is responsive to treatment/prevention of diseases (as described herein) using the antibodies, the dosing regimen, or the methods described herein. In some embodiments, the biomarkers may be used to assess disease state of a subject and/or the duration for administration of the antibodies or doses thereof, as described herein, to the subject.

In some embodiments, the subject has a genetic mutation that causes autosomal-dominant Alzheimer's disease or at a higher risk for developing AD by virtue of carrying one or two APOE ε4 alleles. In particular embodiments, the subject carries one or two APOE ε4 alleles. Such patients, when administered solanezumab have better clinical outcomes than non-carriers.

In some embodiments, the subject has low to moderate tau burden or has been determined to have low to moderate tau burden. The subject has low to moderate tau burden if the tau burden as measured by PET brain imaging (using, *e.g.*, ^{18}F-flortaucipir) is from ≤1.10 standardized uptake value ratio (SUVr) to ≤1.46 SUVr. In some embodiments, the

subject has low to moderate tau burden or has been determined to have low to moderate tau burden and carries one or two APOE ε4 alleles.

In some embodiments, the subject has very low tau burden or has been determined to have very low tau burden. The subject has very low tau burden if the tau burden as measured by PET brain imaging (using, *e.g.*, ^{18}F-flortaucipir) is less than 1.10 SUVr. In some embodiments, the subject has very low tau burden or has been determined to have very low tau burden and carries one or two APOE ε4 alleles.

In some embodiments, the subject has very low to moderate tau burden or has been determined to have very low tau to moderate tau burden. The subject has very low to moderate tau burden if the tau burden as measured by PET brain imaging (using, *e.g.*, ^{18}F-flortaucipir) is ≤1.46 SUVr. In some embodiments, the subject has very low to moderate tau burden or has been determined to have very low to moderate tau burden and carries one or two APOE ε4 alleles.

In some embodiments, the subject does not have a high tau burden or has been determined to not have a high tau burden. In some embodiments, the human subject has high tau burden if the tau burden as measured by PET brain imaging (using, *e.g.*, ^{18}F-flortaucipir) is greater than 1.46 SUVr. In some embodiments, a subject with high tau is not administered the antibodies of the present disclosure. In some embodiments, the subject has does not have high tau burden or has been determined to not have a high tau burden and carries one or two APOE ε4 alleles.

In some embodiments, solanezumab, the dosing regimen, or the methods described the present disclosure is efficacious in human subjects having very low to moderate tau. In some embodiments, solanezumab, the dosing regimen, or the method described the present disclosure is efficacious in human subjects having low to moderate tau. In some embodiments, solanezumab is most efficacious in human subjects having a tau level i) less than or equal to about 1.14 SUVr or ii) from about 1.14 SUVr to about 1.27 SUVr.

In some embodiments, solanezumab, the dosing regimen, or the method described the present disclosure is efficacious in human subjects having very low to moderate tau and carrying one or two APOE ε4 alleles. In some embodiments, solanezumab, the dosing regimen, or the method described the present disclosure is efficacious in human subjects

having low to moderate tau and carrying one or two APOE ε4 alleles. In some embodiments, solanezumab is most efficacious in human subjects.

The tau level of a human subject can be determined by techniques and methods familiar to the diagnosing physician or a person of ordinary skill in the art. In some embodiments, a human subject, who is suffering from a disease characterized by amyloid beta (Aβ) deposits, is determined to have very low to moderate tau, low to moderate tau, or no high tau using techniques and methods familiar to the diagnosing physician or a person of ordinary skill in the art. In some embodiments, such methods can also be used to prescreen, screen, diagnose, evaluate increase or reduction in brain tau burden, and/or to assess the progress achieved in the treatment or prevention of the diseases described herein. In some embodiments, the methods can also be used to stratify subjects into groups and/or to identify which group of subjects is responsive to treatment/prevention of a disease (as described herein) using the antibodies, the dosing regimen, or the methods described herein. In some embodiments, the methods or techniques used to determine/detect tau level of a human subject can be used for prescreening or screening subjects and determining which subjects are responsive to treatment/prevention of a disease (as described herein) using the antibodies, the dosing regimen, or the methods described herein.

For the purposes of the present disclosure, the tau level of a human subject can be determined using techniques or methods that, *e.g.*, detect or quantitate i) brain tau deposition, ii) tau in plasma, or iii) tau in cerebrospinal fluid. In some embodiments, brain tau burden, tau in plasma, or tau in cerebrospinal fluid can be used to stratify subjects into groups and to identify which group of subjects is responsive to treatment/prevention of diseases (described herein) using the antibodies, the dosing regimen, or the methods described herein.

Tau levels in the brain of human subject can be determined using methods, such as, tau imaging with radiolabeled PET compounds (Leuzy *et al.*, "Diagnostic Performance of RO948 F18 Tau Positron Emission Tomography in the Differentiation of Alzheimer Disease from Other Neurodegenerative Disorders," *JAMA Neurology* 77.8:955-965 (2020); Ossenkoppele *et al.*, "Discriminative Accuracy of ^{18}F-flortaucipir Positron Emission Tomography for Alzheimer Disease vs Other Neurodegenerative Disorders," *JAMA* 320, 1151-1162, doi:10.1001/jama.2018.12917 (2018), which are hereby incorporated by reference in their entireties.

In some embodiments, the biomarker ^{18}F-flortaucipir, which is a PET ligand, may be used for the purposes of the present disclosure. PET tau images can be, for example, quantitatively evaluated to estimate an SUVr (standardized uptake value ratio) by published methods (Pontecorvo *et al.*, "A Multicentre Longitudinal Study of Flortaucipir (18F) in Normal Ageing, Mild Cognitive Impairment and Alzheimer's Disease Dementia," *Brain* 142:1723-35 (2019); Devous *et al.*, "Test–Retest Reproducibility for the Tau PET Imaging Agent Flortaucipir F18," *Journal of Nuclear Medicine* 59:937-43 (2018); Southekal *et al.*, "Flortaucipir F18 Quantitation Using Parametric Estimation of Reference Signal Intensity," *J. Nucl. Med.* 59:944-51 (2018), which are hereby incorporated by reference in their entireties) and/or to visually evaluate patients, *e.g.*, to determine whether the patient has an AD pattern (Fleisher *et al.*, "Positron Emission Tomography Imaging With ^{18}F-flortaucipir and Postmortem Assessment of Alzheimer Disease Neuropathologic Changes," *JAMA Neurology* 77:829-39 (2020), which is hereby incorporated by reference in its entirety). Lower SUVr values indicate less tau burden while higher SUVr values indicate a higher tau burden. In an embodiment, quantitative assessment by a flortaucipir scan is accomplished through an automated image processing pipeline as described in Southekal *et al.*, "Flortaucipir F18 Quantitation Using Parametric Estimation of Reference Signal Intensity," *J. Nucl. Med.* 59:944–951 (2018), which is hereby incorporated by reference in its entirety. In some embodiments, counts within a specific target region of interest in the brain (*e.g.*, 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), which is hereby incorporated by reference in its entirety) are compared with a reference region wherein the reference region is, *e.g.*, whole cerebellum, (wholeCere), cerebellar GM (cereCrus), atlas-based white matter (atlasWM), subject-specific WM (ssWM, *e.g.*, using parametric estimate of reference signal intensity (PERSI), *see* Southekal *et al.*, "Flortaucipir F18 Quantitation Using Parametric Estimation of Reference Signal Intensity," *J. Nucl. Med.* 59:944–951 (2018), which is hereby incorporated by reference in its entirety). A preferred method of determining tau burden is a quantitative analysis reported as a standardized uptake value ratio (SUVr), which represents counts within a specific target region of interest in the brain (*e.g.*, MUBADA,) when compared with a reference region (*e.g.*, using PERSI).

In some embodiments, phosphorylated tau (P-tau; either phosphorylated at threonine 181 or 217) can be used to measure the tau load/burden for the purposes of the present disclosure (Barthelemy *et al.*, "Cerebrospinal Fluid Phospho-tau T217 Outperforms T181 as a Biomarker for the Differential Diagnosis of Alzheimer's Disease and PET Amyloid-positive Patient Identification," *Alzheimer's Res. Ther.* 12, 26, doi:10.1186/s13195-020-00596-4 (2020); Mattsson *et al.*, "Aβ Deposition is Associated with Increases in Soluble and Phosphorylated Tau that Precede a Positive Tau PET in Alzheimer's Disease," *Science Advances* 6, eaaz2387 (2020), which are hereby incorporated by reference their entireties). In a particular embodiment, antibodies directed against human tau phosphorylated at threonine at residue 217 can be used to measure the tau load/burden in a subject for the purposes of the present disclosure (*see* International Patent Application Publication No. WO 2020/242963, which is incorporated by reference in its entirety). The present disclosure includes, in some embodiments, the use of anti-tau antibodies disclosed in WO 2020/242963 to measure the tau load/burden in a subject. The anti-tau antibodies disclosed in WO 2020/242963 are directed against isoforms of human tau expressed in the CNS (*e.g.*, recognizing the isoforms expressed in the CNS and not recognizing isoforms of human tau expressed exclusively outside the CNS). Such antibodies against isoforms of human tau expressed in the CNS can be used in a method of identifying/selecting a patient as one or more of: (i) having a disease disclosed herein; (ii) at risk for having a disease disclosed herein; (iii) in need of treatment for a disease disclosed herein; or (iv) in need of neurological imaging.

A subject is positive for amyloid deposits when amyloid is detected in the brain by methods such as, amyloid imaging with radiolabeled PET compounds or using a diagnostic that detects Aβ or a biomarker for Aβ. Exemplary methods that can be used in the present disclosure to measure the brain amyloid load/burden include, *e.g.*, Florbetapir (Carpenter, *et al.*, "The Use of the Exploratory IND in the Evaluation and Development of ^{18}F-PET Radiopharmaceuticals for Amyloid Imaging in the Brain: A Review of One Company's Experience," *The Quarterly Journal of Nuclear Medicine and Molecular Imaging* 53.4:387 (2009), which is hereby incorporated by reference in its entirety); Florbetaben (Syed *et al.*, "[^{18}F]Florbetaben: A Review in β-Amyloid PET Imaging in Cognitive Impairment," *CNS Drugs* 29, 605–613 (2015), which is hereby incorporated by reference in its entirety); and Flutemetamol (Heurling *et al.*, "Imaging β-amyloid Using [^{18}F] Flutemetamol Positron

Emission Tomography: From Dosimetry to Clinical Diagnosis," *European Journal of Nuclear Medicine and Molecular Imaging* 43.2: 362-373 (2016), which is hereby incorporated by reference in its entirety).

^{18}F-florbetapir can provide a qualitative and quantitative measurement of brain plaque load in patients, including patients with prodromal AD or mild AD dementia. For example, the absence of significant ^{18}]-florbetapir signal on a visual read indicates patients clinically manifesting cognitive impairment have sparse to no amyloid plaques. As such, ^{18}F-florbetapir also provides a confirmation of amyloid pathology. ^{18}F-Florbetapir PET also provides quantitative assessment of fibrillar amyloid plaque in the brain and, in some embodiments, can be used to assess amyloid plaque reductions from the brain by antibodies of the present disclosure.

Amyloid imaging with radiolabeled PET compounds can also be used to determine if Aβ deposit in the brain of a human patient is reduced or increased (*e.g.*, to calculate the percentage reduction in Aβ deposit post treatment or to assess the progression of AD). A person of skill in the art can correlate the standardized uptake value ratio (SUVr) values obtained from amyloid imaging (with radiolabeled PET compounds) to calculate the % reduction in Aβ deposit in the brain of the patient before and after treatment. The SUVr values can be converted to standardized centiloid (CL) units, where 100 is average for AD and 0 is average for young controls, allowing comparability amongst amyloid PET tracers, and calculation of reduction according to centiloid units (Klunk *et al.*, "The Centiloid Project: Standardizing Quantitative Amyloid Plaque Estimation by PET," *Alzheimer's & Dementia* 11.1: 1-15 (2015) and Navitsky *et al.*, "Standardization of Amyloid Quantitation with Florbetapir Standardized Uptake Value Ratios to the Centiloid Scale," *Alzheimer's & Dementia* 14.12: 1565-1571 (2018), which are hereby incorporated by reference in their entireties). In some embodiments, the change in brain amyloid plaque deposition from baseline is measured by ^{18}F-florbetapir PET scan.

Cerebrospinal fluid or plasma-based analysis of β-amyloid can also be used to measure the amyloid load/burden for the purposes of the present disclosure. For example, Aβ42 can be used to measure brain amyloid (Palmqvist, S. *et al.*, "Accuracy of Brain Amyloid Detection in Clinical Practice Using Cerebrospinal Fluid Beta-amyloid 42: a Cross-validation Study Against Amyloid Positron Emission Tomography. *JAMA Neurol* 71, 1282-1289 (2014), which is hereby incorporated by reference in its entirety). In some

embodiments, the ratio of Aβ42/Aβ40 or Aβ42/Aβ38 can be used as a biomarker for amyloid beta (Janelidze *et al.*, "CSF Abeta42/Abeta40 and Abeta42/Abeta38 Ratios: Better Diagnostic Markers of Alzheimer Disease," *Ann Clin Transl Neurol* 3, 154-165 (2016), which is hereby incorporated by reference in its entirety).

In some embodiments, deposited brain amyloid plaque or Aβ in CSF or plasma can be used to stratify subjects into groups and to identify which group of subjects is responsive to treatment/prevention of a disease (as described herein) using the antibodies, the dosing regimen, or the methods described herein.

In some embodiment, solanezumab is administered by intravenous infusion. In another embodiment, solanezumab is administered subcutaneously.

Solanezumab binds selectively to Aβ found in the brain. Exemplary embodiments of anti-Aβ antibodies of the present disclosure include solanezumab, which is described in (including methods of making and using it) in the following patent documents, which are expressly incorporated herein by reference: US Patent No. 7,195,761, US Patent Application Publication No. 20060039906, US Patent No. 7,892,545, US Patent No. 8,591,894, US Patent No, 7,771,722, US Patent Application Publication No. 20070190046.

Skilled artisans will recognize that solanezumab is an IgG1 monoclonal antibody having complementarity-determining regions (CDRs). Solanezumab binds to the mid-domain of the Aβ peptide. In some embodiments, the antibody has the following sequence.

Light Chain (SEQ ID NO: 1):
DVVMTQSPLSLPVTLGQPASISCRSSQSLIYSDGNAYLHWFLQKPGQSPRLLIYKV
SNRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCSQSTHVPWTFGQGTKVEI
KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ
ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Heavy Chain (SEQ ID NO: 2):
EVQLVESGGGLVQPGGSLRLSCAASGFTFSRYSMSWVRQAPGKGLELVAQINSV
GNSTYYPDTVKGRFTISRDNAKNTLYLQMNSLRAEDTAVYYCASGDYWGQGTL
VTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDK
THTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY

VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQP
ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL
SLSPGK

The antibody of the preceding sequence (as well the antibodies of the patents noted above in the following patent documents US Patent No. 7,195,761, US Patent Application Publication No. 20060039906, US Patent No. 7,892,545, US Patent No. 8,591,894, US Patent No, 7,771,722, US Patent Application Publication No. 20070190046) may be formulated and referred to as solanezumab. Thus, the present embodiments include antibodies with SEQ ID NOs: 1 and 2 or other antibodies, as well as those antibodies which have been formulated in a composition called solanezumab. Those skilled in the art will appreciate that any of the antibodies recited in the present disclosure may be used.

Information about Solanezumab used in combination with other antibodies is found in US Patent Application Publication No. 20190382471, which is expressly incorporated herein by reference in its entirety.

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.

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 (imgt.cines.fr), or from *The Immunoglobulin FactsBook* by Marie-Paule Lefranc and Gerard Lefranc, Academic 25 Press, 2001, ISBN 012441351.Techinques for generating human or humanized antibodies are well known in the art. In another embodiment of the present disclosure, the antibody, or the nucleic acid encoding the same, 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%.

Solanezumab 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 parental routes (*e.g.*, subcutaneous, intravenous, intraperitoneal, intramuscular). Subcutaneous and intravenous routes are preferred.

The terms "treatment," "treating" or "to treat" and the like include restraining, slowing, or stopping the progression or severity of an existing symptom, condition, disease, or disorder in a subject. The term "subject" refers to a human subject or a patient.

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.

The terms "disease characterized by deposition of Aβ" or a "disease characterized by Aβ deposits" are used interchangeably and refer to a disease that is pathologically characterized by Aβ deposits 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); Alzheimer's Disease Cooperative Study – instrumental items of the Activities of Daily Living Inventory (ADCS-iADL)). 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 patient 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 APOE ε4 alleles.

A reduction or slowing of cognitive decline can be measured by cognitive assessments such as Clinical Dementia Rating – summary of boxes (CDR-SB), Mini-Mental State Exam (MMSE), or Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog). A reduction or slowing of functional decline can be measured by functional assessments such as Alzheimer's Disease Competence Scale- Activities of Daily Living (ADCS-ADL).

As used herein, "mg/kg" means an amount, in milligrams, of antibody or drug administered to a subject based on his or her bodyweight in kilograms. A dose is given at one time. For example, a 10 mg/kg dose of antibody for a subject weighing 70 kg would be a single 700 mg dose of antibody given in a single administration. Similarly, a 20 mg/kg dose of antibody for a subject weighing 70 kg would be a 1400 mg dose of antibody given at a single administration.

As used herein, a human subject has "very low tau" burden if the tau burden is less than 1.10 SUVr (<1.10 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 (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*, *e.g.*, Southekal *et al.*, "Flortaucipir F 18 Quantitation Using Parametric Estimation of Reference Signal Intensity," J. *Nucl. Med.* 59:944–951 (2018)). See also, International Patent Application No. PCT/US2022/011894, which is hereby incorporated by reference in its entirety.

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)). See also, International Patent Application No. PCT/US2022/011894, which is hereby incorporated by reference in its entirety.

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. See also, International Patent Application No. PCT/US2022/011894, which is hereby incorporated by reference in its entirety.

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)). See also, International Patent Application No. PCT/US2022/011894, which is hereby incorporated by reference in its entirety.

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

The terms "human subject" and "patient" are used interchangeably in the present disclosure.

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

The following Figures 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.

Example 1: Clinical Trials for Solanezumab

Expedition-1 and Expedition-2: Alzheimer's patients were studied in two phase 3, double-blind trials (Expedition-1 and Expedition-2, ClinicalTrials.gov numbers, NCT00905372 and NCT00904683, respectively), which randomly assigned 1012 and 1040 patients, respectively, with mild-to-moderate Alzheimer's disease to receive placebo or solanezumab (administered intravenously at a dose of 400 mg) every 4 weeks for 18 months. (Doody, *et al.*, "Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease", *New England Journal of Medicine*, 370; 4, pp. 311-321 (2014), which is hereby incorporated by reference in its entirety). The primary outcomes were the changes from baseline to week 80 in scores on the 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog11; range, 0 to 70, with higher scores indicating greater cognitive impairment) and the Alzheimer's Disease Cooperative Study–Activities of Daily Living scale (ADCS-ADL; range, 0 to 78, with lower scores indicating worse functioning). After analysis of data from Expedition-1, the primary outcome for Expedition-2 was revised to the change in scores on the 14-item cognitive subscale of the Alzheimer's Disease

Assessment Scale (ADAS-Cog14; range, 0 to 90, with higher scores indicating greater impairment), in patients with mild Alzheimer's disease.

Both trials involved otherwise healthy patients 55 years of age or older who had mild-to-moderate Alzheimer's disease without depression. Mild-to-moderate Alzheimer's disease was documented on the basis of a score of 16 to 26 on the Mini–Mental State Examination (MMSE; score range, 0 to 30, with higher scores indicating better cognitive function) and the criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association. The absence of depression was documented on the basis of a score of 6 or less on the Geriatric Depression Scale (score range, 0 to 15, with higher scores indicating more severe depression). Participants were randomly assigned to receive solanezumab (400 mg) or placebo, administered as an intravenous infusion of approximately 70 ml over a period of 30 minutes, once every 4 weeks for 18 months. Concomitant treatment with cholinesterase inhibitors, memantine, or both was allowed.

Expedition-3: A double-blind, placebo-controlled, phase 3 trial involving patients with mild dementia due to Alzheimer's disease, defined as a Mini–Mental State Examination (MMSE) score of 20 to 26 (on a scale from 0 to 30, with higher scores indicating better cognition) and with amyloid deposition shown by means of florbetapir positron-emission tomography or Aβ1-42 measurements in cerebrospinal fluid (Expedition-3, ClinicalTrials.gov number, NCT01900665). Patients were randomly assigned to receive solanezumab at a dose of 400 mg or placebo intravenously every 4 weeks for 76 weeks. The primary outcome was the change from baseline to week 80 in the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog14; scores range from 0 to 90, with higher scores indicating greater cognitive impairment). (Honig, *et al.*, "Trial of Solanezumab for Mild Dementia Due to Alzheimer's Disease," *New England Journal of Medicine*, vol 78, No. 4, pp. 321-300 (2018), which is hereby incorporated by reference in its entirety). This trial included male and female patients, 55 to 90 years of age, who met the diagnostic criteria for probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association. Unlike the Expedition-1 and Expedition-2 trials, the Expedition-3 trial included only patients with mild Alzheimer's disease who had biomarker evidence of amyloid-related disease, determined by means of either florbetapir

positron-emission tomography (PET) scan or Aβ1-42 measurements in cerebrospinal fluid (CSF).

Patients were randomly assigned in double-blind fashion to receive intravenous infusions of either solanezumab at a dose of 400 mg or placebo every 4 weeks for 76 weeks. Patients who completed the double-blind period could participate in an optional 24-month open-label period. Concomitant therapy, including treatments for symptoms of dementia (acetylcholinesterase inhibitors and memantine, alone or in combination) and nondrug treatments, was allowed in order to ensure that patients continued receiving the standard of care for Alzheimer's disease. The primary objective of the trial was to test the hypothesis that solanezumab would slow the cognitive decline of Alzheimer's disease, as compared with placebo, in patients with mild dementia due to Alzheimer's disease.

Analysis of data from Expedition-1, Expedition-2 and Expedition-3 show that solanezumab shows better clinical outcomes in carriers of APOE ε4 than non-carriers. The better clinical outcomes are shown on the Integrated AD Rating Scale (iADRS; a primary endpoint which is a composite tool measuring cognition and daily function), the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB), and ADAS-Cog scale. A 42% slowing in decline on the ADAS-Cog14 scale was observed in Expedition-1 and Expedition-2 trials. In Expedition-3 in Mild AD Dementia patients, there was a 15% slowing in decline.

Table 2 shows that administration of solanezumab to APOE ε4 carriers of Expedition-3 performed better in slowing decline than non-carriers:

Table 2: Change in MMSE based upon APOE ε4 status.

APOE ε4 status	**Placebo**	**Sola**	**Difference**	**% Slowing**
Carrier	-3.65	-2.96	-0.69	18.9%
Non-carrier	-3.65	-3.7	0.05	-1.4%

Table 3: Change in Expedition-3 of CDS-SB by APOE ε4 status.

APOE ε4 status	**Placebo**	**Sola**	**Difference**	**% Slowing**
Carrier	2.03	1.66	0.37	18.2%
Non-carrier	2.4	2.25	0.15	6.3%

Table 4: Change in ADCS-ADL by APOE ε4 status in Expedition-3.

APOE ε4 status	**Placebo**	**Sola**	**Difference**	**% Slowing**

Carrier	-7.66	-6.34	-1.32	17.2%
Non-carrier	-9.06	-8.21	-0.85	9.4%

Thus, as can be seen from this data, when a human subject who is a carrier of APOE ε4 is given solanzumab, that subject performs better on clincial endpoints. In Table 2, the APOE ε4 carriers had a ~19% slowing of cognitive decline vs. placebo on the MMSE scale (Figures 9 and 10A-B). In Table 3, the carriers had a 18% slowing of cognitive decline vs. placebo on the CDR-SB scale (Figures 11 and 12A-B). In Table 4, the carriers had a 17% slowing of cognitive decline vs. placebo on the ADCS-ADL scale (Figures 13 and 14A-B). Additionally, carriers had a 17% slowing of cognitive decline vs. placebo in Expedition-3 and a 28% slowing in pooled data from Expedition-1 and -2 on the ADCS-iADL scale.

The APOE ε4 carriers had a 15% slowing of cognitive decline vs. placebo in Expedition-3 (Figures 4A, 4B) and a 42% slowing in cognitive decline in pooled data from Expedition-1 and -2 (Figures 5A and 5B).

Figure 15 shows a change on the iADRS scale between the carriers and non-carriers of APOE ε4. Specifically, the carriers had a 11% slowing of cognitive decline vs. placebo in Expedition-3.

In Expedition-3, for treatment with low-dose of solanezumab (400mg IV every month), all outcome measures had a larger effect size in the APOE ε4 carrier group relative to the non-carrier group although treatment differences did not reach significance for the iADRS and ADAS-Cog14. In the CDR-SB, solanezumab reduced the clinical decline by 18% ($p=0.009$) at 80 weeks. In the ADCS-iADL and the MMSE, the slowing rates were respectively 17% ($p=0.017$) and 19% ($p=0.005$), and the treatment differences were significant as early as 64 weeks for both scales. Effect sizes were larger in all clinical outcome measures in pooled mild AD dementia data from Expedition-1 and Expedition-2. Low-dose solanezumab slowed the clinical decline by 42% as measured with the ADAS-Cog14 ($p<0.001$) and by 28% in the ADCS-iADL ($p<0.01$) in APOE ε4 carriers. In the 3 clinical studies (Expedition-1, -2, and -3), solanezumab did not affect the clinical state of APOE ε4 non-carriers. Outcome measures show higher effect sizes for carriers compared to non-carriers and often larger and significant treatment differences in the carrier population.

Across all therapeutic clinical trials selected for the presence of amyloid pathology, at baseline, carriers are younger and have higher amyloid loads and higher tau pathology. The clinical decline across all scales for the placebo groups does not differ by carrier status. For placebo groups, comparison of carrier status shows there is no significant longitudinal change in amyloid, however there is a trend toward greater tau change in carriers vs. non-carriers. The relative longitudinal change of amyloid while on therapy shows a greater decrease in non-carriers than carriers. One hypothesis to consider is the interaction of APOE ε4 with tau. It has been known that amyloid deposition concentrates and contains APOE ε4 embedded within the plaque. More recently, it was shown that APOE ε4 is also isolated with tau tangles. Animal data further suggest that there is an APOE ε4 interaction with tau. In addition, a rare mutation in APOE ε4 appeared to protect a subject, carrying an autosomal dominant PSEN1 mutation, well beyond the age of typical onset despite having substantial brain amyloid load but relatively low tau burden. Data suggests that APOE ε4 also influences tau beyond an amyloid interaction and that the rate of tau change may be faster in carriers. Furthermore, the impact of treatment may have a greater influence on tau progression which is more directly linked to clinical progression. Tau progression and spread has been linked to LRP1. (Rauch, *et al.*, "LRP1 is a Master Regulator of Tau Uptake and Spread," *Nature*; 580(7803):381-385 (2020), which is hereby incorporated by reference in its entirety). Recently reported, LRP1 appears to facilitate tau internalization and degradation via an APOE ε4 mediated mechanism. (*See* Cooper *et al.*, "Regulation of Tau Internalization, Degradation, and Seeding by LRP1 Reveals Multiple Pathways for Tau Catabolism," *Journal of Biological Chemistry*, Vol. 296 (2021) (which is hereby incorporated by reference in its entirety). So, LRP1 seems ideally linked given its interaction with APOE ε4 and tau and the interaction of APOE ε4 with amyloid and tau.

WE CLAIM:

1. A method of treating or preventing a disease characterized by amyloid beta (Aβ) deposits in the brain of a human subject having an APOE ε4 allele comprising:

i) administering a therapeutically effective amount of an antibody comprising SEQ ID NO: 1 and SEQ ID NO: 2, or pharmaceutical composition thereof, to the human subject that has one or two alleles of APOE ε4.

2. A method of treating or preventing a disease characterized by amyloid beta (Aβ) deposits in the brain of a human subject having been identified as having an APOE ε4 allele, comprising:

i) administering a therapeutically effective amount of an antibody comprising SEQ ID NO: 1 and SEQ ID NO: 2 to the human subject.

3. A method of treating or preventing a disease characterized by amyloid beta (Aβ) deposits in the brain of a human subject, comprising:

i) identifying or having identified the human subject as having an APOE ε4 allele; and

ii) if the human subject is identified as having an APOE ε4 allele, administering or having administered a therapeutically effective amount of an antibody comprising SEQ ID NO: 1 and SEQ ID NO: 2 to the human subject.

4. A method of treating or preventing a disease characterized by amyloid beta (Aβ) deposits in the brain of a human subject, comprising:

i) administering a therapeutically effective amount of an antibody comprising SEQ ID NO: 1 and SEQ ID NO: 2 to the human subject, wherein the human subject has an APOE ε4 allele.

5. A method according to any of claims 1-4, wherein the antibody is solanezumab.

6. A method according to any of claim 1-5 wherein said step of administering comprises administering one or more than one dose of the antibody.

7. A method according to any of claims 1-6 wherein the human subject has two APOE ε4 alleles.

8. The method according to any one of claims 1-7, wherein the disease characterized by Aβ deposit 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, or pre-clinical cerebral amyloid angiopathy.

9. The method according to any one of claims 1-7, wherein the human subject is administered the antibody for a duration sufficient to treat or prevent the disease.

10. The method according to any one of claims 1-9, wherein the treatment or prevention of the disease slows cognitive or functional decline in the human subject.

11. The method according to any one of claims 1-9, wherein the treatment or prevention of the disease reduces amyloid load in the brain of the human subject.

12. The method according to any one of claims 1-11, the antibody is administered to the subject till amyloid deposits or plaques are cleared from the subject's brain.

13. The method according to claim 11, wherein the reduction in amyloid load in the brain of the human subject is determined by amyloid PET brain imaging or a diagnostic that detects a biomarker for Aβ.

14. The method according to claim 1, wherein the human subject has early symptomatic AD.

15. The method according to claim 14, wherein the human subject has prodromal AD and/or mild dementia due to AD.

16. The method according to claim 1, wherein the human subject has preclinical AD.

17. The method according to claim 16, wherein the human subject has evidence of elevated brain amyloid.

18. The method according to any one of claims 1-17, wherein the antibody is administered at a dose of 400 mg every 4 weeks, 800 mg every 4 weeks, 1200 mg every 4 weeks, 1600 mg every 4 weeks, 2000 mg every 4 weeks, 2400 mg every 4 weeks, 2800 mg every 4 weeks, 3200 mg every 4 weeks, 3600 mg every 4 weeks, 4000 mg every 4 weeks, 4400 mg every 4 weeks, 4800 mg every 4 weeks, 5200 mg every 4 weeks, or 5600 mg every 4 weeks.

19. The method of claim 18, wherein the antibody is administered at an initial dose of 400 mg every 4 weeks and is titrated to 1600 mg every 4 weeks.

20. The method of claim 18, wherein the antibody is administered at an initial dose of 1600 mg every 4 weeks and is titrated to 400 mg every 4 weeks.

21. A method of reducing amyloid load in the brain of a human subject having an APOE ε4 allele comprising:

i) administering a therapeutically effective amount of an antibody comprising SEQ ID NO: 1 and SEQ ID NO: 2, or pharmaceutical composition thereof, to the human subject that has one or two alleles of APOE ε4.

22. A method of reducing amyloid load in the brain of a human subject having been identified as having an APOE ε4 allele, comprising:

i) administering an antibody comprising SEQ ID NO: 1 and SEQ ID NO: 2 to the human subject.

23. A method of reducing amyloid load in the brain of a human subject, comprising:

i) identifying or having identified the human subject as having an APOE ε4 allele; and

ii) if the human subject is identified as having an APOE ε4 allele, administering or having administered an antibody comprising SEQ ID NO: 1 and SEQ ID NO: 2 to the human subject.

24. A method of reducing amyloid load in the brain of a human subject, comprising:

i) administering an antibody comprising SEQ ID NO: 1 and SEQ ID NO: 2 to the human subject, wherein the human subject has an APOE ε4 allele.

25. A method according to any of claims 21-24, wherein the antibody is solanezumab.

26. A method according to any of claim 21-25 wherein said step of administering comprises administering one or more than one dose of the antibody.

27. A method according to any of claims 21-26 wherein the human subject has two APOE ε4 alleles.

28. The method according to any one of claims 21-27, wherein the disease characterized by Aβ deposit 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, or pre-clinical cerebral amyloid angiopathy.

29. The method according to any one of claims 21-27, wherein the human subject is administered the antibody for a duration sufficient to treat or prevent the disease.

30. The method according to any one of claims 21-29, wherein the treatment or prevention of the disease slows cognitive or functional decline in the human subject.

31. The method according to any one of claims 21-30, the antibody is administered to the subject till amyloid deposits or plaques are cleared from the subject's brain.

32. The method according to claim 31, wherein the reduction in amyloid load in the brain of the human subject is determined by amyloid PET brain imaging or a diagnostic that detects a biomarker for Aβ.

33. The method according to claim 21, wherein the human subject has early symptomatic AD.

34. The method according to claim 33, wherein the human subject has prodromal AD and/or mild dementia due to AD.

35. The method according to claim 21, wherein the human subject has preclinical AD.

36. The method according to claim 35, wherein the human subject has evidence of elevated brain amyloid.

37. The method according to any one of claims 21-36, wherein the antibody is administered at a dose of 400 mg every 4 weeks, 800 mg every 4 weeks, 1200 mg every 4 weeks, 1600 mg every 4 weeks, 2000 mg every 4 weeks, 2400 mg every 4 weeks, 2800 mg every 4 weeks, 3200 mg every 4 weeks, 3600 mg every 4 weeks, 4000 mg every 4 weeks, 4400 mg every 4 weeks, 4800 mg every 4 weeks, 5200 mg every 4 weeks, or 5600 mg every 4 weeks.

38. The method of claim 37, wherein the antibody is administered at an initial dose of 400 mg every 4 weeks and is titrated to 1600 mg every 4 weeks.

39. The method of claim 38, wherein the antibody is administered at an initial dose of 1600 mg every 4 weeks and is titrated to 400 mg every 4 weeks.

40. An antibody for use in the treatment or prevention of a disease characterized by Aβ deposits in the brain of a human subject, wherein the human subject carries one or two alleles of APOE ε4 and wherein the antibody comprises a light chain of SEQ ID NO: 1 and a heavy chain of SEQ ID NO: 2.

41. The antibody for use according to claim 40, wherein the disease characterized by Aβ deposit 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, or pre-clinical cerebral amyloid angiopathy.

42. The antibody for use according to any one of claims 40-41, wherein the human subject is an early symptomatic AD patient or wherein the human subject has prodromal AD and mild dementia due to AD.

Effect Sizes Across Trials		
Entire Group	Carrier	Non-Carrier
Exp 3 (67.8% Carrier)		
iADRS	0.10 (13%)	0.029 (3%)
ADAS-Cog	0.098 (15%)	0.000 (0%)
iADL	0.130* (17%)	0.073 (8%)
CDR-SB	0.125* (18%)	0.054 (6%)
MMSE	0.150* (19%)	Worse (-1%)
FAQ	0.083 (10%)	0.001 (0%)
TB1 (73% Carrier)		
iADRS 0.289	0.496* (49%)	Worse
ADAS 0.294	0.432* (54%)	Worse
iADL0.171	0.366* (44%)	Worse
CDR-SB 0.211	0.348* (36%)	Worse
MMSE 0.173	0.202 (25%)	0.010 (1%)

	Statistically sig
	Higher effect size
	Performs worse than placebo

FIG. 1

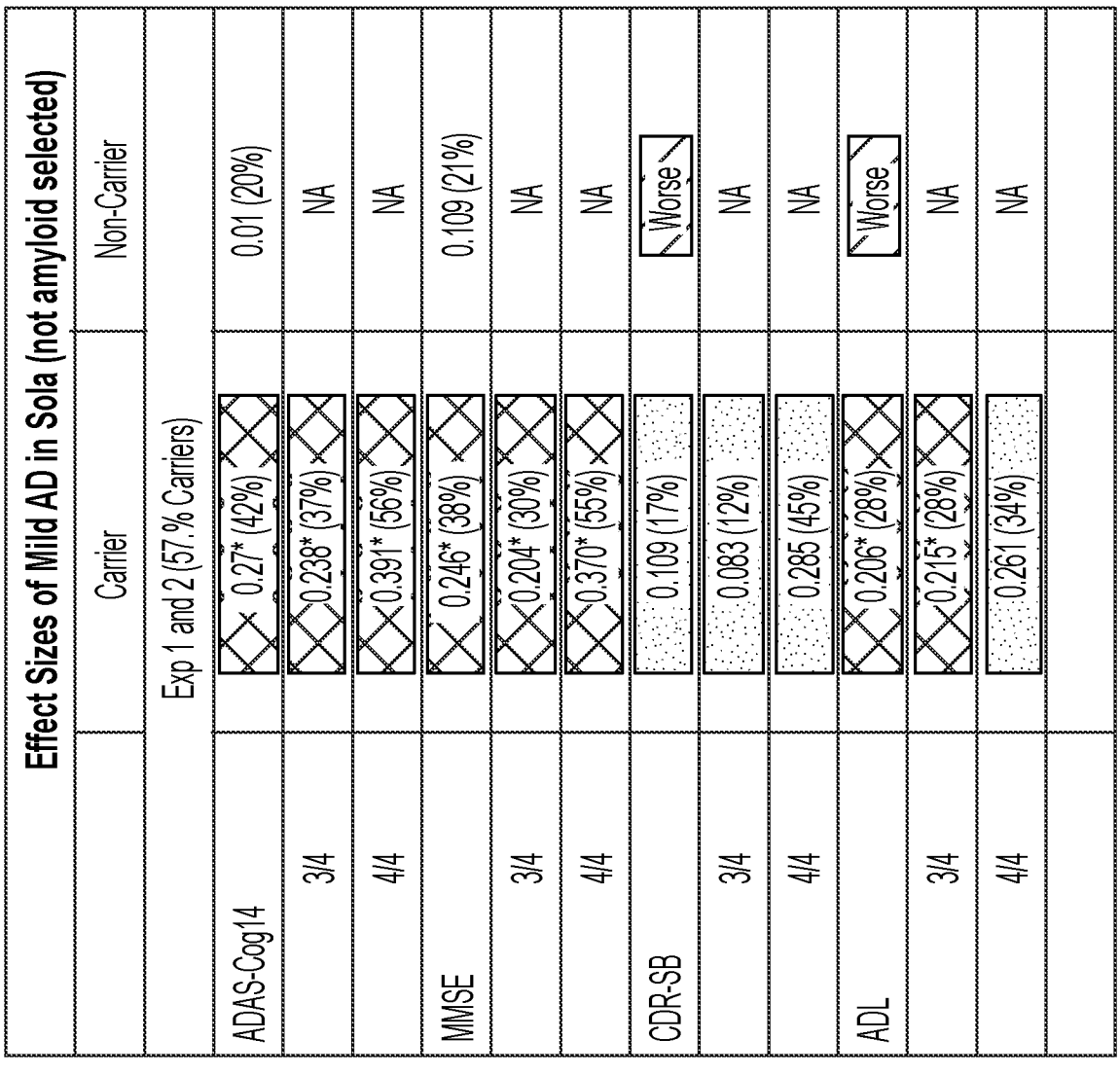
Effect Sizes of Mild AD in Sola (not amyloid selected)
Carrier
Non-Carrier
Exp 1 and 2 (57.% Carriers)
ADAS-Cog14
0.27* (42%)
0.01 (20%)
3/4
0.238* (37%)
NA
4/4
0.391* (56%)
NA
MMSE
0.246* (38%)
0.109 (21%)
3/4
0.204* (30%)
NA
4/4
0.370* (55%)
NA
CDR-SB
0.109 (17%)
Worse
3/4
0.083 (12%)
NA
4/4
0.285 (45%)
NA
ADL
0.206* (28%)
Worse
3/4
0.215* (28%)
NA
4/4
0.261 (34%)
NA
Pop
n
Total
1209
Carrier
696
Non-Carrier
513
3/4
507
4/4
156
Statistically sig
Higher effect size
Performs worse than placebo

FIG. 2

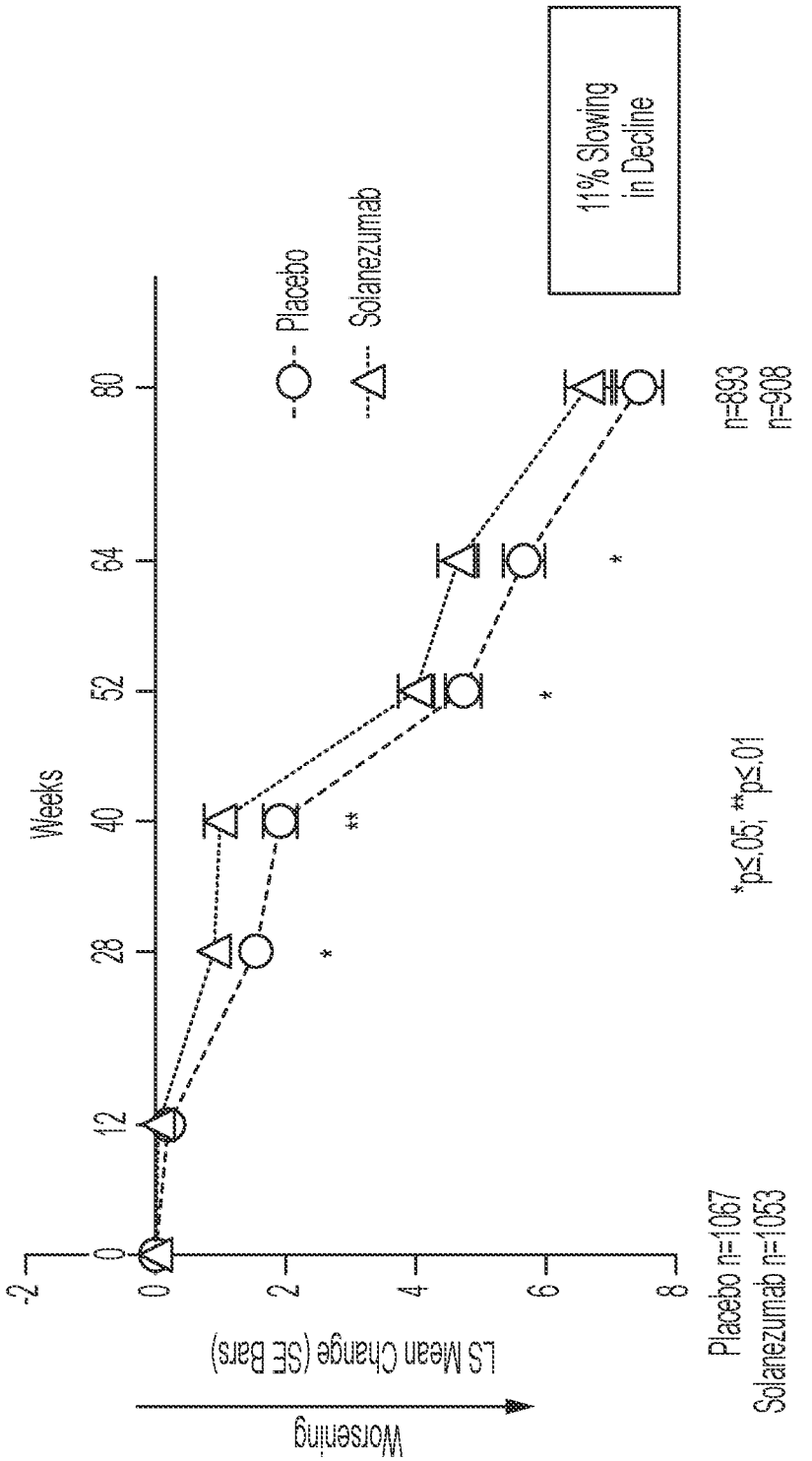
11% Slowing in Decline
Placebo
Solanezumab
Weeks
0
12
28
40
52
64
80
-2
0
2
4
6
8
LS Mean Change (SE Bars)
Worsening
n=893
n=908
*p≤.05; **p≤.01
Placebo n=1067
Solanezumab n=1053

FIG. 3

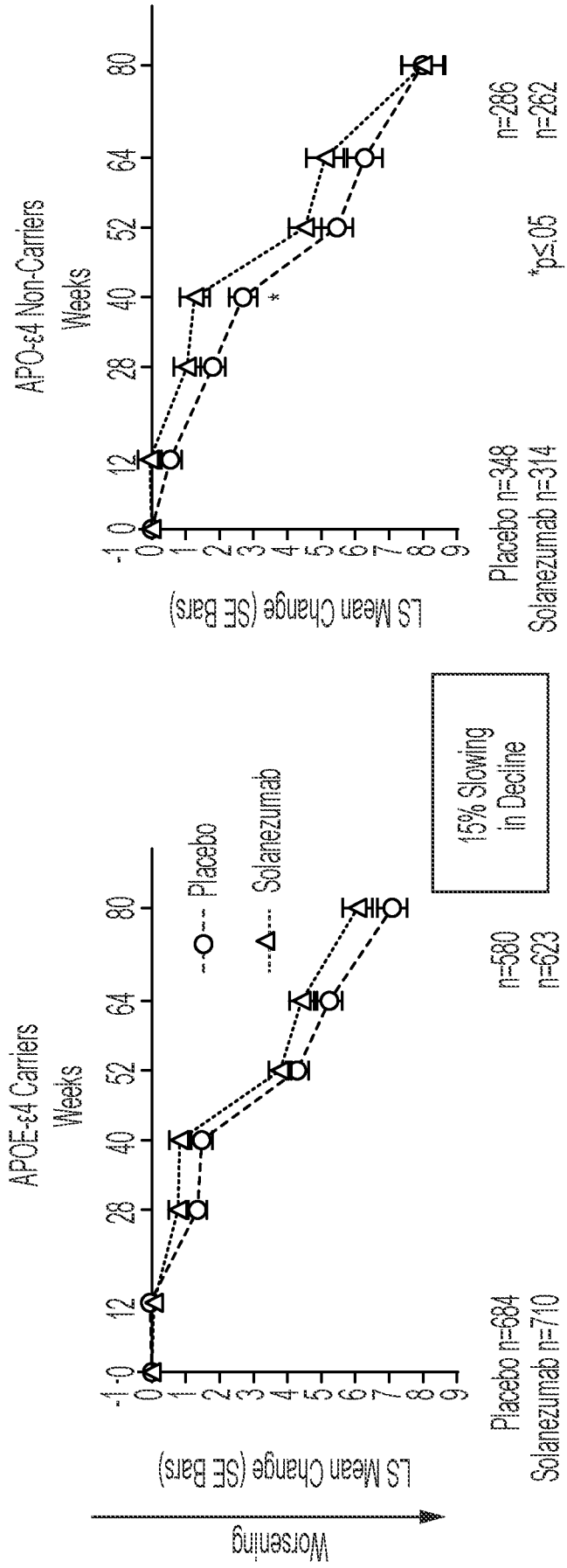
APOE-ε4 Carriers
Weeks
-1 0 12 28 40 52 64 80
0 1 2 3 4 5 6 7 8 9
LS Mean Change (SE Bars)
Worsening
Placebo
Solanezumab
Placebo n=684
Solanezumab n=710
n=580
n=623
15% Slowing in Decline
APO-ε4 Non-Carriers
Weeks
-1 0 12 28 40 52 64 80
0 1 2 3 4 5 6 7 8 9
LS Mean Change (SE Bars)
*
Placebo n=348
Solanezumab n=314
n=286
n=262
*p≤.05
APO-ε4 Carrier Status-by-Treatment interaction p-value=.157

FIG. 4A

FIG. 4B

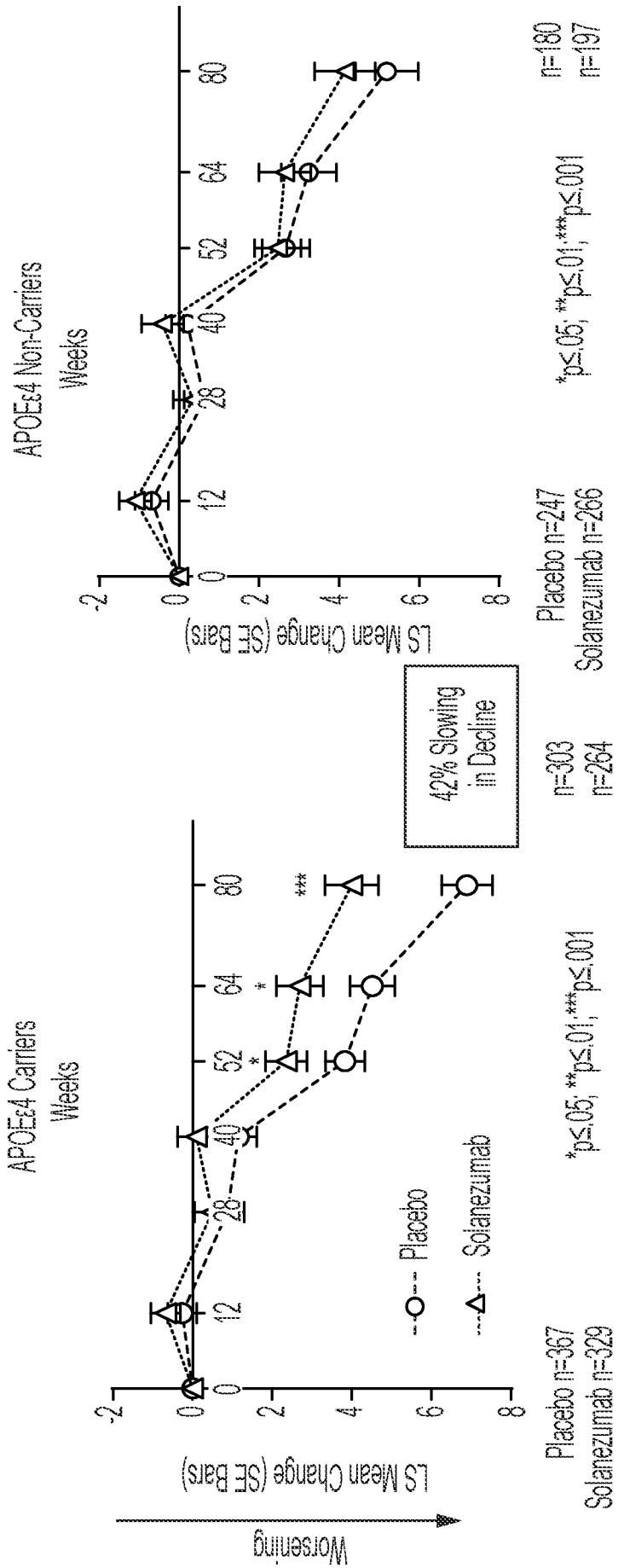
APOEε4 Carriers
Weeks
LS Mean Change (SE Bars)
Worsening
-2
0
2
4
6
8
0
12
28
40
52
64
80
Placebo
Solanezumab
*p≤.05; **p≤.01;***p≤.001
Placebo n=367
Solanezumab n=329
n=303
n=264
42% Slowing in Decline
APOEε4 Non-Carriers
Weeks
LS Mean Change (SE Bars)
Placebo n=247
Solanezumab n=266
*p≤.05; **p≤.01;***p≤.001
n=180
n=197

FIG. 5A

FIG. 5B

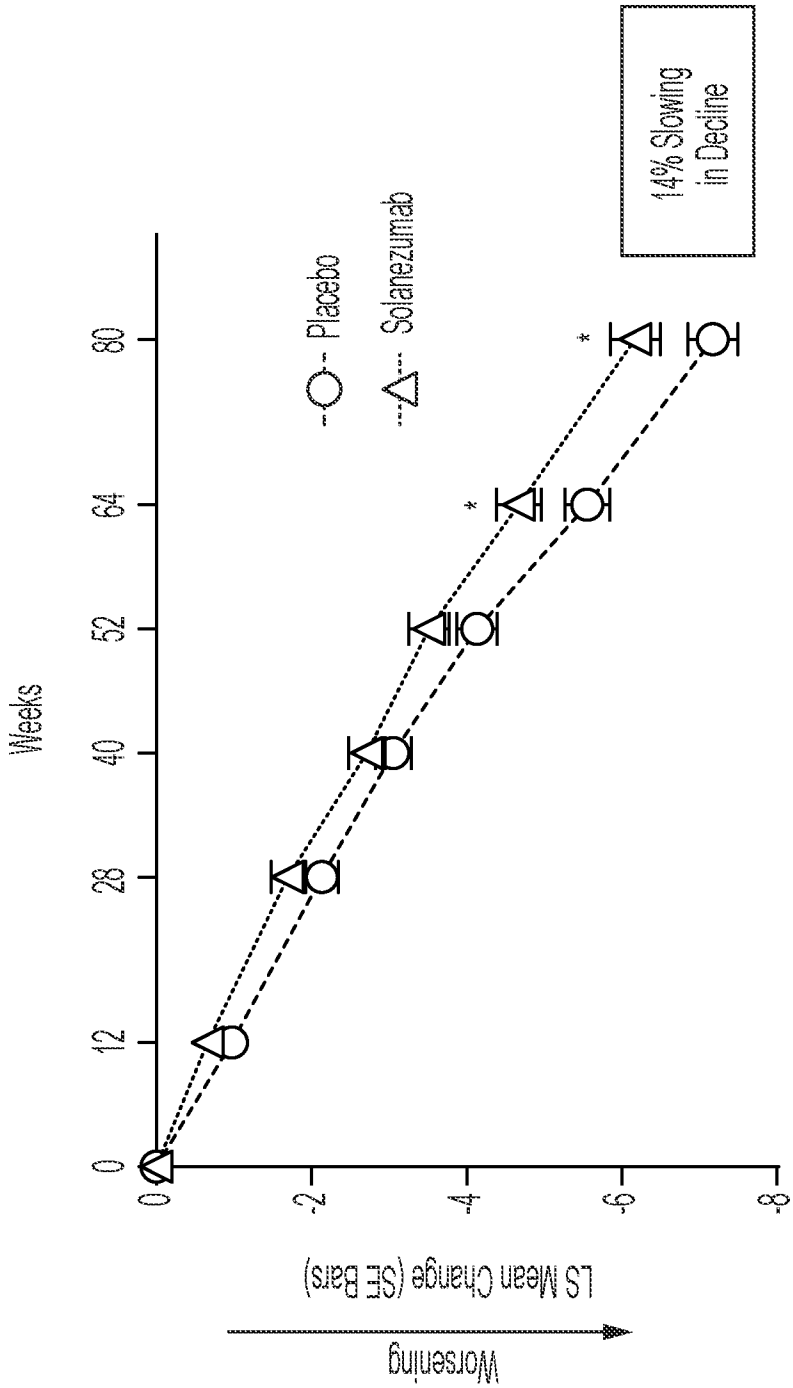
Placebo
Solanezumab
14% Slowing in Decline
Weeks
0
12
28
40
52
64
80
0
-2
-4
-6
-8
LS Mean Change (SE Bars)
Worsening
Placebo n=1063
Solanezumab n=1053
n=896
n=908
*p≤.05
*
*
*

FIG. 6

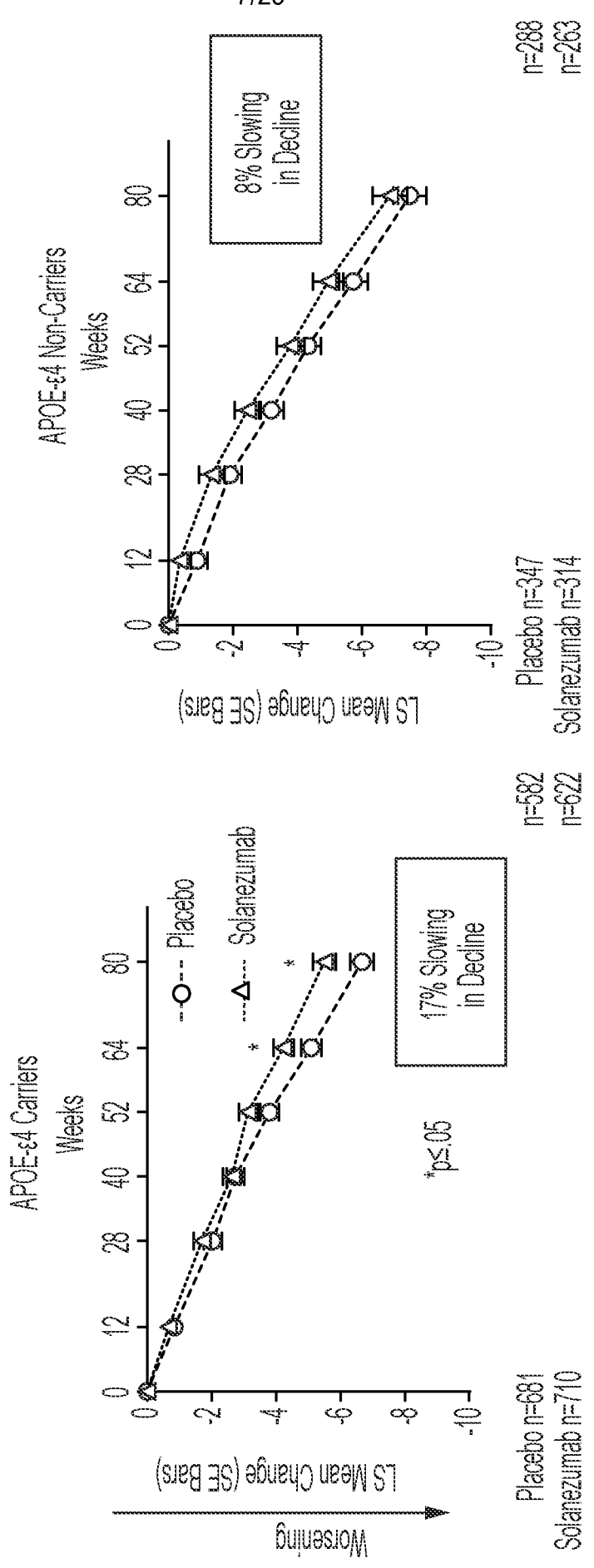
APOE-ε4 Carriers
Weeks
0
12
28
40
52
64
80
-2
-4
-6
-8
-10
LS Mean Change (SE Bars)
Worsening
Placebo
Solanezumab
*
*
*p≤.05
17% Slowing in Decline
Placebo n=681
Solanezumab n=710
n=582
n=622
APOE-ε4 Non-Carriers
Weeks
8% Slowing in Decline
Placebo n=347
Solanezumab n=314
n=288
n=263
APOE-ε4 Carrier Status-by-Treatment interaction p-value=.878

FIG. 7A

FIG. 7B

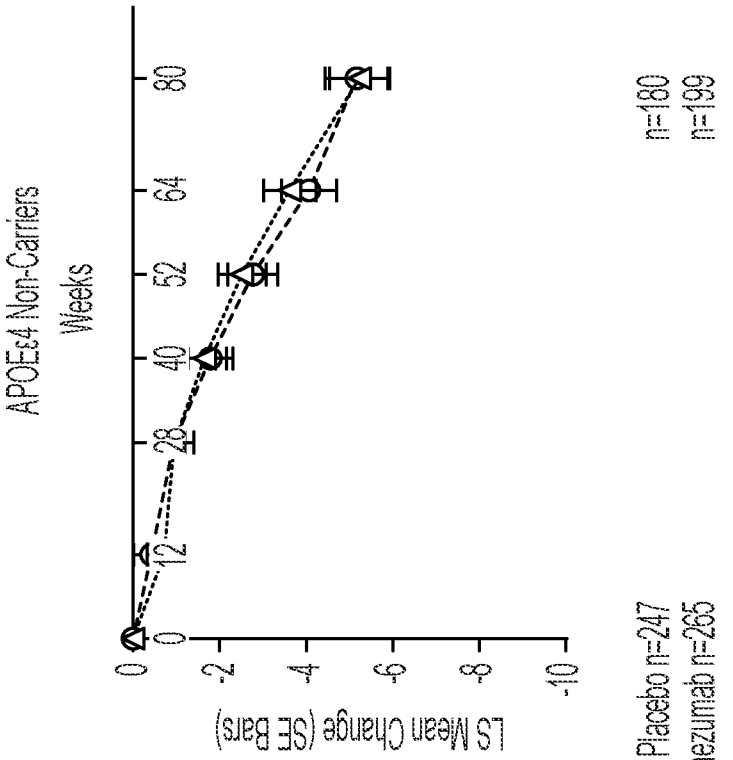
APOE ε4 Non-Carriers
Weeks
LS Mean Change (SE Bars)
0
12
28
40
52
64
80
-2
-4
-6
-8
-10
Placebo n=247
Solanezumab n=265
n=180
n=199

FIG. 8B

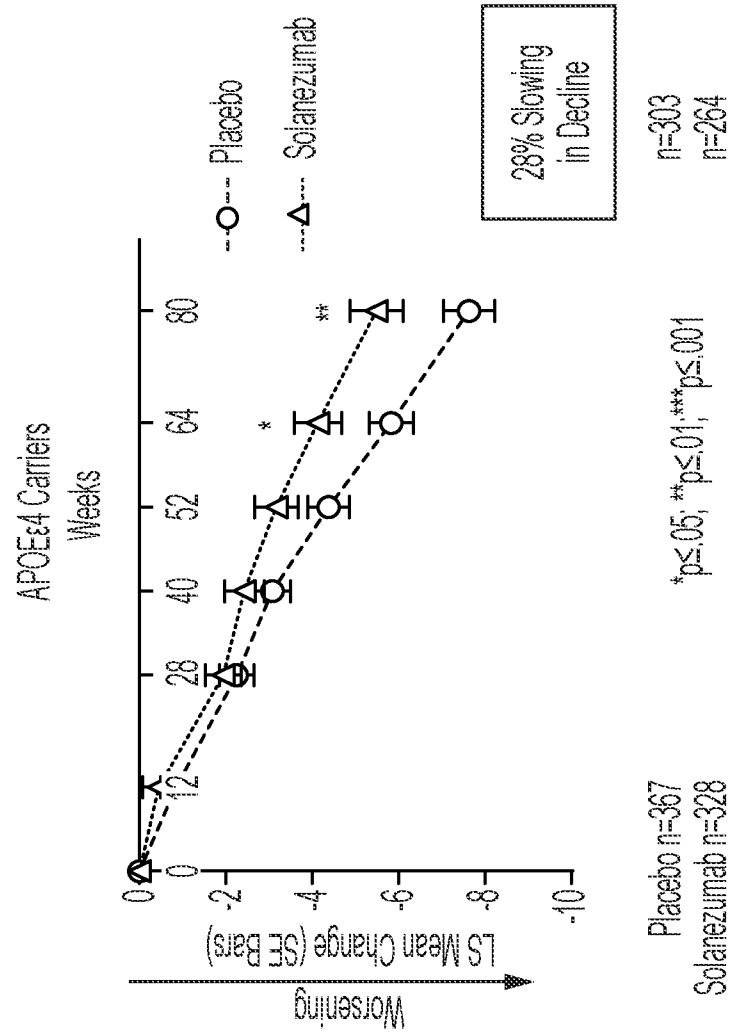
APOE ε4 Carriers
Weeks
LS Mean Change (SE Bars)
Worsening
0
12
28
40
52
64
80
-2
-4
-6
-8
-10
Placebo
Solanezumab
*
**
28% Slowing in Decline
Placebo n=367
Solanezumab n=328
n=303
n=264
*p≤.05; **p≤.01;***p≤.001

FIG. 8A

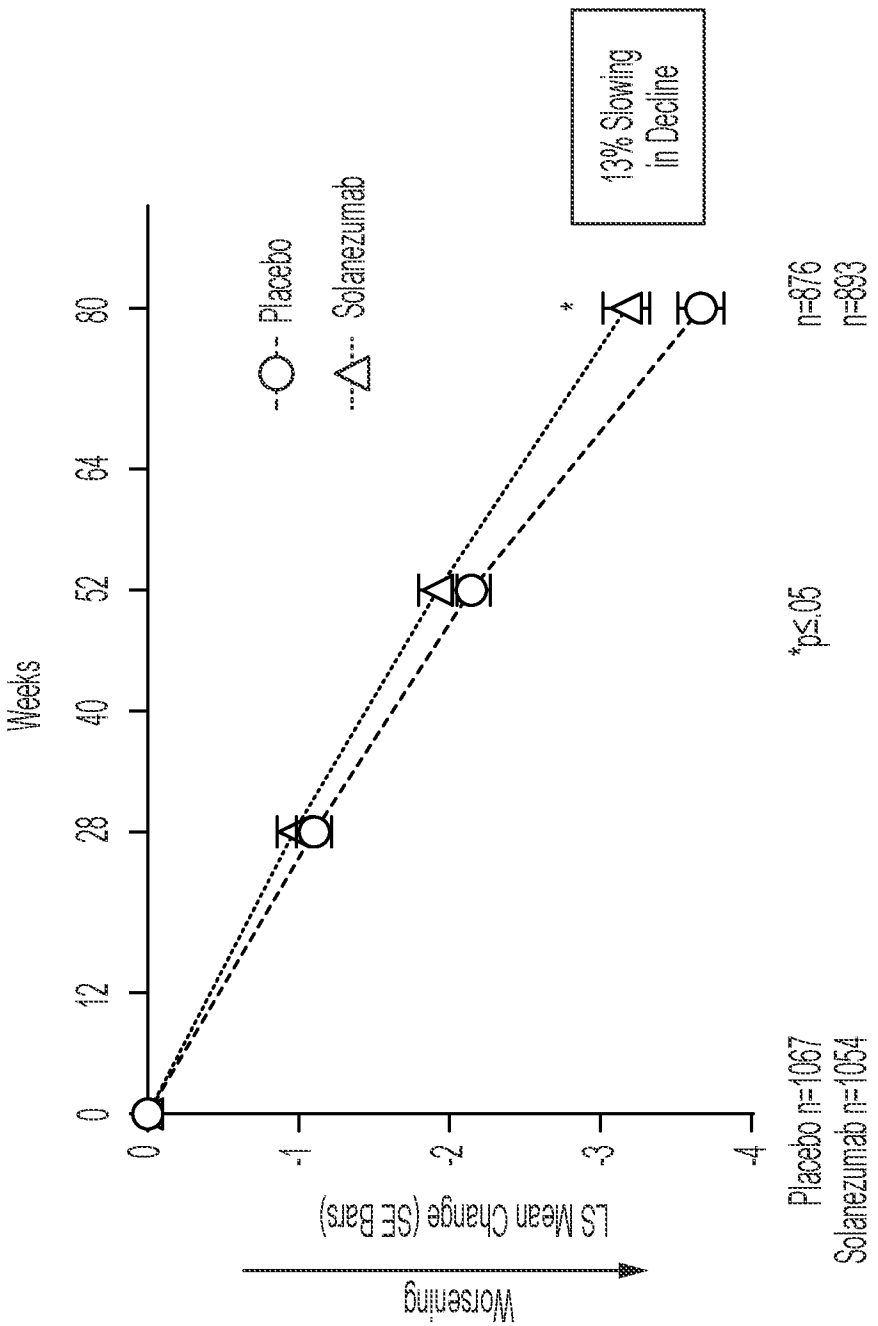
Placebo
Solanezumab
13% Slowing in Decline
Weeks
0
12
28
40
52
64
80
0
-1
-2
-3
-4
LS Mean Change (SE Bars)
Worsening
*
*p≤.05
Placebo n=1067
Solanezumab n=1054
n=876
n=893

FIG. 9

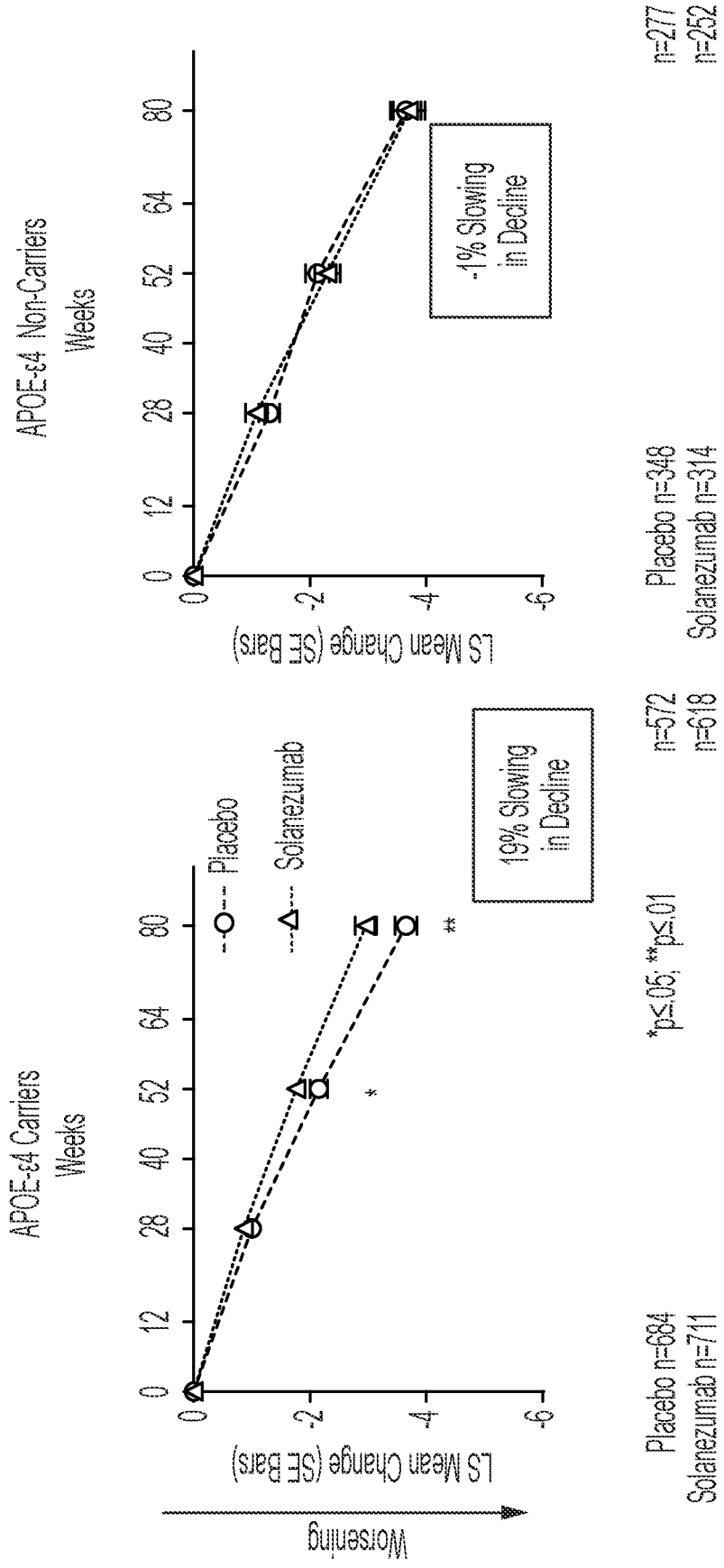

FIG. 10A

FIG. 10B

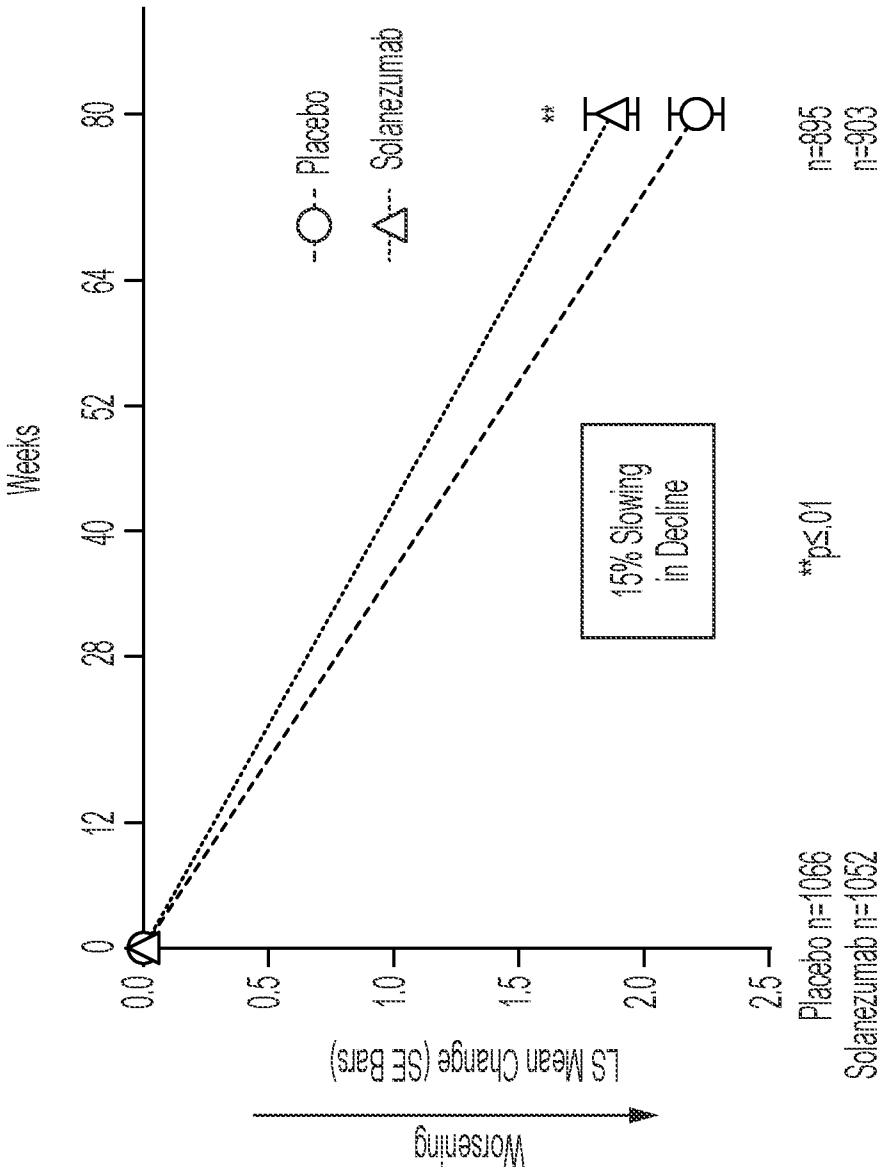
Weeks
0
12
28
40
52
64
80
0.0
0.5
1.0
1.5
2.0
2.5
LS Mean Change (SE Bars)
Worsening
Placebo
Solanezumab
**
15% Slowing in Decline
**p≤.01
Placebo n=1066
Solanezumab n=1052
n=895
n=903

FIG. 11

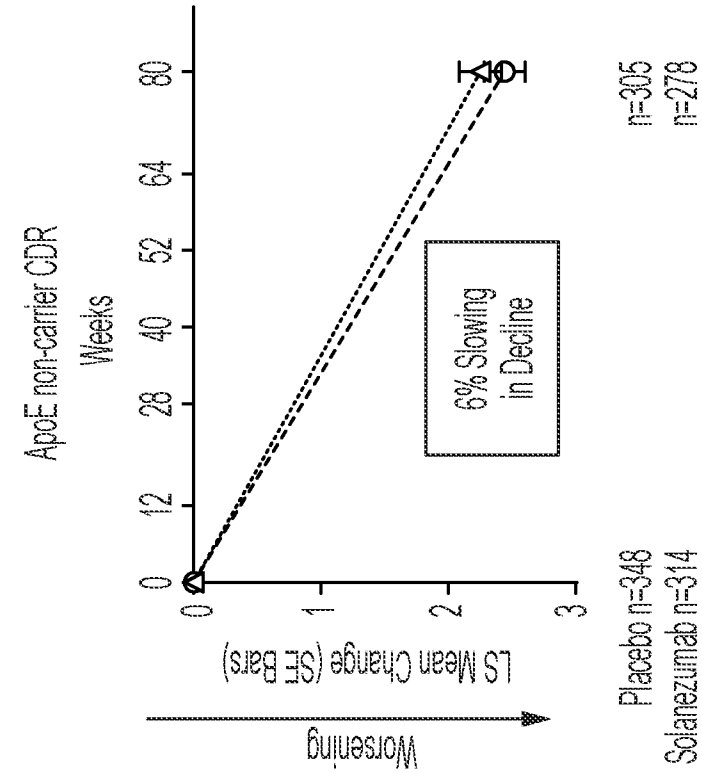

FIG. 12B

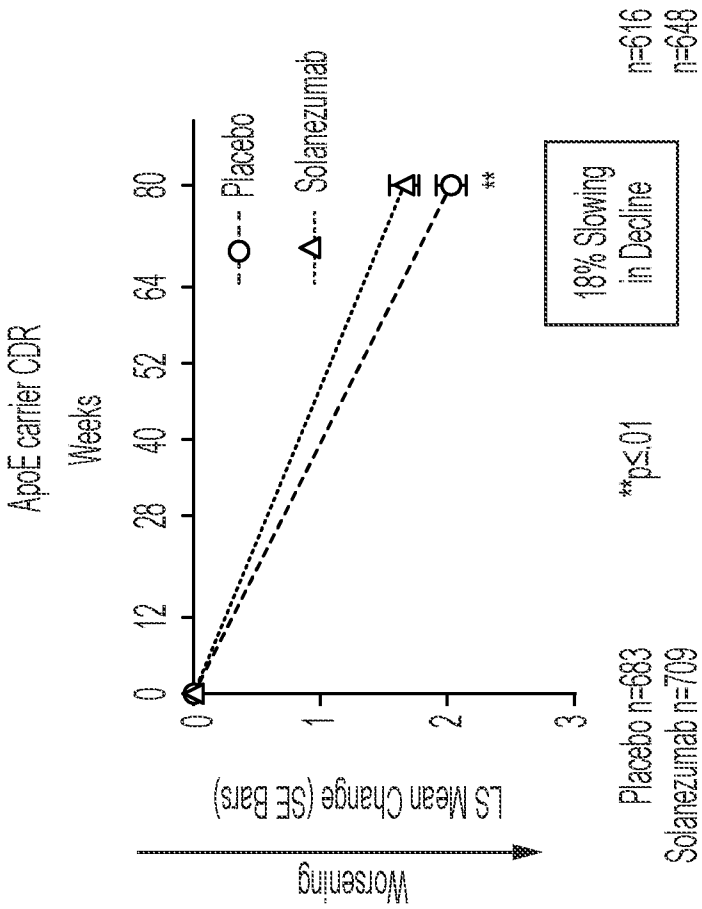

FIG. 12A

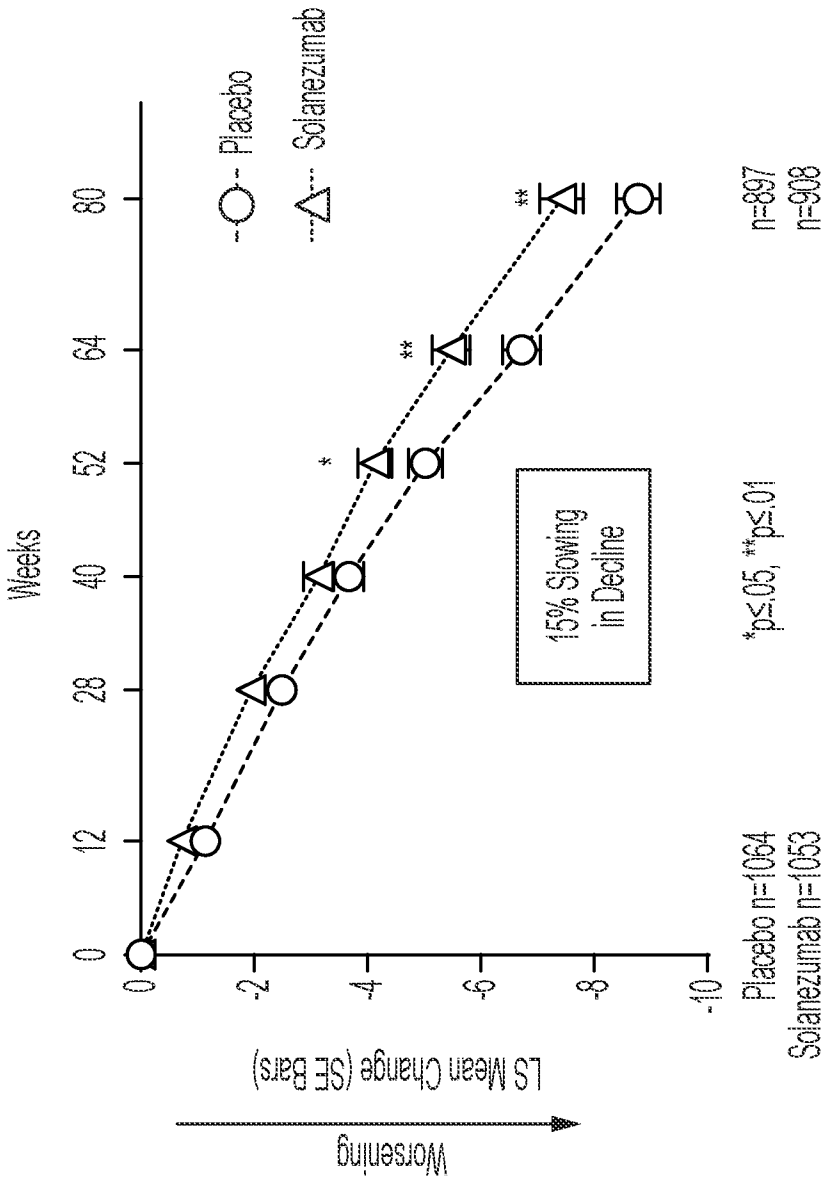
Placebo
Solanezumab
Weeks
0
12
28
40
52
64
80
0
-2
-4
-6
-8
-10
LS Mean Change (SE Bars)
Worsening
*
**
**
15% Slowing in Decline
*p≤.05, **p≤.01
Placebo n=1064
Solanezumab n=1053
n=897
n=908

FIG. 13

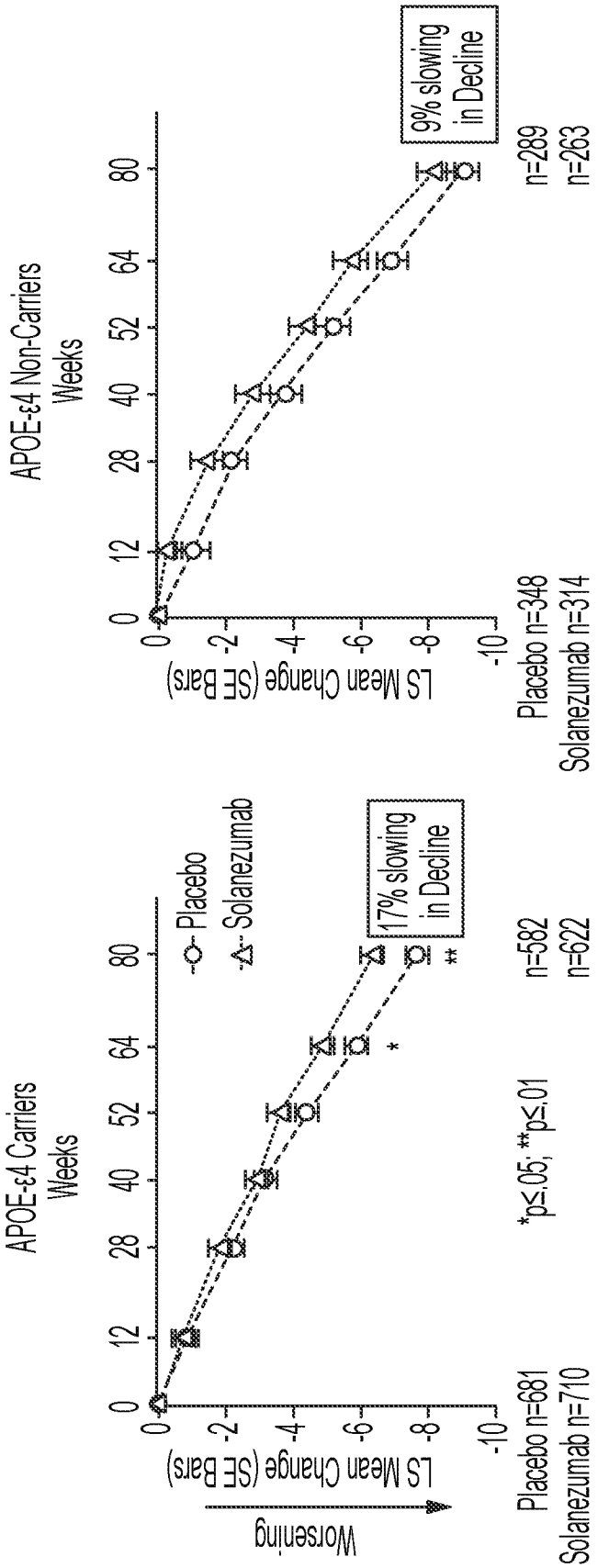

FIG. 14A

FIG. 14B

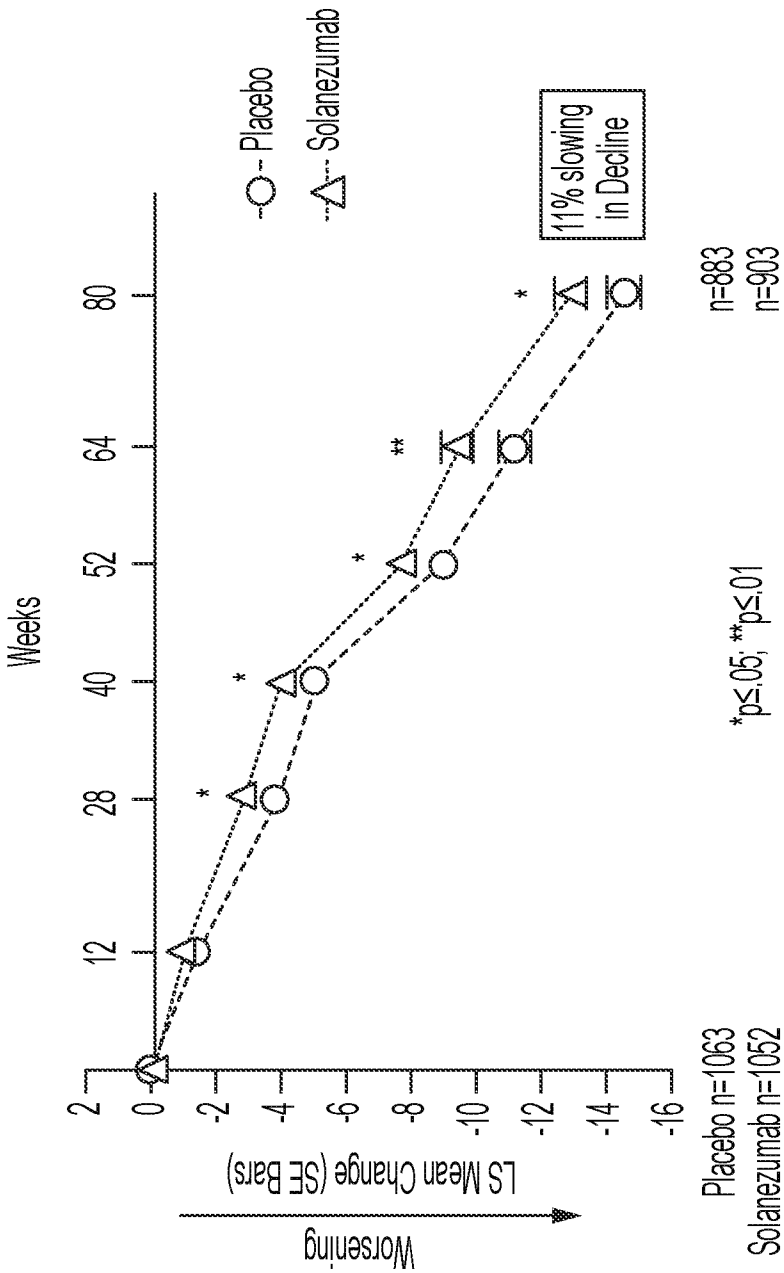
Placebo
Solanezumab
11% slowing in Decline
Weeks
2
12
28
40
52
64
80
0
-2
-4
-6
-8
-10
-12
-14
-16
LS Mean Change (SE Bars)
Worsening
Placebo n=1063
Solanezumab n=1052
n=883
n=903
*p≤.05; **p≤.01

FIG. 15

	LS Mean Change (SE) at 80 Weeks		p-value	Slowing in Decline
	Placebo N≈1072	Solanezumab N≈1057		
ADAS-Cog14	7.44 (0.36)	6.65 (0.36)	.095	11%
ADCS-iADL	-7.17 (0.32)	-6.17 (0.32)	.019	14%
MMSE	-3.66 (0.16)	-3.17 (0.15)	.014	13%
FAQ	5.57 (0.21)	5.17 (0.21)	.140	7%
ADCS-ADL	-8.77 (0.39)	-7.42 (0.39)	.009	15%
iADRS	-14.59 (0.54)	-12.92 (0.53)	.017	11%
CDR-SB	2.21 (0.11)	1.87 (0.10)	.004	15%

FIG. 16

Demographic	Placebo N=660	Solanezumab N=654	p-value
Age, years, mean (SD)	73.3 (7.9)	73.9 (8.1)	.185
Female, n (%)	360 (54.5)	345 (52.8)	.515
Race, n (%)			.503
White	556 (84.2)	526 (80.4)	
Black or African American	12 (1.8)	15 (2.3)	
Asian	90 (13.6)	111 (17.0)	
APOE ε4 carriers, n (%)*	367 (59.8)	329 (55.3)	.116
Education, years, mean (SD)	12.6 (3.9)	12.4 (4.0)	.430
Symptom onset, years, mean (SD)	4.20 (2.6)	4.31 (2.4)	.273
Diagnosis, years, mean (SD)	2.0 (1.9)	1.9 (1.8)	.595

FIG. 17

Parameter	Placebo N=1072	Solanezumab N=1057	p-value
AChEI /Memantine use, n (%)	856 (79.9%)	822 (77.8%)	.244
Measure, mean score (SD)			
ADAS-Cog14	29.7 (8.5)	28.9 (8.3)	.0 16
ADCS-ADL Instrumental	45.4 (8.1)	45.6 (7.9)	.436
MMSE	22.6 (2.9)	22.8 (2.8)	.116
FAQ	10.6 (7.1)	10.3 (6.8)	.363
ADCS-ADL	66.7 (9.1)	67.0 (8.7)	NA
CDR-SB	3.9 (2.0)	3.9 (1.9)	.542

FIG. 18

Demographic	Placebo N=660	Solanezumab N=654	p-value
AChEI / Memantine at baseline, n (%)	584 (88.5)	571 (87.3)	.513
Baseline efficacy measures, score (SD)			
ADAS-Cog14	29.6 (8.8)	30.1 (8.6)	.167
ADCS-ADL Instrumental ADLs	42.9 (9.5)	42.4 (10.0)	.213
MMSE	22.5 (2.8)	22.5 (2.8)	.867
FAQ	N/A	N/A	N/A
ADCS-ADL	63.8 (10.8)	63.4 (11.2)	.315
CDR-SB	4.4 (2.2)	4.4 (2.1)	.777

FIG. 19

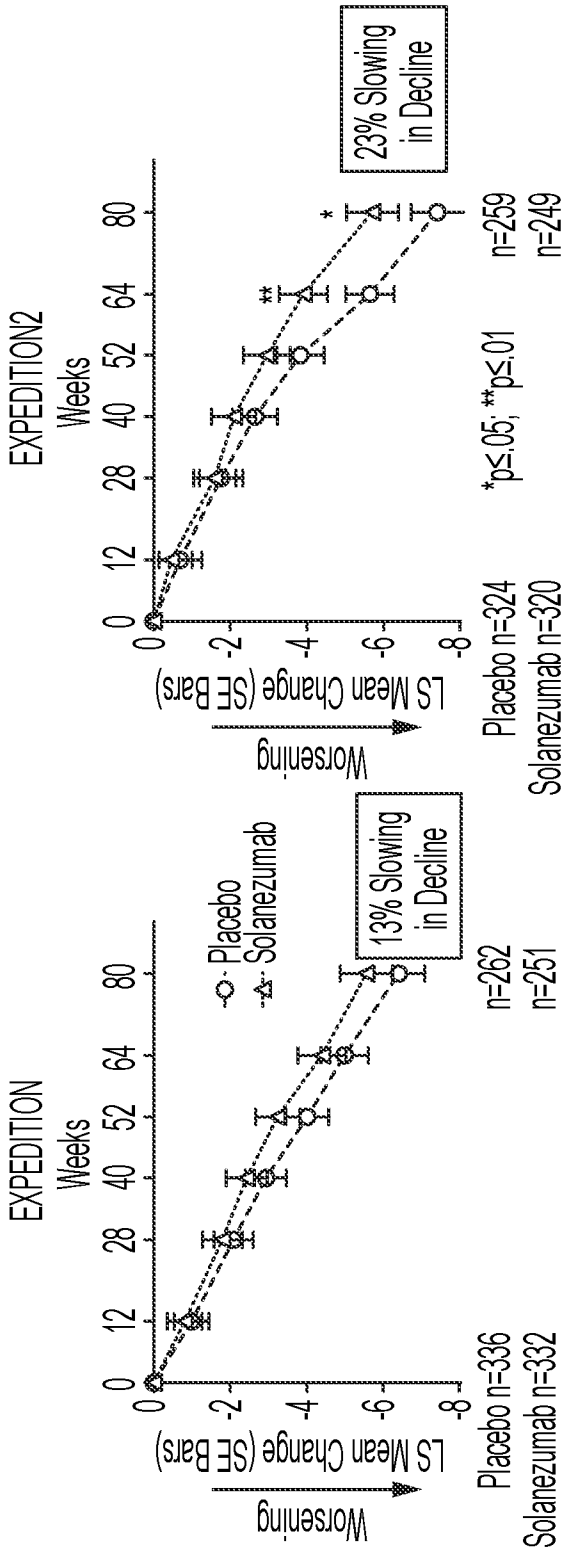

FIG. 20A

FIG. 20B

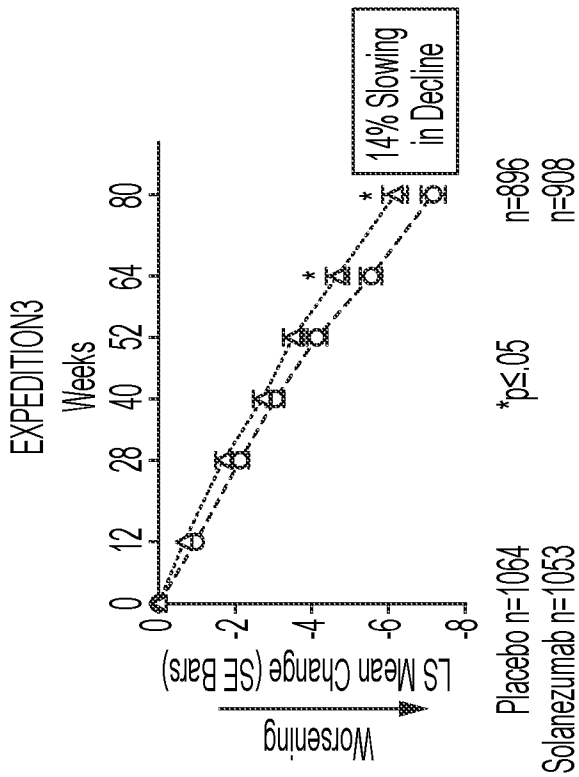

FIG. 20D

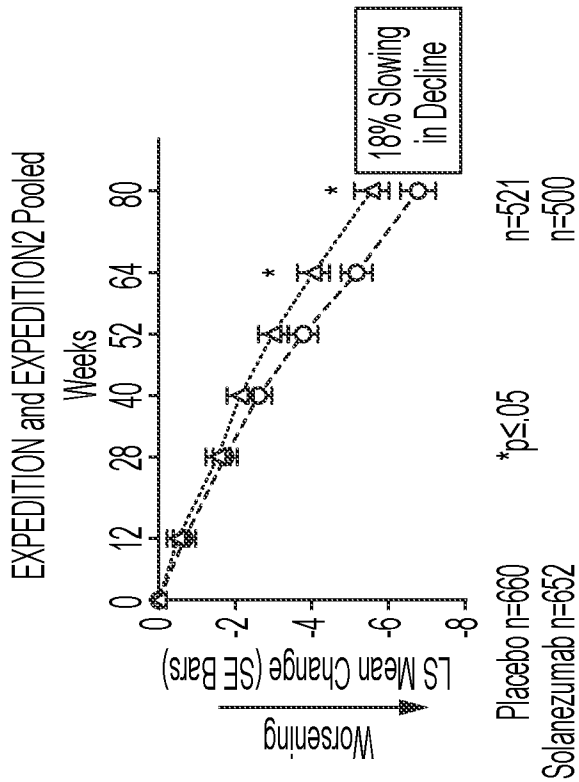

FIG. 20C

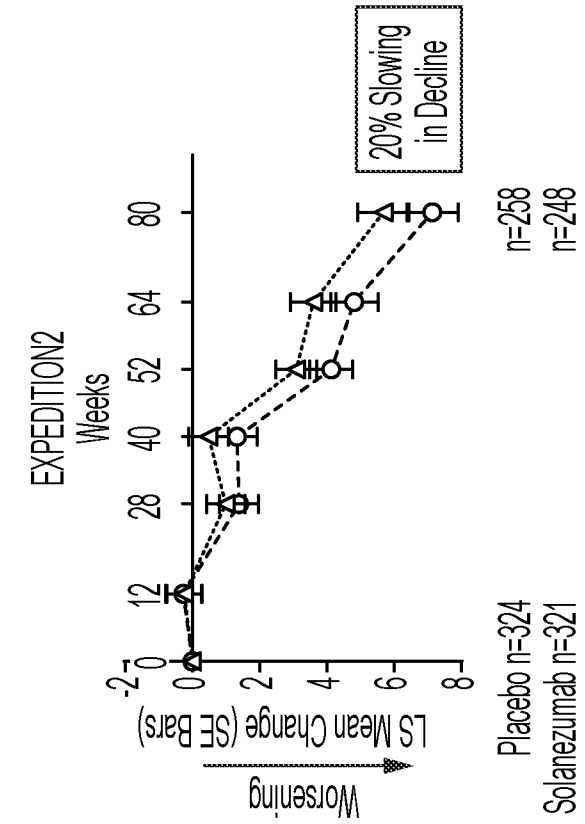

FIG. 21B

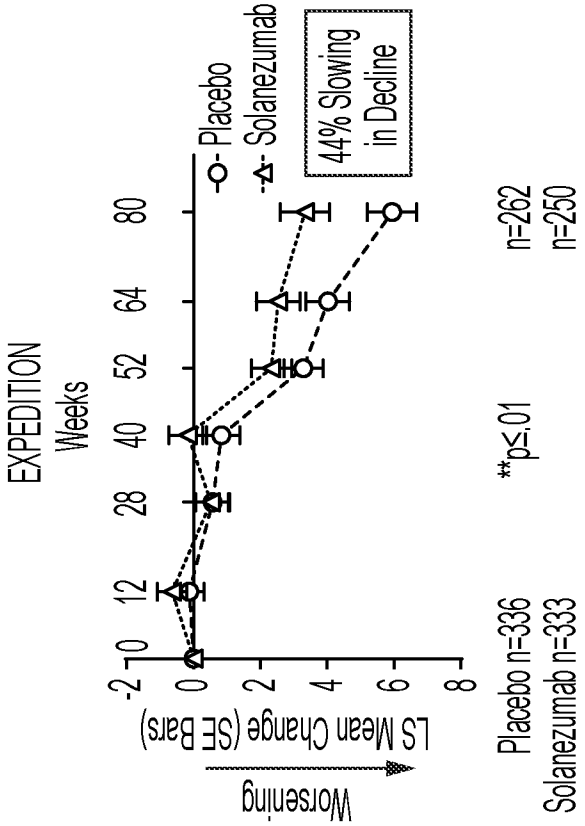

FIG. 21A

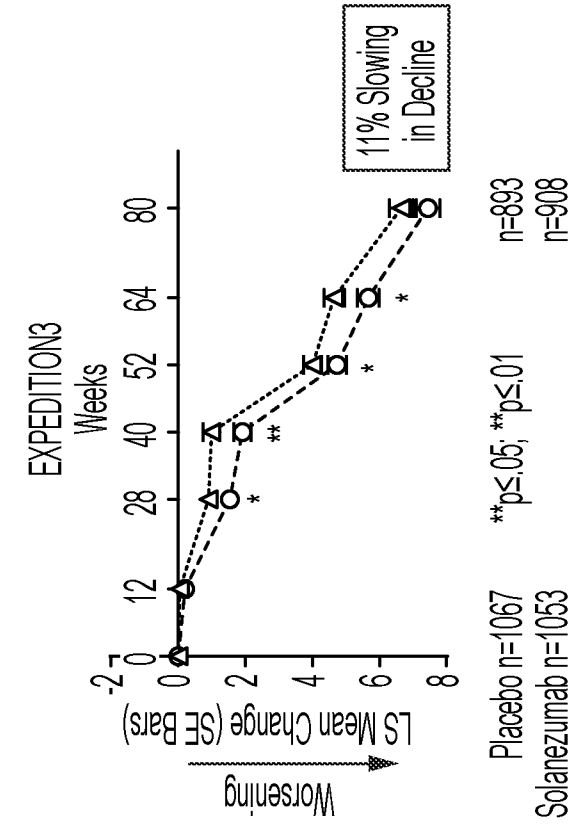

FIG. 21D

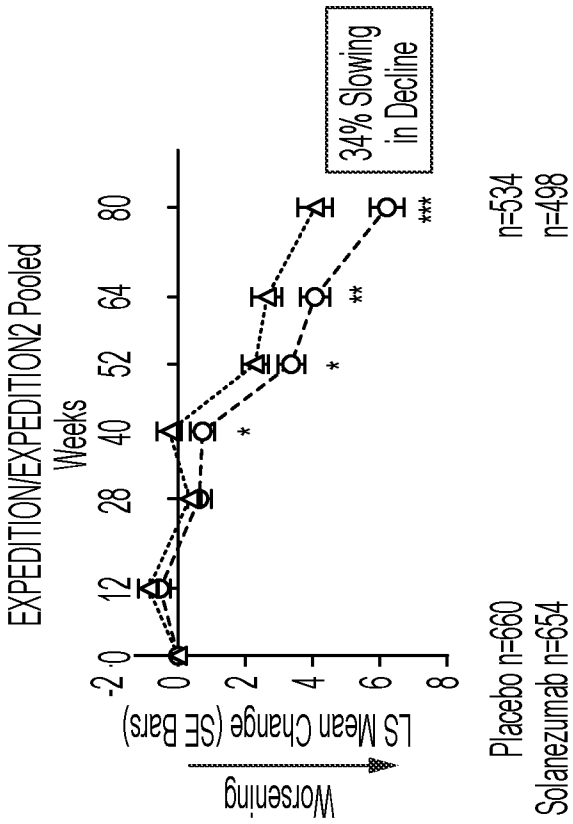

FIG. 21C

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2022/030167

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/395 C07K16/18 A61P25/00
ADD. A61K39/00

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)
C07K A61P A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FARLOW MARTIN ET AL: "Safety and biomarker effects of solanezumab in patients with Alzheimer's disease", ALZHEIMER'S & DEMENTIA, vol. 8, no. 4, 7 June 2012 (2012-06-07), pages 261-271, XP055923662, US ISSN: 1552-5260, DOI: 10.1016/j.jalz.2011.09.224 Retrieved from the Internet: URL:https://onlinelibrary.wiley.com/doi/full-xml/10.1016/j.jalz.2011.09.224> the whole document paragraphs [03.2], [0002] ----- -/--	1-14, 16-42

[x] 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

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Date of the actual completion of the international search	Date of mailing of the international search report
26 August 2022	05/09/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Siaterli, Maria

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KEVIN M. SCHILLING ET AL: "Paper and toner three-dimensional fluidic devices: programming fluid flow to improve point-of-care diagnostics", LAB ON A CHIP, vol. 13, no. 4, 1 January 2013 (2013-01-01), page 628, XP055283832, UK ISSN: 1473-0197, DOI: 10.1039/c2lc40984d the whole document page 313, right-hand column, paragraph 3 -----	1-42
X	EARLEY LAURIEL F. ET AL: "Adeno-associated Virus (AAV) Assembly-Activating Protein Is Not an Essential Requirement for Capsid Assembly of AAV Serotypes 4, 5, and 11", JOURNAL OF VIROLOGY, vol. 91, no. 3, 1 February 2017 (2017-02-01), XP055953369, US ISSN: 0022-538X, DOI: 10.1128/JVI.01980-16 Retrieved from the Internet: URL:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5244341/pdf/e01980-16.pdf> the whole document page 328, left-hand column, paragraph 3 -----	1-42
X	SIEMERS E R ET AL: "Safety and changes in plasma and cerebrospinal fluid amyloid [beta] after a single administration of an amyloid [beta] monoclonal antibody in subjects with Alzheimer disease", CLINICAL NEUROPHARMACOLOGY, RAVEN PRESS, NEW YORK, NY, US, vol. 33, no. 2, 1 January 2010 (2010-01-01), pages 67-73, XP009145612, ISSN: 0362-5664 the whole document page 68, left-hand column, paragraph 4 page 69, right-hand column, paragraph 2 ----- -/--	1-42

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2022/030167

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CARLSON CHRISTOPHER ET AL: "Amyloid-related imaging abnormalities from trials of solanezumab for Alzheimer's disease", ALZHEIMER'S & DEMENTIA: DIAGNOSIS, ASSESSMENT & DISEASE MONITORING, vol. 2, no. 1, 1 March 2016 (2016-03-01), pages 75-85, XP055954467, ISSN: 2352-8729, DOI: 10.1016/j.dadm.2016.02.004 the whole document paragraph [03.5] page 83, right-hand column, paragraph 1 -----	1-42
X	FLEISHER ADAM S ET AL: "Use of white matter reference regions for detection of change in florbetapir positron emission tomography from completed phase 3 solanezumab trials", ALZHEIMER'S & DEMENTIA, vol. 13, no. 10, 10 October 2017 (2017-10-10), pages 1117-1124, XP085225601, ISSN: 1552-5260, DOI: 10.1016/J.JALZ.2017.02.009 the whole document paragraphs [02.1], [03.2]; table 1 -----	1-42

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