

METHODS OF TREATMENT USING P-TAU181 LEVEL

- [1] This invention was partially made with government support under Grant Nos. R01AG054029, R01AG061848, and 5U24AG057437-04, awarded by the National Institutes of Health. The government has certain rights in this invention.
- [2] This Application claims the benefit of and priority to US Provisional Applications 63/306,060 filed February 10, 2022; 63/269,394 filed March 15, 2022; 63/364,617 filed May 12, 2022; each entitled "METHODS OF TREATMENT USING P-TAU181 LEVEL," the contents of which are expressly incorporated herein by reference in their entirety.
- [3] Alzheimer's disease (AD) is a progressive, neurodegenerative disorder of unknown etiology and the most common form of dementia among older people. In 2006, there were 26.6 million cases of AD in the world (range: 11.4-59.4 million) (Brookmeyer, R., *et al.*, Forecasting the global burden of Alzheimer's Disease. *Alzheimer Dement.* 2007; 3:186-91), while there were more than 5 million people in the United States reportedly living with AD (Alzheimer's Association, Alzheimer's Association report, 2010 Alzheimer's disease facts and figures. *Alzheimer Dement.* 2010;6:158-94). By the year 2050, the worldwide prevalence of AD is predicted to grow to 106.8 million (range: 47.2-221.2 million), while in the United States alone the prevalence is estimated to be 11 to 16 million. (Brookmeyer, *supra*, and 2010 Alzheimer's disease facts and figures, *supra*).
- [4] The disease generally involves a global decline of cognitive function that progresses slowly and leaves end-stage subjects bedridden. AD subjects typically survive for only 3 to 10 years after symptom onset, although extremes of 2 and 20 years are known. (Hebert, L.E., *et al.*, Alzheimer disease in the U.S. population: prevalence estimates using the 2000 census. *Arch Neurol.* 2003; 60:1119-1122.) AD is the seventh leading cause of all deaths in the United States and the fifth leading cause of death in Americans older than the age of 65 years, despite the fact that mortality due to AD is greatly underestimated because death certificates rarely attribute the cause of death to AD. (Alzheimer's Association. Alzheimer's Association report. 2010 Alzheimer's disease facts and figures. *Alzheimer Dement.* 2010; 6:158-94.)
- [5] AD represents a significant economic burden across industrialized countries with a substantial impact on healthcare systems and the public purse as well as on subjects and their families. In the United States alone, total payments for 2010 were estimated at \$172 billion, including \$123 billion for Medicare and Medicaid.
- [6] Histologically, the disease is characterized by neuritic plaques, found primarily in the association cortex, limbic system and basal ganglia. The major constituent of these plaques is amyloid beta peptide (A β). A β exists in various conformational states - monomers, oligomers, protofibrils, and insoluble fibrils. Details of the mechanistic relationship between onset of Alzheimer's disease and A β production is unknown. However, some anti-A β antibodies are undergoing clinical study now as potential therapeutic agents for Alzheimer's disease.
- [7] Despite the recent development of treatments for AD, including those targeting A β , there remains a need for better monitoring of treatments, including non-invasive assays to evaluate treatment efficacy and to calibrate treatment regimens in subjects. Currently, disease monitoring is largely dependent upon assays that are expensive and can increase the risk of complications to the subject A β positron emission tomography (PET) and cerebrospinal fluid (CSF) biomarker assays.
- [8] Accordingly, disclosed herein are improved methods of selecting, monitoring, and treating patients with AD. In some embodiments, a patient is selected for treatment by
- a. measuring a concentration of phosphorylated tau181 (p-tau181) in the blood sample obtained from the subject;

- b. optionally, measuring a concentration of amyloid β 1-42 ($A\beta_{42}$) and a concentration of amyloid β 1-40 ($A\beta_{40}$) in a blood sample obtained from the subject to determine an $A\beta_{42}$ to $A\beta_{40}$ ratio ($A\beta_{42}/40$ ratio); and
- c. selecting a patient for treatment who has a p-tau181 concentration above a threshold and, optionally, also has an $A\beta_{42}/40$ ratio below a threshold (for example, a threshold of about 0.092).

[9] In various embodiments, the methods comprise treating Alzheimer's disease (AD) in a subject having or suspected of having AD, comprising

measuring or having measured a first level of phosphorylated tau181 (p-tau181) in a first blood sample obtained from the subject;

administering to the subject a first dose of an anti-amyloid β ($A\beta$) protofibril antibody;

measuring or having measured a second level of p-tau181 in a second blood sample obtained from the subject after the administration of the first dose of the anti- $A\beta$ protofibril antibody (although it is to be understood that additional doses may be administered in between the sampling time points);

if the second level is the same as or higher than the first level, (i) administering a second dose of the anti- $A\beta$ protofibril antibody to the subject that is higher than the first dose of the anti- $A\beta$ protofibril antibody, or (ii) administering a different treatment for AD to the subject, and

if the second level is lower than the first level, administering a second dose of the anti- $A\beta$ protofibril antibody to the subject that is the same as or lower than the first dose of the anti- $A\beta$ protofibril antibody.

[10] In some embodiments, more than one first dose and more than one second dose of the anti- $A\beta$ protofibril antibody is administered. In some embodiments, when administering a second dose that is higher than the first dose, the second dose is administered at a higher amount and/or an increased frequency relative to the first dose. In some embodiments, when administering a second dose that is lower than the first dose, the second dose is administered at a lower amount and/or a decreased frequency relative to the first dose.

[11] In some embodiments, the methods comprise treating AD in a subject having or suspected of having AD, comprising

measuring or having measured a first level of p-tau181 in a first blood sample obtained from the subject;

administering to the subject a first dose of an anti- $A\beta$ protofibril antibody;

measuring or having measured a second level of p-tau181 in a second blood sample obtained from the subject after the administration of the first dose of the anti- $A\beta$ protofibril antibody;

if the second level is lower than the first level, administering a second dose of the anti-A β protofibril antibody to the subject that is the same as or lower than the first dose of the anti-A β protofibril antibody.

[12] In some embodiments, the methods comprise treating AD in a subject having or suspected of having AD, comprising

measuring or having measured a first level of p-tau181 in a first blood sample obtained from the subject;

administering to the subject a first dose of an anti-A β protofibril antibody;

measuring or having measured a second level of p-tau181 in a second blood sample obtained from the subject after the administration of the first dose of the anti-A β protofibril antibody;

if the second level is the same as or higher than the first level, (i) administering a second dose of the anti-A β protofibril antibody that is higher than the first dose of the anti-A β protofibril antibody, or (ii) administering a different treatment for AD to the subject.

[13] In some embodiments, the methods comprise reducing brain amyloid in a subject having or suspected of having AD, comprising

measuring or having measured a first level of p-tau181 in a first blood sample obtained from the subject;

administering to the subject a first dose of an A β protofibril antibody;

measuring or having measured a second level of p-tau181 in a second blood sample obtained from the subject after the administration of the first dose of the anti-A β protofibril antibody;

if the second level is the same as or higher than the first level, (i) administering a second dose of the anti-A β protofibril antibody that is higher than the first dose of the anti-A β protofibril antibody, or (ii) administering a different treatment for AD to the subject, and

if the second level is lower than the first level, administering a second dose of the anti-A β protofibril antibody that is the same as or lower than the first dose of the anti-A β protofibril antibody;

thereby reducing brain amyloid.

[14] In some embodiments, the methods comprise reducing brain amyloid in a subject having or suspected of having AD, comprising

measuring or having measured a first level of p-tau181 in a first blood sample obtained from the subject;

administering to the subject a first dose of an A β protofibril antibody;

measuring or having measured a second level of p-tau181 in a second blood sample obtained from the subject after the administration of the first dose of the anti-A β protofibril antibody;

if the second level is lower than the first level, administering a second dose of the anti-A β protofibril antibody that is the same as or lower than the first dose of the anti-A β protofibril antibody;

thereby reducing brain amyloid.

[15] In some embodiments, the methods comprise reducing brain amyloid in a subject having or suspected of having AD, comprising

measuring or having measured a first level of p-tau181 in a first blood sample obtained from the subject;

administering to the subject a first dose of an A β protofibril antibody;

measuring or having measured a second level of p-tau181 in a second blood sample obtained from the subject after the administration of the first dose of the anti-A β protofibril antibody;

if the second level is the same as or higher than the first level, (i) administering a second dose of the anti-A β protofibril antibody that is higher than the first dose of the anti-A β protofibril antibody, or (ii) administering a different treatment for AD to the subject,

thereby reducing brain amyloid.

[16] In some embodiments, the methods comprise monitoring treatment efficacy in a subject having or suspected of having AD, comprising

administering to the subject a dose of an A β protofibril antibody;

measuring or having measured a post-dose level of p-tau181 in a blood sample obtained from the subject; and

comparing the post-dose level of the blood sample to a blood sample obtained from the subject prior to the administration of the dose of the A β protofibril antibody or to a control level, e.g., a blood sample obtained from a subject not diagnosed with AD, wherein the treatment is considered effective if the post-dose level is lower than the level prior to the dose or the control level.

[17] In some embodiments, the methods comprise detecting a decrease in a brain A β level, comprising

measuring or having measured a first level of p-tau181 in a first blood sample obtained from a subject prior to administration of an anti-A β protofibril antibody;

administering to the subject a first dose of an A β protofibril antibody;

measuring or having measured a second level of p-tau181 in a second blood sample obtained from the subject after the administration of the anti-A β protofibril antibody;

administering to the subject a dose of an A β protofibril antibody;

comparing the first and second levels, wherein a second level that is lower than the first level indicates a decrease in amyloid β in the subject.

[18] In some embodiments, the methods comprise reducing brain amyloid in a subject in need thereof, comprising

measuring or having measured a first level of p-tau181 in a first blood sample obtained from the subject;

administering to the subject a first dose of an A β protofibril antibody;

measuring or having measured a second level of p-tau181 in a second blood sample obtained from the subject after the administration of the first dose of the anti-A β protofibril antibody;

if the second level is the same as or higher than the first level, (i) administering a second dose of the anti-A β protofibril antibody that is higher than the first dose of the anti-A β protofibril antibody, or (ii) administering a different treatment for AD to the subject, and

if the second level is lower than the first level, administering a second dose of the anti-A β protofibril antibody that is the same as or lower than the first dose of the anti-A β protofibril antibody.

[19] In some embodiments, the methods comprise treating pre-Alzheimer's disease (pre-AD) in a subject, comprising:

- a. measuring or having measured a level of p-tau181 in a blood sample obtained from the subject; and
- b. if the subject has a level of p-tau181 above a threshold, administering a treatment comprising a therapeutically effective dose of an anti-amyloid β (A β) protofibril antibody to the subject,

wherein the anti-A β protofibril antibody comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 7 and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 8, and wherein the subject is cognitively normal.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1: Least square mean ($\pm$ SE) change from baseline in plasma p-tau181 over time – overall – PD analysis set.

Fig. 2: Correlation between change from baseline in plasma p-tau181 and amyloid PET SUVR at 18 months – overall – PD analysis set. Only subjects in PET substudy with observed data at 12 and/or 18 months are included. Adjusted mean difference from placebo = least square mean of active treatment - least square mean of placebo, estimated from the primary MMRM analysis. Solid line is the estimated linear regression line.

Fig. 3: Scatterplot of change from baseline in amyloid PET SUVR and plasma p-tau181 – core. The subjects with both plasma p-tau181 and amyloid PET SUVR at Core baseline and Core 18 month are presented. Only PET data using Florbetapir tracer is included.

Fig. 4: Correlation between change from baseline in plasma p-tau181 and CDR-SB at 18 months (core) – overall – PD analysis set. Only subjects in plasma p-tau181 with observed data at 12 and/or 18 months are included. Adjusted mean difference from placebo = least square mean of active treatment - least square mean of placebo, estimated from the primary MMRM analysis. The solid line is the estimated linear regression line.

Fig. 5: Correlation between change from baseline in plasma p-tau181 and ADCOMS at 18 months (core) – overall – PD analysis set. Only subjects in plasma p-tau181 with observed data at 12 and/or 18 months are included. Adjusted mean difference from placebo = least square mean of active treatment - least square mean of placebo, estimated from the primary MMRM analysis. The solid line is the estimated linear regression line.

Fig. 6: Correlation between change from baseline in plasma p-tau181 and ADAS-Cog at 18 months (core) – overall – PD analysis set. Only subjects in plasma p-tau181 with observed data at 12 and/or 18 months are included. Adjusted mean difference from placebo = least square mean of active treatment - least square mean of placebo, estimated from the primary MMRM analysis. The solid line is the estimated linear regression line.

Fig. 7: Line plot of mean change ($\pm$ SE) from OLE baseline in plasma p-tau181 by visit (OLE phase) – OLE PD analysis set. Only PET data using Florbetapir tracer is included. Plots are presented by treatment groups in Core Study.

Fig. 8: Scatter plot of mean change from OLE baseline in plasma p-tau181 and change from OLE baseline in PET SUVR (OLE phase) – OLE PD analysis set. Only PET data using Florbetapir tracer is included. Plots are presented by treatment groups in Core Study.

Fig. 9: Data correlation of plasma PET SUVR, A β 42/40 ratio and p-tau181 during Study 201 Core, Gap, and OLE (OLE enrolled set excluding those who progressed beyond EAD).

Fig. 10: PK/PD model for p-tau181.

Fig. 11: Plasma p-tau181 efficacy model.

Fig. 12: Model-predicted plasma p-tau181 following various dosing regimens. Solid line and shaded area show predicted median and 95% CI, respectively.

Fig. 13: Model-Predicted Curve of CFB in SUVr versus CFB in Plasma p-tau181. Solid line and shaded area show predicted median and 95% CI, respectively.

Fig. 14: Scatterplot of change from baseline in amyloid PET SUVR and plasma p-tau181 at 18 months – study 201 Core (PD Analysis Set). The analyte lower limit of quantitation ($=0.764$ pg/mL; 4 times of the assay lower limit of quantitation $=0.191$ pg/mL) is used to impute the value BQL. The solid line is the estimated linear regression line.

Fig. 15: Correlation between amyloid PET SUVR, plasma A β 42/40 ratio and plasma p-tau181 and CDR-SB during study 201 core, gap period, and 201 OLE phase (OLE Enrolled Set Excluding Those Who Progressed beyond EAD). Data are presented by Core Study treatment assignment. In the OLE Phase, placebo subjects received LEC10-BW. Thick black box indicates treatment-naïve subjects receiving first exposure to lecanemab.

Fig. 16: Correlation between plasma p-tau181 and ADCOMS during study 201 core, gap period, and OLE phase. Data are presented by Core Study treatment assignment (OLE Enrolled Set Excluding Those Who Progressed beyond EAD). In the OLE Phase, placebo subjects received LEC10-BW. Thick black box indicates treatment-naïve subjects receiving first exposure to lecanemab.

Fig. 17: Correlation between plasma p-tau181 and ADAS-Cog14 during study 201 core, gap period, and OLE phase. Data are presented by Core Study treatment assignment (OLE Enrolled Set Excluding Those Who Progressed beyond EAD). In the OLE Phase, placebo subjects received LEC10-BW. Thick black box indicates treatment-naïve subjects receiving first exposure to lecanemab.

Fig. 18: Model-predicted SUVR and plasma A β 42/40 ratio and p-tau181 following 18 months treatment with lecanemab at 10 mg/kg biweekly or 10 mg/kg monthly. Solid line and shaded area show predicted median and 95% CI, respectively. Black dotted line in SUVR plot represents SUVR = 1.17, indicating amyloid negative line. For SUVR, baseline SUVR = 1.38 (median of Study 201) was assumed.

Fig. 19: Model-predicted SUVR and plasma A β 42/40 ratio and p-tau181 following continuous 10 mg/kg biweekly with or without treatment discontinuation. Black dotted line in SUVR plot represents SUVR = 1.17, indicating amyloid negative line. For SUVR, lower bound SUVR = 1.0 (theoretical lower bound) was assumed.

DETAILED DESCRIPTION

[20] The “amyloid hypothesis” proposes that amyloid β (A β) peptides play a central role in the pathogenesis of AD. Specifically, it is hypothesized that neurodegeneration in AD may be caused by deposition of A β plaques in brain tissue due to an imbalance between A β production and A β clearance, leading to formation of neurofibrillary tangles containing tau protein. A β peptides generally exist in a dynamic continuum of conformational states such that species tend to progress from monomeric A β , to soluble A β assemblies that include a range of low molecular weight oligomers to higher molecular weight protofibrils, and finally to insoluble fibrils (plaques). Targeting these soluble and insoluble A β tangles and plaques may provide therapeutic benefit.

[21] A number of immunotherapies have been developed with the intent to reduce the amount of insoluble A β fibrils deposited in the brain. However, a simple correlation between the quantity and progressive accumulation of insoluble amyloid plaques and the clinical course of AD has not been determined. While therapeutic strategies continue to focus on removal of insoluble amyloid plaques, an additional approach to therapy may include reducing the toxic A β aggregates, such as protofibrils, that may contribute to the neuronal degeneration characteristic of AD. (See, e.g., Dodort, J.-C. and May, P., “Overview on rodent models of Alzheimer’s disease.” *Curr. Protocols Neurosci.* 2005; 9:22-1-9:22-6; Englund, H. *et al.*, “Sensitive ELISA detection of amyloid- β protofibrils in biological samples.” *J. Neurochem.* 2007; 103:334-45; and Gotz, J. *et al.*, “Transgenic animal models of Alzheimer’s disease and related disorders: histopathology, behavior and therapy.” *Mol. Psychiat.* 2004; 9:664-83.)

[22] In various embodiments, anti-A β protofibril antibodies, such as BAN2401 and other anti-A β protofibril antibodies, may be used to treat AD, e.g., by slowing AD progression in subjects, e.g., those at early stages of the disease when amyloid had been deposited in the brain but where the downstream neurodegenerative cascade thought to be triggered by the amyloid deposition was still relatively early in its course (i.e., limited brain tissue loss has been produced and associated clinical deficits are at a minimum).

[23] In various embodiments, methods are disclosed herein for treating, monitoring treatment, and altering A β levels in patients receiving anti-A β protofibril antibodies, such as BAN2401, comprising evaluating a level of p-tau181. In some embodiments, the methods comprise measuring the level of p-tau181 in a sample (e.g., a plasma sample) from a subject having or suspected of having AD before treatment and/or again in another sample during treatment (although it is to be understood that additional doses may be administered in between the sampling time points). In some embodiments, a decrease in the level of p-tau181 indicates treatment efficacy, e.g., a reduction in brain A β . In some embodiments, a subsequent dose of treatment is given after the second sampling if a decrease in the level of p-tau181 is detected. In some embodiments, treatment may be titrated on the basis of the change in the p-tau181 level, e.g., dosage or treatment frequency may be reduced if a decrease in the level of p-tau181 is detected, alone or in combination with additional therapies such as BACE inhibitors or anti-tau antibodies. In some embodiments, dosage or treatment frequency may be increased, or an alternate treatment may be selected, if the p-tau181 level does not decrease after the second sampling. In some embodiments, additional patient demographics, such as age and if the subject is a carrier of the apolipoprotein E ϵ 4 gene allele, may be used to predict amyloid positivity (e.g. West et al, *Mol Neurodegen* (2021) 16-30, Jansen et al, *JAMA* (2015) 1924-1938, Ossenkoppele et al, *JAMA* (2015) 1939-1950). In some embodiments, an age and/or apolipoprotein E ϵ 4 gene allele normalized

measurement of the level of p-tau181 from a subject is used to evaluate whether a sample (e.g., a plasma sample) from a subject indicates that the subject is amyloid positive or negative. For example, in some embodiments, a patient who is a carrier of an apolipoprotein E ϵ 4 gene allele may be considered amyloid positive at a lower p-tau181 level than the ratio needed to indicate amyloid positivity in a subject who is not a carrier. Likewise, in another example, an older subject may be considered amyloid positive at a lower p-tau181 level than the ratio required to indicate positivity in a younger subject. In some embodiments, the p-tau181 level is used in a Receiver Operating Characteristic (ROC) analysis to predict amyloid positivity. In some embodiments, additional patient demographics, such as age and if the subject is a carrier of an apolipoprotein E ϵ 4 gene allele, may be used with the p-tau181 level in an ROC analysis to predict amyloid positivity. In some embodiments, the prediction of amyloid positivity in a patient is used to determine the dosage or frequency of treatment.

[24] In some embodiments, the methods comprise measuring a p-tau level in a sample, e.g., a blood sample, from a subject having or suspected of having AD before treatment to identify a patient suitable for treatment and/or again in another sample during treatment to monitor treatment efficacy (although it is to be understood that additional doses may be administered in between the sampling time points). In some embodiments, treatment may be stopped and/or reduced (e.g., reduced frequency and/or dosage) if a decrease in the level of p-tau181 is detected between the first and second samplings. In some embodiments, after treatment has been stopped or reduced, a further measurement of the p-tau181 level may be made in a sample from the subject. In some embodiments, treatment is restarted, dosage is increased, and/or the frequency of administration is increased if an increase in the level of p-tau181 is detected. In some embodiments, the dosage or frequency of treatment is increased to return to the dosage and/or frequency used in a prior treatment, e.g., before a dose reduction and/or lengthening of the dose frequency had commenced. In some embodiments, the methods comprise measuring a p-tau181 level in a sample from a subject during treatment and again after stopping treatment or after the dosage or frequency of treatment has been reduced (it is to be understood that additional doses may be administered in between the sampling time points). In some embodiments, if an increase in p-tau181 level is detected, treatment is resumed, or the dosage or frequency of treatment is increased, in comparison to the dose or frequency during the period in which the level increased. In some embodiments, multiple measurements may be made during a treatment prior to a decision to stop treatment and/or reduce treatment based on an decreased p-tau181 level (e.g., based on a trend showing a decrease in the p-tau181 level at each subsequent measurement). In some embodiments, multiple measurements may be taken after treatment has stopped or been reduced, and a decision to resume treatment and/or increase treatment may be taken based on an increase in the p-tau181 level (e.g., based on a trend showing an increase in p-tau181 level at each subsequent measurement). In some embodiments, following the resumption of treatment or the increased treatment regimen, one or more additional measurements may be made of the p-tau181 level in a sample from a subject. In some embodiments, treatment is continued if a decrease in p-tau181 level is observed in the subsequent measurements. In some embodiments, the measurement of the p-tau181 level is done in conjunction with measuring one or more additional biomarkers (e.g., using a reduction in PET SUVR as an indicator of amyloid plaque reduction during and/or after treatment). In some embodiments, treatment may be stopped if an increase in the p-tau level is detected between the first and a subsequent, e.g., second, third, or fourth, sampling. In some embodiments, treatment may be stopped due to a low therapeutic effect.

[25] In some embodiments, any of the methods that comprise measuring a p-tau181 level may further comprise measuring one or more additional biomarkers, e.g., measuring the level of amyloid β 1-40 (A β 40) and amyloid β 1-42 (A β 42) to determine a ratio of A β 42 to

A β 40 (A β 42/40 ratio). In some embodiments, the measurement of an A β 42/40 ratio is done in a sample, e.g., a blood sample, from a subject having or suspected of having AD before treatment and again in another sample during treatment (although it is to be understood that additional doses may be administered in between the sampling time points). In some embodiments, treatment may be stopped and/or reduced (e.g., reduced frequency and/or dosage) if an increase in the A β 42/40 ratio is detected between the first and second samplings. In some embodiments, after treatment has been stopped or reduced, a further measurement of the A β 42/40 ratio may be made in a sample from the subject. In some embodiments, treatment is restarted, dosage is increased, and/or the frequency of administration is increased if a reduction in the A β 42/40 ratio is detected. In some embodiments, the dosage or frequency of treatment is increased to return to the dosage and/or frequency used in a prior treatment, e.g., before a dose reduction and/or lengthening of the dose frequency had commenced. In some embodiments, the methods comprise measuring an A β 42/40 ratio in a sample from a subject during treatment and again after stopping treatment or after the dosage or frequency of treatment has been reduced (it is to be understood that additional doses may be administered in between the sampling time points). In some embodiments, if a reduction in the A β 42/40 ratio is detected, treatment is resumed, or the dosage or frequency of treatment is increased, in comparison to the dose or frequency during the period in which the ratio decreased. In some embodiments, multiple measurements may be made during a treatment prior to stopping treatment and/or reducing treatment based on an elevated A β 42/40 ratio (e.g., based on a trend showing increase in the A β 42/40 ratio at each subsequent measurement). In some embodiments, multiple measurements may be taken after treatment has stopped or been reduced, before resuming treatment and/or increasing treatment may be taken based on a reduction in A β 42/40 ratio (e.g., based on a trend showing a reduction in the A β 42/40 ratio at each subsequent measurement). In some embodiments, following the resumption of treatment or the increased treatment regimen, one or more additional measurements may be made of the A β 42/40 ratio in a sample from a subject. In some embodiments, treatment is continued if an increase in the A β 42/40 ratio is observed in the subsequent measurements. In some embodiments, the measurement of the A β 42/40 is done in conjunction with measuring one or more additional biomarkers (e.g., using a reduction in PET SUVR as an indicator of amyloid plaque reduction during and/or after treatment). In some embodiments, treatment may be stopped if a decrease in the A β 42/40 ratio is detected between the first and a subsequent, e.g., second, third, or fourth, sampling. In some embodiments, treatment may be stopped due to a low therapeutic effect.

[26] In some embodiments, treatment is stopped and/or reduced (e.g., reduced frequency and/or dosage) if an increase in the A β 42/40 ratio is detected between a first and second samplings in a subject and an decrease in the level of p-tau181 is detected in the samples. In some embodiments, treatment is resumed and/or increased (e.g., increased frequency and/or dosage) if a decrease the A β 42/40 ratio is detected after stopping and/or reducing an initial treatment in a subject and an increase in the level of p-tau181 is detected.

[27] In some embodiments, treatment may be stopped if a decrease in the A β 42/40 ratio is detected between the first and a subsequent, e.g., second, third, or fourth, sampling. In some embodiments, treatment may be stopped due to a low therapeutic effect.

[28] In some embodiments, provided herein is a method of reducing and/or slowing clinical decline in a subject, e.g., one having Pre-AD or early Alzheimer's disease, comprising administering a therapeutically effective amount of at least one anti-A β protofibril antibody (e.g., BAN2401) to a patient having a p-tau181 level above a threshold. In some embodiments, the anti-A β protofibril antibody (e.g., BAN2401) is administered in a therapeutically effective amount to decrease the p-tau181 level below a threshold. In some

embodiments, decreasing the level of p-tau181 slows the cognitive decline of a patient (e.g., one having pre-AD or early AD) relative to the decline in the absence of treatment.

[29] For example, in some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody before switching to a maintenance dose. In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg (e.g., administering BAN2401 at 10 mg/kg), biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative. In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg (e.g., administering BAN2401 at 10 mg/kg), biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to a maintenance dose. In some embodiments, a subject is switched to a maintenance dose without an initial titrating step to the maintenance dose. In some embodiments, a subject is switched to a maintenance dose with at least one titrating step to the maintenance dose, e.g., the subject's dosage or frequency of administration may be reduced in multiple steps until achieving a final maintenance dosing regimen (e.g., a stepwise reduction from a subcutaneous treatment dosing regimen of 720 mg weekly to a maintenance dosing regimen of 360 mg weekly or 720 mg biweekly via intermediate dosing at intermediate amounts or time periods such as 540 mg weekly or 720 mg every 10 days). In some embodiments, a subject's maintenance dose is administered at the same amount and/or frequency as the dose during the treatment period. In some embodiments, a subject's maintenance dose is 50% of the dose during the treatment period. An anti-A β protofibril antibody, such as BAN2401, may be formulated in a pharmaceutical composition as disclosed in PCT/IB2021/000155 (WO2021/186245), which is incorporated herein by reference. In some embodiments, the composition comprises 80 mg/mL to 120 mg/mL BAN2401, 240 mM to 360 mM arginine, 0.03% w/v to 0.08% w/v polysorbate 80, and 30 mM to 70 mM citrate buffer. In some embodiments, the arginine is arginine, arginine hydrochloride, or a combination thereof. In some embodiments, the composition comprises a liquid dosage form comprising 100 mg/mL BAN2401, 50 mmol/L citrate, 350 mmol/L arginine, and 0.05% polysorbate 80. In some embodiments, the composition comprises 80 mg/mL to 240 mg/mL BAN2401, 140 mM to 260 mM arginine hydrochloride, 0.01% w/v to 0.1% w/v polysorbate 80, and 15 mM to 35 mM histidine buffer. In some embodiments, the composition comprises a liquid dosage form comprising 100 mg/mL BAN2401, 25 mmol/L histidine, 200 mmol/L arginine, and 0.05% polysorbate 80. In some embodiments, treatment is continued until a desired improvement in one or more biomarker or other treatment outcome measure is achieved, e.g., when an increase in the A β 42/40 ratio is observed in a sample (e.g., a plasma sample) relative to the ratio in a sample taken from the subject before treatment, e.g., before 18 months of treatment. In some embodiments, a maintenance dosing regimen may further comprise one or more additional treatments in addition to an anti-A β protofibril antibody, e.g., it may comprise administering E2814.

[30] In some embodiments, a treatment comprises subcutaneously administering an anti-A β protofibril antibody, e.g., BAN2401, before switching to a subcutaneous maintenance dose. In some embodiments, a treatment comprises subcutaneously administering BAN2401 weekly, e.g., weekly subcutaneous injection of 720 mg in two concurrent, e.g., sequential, injections of 360 mg (2 x 1.8 mL of 400 mg/2 mL) of the subcutaneous formulation, e.g., until a patient is amyloid-negative or e.g., for at least 18 months. In some embodiments, a treatment comprises subcutaneously administering BAN2401 weekly, e.g., at a dose of 720 mg, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to a weekly, subcutaneous maintenance dose, e.g., a dose of 360 mg. In some embodiments, a treatment comprises subcutaneously administering BAN2401 weekly, e.g., at a dose of 720 mg, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to a biweekly subcutaneous maintenance dose, e.g., a dose of 720 mg. In some embodiments, a

treatment comprises subcutaneously administering BAN2401 weekly, e.g., at a dose of 720 mg, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to a monthly subcutaneous maintenance dose, e.g., a dose of 720 mg. In some embodiments, a subject's maintenance dose is administered at the same amount and/or frequency as the dose during the treatment period. In some embodiments, a subject's maintenance dose is 50% of the dose during the treatment period. In some embodiments, BAN2401, is formulated as disclosed in PCT/IB2021/000155 (WO2021/186245), which is incorporated herein by reference. In some embodiments, the composition comprises 80 mg/mL to 240 mg/mL BAN2401, 140 mM to 260 mM arginine hydrochloride, 0.01% w/v to 0.1% w/v polysorbate 80, and 15 mM to 35 mM histidine buffer. In some embodiments, the composition comprises a liquid dosage form comprising 200 mg/mL BAN2401, 25 mmol/L histidine, 200 mmol/L arginine, and 0.05% polysorbate 80. In some embodiments, a treatment comprises subcutaneously administering BAN2401 twice weekly, e.g., at 720 mg per dose, e.g., for at least 18 months or e.g., until a patient is amyloid-negative. In some embodiments, treatment is continued until a desired improvement in one or more biomarker or other treatment outcome measure is achieved, e.g., when an increase in the A β 42/40 ratio is observed in a sample (e.g., a plasma sample) relative to the ratio in a sample taken from the subject before treatment, e.g., before 18 months of treatment.

[31] In some embodiments, following a treatment period, a maintenance dose is administered. In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody before switching to an intravenous maintenance dose. In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg (e.g., administering BAN2401 at 10 mg/kg), biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to an intravenous maintenance dose. In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody before switching to a subcutaneous maintenance dose. In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg (e.g., administering BAN2401 at 10 mg/kg), biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to a subcutaneous maintenance dose, e.g., 720 mg administered weekly or biweekly, or 360 mg administered weekly. In some embodiments, the maintenance dose is administered intravenously, e.g., after an intravenous treatment period as disclosed above. In some embodiments, an intravenous maintenance dose, e.g., a dosing of 10 mg/kg BAN2401, is administered every week, two weeks, every month, every two months, or every three months (quarterly). In some embodiments, the intravenous maintenance dose is administered every two weeks. In some embodiments, the intravenous maintenance dose is administered every four weeks. In some embodiments, the intravenous maintenance dose is administered every six weeks. In some embodiments, the intravenous maintenance dose is administered every eight weeks (2 months). In some embodiments, the intravenous maintenance dose is administered every three months (quarterly). In some embodiments, the intravenous maintenance dose is administered every 24 weeks (every six months or semi-annually). In some embodiments, the intravenous maintenance dose is 2.5 mg/kg - 10 mg/kg. In some embodiments, the maintenance dose is administered as a biweekly, intravenous dose of 10 mg/kg BAN2401. In some embodiments, the maintenance dose is administered as an intravenous dose of 10 mg/kg every four weeks (monthly). In some embodiments, the maintenance dose is administered as an intravenous dose of 10 mg/kg every six weeks. In some embodiments, the maintenance dose is administered as an intravenous dose of 10 mg/kg every eight weeks (2 months). In some embodiments, the maintenance dose is administered as an intravenous dose of 10 mg/kg every twelve weeks (every three months or quarterly). In some embodiments, the maintenance dose is administered as an intravenously dose of 10 mg/kg every 24 weeks

(every six months or semi-annually). In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg, biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to a weekly intravenous maintenance dose. In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg, biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to a biweekly intravenous maintenance dose. In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg, biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to a monthly intravenous maintenance dose. In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg, biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to an intravenous maintenance dose every six weeks. In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg, biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to an intravenous maintenance dose every eight weeks. In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg, biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to a quarterly intravenous maintenance dose.

[32] In some embodiments, a maintenance dose is administered subcutaneously (e.g., as one or more subcutaneous injections). In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody before switching to a subcutaneous maintenance dose. In other embodiments, a treatment comprises subcutaneously administering an anti-A β protofibril antibody before switching to an intravenous maintenance dose. In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg (e.g., administering BAN2401 at 10 mg/kg), biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to a subcutaneous maintenance dose. In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg, biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to a weekly subcutaneous maintenance dose. In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg, biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to a weekly, 360 mg, subcutaneous maintenance dose. In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg, biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to a weekly, 720 mg, subcutaneous maintenance dose. In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg, biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to a biweekly, 720 mg, subcutaneous maintenance dose. In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg, biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to a monthly, 720 mg, subcutaneous maintenance dose. In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg, biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to a quarterly, 720 mg, subcutaneous maintenance dose.

[33] In some embodiments, a patient will begin treatment comprising administering intravenously an anti-A β protofibril antibody, e.g., at a dose of 10 mg/kg, then switch to a treatment (e.g., a maintenance treatment) comprising subcutaneously administering an anti-A β protofibril antibody, e.g., at a dose of 720 mg. In some embodiments, a patient will begin

treatment comprising administering intravenously an anti-A β protofibril antibody at 10 mg/kg, biweekly, then switch to a treatment comprising subcutaneously administering BAN2401 weekly, e.g., at a dose of 720 mg, e.g., for a total treatment period of at least 18 months or e.g., until the patient is amyloid-negative. In some embodiments, a patient will begin treatment comprising administering intravenously an anti-A β protofibril antibody at 10 mg/kg, biweekly, then switch to a treatment comprising subcutaneously administering BAN2401 weekly, e.g., at a dose of 720 mg, before switching to a weekly, 360 mg, subcutaneous maintenance dose. In some embodiments, a patient will begin treatment comprising administering intravenously an anti-A β protofibril antibody at 10 mg/kg, biweekly, then switch to a treatment comprising subcutaneously administering BAN2401 weekly, e.g., at a dose of 720 mg, before switching to a monthly, 720 mg, subcutaneous maintenance dose.

[34] In some embodiments, the maintenance dose is administered as a subcutaneous injection of the anti-A β protofibril antibody (e.g., BAN2401). In some embodiments, the maintenance dose is administered as a weekly subcutaneous injection of the subcutaneous formulation of the anti-A β protofibril antibody. In some embodiments, the maintenance dose is administered as a weekly, subcutaneous injection of 720 mg comprising two concurrent, e.g., sequential, injections of 360 mg (2 x 1.8 mL of 400 mg/2 mL) of the subcutaneous formulation. In some embodiments, the maintenance dose is administered as a monthly, subcutaneous injection of 720 mg comprising two concurrent, e.g., sequential, injections of 360 mg (2 x 1.8 mL of 400 mg/2 mL) of the subcutaneous formulation. In some embodiments, the maintenance dose is administered as a quarterly, subcutaneous injection of 720 mg comprising two concurrent, e.g., sequential, injections of 360 mg (2 x 1.8 mL of 400 mg/2 mL) of the subcutaneous formulation. In some embodiments, the maintenance dose is administered as a biweekly, subcutaneous injection of 720 mg comprising two concurrent, e.g., sequential, injections of 360 mg (2 x 1.8 mL of 400 mg/2 mL) of the subcutaneous formulation. In some embodiments, the maintenance dose is administered as a monthly, subcutaneous injection of 720 mg comprising two concurrent, e.g., sequential, injections of 360 mg (2 x 1.8 mL of 400 mg/2 mL) of the subcutaneous formulation. In some embodiments, the maintenance dose is administered as a quarterly, subcutaneous injection of 720 mg comprising two concurrent, e.g., sequential, injections of 360 mg (2 x 1.8 mL of 400 mg/2 mL) of the subcutaneous formulation. In some embodiments, the subcutaneous maintenance dose is administered weekly. In some embodiments, the subcutaneous maintenance dose is administered every two weeks. In some embodiments, the subcutaneous maintenance dose is administered every four weeks (monthly). In some embodiments, the subcutaneous maintenance dose is administered every six weeks. In some embodiments, the subcutaneous maintenance dose is administered every eight weeks (2 months). In some embodiments, the subcutaneous maintenance dose is administered every three months (twelve weeks or quarterly). In some embodiments, the subcutaneous maintenance dose is administered weekly, every two weeks, every 4 weeks, every 6 weeks, every 8 weeks, every 10 weeks, every 12 weeks, every 16 weeks, every 24 weeks, every 48 weeks, monthly, every 2 months, every 3 months, every 4 months, every 6 months, or every 12 months. In some embodiments, the subcutaneous maintenance dose comprises an anti-A β protofibril antibody at a dose of 300 mg to 800 mg, 300 mg to 400 mg, 400 mg to 500 mg, 400 mg to 450 mg, 450 mg to 500 mg, 500 mg to 600 mg, 500 mg to 550 mg, 550 mg to 600 mg, 600 mg to 700 mg, 600 mg to 650 mg, 650 mg to 700 mg, 700 mg to 800 mg, 700 mg to 750 mg, or 750 mg to 800 mg. In some embodiments, the maintenance dose is 300 mg, 310 mg, 320 mg, 330 mg, 340 mg, 350 mg, 360 mg, 370 mg, 380 mg, or 390 mg. In some embodiments, the maintenance dose is 400 mg, 410 mg, 420 mg, 430 mg, 440 mg, 450 mg, 460 mg, 470 mg, 480 mg, or 490 mg. In some embodiments, the maintenance dose is 500 mg, 510 mg, 520 mg,

530 mg, 540 mg, 550 mg, 560 mg, 570 mg, 580 mg, or 590 mg. In some embodiments, the maintenance dose is 600 mg, 610 mg, 620 mg, 630 mg, 640 mg, 650 mg, 660 mg, 670 mg, 680 mg, or 690 mg. In some embodiments, the maintenance dose is 700 mg, 710 mg, 720 mg, 730 mg, 740 mg, 750 mg, 760 mg, 770 mg, 780 mg, or 790 mg. In some embodiments, the maintenance dose is 800 mg to 1600 mg, 800 mg to 1000 mg, 800 mg to 900 mg, 900 mg to 1000 mg, 1000 mg to 1200 mg, 1000 mg to 1100 mg, 1100 mg to 1200 mg, 1200 mg to 1400 mg, 1200 mg to 1300 mg, 1300 mg to 1400 mg, 1400 mg to 1600 mg, 1400 mg to 1500 mg, or 1500 mg to 1600 mg. In some embodiments, the maintenance dose is 800 mg, 820 mg, 840 mg, 860 mg, 880 mg, 900 mg, 920 mg, 940 mg, 960 mg, or 980 mg. In some embodiments, the maintenance dose is 1000 mg, 1020 mg, 1040 mg, 1060 mg, 1080 mg, 1100 mg, 1120 mg, 1140 mg, 1160 mg, or 1180 mg. In some embodiments, the maintenance dose is 1200 mg, 1220 mg, 1240 mg, 1260 mg, 1280 mg, 1300 mg, 1320 mg, 1340 mg, 1360 mg, or 1380 mg. In some embodiments, the maintenance dose is 1400 mg, 1420 mg, 1440 mg, 1460 mg, 1480 mg, 1500 mg, 1520 mg, 1540 mg, 1560 mg, or 1580 mg. In some embodiments, the maintenance dose is provided in a single administration, e.g., administered as a single subcutaneous injection of 720 or 1440 mg, or in two or more administrations, e.g., two concurrent administrations of 360 mg for a total of 720 mg or two administrations of 720 mg for a total of 1440 mg. In some embodiments, the maintenance dose is 440 mg. In some embodiments, the maintenance dose is 580 mg. In some embodiments, the maintenance dose is 720 mg. In some embodiments, the maintenance dose is 1440 mg. In some embodiments, the maintenance dose is administered as a weekly, subcutaneous injection of 720 mg. In some embodiments, the maintenance dose is administered as a weekly, subcutaneous injection of 360 mg. In some embodiments, the maintenance dose is administered as a biweekly, subcutaneous injection of 720 mg. In some embodiments, the maintenance dose is administered as a biweekly, subcutaneous injection of 1440 mg. In some embodiments, the maintenance dose is provided in a single, biweekly administration of 1440 mg comprising two concurrent, e.g., sequential administrations of 720 mg of the subcutaneous formulation for a total of 1440 mg.

[35] In some embodiments, a treatment comprises subcutaneously administering an anti-A β protofibril antibody, e.g., BAN2401, before switching to an intravenous maintenance dose. In some embodiments, a treatment comprises subcutaneously administering BAN2401 weekly, e.g., a subcutaneous injection of 720 mg comprising two concurrent, e.g., sequential, injections of 360 mg (2 x 1.8 mL of 400 mg/2 mL), e.g., until a patient is amyloid-negative or e.g., for at least 18 months. In some embodiments, a treatment comprises subcutaneously administering BAN2401 weekly, e.g., at a dose of 720 mg, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, and then switching to a maintenance dose. In some embodiments, a treatment comprises subcutaneously administering BAN2401 weekly, e.g., at a dose of 720 mg, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to an intravenous maintenance dose of 10 mg/kg weekly. In some embodiments, a treatment comprises subcutaneously administering BAN2401 weekly, e.g., at a dose of 720 mg, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to an intravenous maintenance dose of 10 mg/kg biweekly. In some embodiments, a treatment comprises subcutaneously administering BAN2401 weekly, e.g., at a dose of 720 mg, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to an intravenous maintenance dose of 10 mg/kg monthly. In some embodiments, a treatment comprises subcutaneously administering BAN2401 weekly, e.g., at a dose of 720 mg, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to an intravenous maintenance dose of 10 mg/kg every six weeks. In some embodiments, a treatment comprises subcutaneously administering BAN2401 weekly, e.g., at a dose of 720 mg, e.g., for at least 18 months or e.g., until a patient is amyloid-negative,

before switching to an intravenous maintenance dose of 10 mg/kg every eight weeks. In some embodiments, a treatment comprises subcutaneously administering BAN2401 weekly, e.g., at a dose of 720 mg, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to an intravenous maintenance dose of 10 mg/kg quarterly. In some embodiments, a subject's maintenance dose is administered at the same amount and/or frequency as the dose during the treatment period. In some embodiments, a subject's maintenance dose is 50% of the dose during the treatment period.

[36] In some embodiments, the maintenance dose is administered intravenously, e.g., after an intravenous treatment period as disclosed above. In some embodiments, an intravenous maintenance dose, e.g., a dosing of 10 mg/kg BAN2401, is administered every week, two weeks, every month, every two months, or every three months (quarterly). In some embodiments, the intravenous maintenance dose is administered every two weeks. In some embodiments, the intravenous maintenance dose is administered every four weeks. In some embodiments, the intravenous maintenance dose is administered every six weeks. In some embodiments, the intravenous maintenance dose is administered every eight weeks (2 months). In some embodiments, the intravenous maintenance dose is administered every three months (quarterly). In some embodiments, the intravenous maintenance dose is administered every 24 weeks (every six months or semi-annually). In some embodiments, the intravenous maintenance dose is 2.5 mg/kg - 10 mg/kg. In some embodiments, the maintenance dose is administered as a biweekly, intravenous dose of 10 mg/kg BAN2401. In some embodiments, the maintenance dose is administered as an intravenous dose of 10 mg/kg every four weeks (monthly). In some embodiments, the maintenance dose is administered as an intravenous dose of 10 mg/kg every six weeks. In some embodiments, the maintenance dose is administered as an intravenous dose of 10 mg/kg every eight weeks (2 months). In some embodiments, the maintenance dose is administered as an intravenous dose of 10 mg/kg every twelve weeks (every three months or quarterly). In some embodiments, the maintenance dose is administered as an intravenous dose of 10 mg/kg every 24 weeks (every six months or semi-annually). In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg, biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to a weekly intravenous maintenance dose. In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg, biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to a biweekly intravenous maintenance dose. In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg, biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to a monthly intravenous maintenance dose. In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg, biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to an intravenous maintenance dose every six weeks. In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg, biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to an intravenous maintenance dose every eight weeks. In some embodiments, a treatment comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg, biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative, before switching to a quarterly intravenous maintenance dose.

[37] In some embodiments, a patient starts on an intravenous maintenance dose, e.g., a dosing of 10 mg/kg BAN2401 as disclosed above before switching to a subcutaneous maintenance dose, e.g., a subcutaneous injection of 720 mg comprising two concurrent, e.g., sequential, injections of 360 mg (2 x 1.8 mL of 400 mg/2 mL) of the subcutaneous formulation. In some embodiments, a patient starts on a subcutaneous maintenance dose, e.g.,

a subcutaneous injection of 720 mg comprising two concurrent, e.g., sequential, injections of 360 mg (2 x 1.8 mL of 400 mg/2 mL) of the subcutaneous formulation before switching to an intravenous maintenance dose, e.g., a dosing of 10 mg/kg BAN2401 as disclosed above.

[38] In some embodiments, a patient is moved back from a maintenance dose to the initial treatment dose if the patient is determined to no longer be amyloid negative, e.g., as assessed by measuring a p-tau181 level above a threshold in a blood sample taken after switching to a maintenance dose and/or as determined by PET SUVR. In some embodiments, a patient's treatment is discontinued if the patient is determined to no longer be amyloid negative, e.g., as assessed by measuring a p-tau181 level above a threshold in a blood sample taken after switching to a maintenance dose.

[39] In some embodiments, the maintenance dose is administered at least every three months (e.g., quarterly) or every twelve weeks. In some embodiments, after switching to a maintenance dose, the p-tau181 level is measured in a sample (e.g., a plasma sample) from the subject. In some embodiments, the maintenance dose and/or frequency is selected to maintain a p-tau181 level achieved after the completion of the initial treatment (e.g., after 18 months of treatment). In some embodiments, the maintenance dose and/or frequency is selected to maintain the p-tau181 level below the p-tau181 level prior to initial treatment. In some embodiments, a patient's amyloid level may be monitored during the treatment with the maintenance dose, e.g., by a blood biomarker. In some embodiments, a patient's amyloid level may be monitored during the treatment with the maintenance dose by one or more biomarkers such as, but not limited to: (a) amyloid detected by PET scan from either a visual read or semiquantitative thresholds (SUVR or centiloid); (b) cerebrospinal fluid (CSF) A β 1-42, and/or A β 1-42/1-40 ratio; and/or (c) blood biomarkers (such as plasma A β 1-42, total tau (T-tau), and/or phosphorylated tau (P-tau)(e.g., p-tau181)). In some embodiments, a patient's biomarkers may be monitored at least once after switching to the maintenance dose. In some embodiments, a patient's biomarkers are evaluated at least 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 6 months, 12 months, 18 months, or 24 months after switching to the maintenance dose. In some embodiments, the maintenance dose is continued if the p-tau181 level remains unchanged. In some embodiments, a subject is returned to the original dosing (e.g., 10 mg/kg BAN2401 biweekly) if one or more biomarkers worsen, e.g., if the p-tau181 level is increased relative to the level measured in a sample at the end of the earlier treatment period (e.g., at 18 months after the start of treatment). In some embodiments, a subject is administered a higher dose (e.g., a 50% increase in the maintenance dose) if one or more biomarkers worsen, e.g., if the p-tau181 level increases in a sample at the end of the earlier treatment period (e.g., at 18 months after the start of treatment). In some embodiments, a subject is administered a treatment at a higher frequency (e.g., a change from biweekly to weekly administration) if one or more biomarkers worsen, e.g., if the p-tau181 level increases in a sample at the end of the earlier treatment period (e.g., at 18 months after the start of treatment).

[40] In some embodiments, a subject's maintenance dose is administered at the same amount and/or frequency as the dose during the treatment period. In some embodiments, a subject's maintenance dose is 50% of the dose during the treatment period. In some embodiments, a maintenance dose is selected (e.g., in conjunction with the evaluation of a change in the p-tau181 level) based on whether the patient is an ApoE4 carrier, e.g., with a greater decrease in the p-tau181 level required to move from the initial treatment to a maintenance dose for a carrier than for a non-carrier. In some embodiments, the maintenance dose comprises two or more dosings, in which a first dosing is selected from the maintenance dose as exemplified above and a second and/or subsequent dosing comprising a lower amount and/or frequency of dosing than the first or previous dosing, respectively. In some embodiments, the switching to the second or subsequent dosing is determined based on one

or more biomarkers as exemplified above, where the levels of the biomarkers are different from (e.g., improved over) the levels used in switching from initial dose to the first dosing in the maintenance dose.

[41] In some embodiments, after switching to a maintenance dose, a subject's biomarker levels will indicate increasing levels of amyloid in the brain. In some embodiments, after switching to a maintenance dose, a subject's biomarker levels, e.g. the plasma A β 42/40 ratio, will begin to decrease, indicating increasing levels of amyloid in the brain. In some embodiments, a subject on a maintenance dose will have a decrease in the A β 42/40 ratio. In some embodiments, a subject is put on a maintenance dose chosen such that the subject will have a decrease in the A β 42/40 ratio but the A β 42/40 ratio will remain above the threshold for amyloid positivity, e.g. for at least one year (e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 years).

[42] In some embodiments, after switching to a maintenance dose, a subject's biomarker levels, e.g. p-tau181, will begin to increase, indicating increasing levels of amyloid in the brain. In some embodiments, a subject on a maintenance dose will have an increase in plasma p-tau181. In some embodiments, a subject on a maintenance dose will have an increase in p-tau181 but the level p-tau181 will remain below the threshold for amyloid positivity, e.g., for at least one year (e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 years).

[43] In some embodiments, a patient's treatment is discontinued if a patient no longer has early AD, e.g., as assessed by cognitive evaluation, PET SUVR, and/or plasma biomarkers such as the level of p-tau181 (e.g., if the level of p-tau181 is above a threshold and/or an SUVR negativity increases above 1.17 as measured using florbetapir).

[44] In some embodiments, a treatment is discontinued if a favorable biomarker level is achieved. In some embodiments, a treatment is discontinued if a favorable biomarker level is achieved after the completion of the initial treatment. In some embodiments, a treatment is discontinued if a favorable biomarker level is achieved and/or maintained (e.g., for a set period of time such as six months or a year) during a maintenance dosing. In some embodiments, a treatment is discontinued if a low p-tau181 level is achieved, e.g., after the completion of the initial treatment or during a maintenance dosing regimen. In some embodiments, a maintenance dose is discontinued if the p-tau181 level is below the p-tau181 level achieved after the completion of the initial treatment. In some embodiments, a treatment is discontinued if an SUVR amyloid negativity level is at or below 1.17 as measured using florbetapir after the completion of the initial treatment or during a maintenance dosing regimen.

[45] In some embodiments, a maintenance dose is discontinued if a favorable biomarker level is achieved after the completion of a set period of time on the maintenance treatment (e.g., six months or a year). In some embodiments, a maintenance dose is discontinued if a low p-tau181 level is achieved. In some embodiments, a maintenance dose is discontinued if the SUVR amyloid negativity level is at or below 1.17 as measured using florbetapir.

[46] In some embodiments, a maintenance dose is discontinued if a favorable biomarker level is not maintained over the course of a maintenance treatment (e.g., if the p-tau181 level does not decrease compared to the p-tau181 level prior to treatment and/or an SUVR negativity increases above 1.17 as measured using florbetapir). In some embodiments, a maintenance dose is discontinued if a favorable biomarker level is not maintained over the course of a maintenance treatment (e.g., if the p-tau181 level does not decrease compared to the p-tau181 level prior to treatment and/or an SUVR negativity increases above 1.17 as measured using florbetapir).

[47] In some embodiments, a patient's amyloid level may be monitored for regression after treatment discontinuation, e.g., by a blood biomarker. In some embodiments, a patient's amyloid level may be monitored for regression after treatment discontinuation by one or

more biomarkers such as, but not limited to: (a) amyloid detected by PET scan from either a visual read or semiquantitative thresholds (SUVr or centiloid); (b) cerebrospinal fluid (CSF) A β 1-42, and/or A β 1-42/1-40 ratio; and/or (c) blood biomarkers (such as plasma A β 1-42, tau, total tau (T-tau), and/or P-tau (e.g., P-tau181)). In some embodiments, a patient's biomarkers may be monitored at least once after the discontinuation of treatment. In some embodiments, a patient's biomarkers are monitored at least 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 6 months, 12 month, 18 months, or 24 months after treatment discontinuation. In some embodiments, treatment is reinitiated if a patient's biomarker level becomes less favorable, e.g., an increase in the p-tau181 level, e.g., to greater than the p-tau181 level prior to initial treatment.

[48] In some embodiments, the maintenance dose is administered at least every three months (e.g., every three months, every two months, monthly, biweekly, or weekly). In some embodiments, the maintenance dose and/or frequency is selected to maintain a PET SUVr level achieved after the completion of the initial treatment. In some embodiments, the maintenance dose is selected to maintain a PET SUVr level at or below amyloid negativity (e.g. for florbetapir, PET SUVr of 1.17).

[49] In some embodiments, the subject has been diagnosed with early AD. In some embodiments, the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood and/or has been diagnosed as having mild Alzheimer's disease dementia.

[50] In some embodiments, the method of treatment comprises measuring the level of p-tau181 in a first blood sample obtained from the subject. The terms "level of p-tau181" and "p-tau181 level" are used interchangeably. In some embodiments the subject is then administered a therapeutically effective dose of an anti-amyloid β (A β) protofibril antibody. In some embodiments, a second blood sample is obtained after the first sample to determine a second p-tau181 level. In some embodiments, a second blood sample is obtained from a subject after treatment has stopped or been reduced. In some embodiments, a change in the p-tau181 level is used to determine a second therapeutically effective dose. In some embodiments, a subject having a decreased second level relative to the first level is administered a second therapeutically effective dose comprising the same or a lower amount of the anti-A β protofibril antibody than in the first dose to the subject. In some embodiments, a subject having a higher second level relative to the first level is administered a second therapeutically effective dose comprising a higher amount of the anti-A β protofibril antibody than in the first dose. In some embodiments, a subject having a higher second level relative to the first level is administered a different treatment for AD. A first therapeutically effective dose may be administered multiple times (e.g., biweekly or monthly for 6-18 months) before changing to a second therapeutically effective dose or dosing regimen after measuring a second p-tau181 level. In some embodiments, a first therapeutically effective dose may be administered for at least 18 months before switching to a maintenance dose. In some embodiments, a first therapeutically effective dose may be administered until a patient is amyloid negative before switching to a maintenance dose. In some embodiments, a first therapeutically effective dose may be administered until a patient is amyloid negative (e.g., as measured by: amyloid or tau positron emission tomography (PET), a cerebrospinal fluid level of A β 1-42 and/or an A β 1-42/1-40 ratio, a cerebrospinal fluid level of total tau, cerebrospinal fluid level of neurogranin, a cerebrospinal fluid level of neurofilament light peptide (NfL), blood biomarkers as measured in the serum or plasma (e.g. levels of A β 1-42, the ratio of two forms of amyloid- β peptide (A β 1-42/1-40 ratio), plasma levels of plasma total tau (T-tau), levels of phosphorylated tau (P-tau) isoforms (including tau phosphorylated at 181 (P-tau181), 217 (P-tau217), and 231 (P-tau231)), levels of glial fibrillary acidic protein (GFAP) and/or neurofilament light (NfL)) before switching to a maintenance dose. In some

embodiments, a first therapeutically effective dose may be administered until a patient is amyloid negative, e.g., as measured by an A β 42/40 ratio at or above 0.092-0.094 (e.g., at or above 0.092) or a florbetapir amyloid PET SUVR negativity at or below 1.17, before switching to a maintenance dose. In some embodiments, a first therapeutically effective dose may be administered until a patient is amyloid negative, e.g., as measured by a p-tau181 level below a threshold or a florbetapir amyloid PET SUVR negativity at or below 1.17, before switching to a maintenance dose. In some embodiments, a first therapeutically effective dose comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg (e.g., administering BAN2401 at 10 mg/kg), biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative before switching to a maintenance dose.

[51] In some embodiments, a first therapeutically effective dose comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg (e.g., administering BAN2401 at 10 mg/kg), biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative before switching to an intravenous maintenance dose (e.g., at 10 mg/kg, e.g., biweekly, or every 4, 6, 8, 10, or 12 weeks). In some embodiments, a first therapeutically effective dose comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg (e.g., administering BAN2401 at 10 mg/kg), biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative before switching to a biweekly intravenous maintenance dose. In some embodiments, a first therapeutically effective dose comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg (e.g., administering BAN2401 at 10 mg/kg), biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative before switching to a monthly intravenous maintenance dose. In some embodiments, a first therapeutically effective dose comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg (e.g., administering BAN2401 at 10 mg/kg), biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative before switching to an intravenous maintenance dose every six weeks. In some embodiments, a first therapeutically effective dose comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg (e.g., administering BAN2401 at 10 mg/kg), biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative before switching to an intravenous maintenance dose every eight weeks. In some embodiments, a first therapeutically effective dose comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg (e.g., administering BAN2401 at 10 mg/kg), biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative before switching to an intravenous maintenance dose every two months. In some embodiments, a first therapeutically effective dose comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg (e.g., administering BAN2401 at 10 mg/kg), biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative before switching to a quarterly intravenous maintenance dose.

[52] In some embodiments, a first therapeutically effective dose comprises subcutaneously administering an anti-A β protofibril antibody at 720 mg (e.g., administering BAN2401 at 720 mg) weekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative before switching to a subcutaneous maintenance dose (e.g., at 720 mg, e.g., weekly, biweekly, or every 4, 6, 8, 10, or 12 weeks). In some embodiments, the maintenance dose is 360 mg weekly.

[53] In some embodiments, a first therapeutically effective dose comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg (e.g., administering BAN2401 at 10 mg/kg), biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative before switching to a weekly subcutaneous maintenance dose (e.g., at a dose of 720 mg). In some embodiments, a first therapeutically effective dose comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg (e.g., administering BAN2401 at 10 mg/kg), biweekly, e.g., for at least 18 months or e.g., until a patient is

amyloid-negative before switching to a weekly subcutaneous maintenance dose (e.g., at a dose of 360 mg). In some embodiments, a first therapeutically effective dose comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg (e.g., administering BAN2401 at 10 mg/kg), biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative before switching to a biweekly subcutaneous maintenance dose (e.g., at a dose of 720 mg or at a dose of 360 mg). In some embodiments, a first therapeutically effective dose comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg (e.g., administering BAN2401 at 10 mg/kg), biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative before switching to a subcutaneous maintenance dose (e.g., at a dose of 720 mg or at a dose of 360 mg) every month. In some embodiments, a first therapeutically effective dose comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg (e.g., administering BAN2401 at 10 mg/kg), biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative before switching to a subcutaneous maintenance dose (e.g., at a dose of 720 mg or at a dose of 360 mg) every six weeks. In some embodiments, a first therapeutically effective dose comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg (e.g., administering BAN2401 at 10 mg/kg), biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative before switching to a subcutaneous maintenance dose (e.g., at a dose of 720 mg or at a dose of 360 mg) every eight weeks. In some embodiments, a first therapeutically effective dose comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg (e.g., administering BAN2401 at 10 mg/kg), biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative before switching to a subcutaneous maintenance dose (e.g., at a dose of 720 mg or at a dose of 360 mg) every two months. In some embodiments, a first therapeutically effective dose comprises administering intravenously an anti-A β protofibril antibody at 10 mg/kg (e.g., administering BAN2401 at 10 mg/kg), biweekly, e.g., for at least 18 months or e.g., until a patient is amyloid-negative before switching to a quarterly subcutaneous maintenance dose (e.g., at a dose of 720 mg or at a dose of 360 mg).

[54] In some embodiments, a first therapeutically effective dose comprises subcutaneously administering an anti-A β protofibril antibody weekly, e.g., subcutaneous injection of 720 mg comprising two concurrent, e.g., sequential, injections in a given week of 360 mg (2 x 1.8 mL of 400 mg/2 mL) of the subcutaneous formulation, e.g., for at least 18 months or e.g., until a patient is amyloid-negative before switching to a weekly subcutaneous maintenance dose (e.g., at a dose of 720 mg or at a dose of 360 mg). In some embodiments, a first therapeutically effective dose comprises subcutaneously administering an anti-A β protofibril antibody weekly, e.g., subcutaneous injection of 720 mg comprising two concurrent, e.g., sequential, injections in a given week of 360 mg (2 x 1.8 mL of 400 mg/2 mL) of the subcutaneous formulation, e.g., for at least 18 months or e.g., until a patient is amyloid-negative before switching to a biweekly subcutaneous maintenance dose (e.g., at a dose of 720 mg). In some embodiments, a first therapeutically effective dose comprises subcutaneously administering an anti-A β protofibril antibody weekly, e.g., subcutaneous injection of 720 mg comprising two concurrent, e.g., sequential, injections in a given week of 360 mg (2 x 1.8 mL of 400 mg/2 mL) of the subcutaneous formulation, e.g., for at least 18 months or e.g., until a patient is amyloid-negative before switching to a weekly subcutaneous maintenance dose (e.g., a single dose of 360 mg). In some embodiments, a first therapeutically effective dose comprises subcutaneously administering an anti-A β protofibril antibody weekly, e.g., subcutaneous injection of 720 mg comprising two concurrent, e.g., sequential, injections in a given week of 360 mg (2 x 1.8 mL of 400 mg/2 mL) of the subcutaneous formulation, e.g., for at least 18 months or e.g., until a patient is amyloid-negative before switching to a monthly subcutaneous maintenance dose (e.g., at a dose of 720 mg). In some embodiments, a first therapeutically effective dose comprises subcutaneously

administering an anti-A β protofibril antibody weekly, e.g., subcutaneous injection of 720 mg comprising two concurrent, e.g., sequential, injections in a given week of 360 mg (2 x 1.8 mL of 400 mg/2 mL) of the subcutaneous formulation, e.g., for at least 18 months or e.g., until a patient is amyloid-negative before switching to a subcutaneous maintenance dose (e.g., at a dose of 720 mg) every six weeks. In some embodiments, a first therapeutically effective dose comprises subcutaneously administering an anti-A β protofibril antibody weekly, e.g., subcutaneous injection of 720 mg comprising two concurrent, e.g., sequential, injections in a given week of 360 mg (2 x 1.8 mL of 400 mg/2 mL) of the subcutaneous formulation, e.g., for at least 18 months or e.g., until a patient is amyloid-negative before switching to a subcutaneous maintenance dose (e.g., at a dose of 720 mg) every eight weeks. In some embodiments, a first therapeutically effective dose comprises subcutaneously administering an anti-A β protofibril antibody weekly, e.g., subcutaneous injection of 720 mg comprising two concurrent, e.g., sequential, injections in a given week of 360 mg (2 x 1.8 mL of 400 mg/2 mL) of the subcutaneous formulation, e.g., for at least 18 months or e.g., until a patient is amyloid-negative before switching to a subcutaneous maintenance dose (e.g., at a dose of 720 mg) every two months. In some embodiments, a first therapeutically effective dose comprises subcutaneously administering an anti-A β protofibril antibody weekly, e.g., subcutaneous injection of 720 mg comprising two concurrent, e.g., sequential, injections in a given week of 360 mg (2 x 1.8 mL of 400 mg/2 mL) of the subcutaneous formulation, e.g., for at least 18 months or e.g., until a patient is amyloid-negative before switching to a quarterly subcutaneous maintenance dose (e.g., at a dose of 720 mg).

[55] The following are definitions of terms used in the present application.

[56] As used herein, the singular terms “a,” “an,” and “the” include the plural reference unless the context clearly indicates otherwise.

[57] The phrase “and/or,” as used herein, means “either or both” of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Thus, as a non-limiting example, “A and/or B”, when used in conjunction with open-ended language such as “comprising” can refer, in some embodiments, to A only (optionally including elements other than B); in other embodiments, to B only (optionally including elements other than A); in yet other embodiments, to both A and B (optionally including other elements); etc.

[58] As used herein, “at least one” means one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase “at least one” refers, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, “at least one of A and B” (or, equivalently, “at least one of A or B,” or, equivalently “at least one of A and/or B”) can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet another embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

[59] As used herein, “about” when used in connection with doses, amounts, or ratios, include the value of a specified dose, amount, or ratio or a range of the dose, amount, or ratio that is recognized by one of ordinary skill in the art to provide a therapeutic effect equivalent to that obtained from the specified dose, amount, or ratio. The term “about” may refer to an acceptable error for a particular value as determined by one of skill in the art, which depends

in part on how the values is measured or determined. In some embodiments, the term “about” means within 5% of a given value or range.

[60] As used herein, “adjusted mean change from baseline” refers to the use of a statistical analysis to calculate the change in a biomarker value over time. In some embodiments, a linear mixed-effects model (MMRM) is used to account for at least one additional covariate to determine the adjusted mean change from baseline.

[61] When a number is recited, either alone or as part of a numerical range, it should be understood that the numerical value can vary above and below the stated value by up to a variance of +/- 10% of the stated value.

[62] When a range of values is listed herein, it is intended to encompass each value and sub-range within that range. For example, “2.5 mg/kg to 10 mg/kg” is intended to encompass, for example, 2.5 mg/kg, 3 mg/kg, 3.5 mg/kg, 4 mg/kg, 4.5 mg/kg, 5 mg/kg, 5.5 mg/kg, 6 mg/kg, 6.5 mg/kg, 7 mg/kg, 7.5 mg/kg, 8 mg/kg, 8.5 mg/kg, 9 mg/kg, 9.5 mg/kg, 10 mg/kg, 2.5 mg/kg to 3 mg/kg, 2.5 mg/kg to 4.5 mg/kg, 3 mg/kg to 4.5 mg/kg, 4.5 mg/kg to 8 mg/kg, 2.5 mg/kg to 9 mg/kg, and so forth.

[63] Amyloid β 1-42 (A β 42) refers to an amyloid beta monomer from amino acid 1 to 42 of the full-length protein (Table 5, SEQ ID NO:13). Amyloid β 1-40 (A β 1-40) refers to an amyloid beta monomer from amino acid 1 to 42 of the full-length protein (Table 5, SEQ ID NO:14).

[64] P-tau181 is human tau protein phosphorylated at threonine in position 181.

[65] Patients with “preclinical AD” “pre-Alzheimer’s disease” or “pre-AD” as described herein, are cognitively normal individuals with intermediate or elevated levels of amyloid in the brain and can be identified by asymptomatic stages with or without memory complaints and emerging episodic memory and executive function deficits. Cognitively normal can include individuals who are CDR 0, or individuals within the normal ranges of cognitive test scores (MMSE, International Shopping List Task, Logical Memory, etc.). Preclinical AD occurs prior to significant irreversible neurodegeneration and cognitive impairment and is typically characterized by the appearance of in vivo molecular biomarkers of AD and the absence clinical symptoms. Preclinical AD biomarkers that may suggest the future development of Alzheimer’s disease include, but are not limited to, one or more of intermediate or elevated levels of amyloid in the brain by amyloid or tau positron emission tomography (PET) (e.g., a centiloid measure of about 20-40, e.g., a measure of about 20-32), cerebrospinal fluid level of A β 1-42 and/or A β 1-42/1-40 ratio, cerebrospinal fluid level of total tau, cerebrospinal fluid level of neurogranin, cerebrospinal fluid level of neurofilament light peptide (NfL), and blood biomarkers as measured in the serum or plasma (e.g. levels of A β 1-42, the ratio of two forms of amyloid- β peptide (A β 1-42/1-40 ratio, e.g., a ratio of between about 0.092-0.094 or below about 0.092), plasma levels of plasma total tau (T-tau), levels of phosphorylated tau (P-tau) isoforms (including tau phosphorylated at 181 (P-tau181), 217 (P-tau217), and 231 (P-tau231)), glial fibrillary acidic protein (GFAP), and neurofilament light (NfL)). For example, it has been found that subjects treated with elenbecestat (E2609), a β -site amyloid precursor protein cleaving enzyme (BACE) inhibitor, who had amyloid baseline positron emission tomography (PET) standard uptake value ratios (SUVr values) of 1.4 to 1.9, exhibited the greatest slowing of cognitive decline while on treatment. See Lynch, S. Y. et al. “Elenbecestat, a BACE inhibitor: results from a Phase 2 study in subjects with mild cognitive impairment and mild-to-moderate dementia due to Alzheimer’s disease.” Poster P4-389, Alzheimer’s Association International Conference, July 22-26, 2018, Chicago, IL, USA. Similarly, it has been found that subjects having a baseline florbetapir amyloid PET SUVr levels below 1.2 do not exhibit enough cognitive decline to be detectable, whereas subjects having SUVr levels above 1.6 appear to correlate with a plateau effect in which amyloid level has reached a saturation level and treatment does

not result in a change of cognitive measures. See Dhadda, S. et al., “Baseline florbetapir amyloid PET standard update value ratio (SUVR) can predict clinical progression in prodromal Alzheimer’s disease (pAD).” Poster P4-291, Alzheimer’s Association International Conference, July 22-26, 2018, Chicago, IL, USA.

[66] “Early AD”, “EAD”, or “early Alzheimer’s disease,” as used herein, is a continuum of AD severity from mild cognitive impairment due to AD – intermediate likelihood to mild Alzheimer’s disease dementia. Subjects with early AD include subjects with mild Alzheimer’s disease dementia as defined herein and subjects with mild cognitive impairment (MCI) due to AD – intermediate likelihood as defined herein. In some embodiments, subjects with early AD have MMSE scores of 22 to 30 and Clinical Dementia Rating (CDR) global range 0.5 to 1.0. Other methods for detecting early AD disease may employ the tests and assays specified below, including the National Institute of Aging-Alzheimer’s Association (NIA-AA) core clinical criteria for probable Alzheimer’s disease dementia in McKhann, G.M. *et al.*, “The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging – Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease.” *Alzheimer Dement.* 2011; 7:263-9. Other methods include CDR-SB, ADCOMS Composite Clinical Score, the Mini-Mental State Examination, ADAS-Cog, ADAS MCI-ADL, modified iADRS, Wechsler Memory Scale-IV Logical Memory (subscale) I (WMS-IV LMI), and Wechsler Memory Scale-IV Logical Memory (subscale) II (WMS-IV LMII). In some embodiments, a subject with early AD has evidence of elevated amyloid in the brain or a positive amyloid load. In some embodiments, elevated amyloid in the brain or a positive amyloid load is indicated and/or confirmed by PET assessment. In some embodiments, elevated amyloid in the brain or a positive amyloid load is indicated and/or confirmed by a CSF assessment of markers such as A β 1-42 (e.g., a soluble CSF biomarker analysis). In some embodiments, elevated amyloid in the brain or a positive amyloid load is indicated and/or confirmed by measuring the level of p-tau181. In some embodiments, elevated amyloid in the brain or a positive amyloid load is indicated and/or confirmed by an MRI. In some embodiments, elevated amyloid in the brain or a positive amyloid load is indicated by retinal amyloid accumulation. In some embodiments, more than one assessment method is used.

[67] In addition to measuring the level of p-tau181 in a sample from a subject, the subject’s amyloid level may alternatively be detected, or additionally confirmed, by one or more biomarkers such as, but not limited to: (a) amyloid detected by PET scan from either a visual read or semiquantitative thresholds (SUVR or centiloid); (b) cerebrospinal fluid (CSF) A β 1-42, and/or A β 1-42/1-40 ratio; and/or (c) blood biomarkers (such as plasma A β 1-42, tau, and/or total tau (T-tau). Secondary markers may confirm a primary amyloid determination and include but are not limited to markers of neuronal damage such as neurofilament light peptide (NfL) and markers of neuroinflammation such as glial fibrillary acidic protein (GFAP).

[68] “Amyloid” refers to fibers that are unbranched, usually extracellular, and found in vivo; in addition, the fibers bind the dye Congo Red and then show green birefringence when viewed between crossed polarizers. Amyloid-forming proteins have been identified and associated with serious diseases, including amyloid- β peptide (A β) with Alzheimer’s disease (AD), islet amyloid polypeptide (IAPP) with diabetes type 2, and prion protein (PrP) with the spongiform encephalopathies. As used herein, “amyloid,” “brain amyloid,” and “amyloid- β peptide (A β)” are used interchangeably.

[69] In some embodiments, the subject has “elevated amyloid” or “intermediate amyloid.” As one of ordinary skill in the art will recognize, amyloid levels from amyloid PET can be reported using the Centiloid method in “centiloid” units (CL). (Klunk WE et al. The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. *Alzheimer’s*

Dement. 2015; 11:1–15 e1–4). The Centiloid method measures a tracer on a scale of 0 CL to 100 CL, where 0 is deemed the anchor-point and represents the mean in young healthy controls and 100 CL represents the mean amyloid burden present in subjects with mild to moderate severity dementia due to AD. (Id.) As is known to one of ordinary skill in the art, centiloid thresholds may vary, for example may be refined, based on new or additional scientific information. (See, e.g., <http://www.gaain.org/centiloid-project>.) An elevated level of amyloid can be set relative to a baseline threshold in a healthy control determined according to methods known to a person of ordinary skill in the art (POSA). For example, a centiloid value of 32.5 can be used as a threshold value for “elevated amyloid,” and an “intermediate amyloid” level refers to an A β amyloid PET in the range of 20–32.5 CL (e.g., 30 CL). In another example, a centiloid value of 40 can be used as a threshold value for “elevated amyloid,” and an “intermediate amyloid” level refers to an A β amyloid PET in the range of 20–40 CL.

[70] Subjects with “mild Alzheimer’s disease dementia,” or “mild AD dementia” as used herein, are subjects meeting the National Institute of Aging-Alzheimer’s Association (NIA-AA) core clinical criteria for probable Alzheimer’s disease dementia in McKhann, G.M. *et al.*, “The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging – Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease.” *Alzheimer Dement.* 2011; 7:263-9. Also included herein are subjects who have a CDR score of 0.5 to 1.0 and a Memory Box score of 0.5 or greater at screening and baseline and subjects that exhibit change in the score on the Wechsler Memory Scale-Revised Logical Memory subscale II (WMS-R LM II).

[71] Subjects with “MCI due to AD – intermediate likelihood,” as used herein are those identified as such in accordance with the NIA-AA core clinical criteria for mild cognitive impairment due to Alzheimer’s disease – intermediate likelihood (see McKhann *supra*). For example, a subject may be symptomatic but not demented, with evidence of brain amyloid pathology making them less heterogeneous and more similar to mild Alzheimer’s disease dementia subjects in cognitive and functional decline as measured by the ADCOMS Composite Clinical Score defined herein. Also included are subjects who have a CDR score of 0.5 and a Memory Box score of 0.5 or greater at screening and baseline. Furthermore, subjects who report a history of subjective memory decline with gradual onset and slow progression over the last 1 year before screening, which is corroborated by an informant, are also included herein. Memory decline and/or episodic memory impairment can be assessed in a subject by change in the score on the Wechsler Memory Scale-Revised Logical Memory subscale II (WMS-R LM II).

[72] As used herein, “MMSE” refers to the Mini-Mental State Examination, a cognitive instrument commonly used for screening purposes, but also often measured longitudinally in AD clinical trials having a 30 point scale with higher scores indicating less impairment and lower scores indicating more impairment, ranging from 0 (most impaired) to 30 (no impairment). In some embodiments, seven items measuring orientation to time and place, registration, recall, attention, language, and drawing may be assessed as part of the MMSE score. (Folstein, M.F. *et al.*, “Mini-mental state. A practical method for grading the cognitive state of patients for the clinician.” *J. Psychiatr. Res.* 1975;12:189-98.)

[73] As used herein, “ADAS-Cog” refers to Alzheimer’s Disease Assessment Scale-Cognitive. The ADAS-Cog is a widely used cognitive scale in Alzheimer’s disease trials having a structured scale that evaluates memory (word recall, delayed word recall, and word recognition), reasoning (following commands), language (naming, comprehension), orientation, ideational praxis (placing letter in envelope) and constructional praxis (copying geometric designs). (Rosen, W.G. *et al.*, “A new rating scale for Alzheimer’s disease.” *Am. J. Psychiatry* 1984; 141:1356-64.) Ratings of spoken language, language comprehension,

word finding difficulty, ability to remember test instructions, maze, and number cancellation may also be obtained. In some embodiments, ADAS-Cog refers to the use of the Alzheimer Disease Assessment Scale-Cognitive Subscale₁₄ (ADAS-Cog₁₄). In some embodiments, a modified version may be used herein and is scored from 0 to 90 points with a score of 0 indicating no impairment, and a score of 90 indicating maximum impairment. In some embodiments, the ADAS-Cog₁₄ tasks include memory (word recall, delayed word recall, and word recognition), reasoning (following commands), language (naming, comprehension), orientation, ideational praxis (placing letter in envelope), constructional praxis (copying geometric designs), spoken language, language comprehension, word finding difficulty, ability to remember test instructions, maze, and number cancellation (Rosen *et al.*, 1984).

[74] As used herein, “CDR-SB” refers to clinical dementia rating - sum of boxes. The CDR is a clinical scale that describes 5 degrees of impairment in performance on each of 6 categories of function including memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. (Berg, L. *et al.*, “Mild senile dementia of the Alzheimer type: 2. Longitudinal assessment.” *Ann. Neurol.* 1988; 23:477-84.) The ratings of degree of impairment obtained on each of the 6 categories of function are synthesized into 1 global rating of dementia CDR score (ranging from 0 to 3). A sum of boxes score provides an additional measure of change where each category has a maximum possible score of 3 points and the total score is a sum of the category scores giving a total possible score of 0 to 18 with higher scores indicating more impairment. The global score may be used as a clinical measure of severity of dementia.

[75] As used herein, “ADCOMS” refers to Alzheimer’s Disease Composite Score, a composite clinical score based on an analysis of four ADAS-Cog items (delayed word recall, orientation, word recognition, and word finding difficulty), two Mini Mental State Examination (MMSE) items (orientation to time, and drawing), and all six CDR-SB items (personal care, community affairs, home and hobbies, memory, orientation, and judgment and problem solving), as discussed in the Examples and in Wang, J. *et al.*, “ADCOMS: a composite clinical outcome for prodromal Alzheimer’s disease trials.” *J. Neurol. Neurosurg. Psychiatry.* 2016; 87:993-999. ADCOMS was developed to be particularly sensitive to disease progression during early stages of AD (i.e., preclinical AD or early AD).

[76] In some embodiments, ADCOMS can be calculated using the following formula:

$$S(t) = \sum_{i=1}^{12} a_i A_i(t) + \sum_{i=1}^7 b_i B_i(t) + \sum_{i=1}^6 c_i C_i(t)$$

where $A_i(t)$, $B_i(t)$ and $C_i(t)$ are item scores at time t corresponding to items from ADAS-cog, reversed MMSE scores, and CDR-SB, respectively (Wang, J. *et al.*, “ADCOMS: a composite clinical outcome for prodromal Alzheimer’s disease trials). ADCOMS is particularly sensitive to disease progression during early stages of AD, i.e., prodromal and mild AD.

[77] As used herein, “ADCS MCI-ADL” refers to the Alzheimer’s Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL). The ADCS MCI-ADL is a clinical scale that assesses the competence level of a patient at six basic activities of daily living. Additional examples are discussed in Kreutzer J.S., DeLuca J., Caplan B. (eds) *Encyclopedia of Clinical Neuropsychology*. Springer, New York, NY.

[78] As used herein, “modified iADRS” or “iADRS” refers to a composite tool that combines scores from the ADAS Cog₁₄ (all items) and the ADCS MCI-ADL (all items). The modified iADRS score can be used to evaluate disease progression:

$$\text{Modified iADRS score} = [-1(\text{ADAS-cog}_{14}) + 90] + \text{ADCS MCI-ADL}.$$

[79] As used herein, “ApoE4-positive” subjects and “ApoE4 carriers” refer to subjects who harbor the $\epsilon 4$ variant of the apolipoprotein (APOE) gene. The $\epsilon 4$ variant is one of several major alleles of the apolipoprotein gene. The gene is generally responsible for metabolism of fats. It has been found that carriers of the apolipoprotein $\epsilon 4$ show significantly greater rates of amyloid retention when compared to non-carriers. (Drzezga, A. *et al*, “Effect of APOE genotype on amyloid plaque load and gray matter volume in Alzheimer disease.” *Neurology*. 2009; 72:1487-94.) In some embodiments, a subject treated herein is a heterozygous carrier of the apolipoprotein E $\epsilon 4$ gene allele. In some embodiments, the subject is a homozygous carrier of the apolipoprotein E $\epsilon 4$ gene allele. ApoE4 carriers may have a greater response to treatment when administered a composition comprising an anti-A β protofibril antibody (i.e. lecanemab) than ApoE4 non-carriers. The terms “ApoE4-negative” and “ApoE4 non-carriers” are used interchangeably.

[80] As used herein, whether an early AD subject is “amyloid positive” or “amyloid negative” may be determined based on whether the subject has a positive amyloid load. In some embodiments, a subject is determined to be amyloid-positive or amyloid-negative as indicated by longitudinal positron emission tomography (PET) assessment of an amyloid imaging agent uptake into the brain. In some embodiments, a subject is “amyloid negative” if the florbetapir amyloid PET SUVR negativity is below 1.17. In some embodiments, a subject is determined to be amyloid-positive or amyloid-negative by evaluation of the level of p-tau181 in a sample (e.g., a plasma sample) from a subject, alone or in combination with another method such as PET measurement of brain amyloid. In some embodiments, a subject is “amyloid negative” if the A β 42/40 ratio in a sample is at or about above 0.092-0.094 e.g., at about 0.092. In some embodiments, a subject is “amyloid negative” if the A β 42/40 ratio in a sample is above 0.092. In some embodiments, a subject is determined to be amyloid-positive or amyloid-negative by a CSF assessment of the presence of amyloid pathology using assessments of markers such as p-tau181, alone or in combination with another method such as PET measurement of brain amyloid. In some embodiments, a qualitative visual read of PET scans may be used to determine amyloid positive and amyloid negative by categorizing subjects as having either “normal” or “abnormal” uptake on the basis of the PET image pattern. Readers will have been trained and certified to recognize brain PET images with abnormal or normal patterns of uptake, or the detection of amyloid is done through a semi-quantitative or quantitative approach. In some embodiments, a threshold will be set for quantitatively determining from a biomarker (e.g., serum or CSF) and/or PET scan whether an A β brain load indicates a subject is amyloid-positive or negative. In some embodiments, a subject is determined to be amyloid-positive or amyloid-negative by an MRI. In some embodiments, a subject is determined to be amyloid-positive or amyloid-negative by retinal amyloid accumulation. In some embodiments, a subject is determined to be amyloid-positive or amyloid-negative by behavioral/cognitive phenotypes.

[81] As would be understood by one of ordinary skill in the art, digital, computerized, and/or conventional (e.g., pen and paper) cognitive tests may be used to detect early cognitive changes that may signal mild cognitive impairment and/or a risk for developing dementia, and thus may be used to identify subject in need of treatment as disclosed herein. Such tests, for example, may screen for cognitive impairment, and potentially identify individuals with MCI. Tests may use artificial intelligence to analyze cognitive test results to determine whether a case of mild cognitive impairment will escalate into Alzheimer’s within a year. Diagnosing the condition early, before symptoms have begun to appear, may be used to assist physicians identify subjects in need of treatment as disclosed herein sooner, potentially delaying onset or lessening the severity of the neurodegenerative disease.

[82] As used herein, the term “treat” refers to any administration or application of a therapeutic agent for a disease or disorder in a subject, and includes inhibiting the disease,

slowing progression of the disease, delaying progression, arresting its development, reversing progression of disease (e.g., reversing build up of A β fibrils), preventing the onset or development of the disease, relieving or ameliorating one or more symptoms or underlying condition(s) of the disease, curing the disease, improving one or more clinical metrics, or preventing reoccurrence of one or more symptoms of the disease. In some embodiments, treatment of AD in a subject comprises an administration, e.g., an intravenous infusion, of an anti-amyloid β (A β) protofibril antibody.

[83] As used herein, the term “infusion” refers to an active administration of one or more agents with an infusion time of, for example, approximately 60 minutes. In some embodiments, an anti-amyloid β (A β) protofibril antibody, described herein is systemically administered to a human subject via infusion. In some embodiments, an anti-amyloid β (A β) protofibril antibody is alternatively administered to the human subject, e.g., by subcutaneous injection. In some embodiments, the subcutaneous injection is a weekly injection. In some embodiments, the subcutaneous injection is a biweekly injection. In some embodiments, an anti-amyloid β (A β) protofibril antibody is administered to the human subject by intravenous infusion.

[84] In some embodiments, the subject is administered a maintenance dose of a treatment. As used herein, the term “maintenance dose” refers to a dosage administered to a subject to maintain the desired therapeutic effect. In some embodiments, the maintenance dose is administered weekly, every two weeks, monthly, every two months, or every three months (quarterly) or every 24 weeks (every six months or semi-annually). In some embodiments, the maintenance dose comprises an anti-A β protofibril antibody. In some embodiments, the maintenance dose is administered as an intravenous infusion. In some embodiments, the intravenous infusion is administered biweekly (Q2W). In some embodiments, the intravenous infusion is administered every 4 weeks (Q4W). In some embodiments, the intravenous infusion is administered every 3 months (Q3M). In some embodiments, the intravenous infusion is a 10 mg/kg dose of BAN2401. In some embodiments, the intravenous infusion is a 10 mg/kg dose of BAN2401 administered biweekly. In some embodiments, the maintenance dose is administered subcutaneously, orally, or nasally. In some embodiments, the maintenance dose is administered subcutaneously.

[85] In some embodiments, the maintenance dose is administered as a subcutaneous injection. In some embodiments, the maintenance dose is administered as a weekly, subcutaneous injection. In some embodiments, the maintenance dose is administered as a biweekly, subcutaneous injection. In some embodiments, the maintenance dose is administered as a monthly, subcutaneous injection. In some embodiments, the maintenance dose is administered as a quarterly, subcutaneous injection. In some embodiments, the maintenance dose is administered weekly or less frequently, e.g., every two weeks (biweekly), every four weeks, monthly, every six weeks, every eight weeks (2 months), every three months (quarterly) or every six monthly (semi-annually). In some embodiments, the maintenance dose is provided in a single administration, e.g., administered as a single subcutaneous injection of 720 or 1440 mg, or in two or more administrations, e.g., two concurrent administrations of 360 mg for a total of 720 mg or two administrations of 720 mg for a total of 1440 mg, or four administrations of 360 mg for a total of 1440 mg. In some embodiments, the maintenance dose is 120 mg. In some embodiments, the maintenance dose is 180 mg. In some embodiments, the maintenance dose is 240 mg. In some embodiments, the maintenance dose is 360 mg. In some embodiments, the maintenance dose is 440 mg. In some embodiments, the maintenance dose is 480 mg. In some embodiments, the maintenance dose is 540 mg. In some embodiments, the maintenance dose is 440 mg. In some embodiments, the maintenance dose is 580 mg. In some embodiments, the maintenance dose

is 600 mg. In some embodiments, the maintenance dose is administered as a single administration of 720 mg or two administrations of 360 mg. In some embodiments, the maintenance dose is 840 mg. In some embodiments, the maintenance dose is 900 mg. In some embodiments, the maintenance dose is 960 mg. In some embodiments, the maintenance dose is 1080 mg. In some embodiments, the maintenance dose is 1200 mg. In some embodiments, the maintenance dose is 1260 mg. In some embodiments, the maintenance dose is 1320 mg. In some embodiments, the maintenance dose is 1440 mg. In some embodiments, the maintenance dose is administered as a weekly, subcutaneous injection of 720 mg. In some embodiments, the maintenance dose is administered as a weekly, subcutaneous injection of 720 mg comprising two concurrent, e.g., sequential, injections of 360 mg (2 x 1.8 mL of 400 mg/2 mL) of the subcutaneous formulation. In some embodiments, the maintenance dose is administered as a biweekly, subcutaneous injection of 720 mg. In some embodiments, the maintenance dose is administered as a biweekly, subcutaneous injection of 720 mg comprising two concurrent, e.g., sequential, injections of 360 mg (2 x 1.8 mL of 400 mg/2 mL) of the subcutaneous formulation. In some embodiments, the maintenance dose is administered as a biweekly, subcutaneous injection of 1440 mg. In some embodiments, the maintenance dose is provided in a single, biweekly administration of 1440 mg comprising two concurrent, e.g., two sequential administrations of 720 mg of the subcutaneous formulation for a total of 1440 mg or four sequential administrations of 360 mg for a total of 1440 mg.

[86] In some embodiments, the maintenance dose is administered once or multiple times. In some embodiments, the maintenance dose is administered at a lower dose than during an earlier course of treatment and/or is administered less frequently than during the earlier course of treatment.

[87] In some embodiments, after switching to a maintenance dose, a subject's biomarker levels may indicate increasing levels of amyloid in the brain. In some embodiments, after switching to a maintenance dose, a subject's biomarker levels, e.g. the plasma A β 42/40 ratio, may begin to decrease, indicating increasing levels of amyloid in the brain. In some embodiments, a subject on a maintenance dose may have a decrease in the A β 42/40 ratio. In some embodiments, a subject is put on a maintenance dose chosen such that the subject may have a decrease in the A β 42/40 ratio but the A β 42/40 ratio may remain above the threshold for amyloid positivity, e.g. for at least one year (e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 years).

[88] In some embodiments, after switching to a maintenance dose, a subject's biomarker levels, e.g. p-tau181, may begin to increase, indicating increasing levels of amyloid in the brain. In some embodiments, a subject on a maintenance dose may have an increase in plasma p-tau181. In some embodiments, a subject on a maintenance dose may have an increase in p-tau181 but the level p-tau181 may remain below the threshold for amyloid positivity, e.g., for at least one year (e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 years).

[89] As used herein, the term "prevent" refers to obtaining beneficial or desired results including, but not limited to, prophylactic benefit. For prophylactic benefit, the composition may be administered to a subject at risk of developing Alzheimer's disease, to a subject having one or more preclinical symptoms but not clinical symptoms of Alzheimer's disease, or to a subject reporting one or more of the physiological symptoms of Alzheimer's disease, even though a clinical diagnosis of having Alzheimer's has not been made. As used herein "prevention" may further include therapeutic benefit, by which is meant eradication or amelioration of the underlying condition being treated or of one or more of the physiological symptoms associated therewith.

[90] As used herein, the term "ARIA" refers to amyloid-related imaging abnormality as evaluated using MRI. In some embodiments, ARIA includes amyloid related imaging

abnormality edema/effusion (ARIA-E). In some embodiments, ARIA includes amyloid related imaging abnormality hemorrhage (ARIA-H). In some embodiments, subjects with ARIA experience headache, confusion, and/or seizure and these may be used to identify a subject with ARIA or to indicate further evaluation for ARIA. In some embodiments, ARIA is evaluated at specified intervals during treatment. In some embodiments, ARIA is evaluated when the subject experiences symptoms of ARIA. In some embodiments, maximum serum concentration (C_{max}) of anti-A β protofibril antibody can be used as a predictor of the risk of ARIA-E. In some embodiments, the use of a subcutaneous formulation may provide a reduced risk of ARIA-E (e.g., due to a lower C_{max}) compared to an IV administration.

[91] As used herein, the term “clinical decline” refers to a worsening of one or more clinical symptoms of AD. Methods for measuring clinical decline may employ the tests and assays specified herein. In some embodiments, clinical decline is determined by a worsening of ADCOMS. In some embodiments, clinical decline is determined by a worsening of MMSE. In some embodiments, clinical decline is determined by a worsening of ADAS-Cog. In some embodiments, clinical decline is determined by a worsening of FAQ. In some embodiments, clinical decline is determined by a worsening of CDR-SB. In some embodiments, clinical decline is determined by a worsening of Wechsler Memory Scale-IV Logical Memory (subscale) I and/or (subscale) II. In some embodiments, clinical decline is determined by a worsening of CDR score. In some embodiments, clinical decline refers to a worsening in one or more biomarkers of AD or brain measurement (e.g., by PET or MRI), e.g., of brain atrophy and/or amyloid accumulation.

[92] As used herein, the term “blood sample” or “blood” refers to a sample of blood, including serum and/or blood plasma from a human subject. In some embodiments, blood will be collected from subjects to evaluate potential biomarkers of AD that may include amyloid fragments and isoforms, tau, and other protein biomarkers (e.g., NFL) for association with AD diagnosis, amyloid or tau load, or disease modification. In some embodiments, subjects are required to fast if possible before collection at Week 96 and Week 216. In other embodiments and/or at other time points, subjects do not require fasting. Pre-AD biomarker levels that may suggest the development of Alzheimer’s disease include, but are not limited to, brain amyloid level, cerebrospinal fluid level of A β 1-42, cerebrospinal fluid level of total tau, cerebrospinal fluid level of neurogranin, and cerebrospinal fluid level of neurofilament light chain (NfL).

Measurement of p-tau181 level

[93] The disclosure and methods discussed herein depend in part on the surprising discovery that treatment comprising an anti-A β protofibril antibody such as BAN2401 can lead to a decrease in the level of p-tau181 that correlates with reduced brain amyloid load and improved cognitive outcomes in subjects. The change in the level can therefore be used, in various embodiments, as a less invasive measure of treatment efficacy and to allow for monitoring and treatment decisions such as whether to increase or decrease the amount of antibody being administered, whether to increase or decrease the frequency of administration, whether to introduce a further therapeutic agent, and/or whether to discontinue treatment with the anti-A β protofibril antibody.

[94] The p-tau181 level can be measured using an immunoassay (e.g., a QuanterixTM Simoa[®] p-tau assay) and/or mass spectrophotometry (IP/LC-MS/MS) based technology methods. Plasma p-tau181 is elevated in early stages of AD as determined by Braak staging (I-II) and continues to increase as the disease progresses into Braak stage V-VI (Janelidze et al., “Plasma P-tau181 in Alzheimer’s disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer’s dementia,” *Nat. Med.*,

26(3):379-386 (2020)). The biomarker highly correlates with amyloid PET and Tau PET and has demonstrated a 3.5-fold elevation in AD compared to control, with an intermediate increase in the MCI group, and appears to differentiate patients with clinically diagnosed AD from other tauopathies as well (Thijssen et al., "Diagnostic value of plasma phosphorylated tau181 in Alzheimer's disease and frontotemporal lobar degeneration," *Nat. Med.*, 26(3):387-397 (2020); Janelidze et al.).

[95] The measurement of the p-tau181 level may be used alone to evaluate treatment efficacy, or in conjunction with one or more additional criteria, such as PET measurement of A β radiotracer uptake, MRI evaluation of A β plaque, and/or behavioral measures, as discussed herein. Such assays may also be used to diagnose patients eligible for treatment (e.g. by measuring the level of p-tau181 and determining a subject is suitable for treatment because of a higher level than observed in a healthy control subject or a control subject not diagnosed with AD including EAD, alone or in conjunction with measuring one or more additional marker of AD pathology in the subject). In some embodiments, the measurement of the level of p-tau181 may be used in place of another method of measuring brain amyloid levels, such as a PET scan for determining a subject is suitable for treatment. In some embodiments, the measurement of the level of p-tau181 may be used in place of another method of measuring brain amyloid levels, such as a PET scan for determining treatment efficacy and/or making treatment decisions such as whether to continue treatment, switch to a maintenance dose, etc. The determination of treatment efficacy or treatment decision may be performed by comparing the level of p-tau 181 with control level which may be obtained from a healthy subject or a subject not diagnosed with AD including EAD.

[96] In some embodiments, a p-tau181 level measurement may employ a relative change from baseline measurement. In some embodiments, a change in the p-tau181 level may be used to evaluate treatment efficacy. In some embodiments, a decrease in the level of p-tau181 indicates treatment efficacy, e.g., a reduction in brain amyloid levels. In some embodiments, a p-tau181 level measurement may employ a set threshold to determine a change in brain amyloid levels, e.g., to identify and/or select a patient suitable for treatment, e.g., with an anti-A β protofibril antibody, or to determine whether to continue treatment, or to determine whether to switch to a maintenance dose, or to conclude a patient is amyloid negative. In some embodiments, the threshold may be evaluated in conjunction with another measurement of brain amyloid load, such as a PET scan, to assist in determining whether a subject is suitable for treatment or continued treatment. In some embodiments, a p-tau181 level threshold may be used in place of another method of measuring brain amyloid levels, such as a PET scan. In some embodiments, a p-tau181 level threshold at or above about 2.2 to 2.3 pg/mL is used to identify and/or select a patient suitable for treatment, e.g., with an anti-A β protofibril antibody. In some embodiments, a p-tau181 level threshold at or above about 2.2 pg/mL is used to identify and/or select a patient suitable for treatment, e.g., with an anti-A β protofibril antibody. In some embodiments, a p-tau181 level threshold at or above about 2.3 pg/mL is used to identify and/or select a patient suitable for treatment, e.g., with an anti-A β protofibril antibody. In certain such embodiments, the p-tau181 level is measured using a Quanterix™ Simoa® p-tau assay. In some embodiments, the threshold is about 2.3 pg/mL. In some embodiments, the threshold is about 2.2 pg/mL. In some embodiments, an increase in the p-tau181 level above a threshold value may indicate a need to continue treatment or to select an increase in a dosing regimen. In some embodiments, a decrease in the p-tau181 level below a threshold value may be used to indicate a treatment may be terminated (e.g., terminated in favor of a maintenance regimen) and/or to otherwise to determine a decrease in a dosing regimen or discontinuation in treatment. In some embodiments, an increase in the p-tau181 level above a threshold value may be used to determine whether to discontinue a maintenance dosing regimen, e.g., and return to the prior treatment regimen.

Anti-A β protofibril antibodies

[97] In some embodiments, any anti-A β protofibril antibody may be used in the methods disclosed herein. In some embodiments, the antibody comprises one or more of the sequences listed in Tables 1-4, e.g., comprising a complete set of 6 complementarity determining regions (CDRs) and/or a complete set of variable regions and/or a complete set of heavy and light chain sequences from the tables. In some embodiments, the anti-A β protofibril antibody comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO: 1 (HCDR1), SEQ ID NO: 2 (HCDR2), and SEQ ID NO: 3 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO: 4 (LCDR1), SEQ ID NO: 5 (LCDR2), and SEQ ID NO: 6 (LCDR3). In some embodiments, the anti-A β protofibril antibody comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 7 and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 8. In some embodiments, the anti-A β protofibril antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 9 and a light chain comprising an amino acid sequence of SEQ ID NO: 10. "CDRs" used herein in the context of an antibody sequence or structure refers to complementarity determining regions, that provide the main determinants of antigen binding. Generally, the antigen-binding site has six CDRs; three in the VH (HCDR1, HCDR2, HCDR3), and three in the VL (LCDR1, LCDR2, LCDR3). The CDRs may be determined according to the Kabat numbering scheme, which may be determined by according to the Kabat numbering scheme (Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991, hereafter referred to as "Kabat report").

[98] In some embodiments, the at least one anti-A β protofibril antibody comprises a human constant region. In some embodiments, the human constant region of the at least one anti-A β protofibril antibody comprises a heavy chain constant region chosen from IgG1, IgG2, IgG3, IgG4, IgM, IgA, IgE, and any allelic variation thereof as disclosed in the Kabat report. Any one or more of such sequences may be used in the present disclosure. In some embodiments, the heavy chain constant region is chosen from IgG1 and allelic variations thereof. The amino acid sequence of human IgG1 constant region is known in the art and set out in SEQ ID NO: 11.

[99] In some embodiments, the human constant region of the at least one anti-A β antibody comprises a light chain constant region chosen from κ - λ -chain constant regions and any allelic variation thereof as discussed in the Kabat report. Any one or more of such sequences may be used in the present disclosure. In some embodiments, the light chain constant region is chosen from κ and allelic variations thereof. The amino acid sequence of human κ chain constant region is known in the art and set out in SEQ ID NO: 12.

[100] In some embodiments, the at least one anti-A β protofibril antibody comprises human heavy and light chain variable region frameworks. In some embodiments, the at least one anti-A β protofibril antibody comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 7, and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 8. In some embodiments, the at least one anti-A β protofibril antibody comprises a human IgG1 heavy chain constant region, and a human Ig kappa light chain constant region. In some embodiments, the at least one anti-A β protofibril antibody comprises a heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 11, and a light chain constant region comprising an amino acid sequence of SEQ ID NO: 12.

[101] In some embodiments, the at least one anti-A β protofibril antibody is BAN2401, also known as lecanemab. The terms “BAN2401” and “lecanemab” are used interchangeably and refer to a humanized IgG1 monoclonal version of mAb158, which is a murine monoclonal antibody raised to target protofibrils and disclosed in WO 2007/108756 and Journal of Alzheimer’s Disease 43: 575-588 (2015). BAN2401 comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO: 1 (HCDR1), SEQ ID NO: 2 (HCDR2), and SEQ ID NO: 3 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO: 4 (LCDR1), SEQ ID NO: 5 (LCDR2), and SEQ ID NO: 6 (LCDR3) and is described in WO 2007/108756 and in Journal of Alzheimer’s Disease 43:575-588 (2015). BAN2401 comprises (i) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 7 and (ii) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 8. The full length sequences of heavy chain and light chain of BAN2401 are set forth in SEQ ID NOs: 9 and 10 and is described in WO 2007/108756 and in Journal of Alzheimer’s Disease 43:575-588 (2015).

[102] Other non-limiting examples of suitable antibodies for use as the at least one anti-A β protofibril antibody in the present disclosure include aducanumab, as well as those disclosed in WO 2002/003911, WO 2005/123775, WO 2007/108756, WO 2011/001366, WO 2011/104696, and WO 2016/005466.

[103] In some embodiments, the isolated anti-A β protofibril antibody is present in a concentration of at least 80 mg/mL. In some embodiments, the isolated anti-A β protofibril antibody is present in a concentration of at least 100 mg/mL. In some embodiments, the isolated anti-A β protofibril antibody is present in a concentration of at least 200 mg/mL. In some embodiments, the isolated anti-A β protofibril antibody is present in a concentration of at least 250 mg/mL. In some embodiments, the isolated antibody or fragment thereof is present in a concentration ranging from 80 mg/mL to 300 mg/mL. In some embodiments, the isolated anti-A β protofibril antibody is present in a concentration ranging from 85 mg/mL to 275 mg/mL. In some embodiments, the isolated anti-A β protofibril antibody is present in a concentration ranging from 90 mg/mL to 250 mg/mL. In some embodiments, the isolated anti-A β protofibril antibody is present in a concentration ranging from 95 mg/mL to 225 mg/mL. In some embodiments, the isolated anti-A β protofibril antibody is present in a concentration ranging from 100 mg/mL to 200 mg/mL. In some embodiments, the isolated antibody or fragment thereof is present in a concentration of 80 mg/mL, 90 mg/mL, 100 mg/mL, 110 mg/mL, 120 mg/mL, 130 mg/mL, 140 mg/mL, 150 mg/mL, 160 mg/mL, 170 mg/mL, 180 mg/mL, 190 mg/mL, 200 mg/mL, 210 mg/mL, 220 mg/mL, 230 mg/mL, 240 mg/mL, 250 mg/mL, 260 mg/mL, 270 mg/mL, 280 mg/mL, 290 mg/mL, or 300 mg/mL. In some embodiments, the isolated antibody or fragment thereof is present in a concentration of 100 mg/mL. In some embodiments, the isolated antibody or fragment thereof is present in a concentration of 200 mg/mL. In some embodiments, the isolated antibody or fragment thereof is present in a concentration of 250 mg/mL. In some embodiments, the isolated antibody or fragment thereof is present in a concentration of 300 mg/mL. In some embodiments, the isolated antibody or fragment thereof is BAN2401.

[104] As used herein, a “fragment” of an antibody comprises a portion of the antibody, for example comprising an antigen-binding or a variable region thereof. Non-limiting examples of fragments include Fab fragments, Fab' fragments, F(ab')₂ fragments, Fv fragments, diabodies, linear antibodies, and single-chain antibody molecules.

Therapeutically effective amount of at least one anti-A β protofibril antibody

[105] In various embodiments, the methods of the present disclosure comprise administering to a subject a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. As used herein, the term a “therapeutically effective amount” refers to an amount of a compound or pharmaceutical composition sufficient to produce a desired therapeutic effect. In various embodiments, the therapeutically effective amount is an amount sufficient to decrease the p-tau181 level when comparing the level in a sample, e.g., a blood sample, before and after treatment. In some embodiments, the therapeutically effective amount is initially 2.5-15 mg/kg, e.g., about 10 mg/kg. In some embodiments, after administering a first therapeutically effective amount for a period of time, e.g., 6-12 months or more, a second therapeutically effective amount is administered at a lower dosage, e.g., if decrease in the level of p-tau181 is observed before and after administering the first therapeutically effective amount. In some embodiments, the second therapeutically effective amount is accompanied by one or more additional therapy, e.g., a BACE inhibitor and/or anti-tau antibody therapy. In some embodiments, the at least one additional therapeutic agent comprises one or more of BACE inhibitors, gamma secretase inhibitors, gamma secretase modulators, A β peptide generation inhibitors other than said at least one anti-A β protofibril antibody, agents that lower A β peptide levels other than said at least one anti-A β protofibril antibody, and a combination thereof. In some embodiments, the at least one additional therapeutic agent comprises a BACE inhibitor. In some embodiments, the BACE inhibitor is chosen from CNP520, BI-1181181, LY2886721, LY3202626, PF-06751979, RG7129, atabecestat, elenbecestat, lanabecestat, and verubecestat. In some embodiments, the BACE inhibitor is elenbecestat.

[106] One of ordinary skill in the art will understand that the therapeutically effective amount of the at least one anti-A β protofibril antibody administered to a subject may depend upon a number of factors including pharmacodynamic characteristics, route of administration, frequency of treatment, and health, age, and weight of the subject to be treated and, with the information disclosed herein, will be able to determine the appropriate amount for each subject.

[107] In some embodiments, the therapeutically effective amount is a dose chosen to improve efficacy and/or maintain efficacy and improve at least one of safety and tolerability. In some embodiments, the therapeutically effective amount is chosen to lower at least one side effect and simultaneously improve efficacy and/or maintain efficacy.

[108] In some embodiments, 0.5 mg/kg to 45 mg/kg, 0.5 mg/kg to 40 mg/kg, 0.5 mg/kg to 35 mg/kg, 0.5 mg/kg to 30 mg/kg, 0.5 mg/kg to 25 mg/kg, 0.5 mg/kg to 20 mg/kg, 0.5 mg/kg to 15 mg/kg, 0.5 mg/kg to 10 mg/kg, 0.5 mg/kg to 5 mg/kg, or 0.5 mg/kg to 2.5 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject.

[109] In some embodiments, 2.5 mg/kg to 45 mg/kg, 2.5 mg/kg to 40 mg/kg, 2.5 mg/kg to 35 mg/kg, 2.5 mg/kg to 30 mg/kg, 2.5 mg/kg to 25 mg/kg, 2.5 mg/kg to 20 mg/kg, 2.5 mg/kg to 15 mg/kg, 2.5 mg/kg to 10 mg/kg, or 2.5 mg/kg to 5 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject.

[110] In some embodiments, 5 mg/kg to 45 mg/kg, 5 mg/kg to 40 mg/kg, 5 mg/kg to 35 mg/kg, 5 mg/kg to 30 mg/kg, 5 mg/kg to 25 mg/kg, 5 mg/kg to 20 mg/kg, 5 mg/kg to 15 mg/kg, or 5 mg/kg to 10 mg/kg, of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject.

[111] In some embodiments, 7.5 mg/kg to 45 mg/kg, 7.5 mg/kg to 40 mg/kg, 7.5 mg/kg to 35 mg/kg, 7.5 mg/kg to 30 mg/kg, 7.5 mg/kg to 25 mg/kg, 7.5 mg/kg to 20 mg/kg, 7.5

mg/kg to 15 mg/kg, or 7.5 mg/kg to 10 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject.

[112] In some embodiments, from 0.5 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, 13 mg/kg, 14 mg/kg, 15 mg/kg, 16 mg/kg, 17 mg/kg, 18 mg/kg, 19 mg/kg, 20 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject. In some embodiments, up to 20 mg/kg, 19 mg/kg, 18 mg/kg, 17 mg/kg, 16 mg/kg, 15 mg/kg, 14 mg/kg, 13 mg/kg, 12 mg/kg, 11 mg/kg, 10 mg/kg, 9 mg/kg, 8 mg/kg, 7 mg/kg, 6 mg/kg, 5 mg/kg, 4 mg/kg, 3 mg/kg, 2 mg/kg, 1 mg/kg, or 0.5 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject.

[113] In some embodiments, 0.5 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject. In some embodiments, 1 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject. In some embodiments, 2 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject. In some embodiments, 2.5 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject. In some embodiments, 3 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject. In some embodiments, 4 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject. In some embodiments, 5 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject. In some embodiments, 6 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject. In some embodiments, 7 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject. In some embodiments, 7.5 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject. In some embodiments, 8 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject. In some embodiments, 9 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject. In some embodiments, 10 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject. In some embodiments, 11 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject. In some embodiments, 12 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject. In some embodiments, 12.5 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject. In some embodiments, 13 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject. In some embodiments, 14 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject. In some embodiments, 15 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject. In some embodiments, 16, 17, 18, 19, or 20 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject. In some embodiments, 21, 22, 23, 24, or 25 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject.

[114] In some embodiments, 27.5 mg/kg, 30 mg/kg, 32.5 mg/kg, 35 mg/kg, 37.5 mg/kg, 40 mg/kg, 42.5 mg/kg, 45 mg/kg, 47.5 mg/kg, or 50 mg/kg of at least one anti-A β protofibril antibody is administered to the subject relative to body weight of the subject.

[115] As mentioned, in some embodiments, the at least one anti-A β protofibril antibody is BAN2401. Accordingly, in some embodiments, 0.5 mg/kg to 45 mg/kg, 0.5 mg/kg to 40

mg/kg, 0.5 mg/kg to 35 mg/kg, 0.5 mg/kg to 30 mg/kg, 0.5 mg/kg to 25 mg/kg, 0.5 mg/kg to 20 mg/kg, 0.5 mg/kg to 15 mg/kg, 0.5 mg/kg to 10 mg/kg, 0.5 mg/kg to 5 mg/kg, or 0.5 mg/kg to 2.5 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject.

[116] In some embodiments, 2.5 mg/kg to 45 mg/kg, 2.5 mg/kg to 40 mg/kg, 2.5 mg/kg to 35 mg/kg, 2.5 mg/kg to 30 mg/kg, 2.5 mg/kg to 25 mg/kg, 2.5 mg/kg to 20 mg/kg, 2.5 mg/kg to 15 mg/kg, 2.5 mg/kg to 10 mg/kg, or 2.5 mg/kg to 5 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject.

[117] In some embodiments, 5 mg/kg to 45 mg/kg, 5 mg/kg to 40 mg/kg, 5 mg/kg to 35 mg/kg, 5 mg/kg to 30 mg/kg, 5 mg/kg to 25 mg/kg, 5 mg/kg to 20 mg/kg, 5 mg/kg to 15 mg/kg, or 5 mg/kg to 10 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject.

[118] In some embodiments, 7.5 mg/kg to 45 mg/kg, 7.5 mg/kg to 40 mg/kg, 7.5 mg/kg to 35 mg/kg, 7.5 mg/kg to 30 mg/kg, 7.5 mg/kg to 25 mg/kg, 7.5 mg/kg to 20 mg/kg, 7.5 mg/kg to 15 mg/kg, or 7.5 mg/kg to 10 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject.

[119] In some embodiments, from 0.5 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, 13 mg/kg, 14 mg/kg, 15 mg/kg, 16 mg/kg, 17 mg/kg, 18 mg/kg, 19 mg/kg, 20 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, up to 20 mg/kg, 19 mg/kg, 18 mg/kg, 17 mg/kg, 16 mg/kg, 15 mg/kg, 14 mg/kg, 13 mg/kg, 12 mg/kg, 11 mg/kg, 10 mg/kg, 9 mg/kg, 8 mg/kg, 7 mg/kg, 6 mg/kg, 5 mg/kg, 4 mg/kg, 3 mg/kg, 2 mg/kg, 1 mg/kg, or 0.5 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject.

[120] In some embodiments, 0.5 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 1 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 2 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 2.5 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 3 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 4 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 5 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 6 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 7 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 7.5 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 8 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 9 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 10 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 11 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 12 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 12.5 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 13 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 14 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 15 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 16, 17, 18, 19, or 20 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 21,

22, 23, 24, or 25 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 27.5 mg/kg, 30 mg/kg, 32.5 mg/kg, 35 mg/kg, 37.5 mg/kg, 40 mg/kg, 42.5 mg/kg, 45 mg/kg, 47.5 mg/kg, or 50 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject.

[121] In some embodiments, 2.5 mg/kg to 10 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 5 mg/kg to 10 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 2.5 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 5 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 7.5 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, 10 mg/kg of BAN2401 is administered to the subject relative to body weight of the subject. In some embodiments, a reduced concentration of BAN2401 is administered if the initial dosing decreases the level of p-tau181 when comparing the level in a sample, e.g., a blood sample, before and after the initial treatment.

[122] In some embodiments, a subject is administered a first dose of the anti-A β protofibril antibody without an initial titrating step up to the treatment dose (e.g., a subject starts treatment at 10 mg/kg with no titration). In some embodiments, a dose of BAN2401 may be used without the need of a prior titrating step. In some embodiments, a subject is switched to a maintenance dose without an initial titrating step to the maintenance dose. In certain instances, providing a therapeutic dose without a titration step may provide additional therapeutic benefits to the patient, e.g., a faster shift in plasma biomarkers toward amyloid negativity or facilitating identification sooner of patients that do not have a therapeutic change in plasma biomarkers in response to the anti-A β protofibril antibody (non-responders) and who would benefit from alternative treatment.

Dosing regimens for at least one anti-A β protofibril antibody

[123] In various embodiments, the methods of the present disclosure comprise administering to a subject a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody at a schedule that may be fixed and/or adjusted over time. One of ordinary skill in the art will understand that any of the therapeutically effective amounts of the at least one anti-A β protofibril antibody disclosed above may be administered one or more times according to one or more dosing regimens. One of ordinary skill in the art will be able to determine, depending upon a number of factors including pharmacodynamic characteristics, route of administration, dose, and health, age, and weight of the subject to be treated and, with the information disclosed herein, the appropriate dosing regimen(s) for each subject.

[124] In some embodiments, a composition comprising, e.g., 2.5-15 mg/kg, e.g., 10 mg/kg of at least one anti-A β protofibril antibody relative to body weight of the subject, is administered to the subject once every two to four weeks. In some embodiments, the composition is administered to the subject once every month. In various embodiments, the composition is administered, e.g., biweekly or monthly, to decrease the p-tau181 level when comparing the level in a sample, e.g., a blood sample, before and after treatment. In some embodiments, after administering a first composition, e.g., biweekly or monthly for a period of time, e.g., 6-12 months or more, a reduced frequency is used, e.g., every 3, 4, 5, 6, 7, or 8 weeks, or every 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months, or more, if a decrease in the p-tau181 level is observed. In some embodiments, the reduced frequency is accompanied by one or more additional therapy, e.g., a BACE inhibitor and/or anti-tau antibody therapy.

[125] In some embodiments, a composition comprising at least one anti-A β protofibril antibody is administered every day, every other day, every third day, once every week, once every two weeks (“biweekly” or “bw”), once every three weeks, once every four weeks (“four-week interval”), once every month (“mo”), once every five weeks, once every six weeks, once every seven weeks, once every eight weeks, once every two months, once every nine weeks, once every ten weeks, once every eleven weeks, once every twelve weeks, once every three months (quarterly), once every fourteen weeks, once every sixteen weeks, once every four months, once every eighteen weeks, once every twenty weeks, once every five months, once every 22 weeks, once every 24 weeks, once every six months (semi-annually), once every seven months, once every eight months, once every nine months, once every ten months, once every eleven months, once every twelve months (annually), once every thirteen months, once every fourteen months, once every fifteen months, once every sixteen months, once every seventeen months, or once every eighteen months. In some embodiments, a composition comprising at least one anti-A β protofibril antibody is administered every day, every other day, every third day, once every week, once every two weeks (“biweekly”), once every four weeks (“four-week interval”), or once every month. In some embodiments, a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody is administered once every two weeks or once every four weeks. In some embodiments, a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody is administered once every two weeks. In some embodiments, a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody is administered once every four weeks.

[126] In some embodiments, the initial treatment is administered for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or more months. In some embodiments, before and after the initial treatment, the p-tau181 level is measured in a sample, e.g., a blood sample, from the subject.

[127] In some embodiments, a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody is administered once every week. In some embodiments, a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody is administered once every two weeks. In some embodiments, a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody is administered once every three weeks. In some embodiments, a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody is administered once every four weeks. In some embodiments, a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody is administered once every month.

[128] In some embodiments, a composition comprising a therapeutically effective amount of BAN2401 is administered once every week. In some embodiments, a composition comprising a therapeutically effective amount of BAN2401 is administered once every two weeks. In some embodiments, a composition comprising a therapeutically effective amount of BAN2401 is administered once every three weeks. In some embodiments, a composition comprising a therapeutically effective amount of BAN2401 is administered once every four weeks. In some embodiments, a composition comprising a therapeutically effective amount of BAN2401 is administered once every month.

[129] In some embodiments, a composition comprising 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, or 10 mg/kg of at least one anti-A β protofibril antibody relative to body weight of the subject is administered to the subject once every week. In some embodiments, a composition comprising 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, or 10 mg/kg of at least one anti-A β protofibril antibody relative to body weight of the subject is administered to the subject once every two weeks. In some embodiments, a composition comprising 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, or

10 mg/kg of at least one anti-A β protofibril antibody relative to body weight of the subject is administered to the subject once every three weeks. In some embodiments, a composition comprising 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, or 10 mg/kg of at least one anti-A β protofibril antibody relative to body weight of the subject is administered to the subject once every four weeks. In some embodiments, a composition comprising 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, or 10 mg/kg of at least one anti-A β protofibril antibody relative to body weight of the subject is administered to the subject once every month.

[130] In some embodiments, a composition comprising 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, or 10 mg/kg of BAN2401 relative to body weight of the subject is administered to the subject once every week. In some embodiments, a composition comprising 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, or 10 mg/kg of BAN2401 relative to body weight of the subject is administered to the subject once every two weeks. In some embodiments, a composition comprising 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, or 10 mg/kg of BAN2401 relative to body weight of the subject is administered to the subject once every three weeks. In some embodiments, a composition comprising 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, or 10 mg/kg of BAN2401 relative to body weight of the subject is administered to the subject once every four weeks. In some embodiments, a composition comprising 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, or 10 mg/kg of BAN2401 relative to body weight of the subject is administered to the subject once every month.

[131] In some embodiments, a composition comprising 10 mg/kg of BAN2401 relative to body weight of the subject is administered to the subject once every two weeks. In some embodiments, a composition comprising 10 mg/kg of BAN2401 relative to body weight of the subject is administered to the subject once every month. In some embodiments, a reduced dosage frequency of BAN2401 and/or a reduced concentration of BAN2401 is administered if the initial dosing (e.g., every two or four weeks for 6-12 months or more) decreases the p-tau181 level when comparing the level in a sample, e.g., a blood sample, before and after the initial treatment.

Composition comprising at least one anti-A β protofibril antibody

[132] In some embodiments, the at least one anti-A β protofibril antibody is comprised in a composition. In some embodiments, the composition consists of at least one anti-A β protofibril antibody. In some embodiments, the antibody is present at a concentration of 50-250 mg/ML, e.g., 100-200 mg/mL. In some embodiments, the composition comprises at least one anti-A β protofibril antibody and further comprises at least one additional active and/or inactive component. In some embodiments, the at least one additional component can comprise one or more suitable physiologically acceptable excipients for human and/or veterinary use.

[133] The compositions of the present disclosure may be in the form of a tablet, pill, capsule, solution, and/or any other suitable form deemed appropriate by one of ordinary skill in the art. The route of administration of the compositions of the present disclosure may be any suitable route, including intravenous, subcutaneous, oral, and nasal. In some embodiments, the composition is formulated as a sterile, non-pyrogenic liquid for intravenous administration. In some embodiments, the composition is a saline solution.

[134] In some embodiments, the at least one additional component in the composition comprises buffer(s). In some embodiments, the at least one additional component comprises emulsifier(s). In some embodiments, the at least one additional component comprises sodium citrate, sodium chloride, histidine, arginine, arginine hydrochloride, and/or polysorbate 80. In some embodiments, the sodium citrate may be present at a concentration ranging from 1 mM to 150 mM. In some embodiments, the sodium citrate may be present at a concentration of 25 mM. In some embodiments, the sodium citrate may be present at a concentration of 50

mM. In some embodiments, the sodium chloride may be present at a concentration ranging from 25 mM to 250 mM. In some embodiments, the arginine may be present at a concentration ranging from 240 mM to 360 mM. In some embodiments, the arginine hydrochloride may be present at a concentration ranging from 100 mM to 250 mM. In some embodiments, the histidine may be present at a concentration ranging from 10 mM to 50 mM. In some embodiments, the sodium citrate may be present at a concentration of 125 mM. In some embodiments, the polysorbate 80 may be present at a concentration ranging from 0.001% (w/v) to 2% (w/v). In some embodiments, the polysorbate 80 may be present at a concentration of 0.02% (w/v). In some embodiments, the polysorbate 80 may be present at a concentration of 0.05% (w/v).

[135] In some embodiments, the composition is a liquid dosage form comprising at least one anti-A β protofibril antibody, such as BAN2401, and further comprising, for instance, sodium citrate, sodium chloride, and polysorbate 80. In some embodiments, the composition is a liquid dosage form comprising 50 mmol/L citrate, 350 mmol/L arginine, and 0.05% polysorbate 80.

[136] In some embodiments, the composition is a liquid dosage form comprising at least one anti-A β protofibril antibody, such as BAN2401, and further comprising, for instance, arginine hydrochloride, histidine, and polysorbate 80. In some embodiments, the composition is a liquid dosage form comprising 25 mmol/L histidine, 200 mmol/L arginine, 0.05% polysorbate 80. PCT/IB2021/000155 (WO2021/186245) is incorporated herein by reference for suitable intravenous and subcutaneous formulations.

Concomitant administration of at least one anti-A β protofibril antibody and at least one Alzheimer's disease medication other than BAN2401

[137] In some embodiments, provided herein is a method of treating a subject, e.g., one having Pre-AD or early Alzheimer's disease, comprising concomitantly administering a therapeutically effective amount of at least one anti-A β protofibril antibody such as BAN2401 and a therapeutically effective amount of at least one Alzheimer's disease medication other than BAN2401. In some embodiments, provided herein is a method of reducing and/or slowing clinical decline in a subject, e.g., one having Pre-AD or early Alzheimer's disease, comprising concomitantly administering a therapeutically effective amount of at least one anti-A β protofibril antibody such as BAN2401 and a therapeutically effective amount of at least one Alzheimer's disease medication other than BAN2401. The at least one additional therapy may comprise an additional anti-A β antibody such as aducanumab. In some embodiments, the at least one additional therapy may comprise a BACE inhibitor and/or an anti-tau antibody. In some embodiments, the additional therapy is given in place of an anti-A β protofibril antibody such as BAN2401 if initial treatment with the first antibody does not lead to a decrease in the p-tau181 level, or the additional therapy is given in combination with an increased dosage or frequency of the first antibody. In some embodiments, the additional therapy is given in combination with a reduced dosage or administration frequency of an anti-A β protofibril antibody such as BAN2401 if initial treatment with the first antibody leads to a decrease in the p-tau181 level.

[138] In some embodiments, provided herein is a method of treating a subject having pre-AD, or a patient that is symptomatic for Alzheimer's disease (e.g., early Alzheimer's disease), comprising concomitantly administering a therapeutically effective amount of at least one anti-A β protofibril antibody such as BAN2401 and a therapeutically effective amount of an anti-tau antibody or antigen binding fragment thereof that is capable of binding to human tau, e.g., the anti-tau antibody or antigen binding fragment comprises E2814 or an antigen binding fragment thereof. E2814 is disclosed in US 2019/0112364 A1 as clone 7G6-

HCzu25/LCzu18, the sequences of which are incorporated by reference herein. In some embodiments, provided herein is a method of reducing and/or slowing clinical decline in a subject, e.g., one having pre-AD, or a patient that is symptomatic for Alzheimer's disease (e.g., early Alzheimer's disease), comprising concomitantly administering a therapeutically effective amount of at least one anti-A β protofibril antibody such as BAN2401 and a therapeutically effective amount of an anti-tau antibody or antigen binding fragment thereof that is capable of binding to human tau, e.g., the anti-tau antibody or antigen binding fragment comprises E2814 or an antigen binding fragment thereof. E2814 is disclosed in US 2019/0112364 A1 as clone 7G6-HCzu25/LCzu18, the sequences of which are incorporated by reference herein. In some embodiments, the isolated anti-tau antibody or antigen binding fragment thereof that is capable of binding to human tau comprises six CDRs (HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3) comprising the amino acid sequences of SEQ ID NO:15 (HCDR1), SEQ ID NO:16 (HCDR2), SEQ ID NO:17 (HCDR3), SEQ ID NO:18 (LCDR1), SEQ ID NO:19 (LCDR2), and SEQ ID NO:20 (LCDR3). See, e.g., Table 11. In some embodiments, the isolated anti-tau antibody or antigen binding fragment thereof that is capable of binding to human tau comprises six CDRs (HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3) from a heavy chain variable region of SEQ ID NO: 21 and a light chain variable region of SEQ ID NO: 22. In some embodiments, the anti-tau antibody or antigen binding fragment thereof that is capable of binding to human tau comprises a heavy chain variable region of SEQ ID NO: 21 and a light chain variable region of SEQ ID NO: 22. See, e.g., Table 12. In some embodiments, the heavy chain constant region comprises SEQ ID NO: 23. In some embodiments, the heavy chain constant region comprises SEQ ID NO: 24. See, e.g., Table 13.

[139] In some embodiments, a patient that is symptomatic for Alzheimer's disease is administered the anti-A β protofibril antibody (e.g., BAN2401) for at least 24 weeks then administered the isolated anti-tau antibody or antigen binding fragment thereof that is capable of binding to human tau (e.g., E2814) in conjunction with the isolated anti-A β protofibril antibody. In some embodiments, a patient that is symptomatic for Alzheimer's disease is administered the anti-A β protofibril antibody, e.g., for 24 weeks or until the patient's p-tau181 level decreases below a certain threshold, then administered the isolated anti-tau antibody or antigen binding fragment thereof that is capable of binding to human tau in conjunction with the isolated anti-A β protofibril antibody. In some embodiments, a patient that is symptomatic for Alzheimer's disease is administered the anti-A β protofibril antibody for 24 weeks or until the patient is amyloid negative, then administered the isolated anti-tau antibody or antigen binding fragment thereof that is capable of binding to human tau in conjunction with the isolated anti-A β protofibril antibody.

[140] In some embodiments, the patient is asymptomatic for Alzheimer's disease (pre-AD) and is first administered an isolated anti-tau antibody or antigen binding fragment thereof that is capable of binding to human tau (e.g., E2814), e.g., for 52 weeks before being administered the isolated anti-tau antibody or antigen binding fragment thereof that is capable of binding to human tau in conjunction with an isolated anti-A β protofibril antibody (e.g., BAN2401). In some embodiments, a patient that is asymptomatic for Alzheimer's disease is administered the isolated anti-tau antibody or antigen binding fragment thereof that is capable of binding to human tau for 52 weeks or until the patient's p-tau181 level decreases below a certain threshold, then administered the isolated anti-tau antibody or antigen binding fragment thereof that is capable of binding to human tau in conjunction with the isolated anti-A β protofibril antibody. In some embodiments, a patient that is asymptomatic for Alzheimer's disease is administered the isolated anti-tau antibody or antigen binding fragment thereof that is capable of binding to human tau for 52 weeks or until the patient is amyloid negative, then administered the isolated anti-tau antibody or antigen binding

fragment thereof that is capable of binding to human tau in conjunction with the isolated anti-A β protofibril antibody.

[141] In some embodiments, the at least one Alzheimer's disease medication is chosen from elenbecestat, donepezil, galantamine, memantine, and rivastigmine. In some embodiments, the at least one Alzheimer's disease medication is a combination of donepezil and memantine. In some embodiments, the at least one additional therapeutic agent comprises one or more of BACE inhibitors, gamma secretase inhibitors, gamma secretase modulators, A β peptide generation inhibitors other than said at least one anti-A β protofibril antibody, agents that lower A β peptide levels other than said at least one anti-A β protofibril antibody, and a combination thereof. In some embodiments, the at least one additional therapeutic agent is a BACE inhibitor. In some embodiments, the BACE inhibitor is chosen from CNP520, BI-1181181, LY2886721, LY3202626, PF-06751979, RG7129, atabecestat, elenbecestat, lanabecestat, and verubecestat. In some embodiments, the BACE inhibitor is elenbecestat. In some embodiments, the BACE inhibitor is chosen from CNP520, BI-1181181, LY2886721, LY3202626, PF-06751979, RG7129, atabecestat, elenbecestat, lanabecestat, and verubecestat.

[142] In some embodiments, donepezil may be administered at its approved dose. In some embodiments, galantamine may be administered at its approved dose. In some embodiments, memantine may be administered at its approved dose. In some embodiments, rivastigmine may be administered at its approved dose.

[143] In some embodiments, elenbecestat may be administered at a dose ranging from 5 mg/day to 100 mg/day, 10 mg/day to 75 mg/day, 5 mg/day to 50 mg/day, or 15 mg/day to 50 mg/day. In some embodiments, elenbecestat may be administered at a dose ranging from about 5 mg/day to about 100 mg/day, about 10 mg/day to about 75 mg/day, about 5 mg/day to about 50 mg/day, or about 15 mg/day to about 50 mg/day. In some embodiments, elenbecestat may be administered at a dose of 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, 25 mg/day, 30 mg/day, or 50 mg/day dosage. In some embodiments, elenbecestat may be administered at a dose of 5 mg/day. In some embodiments, elenbecestat may be administered at a dose of 15 mg/day. In some embodiments, elenbecestat may be administered at a dose of 50 mg/day.

[144] In some embodiments, elenbecestat may be administered at a dose ranging from 5 mg/day to 100 mg/day, 10 mg/day to 75 mg/day, 5 mg/day to 50 mg/day, or 15 mg/day to 50 mg/day. In some embodiments, elenbecestat may be administered at a dose ranging from about 5 mg/day to about 100 mg/day, about 10 mg/day to about 75 mg/day, about 5 mg/day to about 50 mg/day, or about 15 mg/day to about 50 mg/day. In some embodiments, elenbecestat may be administered at a dose of 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, 25 mg/day, 30 mg/day, or 50 mg/day dosage. In some embodiments, elenbecestat may be administered at a dose of 5 mg/day. In some embodiments, elenbecestat may be administered at a dose of 15 mg/day. In some embodiments, elenbecestat may be administered at a dose of 50 mg/day.

Therapeutic Effect

[145] In various embodiments, provided herein is a method of reducing clinical decline in a subject having early Alzheimer's disease comprising administering to said subject a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein. In some embodiments, the subject having early Alzheimer's disease has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood and/or has been diagnosed as having mild Alzheimer's disease

dementia. In some embodiments, the subject having early Alzheimer's disease is ApoE4-positive.

[146] Any of the anti-A β protofibril antibodies, therapeutically acceptable amounts thereof, dosing regimens therefor, and compositions comprising the same that are disclosed herein may be used in the method of reducing clinical decline in a subject having early Alzheimer's disease. For example, in some embodiments, a composition comprising 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, or 10 mg/kg of at least one anti-A β protofibril antibody such as BAN2401 relative to body weight of the subject is administered to the subject once every week, once every two weeks, once every three weeks, once every four weeks, once every month, once every five weeks, once every six weeks, once every seven weeks, once every eight weeks, once every two months, once every nine weeks, once every ten weeks, once every eleven weeks, once every twelve weeks, once every three months (quarterly), once every fourteen weeks, once every sixteen weeks, once every four months, once every eighteen weeks, once every twenty weeks, once every five months, once every 22 weeks, once every 24 weeks, once every six months (semi-annually), once every seven months, once every eight months, once every nine months, once every ten months, once every eleven months, once every twelve months (annually), once every thirteen months, once every fourteen months, once every fifteen months, once every sixteen months, once every seventeen months, or once every eighteen months. In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, or at least 46% relative to placebo as determined by ADCOMS. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[147] In some embodiments, the clinical decline is reduced by 20% to 35% relative to placebo as determined by ADCOMS. In some embodiments, the clinical decline is reduced by 20% to 30% relative to placebo as determined by ADCOMS. In some embodiments, the clinical decline is reduced by 27% to 35% relative to placebo as determined by ADCOMS. In some embodiments, the clinical decline is reduced by at least 20% relative to placebo as determined by ADCOMS. In some embodiments, the clinical decline is reduced by at least 35% relative to placebo as determined by ADCOMS. In some embodiments, the clinical decline is reduced by at least 20% as determined by ADCOMS. In some embodiments, the clinical decline is reduced by at least 30% as determined by ADCOMS. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[148] In some embodiments, the clinical decline is reduced by at least 45% relative to placebo as determined by ADCOMS after 6 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline is reduced by at least 35% relative to placebo as determined by ADCOMS after 12 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline is reduced by at least 30% relative to placebo as

determined by ADCOMS after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline is reduced by at least 46% relative to placebo as determined by ADCOMS after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the composition comprises 10 mg/kg of at least one anti-A β protofibril antibody and is administered once every two weeks or once every month. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[149] In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, or at least 52% relative to placebo as determined by ADCOMS, wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[150] In some embodiments, the clinical decline is reduced by 28% to 33% relative to placebo as determined by ADCOMS, wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the clinical decline is reduced by at least 20%, such as by at 25% or at least 28%, relative to placebo as determined by ADCOMS, wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the clinical decline is reduced by at least 25%, such as by at least 30% or at least 33%, relative to placebo as determined by ADCOMS, wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the clinical decline is reduced by at least 25%, such as by at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, or at least 52% relative to placebo as determined by ADCOMS, wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the clinical decline is reduced by at least 52% relative to placebo as determined by ADCOMS, wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[151] In some embodiments, the clinical decline in the subject diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood is reduced by at least 30% relative to placebo as determined by ADCOMS after 6 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the subject diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood is reduced by at least 25% relative to placebo as determined by ADCOMS after 12 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the subject

diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood is reduced by at least 30% relative to placebo as determined by ADCOMS after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the subject diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood is reduced by at least 52% relative to placebo as determined by ADCOMS after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the composition comprises 10 mg/kg of at least one anti-A β protofibril antibody and is administered once every two weeks or once every month. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[152] In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, or at least 33% relative to placebo as determined by ADCOMS, wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[153] In some embodiments, the clinical decline is reduced by 28% to 38% relative to placebo as determined by ADCOMS, wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the clinical decline is reduced by at least 20%, such as by at least 25%, at least 28%, or at least 33%, relative to placebo as determined by ADCOMS, wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the clinical decline is reduced by at least 25%, such as by at least 30% or at least 33%, relative to placebo as determined by ADCOMS, wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the clinical decline is reduced by at least 33% relative to placebo as determined by ADCOMS, wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[154] In some embodiments, the clinical decline in the subject diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood is reduced by at least 33% relative to placebo as determined by ADCOMS after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the composition comprises 10 mg/kg of at least one anti-A β protofibril antibody and is administered once every two weeks or once every month. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[155] In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least

31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, or at least 78% relative to placebo as determined by ADCOMS, wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[156] In some embodiments, the clinical decline is reduced by 20% to 80% relative to placebo as determined by ADCOMS, wherein the subject has been diagnosed as having Alzheimer's disease dementia. In some embodiments, the clinical decline is reduced by 35% to 78% relative to placebo as determined by ADCOMS, wherein the subject has been diagnosed as having Alzheimer's disease dementia. In some embodiments, the clinical decline is reduced by at least 35% relative to placebo as determined by ADCOMS, wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the clinical decline is reduced by at least 50%, such as by at least 52% or at least 53% relative to placebo as determined by ADCOMS, wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the clinical decline is reduced by at least 70%, such as by at least 75% or at least 78%, relative to placebo as determined by ADCOMS, wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[157] In some embodiments, the clinical decline in the subject diagnosed as having mild Alzheimer's disease dementia is reduced by at least 70% relative to placebo as determined by ADCOMS after 6 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the subject diagnosed as having mild Alzheimer's disease dementia is reduced by at least 50% relative to placebo as determined by ADCOMS after 12 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the subject diagnosed as having mild Alzheimer's disease dementia is reduced by at least 30% relative to placebo as determined by ADCOMS after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the subject diagnosed as having mild Alzheimer's disease dementia is reduced by at least 52% relative to placebo as determined by ADCOMS after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the composition comprises 10 mg/kg of at least one anti-A β protofibril antibody and is administered once every two weeks or once every month. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[158] In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least

24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, or at least 35% relative to placebo as determined by ADCOMS, wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[159] In some embodiments, the clinical decline is reduced by 28% to 38% relative to placebo as determined by ADCOMS, wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the clinical decline is reduced by at least 20%, such as by at least 25%, at least 28%, or at least 35%, relative to placebo as determined by ADCOMS, wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the clinical decline is reduced by at least 25%, such as by at least 30% or at least 35%, relative to placebo as determined by ADCOMS, wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the clinical decline is reduced by at least 35% relative to placebo as determined by ADCOMS, wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[160] In some embodiments, the clinical decline in the subject diagnosed as having mild Alzheimer's disease dementia is reduced by at least 35% relative to placebo as determined by ADCOMS after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the composition comprises 10 mg/kg of at least one anti-A β protofibril antibody and is administered once every two weeks or once every month. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[161] In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 100%, at least 110%, at least 120%, at least 130%, at least 140%, or at least 150% relative to placebo as determined by ADAS-cog. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[162] In some embodiments, the clinical decline is reduced by 40% to 150% relative to placebo as determined by ADAS-cog. In some embodiments, the clinical decline is reduced by 45% to 145% relative to placebo as determined by ADAS-cog. In some embodiments, the clinical decline is reduced by 45% to 55% relative to placebo as determined by ADAS-cog. In some embodiments, the clinical decline is reduced by at least 30% relative to placebo as

determined by ADAS-cog. In some embodiments, the clinical decline is reduced by at least 35% relative to placebo as determined by ADAS-cog. In some embodiments, the clinical decline is reduced by at least 40% as determined by ADAS-cog. In some embodiments, the clinical decline is reduced by at least 45% as determined by ADAS-cog. In some embodiments, the clinical decline is reduced by at least 47% as determined by ADAS-cog. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[163] In some embodiments, the clinical decline is reduced by at least 100%, such as at least 120% or at least 140%, relative to placebo as determined by ADAS-cog after 6 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline is reduced by at least 40%, such as at least 45%, relative to placebo as determined by ADAS-cog after 12 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline is reduced by at least 40%, such as at least 45%, relative to placebo as determined by ADAS-cog after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline is reduced by at least 47%, relative to placebo as determined by ADAS-cog after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the composition comprises 10 mg/kg of at least one anti-A β protofibril antibody and is administered once every two weeks or once every month. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[164] In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, or at least 58% relative to placebo as determined by ADAS-cog, wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[165] In some embodiments, the clinical decline is reduced by 50% to 70% relative to placebo as determined by ADAS-cog, wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the clinical decline is reduced by at least 50%, such as by at least 52%, at least 55%, or at least 58%, relative to placebo as determined by ADAS-cog, wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the clinical decline is reduced by at least 58% relative to placebo as determined by ADAS-cog, wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the above-recited reduction in clinical decline is determined after 1

month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[166] In some embodiments, the clinical decline in the subject diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood is reduced by at least 58% relative to placebo as determined by ADAS-cog after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the composition comprises 10 mg/kg of at least one anti-A β protofibril antibody and is administered once every two weeks or once every month. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[167] In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, or at least 41% relative to placebo as determined by ADAS-cog, wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[168] In some embodiments, the clinical decline is reduced by 30% to 50% relative to placebo as determined by ADAS-cog, wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the clinical decline is reduced by at least 35%, such as by at 38%, at least 40%, or at least 41%, relative to placebo as determined by ADAS-cog, wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the clinical decline is reduced by at least 41% relative to placebo as determined by ADAS-cog, wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[169] In some embodiments, the clinical decline in the subject diagnosed as having mild Alzheimer's disease dementia is reduced by at least 41% relative to placebo as determined by ADAS-cog after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the composition comprises 10 mg/kg of at least one anti-A β protofibril antibody and is administered once every two weeks or once every month. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[170] In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, or at least 40% relative to placebo as determined by CDR-SB. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the

composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[171] In some embodiments, the clinical decline is reduced by 20% to 60% relative to placebo as determined by CDR-SB. In some embodiments, the clinical decline is reduced by 25% to 60% relative to placebo as determined by CDR-SB. In some embodiments, the clinical decline is reduced by 25% to 50% relative to placebo as determined by CDR-SB. In some embodiments, the clinical decline is reduced by at least 20% relative to placebo as determined by CDR-SB. In some embodiments, the clinical decline is reduced by at least 30% relative to placebo as determined by CDR-SB. In some embodiments, the clinical decline is reduced by at least 25%, such as at least 26% or at least 28%, as determined by CDR-SB. In some embodiments, the clinical decline is reduced by at least 30%, such as at least 35% or at least 38%, as determined by CDR-SB. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[172] In some embodiments, the clinical decline is reduced by at least 30%, such as at least 35% or at least 40%, relative to placebo as determined by CDR-SB after 6 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline is reduced by at least 30%, such as at least 35% or at least 45%, relative to placebo as determined by CDR-SB after 12 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline is reduced by at least 20%, such as at least 25%, relative to placebo as determined by CDR-SB after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the composition comprises 10 mg/kg of at least one anti-A β protofibril antibody and is administered once every two weeks or once every month. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[173] In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, or at least 14% relative to placebo as determined by CDR-SB, wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[174] In some embodiments, the clinical decline is reduced by 10% to 20% relative to placebo as determined by CDR-SB, wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the clinical decline is reduced by at least 5%, such as by at 10%, at least 12%, or at least 14%, relative to placebo as determined by CDR-SB, wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the clinical decline is reduced by at least 14% relative to placebo as determined by CDR-SB, wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[175] In some embodiments, the clinical decline in the subject diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood is reduced by at least 14% relative to placebo as determined by CDR-SB after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the composition comprises 10 mg/kg of at least one anti-A β protofibril antibody and is administered once every two weeks or once every month. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[176] In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, or at least 51% relative to placebo as determined by CDR-SB, wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[177] In some embodiments, the clinical decline is reduced by 40% to 60% relative to placebo as determined by CDR-SB, wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the clinical decline is reduced by at least 45%, such as by at least 48%, at least 50%, or at least 51%, relative to placebo as determined by CDR-SB, wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the clinical decline is reduced by at least 51% relative to placebo as determined by CDR-SB, wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[178] In some embodiments, the clinical decline in the subject diagnosed as having mild Alzheimer's disease dementia is reduced by at least 51% relative to placebo as determined by CDR-SB after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the composition comprises 10 mg/kg of at least one anti-A β protofibril antibody and is administered once every two weeks or once every month. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[179] In some embodiments, the reduction in clinical decline is determined after 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, 13 months, 14 months, 15 months, 16 months, 17 months, 18 months, 19 months, 20 months, 21 months, 22 months, 23 months, 24 months, 30 months, 36 months, 42 months, 48 months, 54 months, 60 months, 63 months, 66 months, and/or 72 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[180] In some embodiments, the reduction in clinical decline is determined after 1 month of administration of the composition comprising a therapeutically effective amount of at least

one anti-A β protofibril antibody. In some embodiments, the reduction in clinical decline is determined after 6 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the reduction in clinical decline is determined after 12 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the reduction in clinical decline is determined after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the reduction in clinical decline is determined after 60 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the reduction in clinical decline is determined after 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[181] In some embodiments, the reduction in clinical decline is determined after administration of a composition comprising a therapeutically effective amount of BAN2401.

[182] In some embodiments, the reduction in clinical decline is determined after 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, 13 months, 14 months, 15 months, 16 months, 17 months, 18 months, 19 months, 20 months, 21 months, 22 months, 23 months, 24 months, 30 months, 36 months, 42 months, 48 months, 54 months, 60 months, 63 months, 66 months, and/or 72 months of administration of the composition comprising a therapeutically effective amount of BAN2401. In some embodiments, the reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of BAN2401. In some embodiments, the reduction in clinical decline is determined after 1 month of administration of the composition comprising a therapeutically effective amount of BAN2401. In some embodiments, the reduction in clinical decline is determined after 6 months of administration of the composition comprising a therapeutically effective amount of BAN2401. In some embodiments, the reduction in clinical decline is determined after 12 months of administration of the composition comprising a therapeutically effective amount of BAN2401. In some embodiments, the reduction in clinical decline is determined after 18 months of administration of the composition comprising a therapeutically effective amount of BAN2401. In some embodiments, the reduction in clinical decline is determined after 60 months of administration of the composition comprising a therapeutically effective amount of BAN2401. In some embodiments, the reduction in clinical decline is determined after 63 months of administration of the composition comprising a therapeutically effective amount of BAN2401.

[183] In some embodiments, the subject is ApoE4-positive.

[184] In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, or at least 74% relative to placebo as determined by ADCOMS, wherein the subject is

ApoE4-positive. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β antibody.

[185] In some embodiments, the clinical decline is reduced by 60% to 80%, such as by 63% to 74%, relative to placebo as determined by ADCOMS, wherein the subject is ApoE4-positive. In some embodiments, the clinical decline is reduced by at least 60%, such as at least 63%, relative to placebo as determined by ADCOMS, wherein the subject is ApoE4-positive. In some embodiments, the clinical decline is reduced by at least 65%, such as at least 67%, relative to placebo as determined by ADCOMS, wherein the subject is ApoE4-positive. In some embodiments, the clinical decline is reduced by at least 70%, such as at least 74%, relative to placebo as determined by ADCOMS, wherein the subject is ApoE4-positive.

[186] In some embodiments, the clinical decline in the ApoE4-positive subject is reduced by at least 70% relative to placebo as determined by ADCOMS after 6 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the ApoE4-positive subject is reduced by at least 60% relative to placebo as determined by ADCOMS after 12 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the ApoE4-positive subject is reduced by at least 50%, such as at least 55% or at least 60%, relative to placebo as determined by ADCOMS after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the ApoE4-positive subject is reduced by at least 63%, relative to placebo as determined by ADCOMS after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the composition comprises 10 mg/kg of at least one anti-A β protofibril antibody and is administered once every two weeks or once every month. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[187] In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 100%, at least 101%, at least 102%, at least 103%, at least 104%, at least 105%, at least 106%, at least 107%, at least 108%, at least 109%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 155%, at least 160%, at least 165%, at least 170%, at least 175%, at least 180%, at least 185%, at least 190%, at least 195%, at least 200%, at least 205%, at least 210%, at least

215%, at least 220%, at least 225%, at least 230%, at least 235%, at least 240%, at least 245%, at least 250%, at least 255%, at least 260%, at least 265%, at least 270%, at least 275%, at least 280%, at least 290%, at least 295%, at least 300%, at least 305%, at least 310%, at least 315%, at least 320%, at least 325%, at least 330%, or at least 331% relative to placebo as determined by ADAS-cog, wherein the subject is ApoE4-positive. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[188] In some embodiments, the clinical decline is reduced 70% to 400%, such as 80% to 350%, relative to placebo as determined by ADAS-cog, wherein the subject is ApoE4-positive. In some embodiments, the clinical decline is reduced by at least 70%, such as at least 75% or at least 80%, relative to placebo as determined by ADAS-cog, wherein the subject is ApoE4-positive. In some embodiments, the clinical decline is reduced by at least 80%, such as at least 90% or at least 100%, relative to placebo as determined by ADAS-cog, wherein the subject is ApoE4-positive. In some embodiments, the clinical decline is reduced by at least 300%, such as at least 330%, relative to placebo as determined by ADAS-cog, wherein the subject is ApoE4-positive. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[189] In some embodiments, the clinical decline in the ApoE4-positive subject is reduced by at least 300% relative to placebo as determined by ADAS-cog after 6 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the ApoE4-positive subject is reduced by at least 80%, such as at least 90% or at least 100%, relative to placebo as determined by ADAS-cog after 12 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the ApoE4-positive subject is reduced by at least 70%, such as at least 75%, at least 80%, or at least 84%, relative to placebo as determined by ADAS-cog after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the ApoE4-positive subject is reduced by at least 84%, relative to placebo as determined by ADAS-cog after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the composition comprises 10 mg/kg of at least one anti-A β protofibril antibody and is administered once every two weeks or once every month. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[190] In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least

80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, or at least 87% relative to placebo as determined by CDR-SB, wherein the subject is ApoE4-positive. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[191] In some embodiments, the clinical decline is reduced by 35% to 150%, such as 40% to 100% or 45% to 90%, relative to placebo as determined by CDR-SB, wherein the subject is ApoE4-positive. In some embodiments, the clinical decline is reduced by at least 35%, such as at least 40% or at least 45%, relative to placebo as determined by CDR-SB, wherein the subject is ApoE4-positive. In some embodiments, the clinical decline is reduced by at least 50%, such as at least 55% or at least 60%, relative to placebo as determined by CDR-SB, wherein the subject is ApoE4-positive. In some embodiments, the clinical decline is reduced by at least 70%, such as at least 80% or at least 85%, relative to placebo as determined by CDR-SB, wherein the subject is ApoE4-positive. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[192] In some embodiments, the clinical decline in the ApoE4-positive subject is reduced by at least 35%, such as at least 40% or at least 45%, relative to placebo as determined by CDR-SB after 6 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the ApoE4-positive subject is reduced by at least 70%, such as at least 75% or at least 80%, relative to placebo as determined by CDR-SB after 12 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the ApoE4-positive subject is reduced by at least 50%, such as at least 55% or at least 60%, relative to placebo as determined by CDR-SB after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the ApoE4-positive subject is reduced by at least 60%, relative to placebo as determined by CDR-SB after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the composition comprises 10 mg/kg of at least one anti-A β protofibril antibody and is administered once every two weeks or once every month. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[193] In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, or at least 59% relative to placebo as determined by ADCOMS, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[194] In some embodiments, the clinical decline is reduced by 30% to 70%, such as 38% to 59%, relative to placebo as determined by ADCOMS, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the clinical decline is reduced by at least 30%, such as at least 35% or at least 38%, relative to placebo as determined by ADCOMS, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the clinical decline is reduced by at least 45%, such as at least 50% or at least 53%, relative to placebo as determined by ADCOMS, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the clinical decline is reduced by at least 50%, such as at least 55% or at least 59%, relative to placebo as determined by ADCOMS, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[195] In some embodiments, the clinical decline in the ApoE4-positive subject diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood is reduced by at least 50%, such as at least 55%, relative to placebo as determined by ADCOMS after 6 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the ApoE4-positive subject diagnosed as mild cognitive impairment due to Alzheimer's disease - intermediate likelihood is reduced by at least 30%, such as at least 35%, relative to placebo as determined by ADCOMS after 12 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the ApoE4-positive subject diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood is reduced by at least 45%, such as at least 50% or at least 55%, relative to placebo as determined by ADCOMS after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the composition comprises 10 mg/kg of at least one anti-A β protofibril antibody and is administered once every two weeks or once every month. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[196] In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 100%, at

least 101%, at least 102%, at least 103%, at least 104%, at least 105%, at least 106%, at least 107%, at least 108%, at least 109%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 155%, at least 160%, at least 165%, at least 170%, at least 175%, at least 180%, at least 185%, at least 190%, at least 195%, at least 200%, at least 205%, at least 210%, or at least 211% relative to placebo as determined by ADCOMS, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[197] In some embodiments, the clinical decline in the ApoE4-positive subject diagnosed as having mild Alzheimer's disease dementia is reduced by at least 100%, such as at least 110%, relative to placebo as determined by ADCOMS after 6 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the ApoE4-positive subject diagnosed as having mild Alzheimer's disease dementia is reduced by at least 100%, such as at least 110%, relative to placebo as determined by ADCOMS after 12 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the ApoE4-positive subject diagnosed as having mild Alzheimer's disease dementia is reduced by at least 65%, such as at least 70% or at least 75%, relative to placebo as determined by ADCOMS after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the composition comprises 10 mg/kg of at least one anti-A β protofibril antibody and is administered once every two weeks or once every month. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[198] In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 100%, at least 101%, at least 102%, at least 103%, at least 104%, at least 105%, at least 106%, at least 107%, at least 108%, at least 109%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 155%, at least 160%, at least 165%, at least 170%, at least 175%, at least 180%, at least 185%, at least 190%, at least 195%, at least 200%, at least 205%, at least 210%, or at least 211% relative to placebo as determined by ADAS-Cog, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the above-

recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[199] In some embodiments, the clinical decline is reduced by 40% to 300%, such as 45% to 250% or 50% to 250%, relative to placebo as determined by ADAS-Cog, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the clinical decline is reduced by at least 40%, such as at least 45% or at least 50%, relative to placebo as determined by ADAS-Cog, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the clinical decline is reduced by at least 60, such as at least 70%, at least 75%, or at least 80%, relative to placebo as determined by ADAS-Cog, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the clinical decline is reduced by at least 100%, such as at least 150% or at least 200% relative to placebo as determined by ADAS-Cog, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[200] In some embodiments, the clinical decline in the ApoE4-positive subject diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood is reduced by at least 100%, such as at least 150% or at least 200%, relative to placebo as determined by ADAS-cog after 6 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the ApoE4-positive subject diagnosed as mild cognitive impairment due to Alzheimer's disease - intermediate likelihood is reduced by at least 40%, such as at least 45% or at least 50%, relative to placebo as determined by ADAS-cog after 12 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the ApoE4-positive subject diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood is reduced by at least 50%, such as at least 60%, at least 70%, or at least 75%, relative to placebo as determined by ADAS-cog after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the composition comprises 10 mg/kg of at least one anti-A β protofibril antibody and is administered once every two weeks or once every month. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[201] In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, or at least 45% relative to placebo as determined by CDR-SB, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the above-

recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[202] In some embodiments, the clinical decline is reduced by 20% to 90%, such as 25% to 80% or 30% to 75%, relative to placebo as determined by CDR-SB, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the clinical decline is reduced by at least 25%, such as at least 30%, relative to placebo as determined by CDR-SB, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the clinical decline is reduced by at least 30%, such as at least 35% or 40%, relative to placebo as determined by CDR-SB, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the clinical decline is reduced by at least 35%, such as at least 40% or 45%, relative to placebo as determined by CDR-SB, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[203] In some embodiments, the clinical decline in the ApoE4-positive subject diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood is reduced by at least 35%, such as at least 40% or at least 45%, relative to placebo as determined by CDR-SB composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the ApoE4-positive subject diagnosed as mild cognitive impairment due to Alzheimer's disease - intermediate likelihood is reduced by at least 20%, such as at least 25% or at least 30%, relative to placebo as determined by CDR-SB after 12 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the ApoE4-positive subject diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood is reduced by at least 35%, such as at least 40%, relative to placebo as determined by CDR-SB after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the composition comprises 10 mg/kg of at least one anti-A β protofibril antibody and is administered once every two weeks or once every month. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[204] In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least

80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 100%, at least 101%, at least 102%, at least 103%, at least 104%, at least 105%, at least 106%, at least 107%, at least 108%, at least 109%, at least 110%, at least 111%, at least 112%, at least 113%, at least 114%, at least 115%, at least 116%, at least 117%, at least 118%, or at least 119% relative to placebo as determined by ADCOMS, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[205] In some embodiments, the clinical decline is reduced by 76% to 119% relative to placebo as determined by ADCOMS, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the clinical decline is reduced by 76% relative to placebo as determined by ADCOMS, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the clinical decline is reduced by 113% relative to placebo as determined by ADCOMS, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the clinical decline is reduced by 119% relative to placebo as determined by ADCOMS, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[206] In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 100%, at least 101%, at least 102%, at least 103%, at least 104%, at least 105%, at least 106%, at least 107%, at least 108%, at least 109%, at least 110%, at least 111%, at least 112%, at least 113%, at least 114%, at least 115%, at least 116%, at least 117%, at least 118%, at least 119%, at least 120%, at least 121%, at least 122%, at least 123%, at least 124%, at least 125%, at least 126%, at least 127%, at least 128%, at least 129%, at least 130%, at least 131%, at least 132%, at least 133%, at least 134%, at least 135%, at least 136%, at least 137%, at least 138%, at least 139%, at least 140%, at least 141%, at least 142%, at least 143%, at least 144%, at least 145%, at least 146%, at least 147%, at least 148%, at least

149%, at least 150%, at least 151%, at least 152%, at least 153%, at least 154%, at least 155%, at least 156%, at least 157%, at least 158%, at least 159%, at least 160%, at least 161%, at least 162%, at least 163%, at least 164%, at least 165%, at least 166%, at least 167%, at least 168%, at least 169%, at least 170%, at least 171%, at least 172%, at least 173%, at least 174%, at least 175%, at least 176%, at least 177%, at least 178%, at least 179%, at least 180%, at least 190%, at least 200%, at least 210%, at least 220%, at least 230%, at least 240%, at least 250%, at least 275%, at least 300%, at least 325%, at least 350%, at least 375%, at least 400%, at least 425%, at least 450%, at least 475%, at least 500%, at least 550%, at least 600%, at least 650%, at least 700%, at least 750%, at least 800%, at least 850%, at least 900%, at least 950%, at least 1000%, at least 1001%, at least 1002%, at least 1003%, at least 1004%, at least 1005%, at least 1006%, at least 1007%, at least 1008%, at least 1009%, at least 1010%, at least 1011%, at least 1012%, at least 1013%, at least 1014%, at least 1015%, at least 1016%, at least 1017%, at least 1018%, at least 1019%, at least 1020%, at least 1021%, at least 1022%, or at least 1023% relative to placebo as determined by ADAS-Cog, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[207] In some embodiments, the clinical decline is reduced by 58% to 1023% relative to placebo as determined by ADAS-Cog, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the clinical decline is reduced by 58% relative to placebo as determined by ADAS-Cog, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the clinical decline is reduced by 171% relative to placebo as determined by ADAS-Cog, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the clinical decline is reduced by 1023% relative to placebo as determined by ADAS-Cog, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[208] In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 100%, at least 101%, at least 102%, at least 103%, at least 104%, at least 105%, at least 106%, at least

107%, at least 108%, at least 109%, at least 110%, at least 111%, at least 112%, at least 113%, at least 114%, at least 115%, at least 116%, at least 117%, at least 118%, at least 119%, at least 120%, at least 121%, at least 122%, at least 123%, at least 124%, at least 125%, at least 126%, at least 127%, at least 128%, at least 129%, at least 130%, at least 131%, at least 132%, at least 133%, at least 134%, at least 135%, at least 136%, at least 137%, at least 138%, at least 139%, at least 140%, at least 141%, at least 142%, at least 143%, at least 144%, at least 145%, at least 146%, at least 147%, at least 148%, at least 149%, at least 150%, at least 151%, at least 152%, at least 153%, at least 154%, at least 155%, at least 156%, at least 157%, at least 158%, at least 159%, at least 160%, at least 161%, at least 162%, at least 163%, at least 164%, at least 165%, at least 166%, at least 167%, at least 168%, at least 169%, at least 170%, at least 171%, at least 172%, at least 173%, or at least 174% relative to placebo as determined by CDR-SB, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[209] In some embodiments, the clinical decline is reduced by 70% to 200%, such as 75% to 180% or 82% to 174%, relative to placebo as determined by CDR-SB, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the clinical decline is reduced by at least 70%, such as at least 80% relative to placebo as determined by CDR-SB, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the clinical decline is reduced by at least 75%, such as at least 80% or at least 85%, relative to placebo as determined by CDR-SB, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the clinical decline is reduced by at least 150%, such as at least 160% or 170%, relative to placebo as determined by CDR-SB, wherein the subject is ApoE4-positive, and wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[210] In some embodiments, the clinical decline in the ApoE4-positive subject diagnosed as having mild Alzheimer's disease dementia is reduced by at least 70%, such as at least 75%, at least 80%, or at least 85%, relative to placebo as determined by CDR-SB composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the ApoE4-positive subject diagnosed as having mild Alzheimer's disease dementia is reduced by at least 130%, such as at least 140%, at least 150%, at least 160%, or at least 170%, relative to placebo as determined by CDR-SB after 12 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the ApoE4-positive subject diagnosed as having mild Alzheimer's disease dementia is reduced by at least 65%, such as at least 70%, at least 75%, or at least 80%, relative to placebo as determined by CDR-SB after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the composition comprises 10 mg/kg of at least one anti-A β protofibril antibody and is administered once every two weeks or once every month. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[211] In some embodiments, the subject is ApoE4-negative.

[212] In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, or at least 12% relative to placebo as determined by ADCOMS, wherein the subject is ApoE4-negative. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[213] In some embodiments, the clinical decline is reduced by 5% to 15% relative to placebo as determined by ADCOMS, wherein the subject is ApoE4-negative. In some embodiments, the clinical decline is reduced by at least 5%, such as at least 7%, relative to placebo as determined by ADCOMS, wherein the subject is ApoE4-negative. In some embodiments, the clinical decline is reduced by at least 10%, such as at least 12%, relative to placebo as determined by ADCOMS, wherein the subject is ApoE4-negative. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[214] In some embodiments, the clinical decline in the ApoE4-negative subject is reduced by at least -2% relative to placebo as determined by ADCOMS after 6 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the ApoE4-negative subject is reduced by at least 10% relative to placebo as determined by ADCOMS after 12 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the ApoE4-negative subject is reduced by at least 5%, such as at least 7%, relative to placebo as determined by ADCOMS after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the ApoE4-negative subject is reduced by at least 7%, relative to placebo as determined by ADCOMS after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the composition comprises 10 mg/kg of at least one anti-A β protofibril antibody and is administered once every two weeks or once every month. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[215] In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, or at least 72% relative to placebo as determined by ADAS-cog, wherein the subject is ApoE4-negative. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[216] In some embodiments, the clinical decline is reduced by 40% to 80% relative to placebo as determined by ADAS-cog, wherein the subject is ApoE4-negative. In some embodiments, the clinical decline is reduced by at least 35%, such as at least 40% or at least 43%, relative to placebo as determined by ADAS-cog, wherein the subject is ApoE4-negative. In some embodiments, the clinical decline is reduced by at least 40%, such as at least 45% or at least 46%, relative to placebo as determined by ADAS-cog, wherein the subject is ApoE4-negative. In some embodiments, the clinical decline is reduced by at least 65%, such as at least 70% or at least 72%, relative to placebo as determined by ADAS-cog, wherein the subject is ApoE4-negative. In some embodiments, the clinical decline is reduced by at least 43%, relative to placebo as determined by ADAS-cog, wherein the subject is ApoE4-negative. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[217] In some embodiments, the clinical decline is increased by 7%, 6%, 5%, 5%, 3%, 2%, or 1% relative to placebo as determined by CDR-SB, wherein the subject is ApoE4-negative. In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, or at least 3% relative to placebo as determined by CDR-SB, wherein the subject is ApoE4-negative. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[218] In some embodiments, the clinical decline is reduced by 3% relative to placebo as determined by CDR-SB, wherein the subject is ApoE4-negative. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, or at least 26% relative to placebo as determined by ADCOMS, wherein the subject is ApoE4-negative, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[219] In some embodiments, the clinical decline is reduced by 15% to 26% relative to placebo as determined by ADCOMS, wherein the subject is ApoE4-negative, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the clinical decline is reduced by 15% relative to placebo as determined by ADCOMS, wherein the subject is ApoE4-negative, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the clinical decline is reduced by 26% relative to placebo as determined by ADCOMS, wherein the subject is ApoE4-negative, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[220] In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 100%, at least 101%, at least 102%, at least 103%, at least 104%, at least 105%, at least 106%, at least 107%, at least 108%, at least 109%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 155%, at least 160%, at least 165%, or at least 166% relative to placebo as determined by ADAS-Cog, wherein the subject is ApoE4-negative, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[221] In some embodiments, the clinical decline is reduced by 50% to 200%, such as 60% to 180% or 65% to 170%, relative to placebo as determined by ADAS-Cog, wherein the subject is ApoE4-negative, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the clinical decline is reduced by at least 50%, such as at least 55% or at least 65%, relative to placebo as determined by ADAS-Cog, wherein the subject is ApoE4-negative, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the clinical decline is reduced by at least 70%, such as at least 75% or at least 80%, relative to placebo as determined by ADAS-Cog, wherein the subject is ApoE4-negative, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the clinical decline is reduced by at least 150%, such as at least 160%, relative to placebo as determined by ADAS-Cog, wherein the subject is ApoE4-negative, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[222] In some embodiments, the clinical decline in the ApoE4-negative subject is reduced by at least 150%, such as at least 160%, relative to placebo as determined by ADAS-Cog after 6 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the ApoE4-negative subject is reduced by at least 70%, such as at least 75% or at least 80%, relative to placebo as determined by ADAS-Cog after 12 months of

administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the clinical decline in the ApoE4-negative subject is reduced by at least 50%, such as at least 60% or at least 65%, relative to placebo as determined by ADAS-Cog after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the composition comprises 10 mg/kg of at least one anti-A β protofibril antibody and is administered once every two weeks or once every month. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[223] In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, or at least 5% relative to placebo as determined by CDR-SB, wherein the subject is ApoE4-negative, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[224] In some embodiments, the clinical decline is reduced by at least 5% relative to placebo as determined by CDR-SB, wherein the subject is ApoE4-negative, and wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[225] In some embodiments, the clinical decline is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12% relative to placebo as determined by CDR-SB, wherein the subject is ApoE4-negative, and wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[226] In some embodiments, the clinical decline is reduced by at least 10%, such as at least 12%, relative to placebo as determined by CDR-SB, wherein the subject is ApoE4-negative, and wherein the subject has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the above-recited reduction in clinical decline is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

Conversion of a subject from amyloid positive to amyloid negative

[227] In various embodiments, a subject is administered a composition comprising at least one anti-A β protofibril antibody disclosed herein before exhibiting cognitive symptoms of AD (pre-AD). In some embodiments, the pre-AD patient is amyloid negative, e.g., as determined by PET SUVR and/or by plasma biomarkers such as a p-tau181 level in a blood sample. In some embodiments, the pre-AD patient has a p-tau181 level below a certain threshold, and optionally the patient has intermediate amyloid β , e.g., as measured by PET SUVR prior to treatment. In some embodiments, a patient with pre-AD may be administered a treatment regimen comprising an anti-A β protofibril antibody (i.e. lecanemab) to prevent amyloid positivity. In some embodiments, a patient with pre-AD may be administered a

treatment regimen comprising an anti-A β protofibril antibody (i.e. lecanemab) to delay onset of amyloid positivity. In some embodiments, a patient with pre-AD may be administered a treatment regimen comprising an anti-A β protofibril antibody (i.e. lecanemab) to prevent a worsening in one or more biomarkers of AD or brain measurement (e.g., by PET or MRI), e.g., of brain atrophy and/or amyloid accumulation. In some embodiments, a pre-AD patient who is amyloid negative is administered a reduced dose or dosing frequency as compared to a dose or frequency given to a patient who is amyloid positive (e.g., an intravenous infusion is given at less than 10 mg/kg or less than biweekly, or a subcutaneous administration is provided at less than 720 mg or less than weekly). In some embodiments, a pre-AD patient who is amyloid negative is moved to a maintenance dosing regimen sooner (e.g., in less than 18 months).

[228] In some embodiments, a pre-AD patient has a p-tau181 level above a threshold, and the patient is administered a treatment regimen comprising an anti-A β protofibril antibody (i.e. lecanemab) to decrease the p-tau181 level below a threshold. In some embodiments, the patient has intermediate amyloid β , e.g., as measured by PET SUVR prior to treatment. In some embodiments, treatment reduces the amyloid β , e.g., as measured by PET SUVR. In some embodiments, treatment converts the patient from amyloid positive to amyloid negative status, e.g., as assessed by the p-tau181 level and/or PET SUVR).

[229] In various embodiments, also provided herein is a method of converting an amyloid-positive subject to an amyloid-negative subject. In some embodiments, said method comprises administering to said subject a composition comprising at least one anti-A β protofibril antibody disclosed herein. In some embodiments, said subject having early Alzheimer's disease has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood and/or has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the method further comprises evaluating the efficacy of a treatment by measuring the level of p-tau181 before administering a first dose of the composition comprising the anti-A β protofibril antibody, and measuring again after administering the antibody, e.g., after 6-12 or 18 or 24 or 36 months of treatment. In some embodiments, a decrease in the p-tau181 level after administration of the first dose of the composition comprising the anti-A β protofibril antibody indicates a change from amyloid positive to amyloid negative in the brain of the subject. In some embodiments, an increase in the A β 42/40 ratio after administration of the first dose of the composition comprising the anti-A β protofibril antibody, e.g., an increase to a ratio above 0.092, indicates a change from amyloid positive to amyloid negative in the brain of the subject. In some embodiments, an increase in the A β 42/40 ratio after 6 months or after 12 months or after 18 months or after 24 months or after 36 months following the start of administration of the composition comprising the anti-A β protofibril antibody, e.g., an increase to a ratio of about 0.05-0.1, e.g., about 0.08-0.1, e.g., about 0.092, indicates a change from amyloid positive to amyloid negative in the brain of the subject. In some embodiments, a decrease in the level of p-tau181 after administration of the first dose of the composition comprising the anti-A β protofibril antibody indicates treatment efficacy, e.g., a reduction in brain A β . In some embodiments, a subject who changes to amyloid negative is given a reduced dose or frequency of the anti-A β protofibril antibody, alone or in combination with at least one additional therapy, e.g., a BACE inhibitor and/or anti-tau antibody.

[230] Any of the anti-A β protofibril antibodies, therapeutically acceptable amounts thereof, dosing regimens therefor, and compositions comprising the same that are disclosed herein may be used in the method of converting an amyloid-positive subject to an amyloid-negative subject. For example, in some embodiments, a composition comprising 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, or 10 mg/kg of at least one anti-A β protofibril antibody such as BAN2401 relative to body weight of the subject is administered to the subject once every

week, once every two weeks, once every three weeks, once every four weeks, once every month, once every five weeks, once every six weeks, once every seven weeks, once every eight weeks, once every two months, once every nine weeks, once every ten weeks, once every eleven weeks, once every twelve weeks, once every three months (quarterly), once every fourteen weeks, once every sixteen weeks, once every four months, once every eighteen weeks, once every twenty weeks, once every five months, once every 22 weeks, once every 24 weeks, once every six months (semi-annually), once every seven months, once every eight months, once every nine months, once every ten months, once every eleven months, once every twelve months (annually), once every thirteen months, once every fourteen months, once every fifteen months, once every sixteen months, once every seventeen months, or once every eighteen months.

[231] In some embodiments, the method comprises measuring the p-tau181 level before administering a first dose of the composition comprising the anti-A β protofibril antibody, and measuring again after administering the antibody, e.g., after 6-12 or 18 or 24 months of treatment. In some embodiments, a decrease in the p-tau181 level indicates a change from amyloid positive to amyloid negative in the brain of the subject. In some embodiments, an increase in the A β 42/40 ratio, e.g., to a ratio above 0.092, indicates a change from amyloid positive to amyloid negative in the brain of the subject. In some embodiments, a subject who changes to amyloid negative is given a reduced dose or frequency of the anti-A β protofibril antibody, alone or in combination with at least one additional therapy, e.g., a BACE inhibitor and/or anti-tau antibody.

[232] In some embodiments, administration of the composition results in at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, or at least 81% of the subjects being converted from amyloid positive to amyloid negative, as determined by visual reads of amyloid PET images.

[233] In some embodiments, administration of the composition results in a conversion of 50% to 100%, such as 60% to 90%, of subjects from amyloid positive to amyloid negative, as determined by visual reads of amyloid PET images. In some embodiments, administration of the composition results in at least 55%, such as at least 60% or at least 65%, of the subjects being amyloid negative, as determined by visual reads of amyloid PET images, after 12 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, administration of the composition results in at least 70%, such as at least 75% or at least 80%, of the subjects being amyloid negative, as determined by visual reads of amyloid PET images, after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the composition comprises 10 mg/kg of at least one anti-A β protofibril antibody and is administered once every two weeks or once every month. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[234] In some embodiments, administration of the composition results in at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% of the subjects being amyloid negative, as determined by visual reads of amyloid PET images, wherein the subjects are ApoE4-positive.

[235] In some embodiments, administration of the composition results in 75% to 100%, such as 80% to 100% or 85% to 100% of the subjects being amyloid negative, as determined by visual reads of amyloid PET images, wherein the subjects are ApoE4-positive. In some embodiments, administration of the composition results in at least 75%, such as at least 80% or at least 85%, of the subjects being amyloid negative, as determined by visual reads of amyloid PET images, wherein the subjects are ApoE4-positive. In some embodiments, administration of the composition results in 100% of the subjects being amyloid negative, as determined by visual reads of amyloid PET images, wherein the subjects are ApoE4-positive.

[236] In some embodiments, at least 75%, such as at least 80% or at least 85%, of the ApoE4-positive subjects are amyloid negative, as determined by visual reads of amyloid PET images, after 12 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, at least 75%, such as at least 80%, at least 85%, at least 90%, or at least 95%, of the ApoE4-positive subjects are amyloid negative, as determined by visual reads of amyloid PET images, after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the composition comprises 10 mg/kg of at least one anti-A β protofibril antibody and is administered once every two weeks or once every month. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[237] In some embodiments, administration of the composition results in at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, or at least 79% of the subjects being amyloid negative, as determined by visual reads of amyloid PET images, wherein the subjects are ApoE4-negative.

[238] In some embodiments, administration of the composition results in 50% to 100%, such as 55% to 90%, of the subjects being amyloid negative, as determined by visual reads of amyloid PET images, wherein the subjects are ApoE4-negative. In some embodiments, administration of the composition results in at least 50% of the subjects being amyloid negative, as determined by visual reads of amyloid PET images, wherein the subjects are ApoE4-negative. In some embodiments, administration of the composition results in at least 70% of the subjects being amyloid negative, as determined by visual reads of amyloid PET images, wherein the subjects are ApoE4-negative.

Reduction of brain amyloid level

[239] In various embodiments, also provided herein is a method of reducing brain amyloid level in a subject in need thereof. In some embodiments, the method comprises measuring the level of p-tau181 before administering a first dose of a composition comprising the anti-A β protofibril antibody, and measuring again after administering the antibody, e.g., after 6-12 months of treatment. In some embodiments, decrease in the p-tau181 level indicates a reduction in brain amyloid in the brain of the subject. In some embodiments, a subject who exhibits a reduction in brain amyloid as determined by the change in the p-tau181 level is given a reduced dose or frequency of the anti-A β protofibril antibody, alone or in combination with at least one additional therapy, e.g., a BACE inhibitor and/or anti-tau antibody.

[240] In some embodiments, the subject has early Alzheimer's disease. In some embodiments, the subject has Alzheimer's disease, Down's Syndrome, chronic traumatic encephalopathy, cerebral amyloid angiopathy, Lewy Body Dementia, or another brain disease or conditions with A β peptide-containing soluble and/or insoluble A β aggregates.

[241] One of ordinary skill in the art will understand that, in addition to subjects having Alzheimer's disease, A β plaque deposits are present in the brains of subjects having other neurodegenerative diseases and conditions and thus that the methods disclosed herein may be beneficial for subjects having such neurodegenerative diseases and/or conditions. Such diseases and conditions are known to include, for example, Down's Syndrome, chronic traumatic encephalopathy, cerebral amyloid angiopathy, and Lewy Body Dementia. (See, e.g., Catafau et al., "Amyloid PET imaging: applications beyond Alzheimer's disease," Clin. Transl. Imaging 3(1): 39-55 (2015); and Banerjee, G. et al., "The increasing impact of cerebral amyloid angiopathy: essential new insights for clinical practice," J. Neurol. Neurosurg. Psychiatry 88: 982-994 (2017).)

[242] In some embodiments, the subject having early Alzheimer's disease has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood and/or has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the subject having early Alzheimer's disease is ApoE4-positive.

[243] Any of the anti-A β protofibril antibodies, therapeutically acceptable amounts thereof, dosing regimens therefor, and compositions comprising the same that are disclosed herein may be used in the method of reducing brain amyloid level in a subject having early Alzheimer's disease. For example, in some embodiments, a composition comprising 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, or 10 mg/kg of at least one anti-A β protofibril antibody such as BAN2401 relative to body weight of the subject is administered to the subject once every week, once every two weeks, once every three weeks, once every four weeks, once every month, once every five weeks, once every six weeks, once every seven weeks, once every eight weeks, once every two months, once every nine weeks, once every ten weeks, once every eleven weeks, once every twelve weeks, once every three months (quarterly), once every fourteen weeks, once every sixteen weeks, once every four months, once every eighteen weeks, once every twenty weeks, once every five months, once every 22 weeks,

once every 24 weeks, once every six months (semi-annually), once every seven months, once every eight months, once every nine months, once every ten months, once every eleven months, once every twelve months (annually), once every thirteen months, once every fourteen months, once every fifteen months, once every sixteen months, once every seventeen months, or once every eighteen months. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[244] In some embodiments, said method results in a reduced brain amyloid level after administration relative to the brain amyloid level prior to said administration. In some embodiments, the brain amyloid level is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% relative to the brain amyloid level prior to said administration. In some embodiments, the above-recited reductions in brain amyloid levels are determined by visual reads of amyloid PET images and are expressed as PET standard uptake value ratios (SUVr values).

[245] As used herein, the term “PET” or “Amyloid PET” refers to Amyloid positron emission tomography imaging. In some embodiments, PET imaging (also referred to as a PET scan) is performed to assess for amyloid pathology. In some embodiments, amyloid PET is assessed with a PET tracer and uses the same tracer in follow-up assessments. In some embodiments, the PET imaging uses a florbetapir tracer. In some embodiments, the PET imaging uses a flutemetamol tracer.

[246] Amyloid positron emission tomography (PET) imaging can be used to confirm the presence of amyloid pathology in the brain of early AD subjects in the screening phase of the study and/or to evaluate the effects of the at least one anti-AB antibody on amyloid levels in the brain, both by whole brain analysis (e.g., the average of 5-6 cortical regions) and brain region analysis. In some embodiments, the PET scan uses florbetapir. In some embodiments, amyloid plaque load can be identified by a PET imaging uptake visual read, e.g., by a trained radiologist. In some embodiments, 2 readers (1 designated as Primary Reader) visually assess the images to determine whether the scan is positive or negative for amyloid. In further embodiments, four regions of the brain are assessed for uptake of the imaging agent: the temporal lobes, the occipital lobes, the prefrontal cortex, and the parietal cortex and a positive amyloid scan has either 1 region with intense gray matter uptake that is greater than the white matter uptake and extends to the outer edges of the brain, or 2 regions with areas of reduced gray-white contrast. In further embodiments, if disagreement occurs between 2 readers, both meet to review the scan for a consensus read.

[247] In some embodiments, amyloid plaque load can be identified by a standard uptake value ratio (SUVr) as compared to a reference region. Methods for calculating PET SUVr are known in the art and may include those described herein. In some embodiments, a Standard Uptake Value Ratio Quantitative analysis of amyloid levels is completed using PMOD

Biomedical Image Quantification Software (PMOD Technologies, Zurich, Switzerland). In some embodiments, PET images are first assessed for subject movement in the X, Y, and Z planes and corrected for motion, if needed, before individual images (e.g., 5-minute emission frames) are averaged, e.g., using a PMOD Averaging Function (PET frames averaged to increase the signal to noise ratio). In some embodiments, corresponding MRIs from subjects are prepared (e.g., using matrix size reduction processing, cropping of the MRI to include only the brain, segmentation to separate images into binary maps of gray matter, white matter, and CSF, and stripping the image of skull leaving only brain mask). In some embodiments, the averaged PET images and prepared MRIs are matched using the PMOD Matching Function, placing the images in the same orientation. In some embodiments, a Brain Normalization function, e.g., as provided by PMOD software, is used along with Brain Norm and Rigid Matching transformation matrices, to produce an averaged PET. In some embodiments, this averaged PET which is normalized to the MNI space (Senjem et al, 2005) that is in the same orientation as the subject's segmented MRI for quantitative analysis. In some embodiments, the PMOD Mask Function is used to mask the brain and zero the image outside of the mask to create a Normalized Gray Matter PET and a Normalized White Matter PET. Standard uptake values (SUVs) may be calculated for all gray matter mapped regions and the 3 white matter regions (pons, cerebellar white, and subcortical white) using PMOD software calculated using the normalized PET, subject weight, and injected dose of tracer to arrive at the units of SUVs. In some embodiments, the SUV_r is the ratio of the global cortical average as compared to a reference region of choice. In some embodiments, a whole cerebellum mask is used as the reference region. In some embodiments, the reference region is subcortical white matter, derived whole cerebellum, whole cerebellum adjusted by subcortical white matter, cerebellar gray matter, and composite reference regions consisting of cerebellar cortex, pons subcortical white matter, and cerebella white matter.

[248] In some embodiments, after administration of the first dose of the composition the adjusted mean change from baseline in a subject's PET SUV_r value is reduced by at least -0.10, at least -0.15, at least -0.20, at least -0.25, at least -0.30, at least -0.35, at least -0.40, at least -0.45, at least -0.50, at least -0.55, at least -0.60, at least -0.65, at least -0.70, at least -0.75, at least -0.80, at least -0.85, at least -0.90, or at least -0.95 relative to baseline. In some embodiments, the adjusted mean change from baseline in a subject's PET SUV_r value is reduced by -0.20 to -0.30.

[249] In some embodiments, the amyloid beta plaque levels in the brain are evaluated using PET imaging. In some embodiments, the PET imaging uses a florbetapir tracer. In some embodiments, the PET imaging used a flutemetamol tracer. In some further embodiments, different tracers may yield different results. In some embodiments, the adjusted mean reduction threshold is dependent upon the tracer used. In some embodiments, comparing global cortical average versus whole cerebellum reference, the adjusted mean change from baseline in a subject's PET SUV_r value is reduced by at least -0.20, such as at least -0.25, after 12 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the adjusted mean change from baseline in a subject's PET SUV_r value is reduced by at least -0.25, such as at least -0.30, after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[250] In some embodiments, the reduction of amyloid in the brain is determined by imaging using binding of radiotracers for brain A β amyloid and visualized with PET. In some embodiments, the reduction in the adjusted mean change from baseline is at least -50, such as at least -55 or at least -59 centiloid after 12 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the reduction in the adjusted mean change from baseline is

at least -60, such as at least -65 or at least -70 centiloid after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[251] In some embodiments, said method results in an increased cerebrospinal fluid A β 1-42 level relative to the cerebrospinal fluid A β 1-42 level prior to said administration. In some embodiments, said method results in an increase of cerebrospinal fluid A β 1-42 level of at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% relative to the cerebrospinal fluid A β 1-42 level prior to said administration.

[252] In some embodiments, administration of the composition results in a brain amyloid level reduction of -0.20 to -0.45, such as from -0.25 to -0.35 as determined by visual reads of amyloid PET images, wherein the subject is ApoE4-positive. In some embodiments, administration of the composition results in a brain amyloid level reduction of at least -0.25, as determined by visual reads of amyloid PET images, wherein the subject is ApoE4-positive. In some embodiments, administration of the composition results in a brain amyloid level reduction of at least 0.30, as determined by visual reads of amyloid PET images, wherein the subject is ApoE4-positive.

[253] In some embodiments, a subject's brain amyloid level is determined by visual reads of amyloid PET images and expressed as a PET standard uptake value ratio (SUVR value). In some embodiments, administration of the composition results in a brain amyloid level reduction, as measured by a PET SUVR value, of at least -0.01, at least -0.02, at least -0.03, at least -0.04, at least -0.05, at least -0.06, at least -0.07, at least -0.08, at least -0.09, at least -0.10, at least -0.11, at least -0.12, at least -0.13, at least -0.14, at least -0.15, at least -0.16, at least -0.17, at least -0.18, at least -0.19, at least -0.20, at least -0.21, at least -0.22, at least -0.23, at least -0.24, at least -0.25, at least -0.26, at least -0.27, at least -0.28, or at least -0.29 relative to placebo, wherein the subject is ApoE4-negative.

[254] In some embodiments, administration of the composition results in a brain amyloid level reduction of -0.10 to -0.40, as measured by a PET SUVR value, wherein the subject is ApoE4-negative. In some embodiments, administration of the composition results in a brain amyloid level reduction of at least -0.20, as measured by a PET SUVR value, wherein the subject is ApoE4-negative. In some embodiments, administration of the composition results in a brain amyloid level reduction of at least -0.25, as measured by a PET SUVR value, wherein the subject is ApoE4-negative.

[255] In some embodiments, a subject's brain amyloid level is determined by visual reads of amyloid PET images and expressed as a PET standard uptake value ratio (SUVR value). In some embodiments, administration of the composition results in a brain amyloid level reduction of -0.10 to -0.40, as measured by a PET SUVR value, wherein the subject is ApoE4-negative. In some further embodiments, the subject has an increase in the A β 42/40

ratio after administration of the first dose of the composition comprising the anti-A β protofibril antibody, e.g., an increase to a ratio of about 0.05-0.1, e.g., about 0.08-0.1, e.g., about 0.092, indicating a change from amyloid positive to amyloid negative in the brain of the subject. In some further embodiments, the subject has an increase in the A β 42/40 ratio after administration of the first dose of the composition comprising the anti-A β protofibril antibody, e.g., an increase to a ratio above 0.092, indicating a change from amyloid positive to amyloid negative in the brain of the subject. In some embodiments, the subject has an increase in the A β 42/40 ratio after 6 months or after 12 months or after 18 months or after 24 months of administration of the first dose of the composition comprising the anti-A β protofibril antibody, e.g., an increase to a ratio of about 0.05-0.1, e.g., about 0.08-0.1, e.g., about 0.092, indicating a change from amyloid positive to amyloid negative in the brain of the subject. In some embodiments, the subject has an increase in the A β 42/40 ratio after 6 months or after 12 months or after 18 months or after 24 months of administration of the first dose of the composition comprising the anti-A β protofibril antibody, e.g., an increase to a ratio above 0.092, indicating a change from amyloid positive to amyloid negative in the brain of the subject. In some embodiments, an increase in the A β 42/40 ratio indicates a reduction in brain amyloid level, as determined by visual reads of amyloid PET images. In some embodiments, a subject with a reduction in brain amyloid level is given a reduced dose or frequency of the anti-A β protofibril antibody, alone or in combination with at least one additional therapy, e.g., a BACE inhibitor and/or anti-tau antibody.

Additional biomarker changes

Cerebrospinal Fluid Level of Neurogranin

[256] In some embodiments, administration of a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein to a subject results in a reduction in cerebrospinal fluid level of neurogranin in the subject. In some embodiments, the administration to a subject of a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein results in a reduction of at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, or at least 10%, relative to baseline, in cerebrospinal fluid level of neurogranin.

[257] In some embodiments, administration to a subject of a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein results in a reduction in cerebrospinal fluid level of neurogranin after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, administration to a subject of a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein results in a reduction of at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, or at least 10%, relative to baseline, cerebrospinal fluid level of neurogranin after 18 months of administration of the composition.

[258] In some embodiments, administration to a subject of a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein results in a reduction of at least about 25 pg/mL, at least about 30 pg/mL, at least about 35 pg/mL, at least about 40 pg/mL, at least about 45 pg/mL, at least about 50 pg/mL, at least about 55 pg/mL, at least about 60 pg/mL, or at least about 65 pg/mL, relative to baseline, cerebrospinal fluid level of neurogranin. In some embodiments, administration to a subject of a composition comprising a therapeutically effective amount of at least one anti-A β

protofibril antibody disclosed herein results in a reduction of at least about 65 pg/mL, relative to baseline, cerebrospinal fluid level of neurogranin.

[259] In some embodiments, administration to a subject of a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein results in a reduction of at least about 25 pg/mL, at least about 30 pg/mL, at least about 35 pg/mL, at least about 40 pg/mL, at least about 45 pg/mL, at least about 50 pg/mL, at least about 55 pg/mL, at least about 60 pg/mL, or at least about 65 pg/mL, relative to baseline, of cerebrospinal fluid level of neurogranin after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, administering to a subject a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein results in a reduction of at least 65 pg/mL, relative to baseline, of cerebrospinal fluid level of neurogranin after 18 months of administration of the composition.

[260] In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[261] In some embodiments, the therapeutically effective amount of at least one anti-A β protofibril antibody is 10 mg/kg. In some embodiments, the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein is administered bi-weekly or monthly. In some embodiments, a composition comprising 10 mg/kg of BAN2401 is administered bi-weekly. In some embodiments, a composition comprising 10 mg/kg of BAN2401 is administered monthly.

[262] Cerebrospinal Fluid Level of Neurofilament Light Chain

[263] In some embodiments, administration to a subject of a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein results in a reduction, relative to placebo, in cerebrospinal fluid level of neurofilament light chain. In some embodiments, administration to a subject of a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein results in a reduction of at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, or at least 50%, relative to placebo, in cerebrospinal fluid level of neurofilament light chain.

[264] In some embodiments, administration to a subject of a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein results in a reduction, relative to placebo, in cerebrospinal fluid level of neurofilament light chain after 18 months of administration of the composition. In some embodiments, administration to a subject of a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein results in a reduction, relative to placebo, of at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, or at least 50%, relative to baseline, in cerebrospinal fluid level of neurofilament light chain after 18 months of administration of the composition.

[265] In some embodiments, administration to a subject of a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein results in production of more than about 35 pg/mL, about 40 pg/mL, about 45 pg/mL, about 50 pg/mL, about 55 pg/mL, about 60 pg/mL, about 65 pg/mL, about 70 pg/mL, about 75 pg/mL, relative to baseline, of cerebrospinal fluid level of neurofilament light chain. In some embodiments, administration to a subject of a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein results in production of no more than about 75 pg/mL, relative to baseline, of cerebrospinal fluid level of neurofilament light chain.

[266] In some embodiments, administration to a subject of a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein results in production of more than about 35 pg/mL, about 40 pg/mL, about 45 pg/mL, about

50 pg/mL, about 55 pg/mL, about 60 pg/mL, about 65 pg/mL, about 70 pg/mL, about 75 pg/mL, relative to baseline, of cerebrospinal fluid level of neurofilament light chain after 18 months of administration of the composition. In some embodiments, administration to a subject of a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein results in production of no more than about 75 pg/mL, relative to baseline, of cerebrospinal fluid level of neurofilament light chain after 18 months of administration of the composition.

[267] In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[268] In some embodiments, the therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein is 10 mg/kg. In some embodiments, a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein is administered bi-weekly or monthly. In some embodiments, a composition comprising 10 mg/kg of BAN2401 is administered bi-weekly. In some embodiments, a composition comprising 10 mg/kg of BAN2401 is administered monthly.

[269] Cerebrospinal Fluid Level of Phospho-Tau

[270] In some embodiments, administration to a subject of a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein results in a reduction in cerebrospinal fluid level of phospho-Tau (p-tau). In some embodiments, administration to a subject of a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein results in a reduction of at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, or at least 13% relative to baseline, of cerebrospinal fluid level of phospho-Tau.

[271] In some embodiments, administration to a subject of a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein results in a reduction in cerebrospinal fluid level of phospho-Tau after 18 months of administration of the composition. In some embodiments, administration to a subject of a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein results in a reduction of at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, or at least 13%, relative to baseline, of cerebrospinal fluid level of phospho-Tau after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[272] In some embodiments, administration to a subject of a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein results in a reduction of at least about 65 pg/mL, at least about 70 pg/mL, at least about 75 pg/mL, at least about 80 pg/mL, at least about 85 pg/mL, at least about 90 pg/mL, or at least about 95 pg/mL, relative to baseline, of cerebrospinal fluid level of phospho-Tau. In some embodiments, administration to a subject of a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein results in a reduction of at least about 95 pg/mL, relative to baseline, of cerebrospinal fluid level of phospho-Tau.

[273] In some embodiments, administration to a subject of a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein results in a reduction of at least about 65 pg/mL, at least about 70 pg/mL, at least about 75 pg/mL, at least about 80 pg/mL, at least about 85 pg/mL, at least about 90 pg/mL, or at least about 95 pg/mL, relative to baseline, of cerebrospinal fluid level of phospho-Tau after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, administration to a subject of a composition comprising a therapeutically effective amount of at least one anti-A β

protofibril antibody disclosed herein results in a reduction of at least 95 pg/mL, relative to baseline, of cerebrospinal fluid level of phospho-Tau after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[274] In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[275] In some embodiments, the therapeutically effective amount of at least one anti-A β protofibril antibody is 10 mg/kg. In some embodiments, the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein is administered bi-weekly or monthly. In some embodiments, a composition comprising 10 mg/kg of BAN2401 is administered bi-weekly. In some embodiments, a composition comprising 10 mg/kg of BAN2401 is administered monthly.

[276] Brain Volume

[277] In some embodiments, administration to a subject of a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein results in an improvement, relative to placebo, of total hippocampal atrophy as measured by volumetric MRI (vMRI). In some embodiments, a subject's brain volume (e.g., total ventricular volume, total, right and/or left hippocampal volumes) is measured before treatment. In some embodiments, a subject's brain volume (e.g., total ventricular volume, total, right and/or left hippocampal volumes) is measured at 6 and 12 months after treatment. In some embodiments, administration to a subject of a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein results in an improvement, relative to placebo, of brain volume atrophy as measured by vMRI.

Treating a subject having early Alzheimer's disease resulting in reduction of severity of symptom relative to severity prior to treatment

[278] In various embodiments, also provided herein is a method of treating a subject having early Alzheimer's disease. In some embodiments, the method comprises administering to said subject a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody disclosed herein. In some embodiments, the subject having early Alzheimer's disease has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood and/or has been diagnosed as having mild Alzheimer's disease dementia. In some embodiments, the subject having early Alzheimer's disease is ApoE4-positive. In some embodiments, the method comprises measuring the level of p-tau181 in a subject before administering a first dose of a composition comprising the anti-A β protofibril antibody, and measuring again after administering the antibody, e.g., after 6-12 months of treatment. In some embodiments, a reduction in the p-tau181 level indicates a reduction in the severity of at least one symptom associated with Alzheimer's disease, wherein the severity of at least one symptom associated with Alzheimer's disease is reduced by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95% relative to the severity of the same symptom in the same subject prior to treatment. In some embodiments, the severity of the at least one symptom associated with Alzheimer's disease is determined by ADCOMS, PET, MMSE, CDR-SB, and/or ADAS-Cog. In some embodiments, the at least one symptom associated with Alzheimer's disease is chosen from clinical decline and brain amyloid level.

[279] In some embodiments, the severity of at least one symptom associated with Alzheimer's disease is reduced by at least 1%. In some embodiments, the severity of at least one symptom associated with Alzheimer's disease is reduced by at least 10%. In some embodiments, the severity of at least one symptom associated with Alzheimer's disease is

reduced by at least 20%. In some embodiments, the severity of at least one symptom associated with Alzheimer's disease is reduced by at least 30%. In some embodiments, the severity of at least one symptom associated with Alzheimer's disease is reduced by at least 40%. In some embodiments, the severity of at least one symptom associated with Alzheimer's disease is reduced by at least 50%. In some embodiments, the severity of at least one symptom associated with Alzheimer's disease is reduced by at least 60%. In some embodiments, the severity of at least one symptom associated with Alzheimer's disease is reduced by at least 70%. In some embodiments, the severity of at least one symptom associated with Alzheimer's disease is reduced by at least 80%. In some embodiments, the severity of at least one symptom associated with Alzheimer's disease is reduced by at least 90%. In some embodiments, the severity of at least one symptom associated with Alzheimer's disease is reduced by at least 95%.

[280] In some embodiments, the above-recited reduction in severity is determined after 1 month, 6 months, 12 months, 18 months, 60 months, and/or 63 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[281] In some embodiments, a subject with a reduction in brain amyloid as determined by a decreased p-tau181 level exhibits a reduction in the severity of at least one symptom associated with Alzheimer's disease. In some embodiments, a subject with a decreased p-tau181 level is given a reduced dose or frequency of the anti-A β protofibril antibody, alone or in combination with at least one additional therapy, e.g., a BACE inhibitor and/or anti-tau antibody.

[282] Prevention and/or delay of onset of Alzheimer's disease

[283] In various embodiments, also provided herein is a method of preventing and/or delaying onset of Alzheimer's disease, e.g., in ApoE4-positive subjects. In some embodiments, said method comprises determining the brain amyloid level of a subject and then, if the brain amyloid level of the subject is above a first predetermined level, administering a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[284] In some embodiments, the subject is pre-symptomatic (cognitively unimpaired or cognitively normal) and is selected for treatment (e.g., treatment comprising at least one anti-A β protofibril antibody such as BAN2401) based on an increased p-tau181 level in a blood (e.g., plasma) sample relative to the ratio in a blood sample from a healthy subject or an average ratio from a population of such healthy subjects. In some embodiments, the pre-symptomatic subject is ApoE4-positive. In some embodiments, treatment prevents or delays the onset of AD symptoms. In some embodiments, the subject is aged 55-80.

[285] In some embodiments, the method further comprises measuring the post-administration brain amyloid level of the subject. In some embodiments, treatment decreases the p-tau181 level in a blood sample relative to the level in a sample from the subject prior to treatment comprising the anti-A β protofibril antibody. In some embodiments, treatment is continued if a decrease in the p-tau181 level relative to the level in a sample from the subject prior to treatment comprising the anti-A β protofibril antibody is observed.

[286] In various embodiments, one or more additional biomarker is measured to identify and/or select a pre-symptomatic subject for treatment and/or to monitor treatment efficacy.

[287] In some embodiments, brain amyloid levels are measured by PET in a subject in conjunction with measuring the p-tau181 level in a blood sample from the subject. In some embodiments, brain amyloid levels are not measured by PET (e.g., to reduce cost or increase speed of screening). In some embodiments, the p-tau181 level in a blood sample from a subject is measured with or without the brain amyloid measurement by PET prior to the treatment for screening or selecting a subject to be treated with lecanemab. In some

embodiments, the method further comprises determining a cerebrospinal fluid level of A β 1-42 and/or cerebrospinal fluid total tau level. In some embodiments, a total tau level in blood is measured. In some embodiments, a p-tau level in blood is measured, e.g., p-217 tau.

[288] In some embodiments, the method further comprises determining a cerebrospinal fluid level of neurogranin.

[289] In some embodiments, the method further comprises determining a cerebrospinal fluid level of neurofilament light chain.

[290] In some embodiments, said method further comprises administering the composition if the post-administration brain amyloid level is above a second predetermined level.

[291] In some embodiments, said method further comprises monitoring the brain amyloid level of the subject after administration until the brain amyloid level of the subject is below a first predetermined level.

[292] In some embodiments, said method further comprises administering the composition if the post-administration cerebrospinal fluid level of A β 1-42 and/or cerebrospinal fluid total tau level is above a predetermined level.

[293] In some embodiments, said method further comprises administering the composition if the post-administration cerebrospinal fluid level of neurogranin is above a predetermined level.

[294] In some embodiments, said method further comprises administering the composition if the post-administration neurofilament light chain is above a predetermined level.

[295] In some embodiments, said method further comprises administering at least one additional therapeutic agent. In some embodiments, the at least one additional therapeutic agent is chosen from BACE inhibitors, gamma secretase inhibitors, gamma secretase modulators, A β peptide generation inhibitors other than said at least one anti-A β protofibril antibody, agents that lower A β peptide levels other than said at least one anti-A β protofibril antibody, and a combination thereof. In some embodiments, the at least one additional therapeutic agent is a BACE inhibitor. In some embodiments, the BACE inhibitor is chosen from CNP520, BI-1181181, LY2886721, LY3202626, PF-06751979, RG7129, atabecestat, elenbecestat, lanabecestat, and verubecestat. In some embodiments, the BACE inhibitor is elenbecestat.

[296] Any of the anti-A β protofibril antibodies, therapeutically acceptable amounts thereof, dosing regimens therefor, and compositions comprising the same that are disclosed herein may be used in the method of reducing brain amyloid level in a subject having early Alzheimer's disease. For example, in some embodiments, a composition comprising 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, or 10 mg/kg of at least one anti-A β protofibril antibody such as BAN2401 relative to body weight of the subject is administered to the subject once every week, once every two weeks, once every three weeks, once every four weeks, once every month ("mo"), once every five weeks, once every six weeks, once every seven weeks, once every eight weeks, once every two months, once every nine weeks, once every ten weeks, once every eleven weeks, once every twelve weeks, once every three months (quarterly), once every fourteen weeks, once every sixteen weeks, once every four months, once every eighteen weeks, once every twenty weeks, once every five months, once every 22 weeks, once every 24 weeks, once every six months semi-annually, once every seven months, once every eight months, once every nine months, once every ten months, once every eleven months, once every twelve months (annually), once every thirteen months, once every fourteen months, once every fifteen months, once every sixteen months, once every seventeen months, or once every eighteen months.

[297] In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[298] In some embodiments, administration of the composition comprising at least one anti-A β protofibril antibody results in at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% of the subjects being amyloid negative, as determined by visual reads of amyloid PET images.

[299] In some embodiments, administration of the composition comprising at least one anti-A β protofibril antibody results in 75% to 100%, such as 80% to 100% or 85% to 100% of the subjects being amyloid negative, as determined by visual reads of amyloid PET images. In some embodiments, administration of the composition comprising at least one anti-A β protofibril antibody results in at least 75%, such as at least 80% or at least 85%, of the subjects being amyloid negative, as determined by visual reads of amyloid PET images. In some embodiments, administration of the composition comprising at least one anti-A β protofibril antibody results in 100% of the subjects being amyloid negative, as determined by visual reads of amyloid PET images.

[300] In some embodiments, at least 75%, such as at least 80% or at least 85%, of the subjects are amyloid negative, as determined by visual reads of amyloid PET images, after 12 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, at least 75%, such as at least 80%, at least 85%, at least 90%, or at least 95%, of the subjects are amyloid negative, as determined by visual reads of amyloid PET images, after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the composition comprises 10 mg/kg of at least one anti-A β protofibril antibody and is administered once every two weeks or once every month. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[301] In some embodiments, the method results in a reduced brain amyloid level after administration relative to the brain amyloid level prior to the administration. In some embodiments, the brain amyloid level is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least

81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% relative to the brain amyloid level prior to said administration. In some embodiments, the above-recited reductions in brain amyloid levels are determined by visual reads of amyloid PET images and are expressed as PET standard uptake value ratios (SUVr values).

[302] In some embodiments, the adjusted mean change in a subject's PET SUVr value is reduced by at least -0.10, at least -0.15, at least -0.20, at least -0.25, at least -0.30, at least -0.35, at least -0.40, at least -0.45, at least -0.50, at least -0.55, at least -0.60, at least -0.65, at least -0.70, at least -0.75, at least -0.80, at least -0.85, at least -0.90, or at least -0.95 relative to the brain amyloid level prior to administration of the composition comprising at least one anti-A β protofibril antibody. In some embodiments, the adjusted mean change in a subject's PET SUVr value from the brain amyloid level prior to the administration of the composition comprising at least one anti-A β protofibril antibody is reduced by -0.20 to -0.30.

[303] In some embodiments, comparing global cortical average versus whole cerebellum reference, the adjusted mean change from the brain amyloid level prior to the administration of the composition comprising at least one anti-A β protofibril antibody in a subject's PET SUVr value is reduced by at least -0.20, such as at least -0.25, after 12 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the adjusted mean change in a subject's PET SUVr value is reduced by at least -0.25, such as at least -0.30, relative to the subject's PET SUVr value prior to the administration, after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[304] In some embodiments, the reduction of amyloid in the brain is determined by imaging using binding of radiotracers for brain A β amyloid and visualized with PET. In some embodiments, the reduction in the adjusted mean change from the subject's level prior to the administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody is at least -50, such as at least -55 or at least -59 centiloid after 12 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody. In some embodiments, the reduction in the adjusted mean change from the subject's level prior to the administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody is at least -60, such as at least -65 or at least -70 centiloid after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody.

[305] In some embodiments, the method results in an increased cerebrospinal fluid A β 1-42 level relative to the cerebrospinal fluid A β 1-42 level prior to the administration. In some embodiments, the method results in an increase of cerebrospinal fluid A β 1-42 level of at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at

least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% relative to the cerebrospinal fluid A β 1-42 level prior to the administration.

[306] In some embodiments, administration of the composition comprising at least one anti-A β protofibril antibody results in a brain amyloid level reduction of -0.20 to -0.45, such as from -0.25 to -0.35 as determined by visual reads of amyloid PET images, relative to the brain amyloid level prior to administration of the composition comprising at least one anti-A β protofibril antibody. In some embodiments, administration of the composition comprising at least one anti-A β protofibril antibody results in a brain amyloid level reduction of at least -0.25, as determined by visual reads of amyloid PET images, relative to the brain amyloid level prior to administration of the composition comprising at least one anti-A β protofibril antibody. In some embodiments, administration of the composition comprising at least one anti-A β protofibril antibody results in a brain amyloid level reduction of at least 0.30, as determined by visual reads of amyloid PET images, relative to the brain amyloid level prior to administration of the composition comprising at least one anti-A β protofibril antibody.

[307] Also provided herein is another method of preventing and/or delaying onset Alzheimer's disease in ApoE4-positive subjects. In some embodiments, said method comprises determining the brain amyloid level of a subject and then, if the brain amyloid level of the subject is above a first predetermined level, administering a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody and a composition comprising a therapeutically effective amount of at least one therapeutic agent chosen from BACE inhibitors, gamma secretase inhibitors, gamma secretase modulators, A β peptide generation inhibitors other than said at least one anti-A β protofibril antibody, and agents that lower the levels of A β peptide other than said at least one anti-A β protofibril antibody.

[308] In some embodiments, the method further comprises measuring the post-administration brain amyloid level of the subject.

[309] In some embodiments, the method further comprises determining a cerebrospinal fluid level of A β 1-42 and/or cerebrospinal fluid total tau level.

[310] In some embodiments, the method further comprises determining a cerebrospinal fluid level of neurogranin.

[311] In some embodiments, the method further comprises determining a cerebrospinal fluid level of neurofilament light chain.

[312] In some embodiments, said method further comprises administering a composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody and a composition comprising a therapeutically effective amount of at least one therapeutic agent chosen from BACE inhibitors, gamma secretase inhibitors, gamma secretase modulators, A β peptide generation inhibitors other than said at least one anti-A β protofibril antibody, and agents that lower the levels of A β peptide other than said at least one anti-A β protofibril antibody if the post-administration brain amyloid level is above a second predetermined level.

[313] In some embodiments, said method further comprises administering the composition if the post-administration cerebrospinal fluid level of A β 1-42 and/or cerebrospinal fluid total tau level is above a predetermined level.

[314] In some embodiments, said method further comprises administering the composition if the post-administration cerebrospinal fluid level of neurogranin is above a predetermined level.

[315] In some embodiments, said method further comprises administering the composition if the post-administration cerebrospinal fluid level of neurofilament light chain is above a predetermined level.

[316] In some embodiments, said method further comprises monitoring the brain amyloid level of the subject after administration until the brain amyloid level of the subject is below a first predetermined level.

[317] In some embodiments, said method further comprises administering at least one additional therapeutic agent. In some embodiments, the at least one additional therapeutic agent is chosen from BACE inhibitors, gamma secretase inhibitors, gamma secretase modulators, A β peptide generation inhibitors other than said at least one anti-A β protofibril antibody, agents that lower A β peptide levels other than said at least one anti-A β protofibril antibody, and a combination thereof.

[318] In some embodiments, the at least one additional therapeutic agent is a BACE inhibitor. In some embodiments, the BACE inhibitor is elenbecestat.

[319] Any of the anti-A β protofibril antibodies, therapeutically acceptable amounts thereof, dosing regimens therefor, and compositions comprising the same that are disclosed herein may be used in the method of reducing brain amyloid level in a subject having early Alzheimer's disease. For example, in some embodiments, a composition comprising 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, or 10 mg/kg of at least one anti-A β protofibril antibody such as BAN2401 relative to body weight of the subject is administered to the subject once every week, once every two weeks, once every three weeks, once every four weeks, once every month ("mo"), once every five weeks, once every six weeks, once every seven weeks, once every eight weeks, once every two months, once every nine weeks, once every ten weeks, once every eleven weeks, once every twelve weeks, once every three months (quarterly), once every fourteen weeks, once every sixteen weeks, once every four months, once every eighteen weeks, once every twenty weeks, once every five months, once every 22 weeks, once every 24 weeks, once every six months (semi-annually), once every seven months, once every eight months, once every nine months, once every ten months, once every eleven months, once every twelve months (annually), once every thirteen months, once every fourteen months, once every fifteen months, once every sixteen months, once every seventeen months, or once every eighteen months.

[320] In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[321] In some embodiments, the at least one therapeutic agent is a BACE inhibitor. In some embodiments, the BACE inhibitor is elenbecestat.

[322] In some embodiments, administration of the composition comprising at least one anti-A β protofibril antibody and the composition comprising a therapeutically effective amount of at least one therapeutic agent results in at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%,

at least 96%, at least 97%, at least 98%, at least 99%, or 100% of the subjects being amyloid negative, as determined by visual reads of amyloid PET images.

[323] In some embodiments, administration of the composition comprising at least one anti-A β protofibril antibody and the composition comprising a therapeutically effective amount of at least one therapeutic agent results in 75% to 100%, such as 80% to 100% or 85% to 100% of the subjects being amyloid negative, as determined by visual reads of amyloid PET images. In some embodiments, administration of the composition comprising at least one anti-A β protofibril antibody and the composition comprising a therapeutically effective amount of at least one therapeutic agent results in at least 75%, such as at least 80% or at least 85%, of the subjects being amyloid negative, as determined by visual reads of amyloid PET images. In some embodiments, administration of the composition comprising at least one anti-A β protofibril antibody and the composition comprising a therapeutically effective amount of at least one therapeutic agent results in 100% of the subjects being amyloid negative, as determined by visual reads of amyloid PET images.

[324] In some embodiments, at least 75%, such as at least 80% or at least 85%, of the subjects are amyloid negative, as determined by visual reads of amyloid PET images, after 12 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody and the composition comprising a therapeutically effective amount of at least one therapeutic agent. In some embodiments, at least 75%, such as at least 80%, at least 85%, at least 90%, or at least 95%, of the subjects are amyloid negative, as determined by visual reads of amyloid PET images, after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody and the composition comprising a therapeutically effective amount of at least one therapeutic agent. In some embodiments, the composition comprises 10 mg/kg of at least one anti-A β protofibril antibody and is administered once every two weeks or once every month. In some embodiments, the at least one anti-A β protofibril antibody is BAN2401.

[325] In some embodiments, the method results in a reduced brain amyloid level after administration relative to the brain amyloid level prior to the administration. In some embodiments, the brain amyloid level is reduced by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% relative to the brain amyloid level prior to said administration. In some embodiments, the above-recited reductions in brain amyloid levels are determined by visual reads of amyloid PET images and are expressed as PET standard uptake value ratios (SUVr values).

[326] In some embodiments, the adjusted mean change in a subject's PET SUVr value is reduced by at least -0.10, at least -0.15, at least -0.20, at least -0.25, at least -0.30, at least -0.35, at least -0.40, at least -0.45, at least -0.50, at least -0.55, at least -0.60, at least -0.65, at

least -0.70, at least -0.75, at least -0.80, at least -0.85, at least -0.90, or at least -0.95 relative to the brain amyloid level prior to administration of the composition comprising at least one anti-A β protofibril antibody and the composition comprising a therapeutically effective amount of at least one therapeutic agent. In some embodiments, the adjusted mean change in a subject's PET SUVR value from the brain amyloid level prior to the administration of the composition comprising at least one anti-A β protofibril antibody and the composition comprising a therapeutically effective amount of at least one therapeutic agent is reduced by -0.20 to -0.30.

[327] In some embodiments, comparing global cortical average versus whole cerebellum reference, the adjusted mean change from the brain amyloid level prior to the administration of the composition comprising at least one anti-A β protofibril antibody and the composition comprising a therapeutically effective amount of at least one therapeutic agent in a subject's PET SUVR value is reduced by at least -0.20, such as at least -0.25, after 12 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody and the composition comprising a therapeutically effective amount of at least one therapeutic agent. In some embodiments, the adjusted mean change in a subject's PET SUVR value is reduced by at least -0.25, such as at least -0.30, relative to the subject's PET SUVR value prior to the administration, after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody and the composition comprising a therapeutically effective amount of at least one therapeutic agent.

[328] In some embodiments, the reduction of amyloid in the brain is determined by imaging using binding of radiotracers for brain A β amyloid and visualized with PET. In some embodiments, the reduction in the adjusted mean change from the subject's level prior to the administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody and the composition comprising a therapeutically effective amount of at least one therapeutic agent is at least -50, such as at least -55 or at least -59 centiloid after 12 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody and the composition comprising a therapeutically effective amount of at least one therapeutic agent. In some embodiments, the reduction in the adjusted mean change from the subject's level prior to the administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody is at least -60, such as at least -65 or at least -70 centiloid after 18 months of administration of the composition comprising a therapeutically effective amount of at least one anti-A β protofibril antibody and the composition comprising a therapeutically effective amount of at least one therapeutic agent.

[329] In some embodiments, the method results in an increased cerebrospinal fluid A β 1-42 level relative to the cerebrospinal fluid A β 1-42 level prior to the administration. In some embodiments, the method results in an increase of cerebrospinal fluid A β 1-42 level of at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 11%, at least 12%, at least 13%, at least 14%, at least 15%, at least 16%, at least 17%, at least 18%, at least 19%, at least 20%, at least 21%, at least 22%, at least 23%, at least 24%, at least 25%, at least 26%, at least 27%, at least 28%, at least 29%, at least 30%, at least 31%, at least 32%, at least 33%, at least 34%, at least 35%, at least 36%, at least 37%, at least 38%, at least 39%, at least 40%, at least 41%, at least 42%, at least 43%, at least 44%, at least 45%, at least 46%, at least 47%, at least 48%, at least 49%, at least 50%, at least 51%, at least 52%, at least 53%, at least 54%, at least 55%, at least 56%, at least 57%, at least 58%, at least 59%, at least 60%, at least 61%, at least 62%, at least 63%, at least 64%, at least 65%, at least 66%, at least 67%, at least 68%, at least 69%, at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at

least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% relative to the cerebrospinal fluid A β 1-42 level prior to the administration.

[330] In some embodiments, administration of the composition comprising at least one anti-A β protofibril antibody and the composition comprising a therapeutically effective amount of at least one therapeutic agent results in a brain amyloid level reduction of -0.20 to -0.45, such as from -0.25 to -0.35 as determined by visual reads of amyloid PET images, relative to the brain amyloid level prior to administration of the composition comprising at least one anti-A β protofibril antibody and the composition comprising a therapeutically effective amount of at least one therapeutic agent. In some embodiments, administration of the composition comprising at least one anti-A β protofibril antibody and the composition comprising a therapeutically effective amount of at least one therapeutic agent results in a brain amyloid level reduction of at least -0.25, as determined by visual reads of amyloid PET images, relative to the brain amyloid level prior to administration of the composition comprising at least one anti-A β protofibril antibody. In some embodiments, administration of the composition comprising at least one anti-A β protofibril antibody and the composition comprising a therapeutically effective amount of at least one therapeutic agent results in a brain amyloid level reduction of at least 0.30, as determined by visual reads of amyloid PET images, relative to the brain amyloid level prior to administration of the composition comprising at least one anti-A β protofibril antibody and the composition comprising a therapeutically effective amount of at least one therapeutic agent.

EXEMPLARY EMBODIMENTS

1. A method of treating Alzheimer's disease (AD) in a subject having or suspected of having AD, comprising

measuring or having measured a first level of phosphorylated tau181 (p-tau181) in a first blood sample obtained from the subject;

administering to the subject a first dose of an anti-amyloid β (A β) protofibril antibody;

measuring or having measured a second level of p-tau181 in a second blood sample obtained from the subject after the administration of the first dose of the anti-A β protofibril antibody;

if the second level is the same as or higher than the first level, (i) administering a second dose of the anti-A β protofibril antibody to the subject that is higher than the first dose of the anti-A β protofibril antibody, or (ii) administering a different treatment for AD to the subject, and

if the second level is lower than the first level, administering a second dose of the anti-A β protofibril antibody to the subject that is the same as or lower than the first dose of the anti-A β protofibril antibody.

2. A method of treating AD in a subject having or suspected of having AD, comprising

measuring or having measured a first level of p-tau181 in a first blood sample obtained from the subject;

administering to the subject a first dose of an anti-A β protofibril antibody;

measuring or having measured a second level of p-tau181 in a second blood sample obtained from the subject after the administration of the first dose of the anti-A β protofibril antibody;

if the second level is lower than the first level, administering a second dose of the anti-A β protofibril antibody to the subject that is the same as or lower than the first dose of the anti-A β protofibril antibody.

3. A method of treating AD in a subject having or suspected of having AD, comprising

measuring or having measured a first level of p-tau181 in a first blood sample obtained from the subject;

administering to the subject a first dose of an anti-A β protofibril antibody;

measuring or having measured a second level of p-tau181 in a second blood sample obtained from the subject after the administration of the first dose of the anti-A β protofibril antibody;

if the second level is the same as or higher than the first level, (i) administering a second dose of the anti-A β protofibril antibody that is higher than the first dose of the anti-A β protofibril antibody, or (ii) administering a different treatment for AD to the subject.

4. The method of embodiment 1 or embodiment 3, wherein if the second level is the same as or higher than the first level, a second dose of the anti-A β protofibril antibody is administered to the subject that is higher than the first dose of the anti-A β protofibril antibody.

5. The method of embodiment 1 or 3, wherein if the second level is the same as or higher than the first level, a different treatment for AD is administered to the subject.

6. The method of any one of the embodiments 1-5, wherein the subject has AD.

7. The method of any one of the embodiments 1-5, wherein the subject has been diagnosed with early AD.

8. The method of any one of the embodiments 1-5, wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood and/or has been diagnosed as having mild Alzheimer's disease dementia.

9. The method of embodiment 8, wherein the subject has been diagnosed with mild cognitive impairment due to Alzheimer's disease - intermediate likelihood by National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria.

10. The method of embodiment 9, wherein the subject has been diagnosed with mild cognitive impairment due to Alzheimer's disease - intermediate likelihood by a CDR global score of 0.5 and a Memory Box score of 0.5 or greater before the method of treatment.
11. The method of embodiment 9, wherein the subject has been diagnosed with mild cognitive impairment due to Alzheimer's disease - intermediate likelihood by a history of subjective memory decline with gradual onset and slow progression over the last 1 year before the method of treatment, e.g., as corroborated by an informant.
12. The method of embodiment 9, wherein the subject has been diagnosed with mild Alzheimer's disease dementia by the NIA-AA core clinical criteria for probable Alzheimer's disease dementia.
13. The method of embodiment 9, wherein the subject has been diagnosed with mild Alzheimer's disease dementia by a CDR score of 0.5 to 1.0 and a Memory Box score of 0.5 or greater before the method of treatment.
14. The method of any one of the embodiments 1-13, wherein the subject is amyloid-positive prior to administration, e.g., as indicated by a PET assessment, a CSF assessment of A β (1-42), MRI, retinal amyloid accumulation, and/or specific behavioral/cognitive phenotypes.
15. The method of any one of the embodiments 1-14, wherein the subject has at least one copy of the ApoE4 gene.
16. The method of any one of the embodiments 1-15, wherein the anti-A β protofibril antibody comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO: 1 (HCDR1), SEQ ID NO: 2 (HCDR2), and SEQ ID NO: 3 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO: 4 (LCDR1), SEQ ID NO: 5 (LCDR2), and SEQ ID NO: 6 (LCDR3).
17. The method of embodiment 16, wherein the anti-A β protofibril antibody comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 7 and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 8.
18. The method of embodiment 16 or embodiment 17, wherein the anti-A β protofibril antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 9 and a light chain comprising an amino acid sequence of SEQ ID NO: 10.
19. The method of any one of the embodiments 1-18, wherein the second blood sample is obtained at least 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 6 months, 12 month, 18 months, or 24 months after the first sample.
20. The method of any one of the embodiments 1-19, wherein the anti-A β protofibril antibody is administered as an infusion.
21. The method of any one of the embodiments 1-20, wherein the P-tau181 is measured using an LC MS/MS platform.

22. The method of any one of the embodiments 1-21, wherein the first dose of the anti-A β protofibril antibody comprises 2.5 mg/kg to 15 mg/kg relative to the weight of the subject, e.g., about 10 mg/kg.
23. The method of any one of the embodiments 1-22, wherein the first or second dose of the anti-A β protofibril antibody comprises 10 mg/kg relative to the weight of the subject, wherein the dose is administered once every 2 weeks.
24. The method according to embodiment 22, wherein the anti-A β protofibril antibody is administered once every 2 weeks or once every month.
25. The method of any one of the embodiments 1, 2, or 6-24, wherein if the second level is lower than the first level, the frequency of administration is reduced in the subject, e.g., to monthly, bimonthly, quarterly, or semi-annual administration.
26. The method of any one of the embodiments 1, 3-5-24, wherein if the second level is the same as or higher than the first level, the frequency of administration is increased in the subject.
27. The method any one of the embodiments 1, 2, or 6-22, wherein if the second level is lower than the first level, the subject is indicated as converted from amyloid-positive to amyloid-negative.
28. The method of embodiment 1 or embodiment 2, wherein if the second level is lower than the first level, the amount of the anti-A β protofibril antibody in the second dose is lower than the amount of the anti-A β protofibril antibody in the first dose and/or the frequency of administration is reduced, e.g., from biweekly to monthly or to every six months.
30. The method of any one of the embodiments 1-29, wherein the subject is sequentially or simultaneously administered at least one additional AD medication.
31. The method any one of the embodiments 1-30, wherein the second dose is administered in combination with a second therapeutic.
32. The method of any one of the embodiments 1-31, wherein the method results in a reduction of a cerebrospinal fluid level of A β 1-42, total tau, and/or neurogranin, and/or results in a slowing of increase in cerebrospinal fluid level of neurofilament light chain as compared to before the method of treatment.
33. The method of any one of the embodiments 1-32, further comprising measuring brain amyloid level in the subject before and/or after administration of the first dose of the anti-A β protofibril antibody, e.g., by measuring a PET SUVR value.
35. The method of any one of the embodiments 1-34, wherein the method reduces brain amyloid level in the subject, as measured by an adjusted mean change from baseline in a PET SUVR value.
36. The method of embodiment 35, wherein the adjusted mean change from baseline in the PET SUVR value is a reduction of at least about 0.10, or 0.15, or 0.20, e.g., after 12 months of the method of treatment.

37. The method of any one of the embodiments 1-36, wherein the method of treatment delays clinical decline as determined by ADCOMS.
38. The method of any one of the embodiments 1-36, wherein the method of treatment delays clinical decline as determined by ADAS MCI-ADL.
39. The method of any one of the embodiments 1-36, wherein the method of treatment delays clinical decline as determined by iADRS.
40. The method of any one of the embodiments 1-36, wherein the method of treatment delays clinical decline as measured by a CDR-SB.
41. The method of any one of the embodiments 1-36, wherein the method of treatment delays clinical decline as measured by an ADAS-Cog.
42. The method of any one of the embodiments 1-41, wherein the method of treatment further comprises monitoring for ARIA, e.g., ARIA-E and/or ARIA-H, e.g., as observed by MRI.
43. The method of any one of the embodiments 1, 2, or 6-42, wherein the method reduces a risk of ARIA, e.g., ARIA-E and/or ARIA-H, e.g., as observed by MRI.
44. The method of embodiment 43, wherein ARIA-E does not increase in size or number after the method of treatment, e.g., as measured by MRI.
45. The method of embodiment 43, wherein ARIA-H does not increase in size or number after the method of treatment, e.g., as measured by MRI.
46. A method of reducing brain amyloid beta in a subject having or suspected of having AD, comprising
- measuring or having measured a first level of p-tau181 in a first blood sample obtained from the subject;
 - administering to the subject a first dose of an A β protofibril antibody;
 - measuring or having measured a second level of p-tau181 in a second blood sample obtained from the subject after the administration of the first dose of the anti-A β protofibril antibody;
 - if the second level is the same as or higher than the first level, (i) administering a second dose of the anti-A β protofibril antibody that is higher than the first dose of the anti-A β protofibril antibody, or (ii) administering a different treatment for AD to the subject, and
 - if the second level is lower than the first level, administering a second dose of the anti-A β protofibril antibody that is the same as or lower than the first dose of the anti-A β protofibril antibody.

47. A method of reducing brain amyloid beta in a subject having or suspected of having AD, comprising

measuring or having measured a first level of p-tau181 in a first blood sample obtained from the subject;

administering to the subject a first dose of an anti-A β protofibril antibody;

measuring or having measured a second level of p-tau181 in a second blood sample obtained from the subject after the administration of the first dose of the anti-A β protofibril antibody;

if the second level is lower than the first level, administering a second dose of the anti-A β protofibril antibody that is the same as or lower than the first dose of the anti-A β protofibril antibody;

thereby reducing brain amyloid beta in the subject.

48. A method of reducing brain amyloid beta in a subject having or suspected of having AD, comprising

measuring or having measured a first level of p-tau181 in a first blood sample obtained from the subject;

administering to the subject a first dose of an anti-A β protofibril antibody;

measuring or having measured a second level of p-tau181 in a second blood sample obtained from the subject after the administration of the first dose of the anti-A β protofibril antibody;

if the second level is the same as or higher than the first level, (i) administering a second dose of the anti-A β protofibril antibody to the subject that is higher than the first dose of the anti-A β protofibril antibody, or (ii) administering a different treatment for AD to the subject,

thereby reducing brain amyloid beta in the subject.

49. The method of embodiment 48, wherein if the second level is the same as or higher than the first level, a second dose of the anti-A β protofibril antibody is administered to the subject that is higher than the first dose of the anti-A β protofibril antibody.

50. The method of embodiment 48, wherein if the second level is the same as or higher than the first level, a different treatment for AD is administered to the subject.

51. The method of any one of the embodiments 46-50, wherein the subject has AD.

52. The method of any one of the embodiments 46-50, wherein the subject has been diagnosed with early AD.

53. The method of any one of the embodiments 46-50, wherein the subject has been diagnosed as having mild cognitive impairment due to Alzheimer's disease - intermediate likelihood and/or has been diagnosed as having mild Alzheimer's disease dementia.
54. The method of embodiment 53, wherein the subject has been diagnosed with mild cognitive impairment due to Alzheimer's disease - intermediate likelihood by National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria.
55. The method of embodiment 53, wherein the subject has been diagnosed with mild cognitive impairment due to Alzheimer's disease - intermediate likelihood by a CDR global score of 0.5 and a Memory Box score of 0.5 or greater before the method of treatment.
56. The method of embodiment 53, wherein the subject has been diagnosed with mild cognitive impairment due to Alzheimer's disease - intermediate likelihood by a history of subjective memory decline with gradual onset and slow progression over the last 1 year before the method of treatment, e.g., as corroborated by an informant.
57. The method of embodiment 53, wherein the subject has been diagnosed with mild Alzheimer's disease dementia by the NIA-AA core clinical criteria for probable Alzheimer's disease dementia.
58. The method of embodiment 53, wherein the subject has been diagnosed with mild Alzheimer's disease dementia by a CDR score of 0.5 to 1.0 and a Memory Box score of 0.5 or greater before the method of treatment.
59. The method of any one of the embodiments 46-58, wherein the subject is amyloid-positive prior to administration, e.g., as indicated by a PET assessment, a CSF assessment of A β (1-42), MRI, retinal amyloid accumulation, and/or specific behavioral/cognitive phenotypes.
60. The method of any one of the embodiments 46-59, wherein the subject has at least one copy of the ApoE4 gene.
61. The method of any one of the embodiments 46-60, wherein the anti-A β protofibril antibody comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO: 1 (HCDR1), SEQ ID NO: 2 (HCDR2), and SEQ ID NO: 3 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO: 4 (LCDR1), SEQ ID NO: 5 (LCDR2), and SEQ ID NO: 6 (LCDR3).
62. The method of embodiment 61, wherein the anti-A β protofibril antibody comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 7 and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 8.
63. The method of embodiment 61 or embodiment 62, wherein the anti-A β protofibril antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 9 and a light chain comprising an amino acid sequence of SEQ ID NO: 10.

64. The method of any one of the embodiments 46-63, wherein the second level is obtained at least 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 6 months, 12 month, 18 months or 24 months after the first sample.
65. The method of any one of the embodiments 46-64, wherein the anti-A β protofibril antibody is administered as an infusion.
66. The method of any one of the embodiments 46-65, wherein the p-tau181 is measured using an LC MS/MS platform.
67. The method of any one of the embodiments 46-66, wherein the first dose of the anti-A β protofibril antibody comprises 2.5 mg/kg to 15 mg/kg relative to the weight of the subject, e.g., about 10 mg/kg.
68. The method of any one of the embodiments 46-67, wherein the first or second dose of the anti-A β protofibril antibody comprises 10 mg/kg relative to the weight of the subject, wherein the dose is administered once every 2 weeks.
69. The method according to embodiment 68, wherein the anti-A β protofibril antibody is administered once every 2 weeks or once every month.
70. The method of any one of the embodiments 46, 47, or 51-69, wherein if the second level is lower than the first level, the frequency of administration is reduced in the subject, e.g., to monthly, bimonthly, quarterly, or semi-annual administration.
71. The method of any one of the embodiments 46 or 48-69, wherein if the second level is the same as or higher than the first level, the frequency of administration is increased in the subject.
72. The method of any one of the embodiments 46, 47, or 51-70, wherein if the second level is lower than the first level, the subject is indicated as converted from amyloid-positive to amyloid-negative.
73. The method of embodiment 46 or embodiment 47, wherein if the second level is lower than the first level, the amount of the anti-A β protofibril antibody in the second dose is lower than the amount of the anti-A β protofibril antibody in the first dose and/or the frequency of administration is reduced, e.g., from biweekly to monthly or to every six months.
74. The method of any one of the embodiments 46-73, wherein the second dose is administered in combination with a second therapeutic.
75. The method of any one of the embodiments 46-74, wherein the subject is sequentially or simultaneously administered at least one additional AD medication.
76. The method of any one of the embodiments 46-75, wherein the method results in a reduction of a cerebrospinal fluid level of A β 1-42, total tau, and/or neurogranin, and/or results in a slowing of increase in cerebrospinal fluid level of neurofilament light chain as compared to before the method of treatment.

77. The method of any one of the embodiments 46-76, further comprising measuring brain amyloid level in the subject before and/or after the method of treatment, e.g., by measuring a PET SUV_r value.
78. The method of any one of the embodiments 46-76, wherein the method reduces brain amyloid level in the subject, as measured by an adjusted mean change from baseline in a PET SUV_r value.
79. The method of embodiment 78, wherein the adjusted mean change from baseline in the PET SUV_r value is a reduction of at least about 0.10, or 0.15, or 0.20, e.g., after 12 months of the method of treatment.
80. The method of any one of the embodiments 46-79, wherein the method of treatment delays clinical decline as determined by ADCOMS.
81. The method of any one of the embodiments 46-79, wherein the method of treatment delays clinical decline as determined by ADAS MCI-ADL.
82. The method of any one of the embodiments 46-79, wherein the method of treatment delays clinical decline as determined by iADRS.
83. The method of any one of the embodiments 46-79, wherein the method of treatment delays clinical decline as measured by a CDR-SB.
84. The method of any one of the embodiments 46-79, wherein the method of treatment delays clinical decline as measured by an ADAS-Cog.
85. The method of any one of the embodiments 46-84, wherein the method of treatment further comprises monitoring for ARIA, e.g., ARIA-E and/or ARIA-H, e.g., as observed by MRI.
86. The method of any one of the embodiments 46, 47, or 51-85, wherein the method of treatment reduces a risk of ARIA, e.g., ARIA-E and/or ARIA-H, e.g., as observed by MRI.
87. The method of embodiment 86, wherein ARIA-E does not increase in size or number after the method of treatment, e.g., as measured by MRI.
88. The method of embodiment 86, wherein ARIA-H does not increase in size or number after the method of treatment, e.g., as measured by MRI.
89. A method of monitoring treatment efficacy in a subject having or suspected of having AD, comprising:

administering to the subject a dose of an anti-A β protofibril antibody;

measuring or having measured a post-dose level of p-tau181 in a blood sample obtained from the subject; and

comparing the post-dose level of the blood sample to a blood sample obtained from the subject prior to the administration of the first dose of the anti-A β protofibril antibody or to a control level, e.g., a blood sample obtained from a subject not diagnosed with AD, wherein the treatment is considered effective if the post-dose level is lower than the level prior to the first dose or the control level.

90. The method of embodiment 89, wherein if the post-first dose level is lower than the level prior to the administration of the A β protofibril antibody or lower than the level in the control, the subject is indicated as having a reduction in a brain A β level.

91. The method of embodiment 89, further comprising comparing brain amyloid level in the subject before and/or after administration of the first dose of the anti-A β protofibril antibody, e.g., by measuring a PET SUVR value.

92. The method of embodiment 91, wherein the adjusted mean change from baseline in the PET SUVR value is a reduction of at least about 0.10, or 0.15, or 0.20, e.g., after 12 months of the method of monitoring treatment efficacy with the dose.

93. The method of embodiment 91, wherein the method of monitoring treatment efficacy is confirmed by a visual read of PET images to confirm the subject is amyloid-negative.

94. A method of detecting a decrease in a brain A β level, comprising:

measuring or having measured a first level of p-tau181 in a first blood sample obtained from a subject prior to administration of an anti-A β protofibril antibody;

administering to the subject a dose of the anti-A β protofibril antibody;

measuring or having measured a second level of p-tau181 in a second blood sample obtained from the subject after administration of the anti-A β protofibril antibody;

comparing the first and second levels,
wherein a second level that is lower than the first level indicates a decrease of brain amyloid β in the subject.

95. A method of reducing brain amyloid level in a subject in need thereof comprising:

measuring or having measured a first level of p-tau181 in a first blood sample obtained from the subject;

administering to the subject a first dose of an anti-A β protofibril antibody;

measuring or having measured a second level of p-tau181 in a second blood sample obtained from the subject after the administration of the first dose of the anti-A β protofibril antibody;

if the second level is the same as or higher than the first level, (i) administering a second dose of the anti-A β protofibril antibody to the subject that is higher than the first dose of the anti-A β protofibril antibody, or (ii) administering a different treatment for AD to the subject, and

if the second level is lower than the first level, administering a second dose of the anti-A β protofibril antibody that is the same as or lower than the first dose of the anti-A β protofibril antibody.

96. The method according to embodiment 95, wherein the subject has Alzheimer's disease, Down's Syndrome, chronic traumatic encephalopathy, cerebral amyloid angiopathy, Lewy Body Dementia, or another brain disease or condition with A β peptide-containing soluble and/or insoluble A β aggregates.

97. The method of embodiment 95 or embodiment 96, wherein the anti-A β protofibril antibody comprises three heavy chain complementarity determining regions (HCDR1, HCDR2, and HCDR3) comprising amino acid sequences of SEQ ID NO: 1 (HCDR1), SEQ ID NO: 2 (HCDR2), and SEQ ID NO: 3 (HCDR3); and three light chain complementarity determining regions (LCDR1, LCDR2, and LCDR3) comprising amino acid sequences of SEQ ID NO: 4 (LCDR1), SEQ ID NO: 5 (LCDR2), and SEQ ID NO: 6 (LCDR3).

98. The method of embodiment 97, wherein the anti-A β protofibril antibody comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 7 and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 8.

99. The method of embodiment 97 or embodiment 98, wherein the anti-A β protofibril antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 9 and a light chain comprising an amino acid sequence of SEQ ID NO: 10.

100. The method of any one of the embodiments 1-99, wherein the subject is administered a maintenance dose.

101. The method of embodiment 100, wherein the maintenance dose comprises an anti-amyloid β (A β) protofibril antibody

102. The method of embodiment 101, wherein the maintenance dose is administered once or multiple times.

103. The method of embodiment 102, wherein the maintenance dose is administered at a dose frequency selected to maintain a PET SUVR level achieved during treatment.

104. The method of embodiment 102, wherein the maintenance dose is administered at a dose frequency selected to maintain a PET SUVR level at or below amyloid negativity (e.g. for florbetapir, PET SUVR of 1.17).

105. The method of any one of the embodiments 102-104, wherein the maintenance dose is administered every three months at a dosage of 10 mg/kg.

106. The method of any one of the embodiments 102-104, wherein the maintenance dose is administered every month at a dosage of 10 mg/kg.

107. The method of embodiment 102, wherein the maintenance dose is administered at a dose frequency selected to maintain a p-tau181 level achieved during treatment.

108. The method of embodiment 107, wherein the maintenance dose is administered every month at a dosage of 10 mg/kg.
109. The method of embodiment 101 or embodiment 102, wherein the maintenance dose is administered at a lower dose than during an earlier course of treatment.
110. The method of embodiment 101 or embodiment 102, wherein the maintenance dose is administered less frequently than during the earlier course of treatment.
111. The method of embodiment 102, wherein the maintenance dose is administered weekly, every two weeks, monthly, or every 3 months.
112. The method of embodiment 102, wherein the maintenance dose is administered after a subject obtains a reduced p-tau181 level, e.g., below the p-tau181 level prior to treatment.
113. The method of any one of the embodiments 100-102, wherein the maintenance dose comprises 2.5 mg/kg to 15 mg/kg relative to the weight of the subject.
114. The method of embodiment 113, wherein the maintenance dose comprises 10 mg/kg.
115. The method of any one of the embodiments 1-113, wherein administering to the subject a first therapeutically effective dose of an anti-A β protofibril antibody does not require a titration step.
116. A method of selecting a subject for treatment with an anti-amyloid β (A β) protofibril antibody, comprising
- a. measuring or having measured a p-tau181 level in a blood sample obtained from the subject; and
 - b. selecting the subject for treatment with an anti-amyloid β (A β) protofibril antibody if the level is above a threshold value (e.g., the level is above about 2.2 or 2.3 pg/ml as measured in a Quanterix™ Simoa® assay).
117. A method of treating AD in a subject having or suspected of having AD, comprising
- measuring or having measured a first level of p-tau181 in a first blood sample obtained from the subject;
 - measuring or having measured a concentration of amyloid β 1-42 (A β 42) and a concentration of amyloid β 1-40 (A β 40) in the first blood sample obtained from the subject to determine a first ratio of A β 42 to A β 40 (A β 42/40 ratio);
 - administering to the subject a first dose of an anti-A β protofibril antibody;
 - measuring or having measured a second level of p-tau181 in a second blood sample obtained from the subject after the administration of the first dose of the anti-A β protofibril antibody; and

measuring or having measured a second concentration of amyloid β 1-42 ($A\beta_{42}$) and amyloid β 1-40 ($A\beta_{40}$) in a second blood sample obtained from the subject after the first sampling to determine a second $A\beta_{42}/40$ ratio;

- i) if the second level of p-tau181 is lower than the first level; or
- ii) if the second $A\beta_{42}/40$ ratio is elevated relative to the first ratio; or
- iii) if both the second level of p-tau181 is lower than the first level and the second $A\beta_{42}/40$ ratio is elevated relative to the first ratio;

administering a second dose of the anti- $A\beta$ protofibril antibody to the subject that is the same as or lower than the first dose of the anti- $A\beta$ protofibril antibody.

118. A method of treating Alzheimer's disease (AD) in a subject having or suspected of having AD, comprising

- a. measuring a level of p-tau181 in a blood sample obtained from the subject; and
- b. administering a treatment comprising a therapeutically effective dose of an anti-amyloid β ($A\beta$) protofibril antibody to the subject having p-tau181 level above a threshold value (e.g., the level is above about 2.2 or 2.3 pg/ml as measured in a Quanterix™ Simoa® assay).

119. The method of any one of the embodiments 1-118, wherein administering to the subject a first therapeutically effective dose of an anti- $A\beta$ protofibril antibody does not require a titration step.

120. The method of any one of the embodiments 100-119, wherein the subject has early AD.

121. The method of any one of the embodiments 100-119, wherein the subject has pre-AD.

122. The method of any one of the embodiments 1-121, wherein a level of p-tau181 is measured in a blood sample from the subject prior to treatment.

123. The method of embodiment 122, wherein the level of p-tau181 is measured without a brain amyloid measurement by PET.

124. A method of treating Alzheimer's disease (AD) in a subject having or suspected of having AD, comprising

- a. measuring a first level of p-tau181 in a first blood sample obtained from the subject;
- b. administering to the subject a first therapeutically effective dose of an anti-amyloid β ($A\beta$) protofibril antibody;
- c. measuring a second level of p-tau181 in a second blood sample obtained from the subject from the subject after the first sampling; and
- d. administering a second therapeutically effective dose comprising the same or a lower amount of the anti- $A\beta$ protofibril antibody than in the first dose to the subject having a lower second level of p-tau181 relative to the first level.

125. A method of treating AD in a subject having or suspected of having AD, comprising

- a. measuring a first level of p-tau181 in a first blood sample obtained from the subject;
- b. administering to the subject a first therapeutically effective dose of an anti-A β protofibril antibody;
- c. measuring a second level of p-tau181 in a second blood sample obtained from the subject after the first sampling; and
- d. administering a second therapeutically effective dose comprising a higher amount of the anti-A β protofibril antibody than in the first dose or a different treatment for AD to the subject having the same or a higher level of p-tau181 relative to the first level.

SEQUENCE TABLES

Table 1. Amino acid sequences of monoclonal antibody (mAb)CDRs

mAb	IgG chain	SEQ ID NO	Amino acid sequence
BAN2401	HCDR1	1	SFGMH
	HCDR2	2	YISSGSSTIYYGDTVKG
	HCDR3	3	EGGYYYGRSYTMDY
BAN2401	LCDR1	4	RSSQSIVHSNGNTYLE
	LCDR2	5	KVSNRFS
	LCDR3	6	FQGSHPPT

Table 2. Amino acid sequences of mAb variable regions

mAb	IgG chain	SEQ ID NO	Amino acid sequence
BAN2401	Heavy chain variable region	7	EVQLVESGGGLVQPGGSLRLSCSASGF TFSSFGMHWVRQAPGKGLEWVAYISS GSSTIYYGDTVKGGRFTISRDNKNSLFL QMSSLRAEDTAVYYCAREGGYYYGRS YYTMDYWGQGTTVTVSS
BAN2401	Light chain variable region	8	DVVMTQSPLSLPVTGPAPASISCRSSQSI VHSNGNTYLEWYLQKPGQSPKLLIYKV SNRFSGVPDRFSGSGSGTDFTLRISRVE AEDVGIYYCFQGSHPPTFGPGTKLEIK

Table 3. Amino acid sequences of mAb heavy and light chains

mAb	IgG chain	SEQ ID NO	Amino acid sequence
BAN2401	Heavy chain	9	EVQLVESGGGLVQPGGSLRLSCSASG FTFSSFGMHWRQAPGKGLEWVAYI SSGSSTIYYGDTVKGRTISRDNKNS LFLQMSSLRAEDTAVYYCAREGGYY YGRSYTMDYWGGQGTTVTVSSASTK GPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAV LQSSGLYSLSSVVPSSSLGTQTYICN VNHKPSNTKVDKRVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTP EVTCTVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEM TKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFCSSVMHEALHN HYTQKSLSLSPGK
BAN2401	Light chain	10	light chain: DVVMTQSPLSLPVTPGAPASISCRSSQ SIVHSNGNTYLEWYLQKPGQSPKLLI YKVSNRFGVPDRFSGSGSGTDFTLRI SRVEAEDVGIYYCFQGSHVPPTFGPGT KLEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC

Table 4. Amino acid sequences of mAb constant regions

mAb	IgG chain	Class	SEQ ID NO	Amino acid sequence
BAN2401	Heavy chain	IgG1	11	ASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKRVEPKSCDK THTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQV YTLPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPENN YKTTTPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK
BAN2401	Light chain	kappa	12	RTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWK VDNALQSGNSQESVTEQDSK DSTYLSSTLTLSKADYEEKHK VYACEVTHQGLSSPVTKSFNR GEC

Table 5. Amino acid sequences of Amyloid β

Amyloid β	SEQ ID NO	Amino acid sequence
Amyloid β 1-42	13	DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA
Amyloid β 1-40	14	DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVV

Table 11. Amino acid sequences of E2814 CDRs

mAb	IgG chain	SEQ ID NO	Amino acid sequence
E2814 Heavy Chain	HCDR1	15	TYWIT
	HCDR2	16	DIYPGSSISNYNEKFKS
	HCDR3	17	EDGYDAWFAY
E2814 Light Chain	LCDR1	18	RSSQSILHSNGNTYLE
	LCDR2	19	KVSNRFS
	LCDR3	20	FQGSHVPFT

Table 12. Amino acid sequences of E2814 variable regions

mAb	IgG chain	SEQ ID NO	Amino acid sequence
E2814	Heavy chain variable region	21	EVQLLESGGGLVQPGGSLRLSCAASGY TFTTYWITWVRQAPGKGLEWVSDIYPG SSISNYNEKFKSRFTISVDNSKNTLYLQ MNSLRAEDTAVYYCAREDGYDAWFA YWGQGTLLTVSS
E2814	Light chain variable region	22	DIQMTQSPSSLSASVGDRVITTCRSSQSI LHSNGNTYLEWYQQKPGKAPKLLISKV SNRFSGVPSRFSGSGSGTDFTLTISSLQP EDFATYYCFQGSHVPFTFGQGTKLEIK

Table 13. Amino acid sequences of E2814 constant regions

mAb	IgG chain	Class	SEQ ID NO	Amino acid sequence
E2814	Heavy chain	IgG1	23	ASTKGPSVFPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWN SGALTSGVHTFPAVLQSSGLY SLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDK THTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVVD VSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQV YTLPPSRDELTKNQVSLTCLV KGFYPSDIAVEWESNGQPENN YKTTTPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK
E2814	Light chain	kappa	24	RTVAAPSVFIFPPSDEQLKSGT ASVVCLLNFPYPREAKVQWK VDNALQSGNSQESVTEQDSK DSTYLSSTLTLSKADYEKHK VYACEVTHQGLSSPVTKSFNR GEC

Table 14. Amino acid sequence of Tau

	SEQ ID NO	Amino acid sequence
Tau	25	MAEPRQEFVEMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKES PLQPTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPH EIPGTTAEAEAGIGDTPSLEDEAAGHVTQARMVSKSKDGTGSDDKKAK GADGKTKIATPRGAAPPQKGQANATRIAPKTPAPKTPSSGEPKSG DRSGYSSPGSPGTPGSRRTPSLPTPPTREPCKVAVVRTPPKSPSSAKSRL QTAPVPMPLKKNVSKIGSTENLKHQPGGGKVQIINKKLDLSNVQSKC GSKDNIKHVPGGGSVQIVYKPDLSKVTSCGSLGNIHHKPGGGQVEV KSEKLDKDRVQSKIGSLDNITHVPGGGNKKIETHKLTFRNAKAKTDH GAEIVYKSPVVSGDTSRHLNSVSTGSIDMVDSPQLATLADEVSA SLAKQGL

EXAMPLES

[331] The present disclosure is further illustrated by the following examples that should not be construed as limiting. The contents of all references, patents, and published patent applications cited throughout this application, as well as the figures, are incorporated herein by reference in their entirety for all purposes.

1. Methods for treatment of subjects having early Alzheimer's disease with BAN2401 lecanemab

[332] BAN2401-G000-201 (Study 201, NCT01767311) is a double-blind, parallel-group, placebo-controlled, multicenter and multinational study that utilized a dose-finding response adaptive randomization (RAR) design to evaluate the safety, tolerability, and efficacy of BAN2401 in subjects with MCI due to AD – intermediate likelihood, or with mild AD dementia (collectively designated as early AD in this study). 854 subjects were randomized for treatment. MCI due to AD – intermediate likelihood and mild AD dementia are defined by the National Institute of Aging - Alzheimer's Association (NIA-AA) core clinical criteria.

[333] The core study consisted of a Prerandomization Phase (Screening Period and Baseline Period), and a Randomization Phase with a planned 18-month treatment period followed by a 3-month Follow-Up Period. An Open-Label Extension Phase was implemented to allow for up to 60 months (5 years) of additional treatment. There was an intervening gap period off-treatment between the core study and the Open-Label Extension ranging from 9-59 months (mean 24 months).

Core Study

Prerandomization Phase

[334] The Prerandomization Phase lasted up to 60 days, and consisted of a Screening Period (up to 30 days duration) and a Baseline Period (up to 30 days duration). During the Screening Period and Baseline Period, all subjects were assessed for eligibility using clinical tests, safety MRIs, and amyloid PET assessments to confirm that subjects meet the diagnostic criteria for MCI due to AD – intermediate likelihood or mild Alzheimer's disease dementia and that they do not have other medical conditions that may interfere with study participation. All subjects were confirmed amyloid positive via amyloid positron emission tomography (PET) or cerebrospinal fluid (CSF) A β 1–42 for eligibility.

[335] Further assessments were conducted during the Baseline Period, including additional clinical evaluations, mandatory blood sampling for pharmacogenomics (APOE4 status), and CSF sampling for those who consent to soluble CSF biomarker analysis. At the Baseline Visit, clinical assessments: MMSE, CDR, ADAS-Cog, and FAQ, were conducted.

Randomization Phase

[336] Subjects were randomized to receive placebo or 1 of 5 doses of BAN2401 (2.5, 5, or 10 mg/kg given biweekly, or 5 or 10 mg/kg given every 4 weeks [monthly]), administered by intravenous (IV) infusion for the duration of the Randomization Phase (18 months). Table 6 is summary of patient demographics and dosing regimen for patients in the Study 201 Core used in the full dataset analysis.

Table 6: Patient demographics for patients in the Study 201 Core used in the full dataset analysis

Category		Lecanemab							Combined Total (N=825)
		Placebo (PBO) (N=238)	2.5 mg/kg Biweekly (LEC2.5-BW) (N=52)	5 mg/kg Monthly (LEC5-M) (N=48)	5 mg/kg Biweekly (LEC5-BW) (N=89)	10 mg/kg Monthly (LEC10-M) (N=246)	10 mg/kg Biweekly (LEC10-BW) (N=152)	Total (N=587)	
Age (year) ^a	n	238	52	48	89	246	152	587	825
	Mean (SD)	71.11 (8.892)	70.50 (8.257)	70.42 (7.514)	70.64 (7.446)	71.26 (7.455)	72.64 (8.777)	71.39 (7.907)	71.31 (8.198)
	Median	72.00	70.50	71.00	72.00	71.00	73.00	72.00	72.00
	Min, max	50.0, 89.0	50.0, 86.0	55.0, 84.0	52.0, 87.0	53.0, 90.0	51.0, 88.0	50.0, 90.0	50.0, 90.0
Age group, n (%)	<65 years	55 (23.1)	11 (21.2)	9 (18.8)	20 (22.5)	44 (17.9)	27 (17.8)	111 (18.9)	166 (20.1)
	≥65 to <80 years	144 (60.5)	35 (67.3)	35 (72.9)	60 (67.4)	168 (68.3)	94 (61.8)	392 (66.8)	536 (65.0)
	≥80 years	39 (16.4)	6 (11.5)	4 (8.3)	9 (10.1)	34 (13.8)	31 (20.4)	84 (14.3)	123 (14.9)
Sex, n (%)	Male	101 (42.4)	26 (50.0)	24 (50.0)	41 (46.1)	136 (55.3)	88 (57.9)	315 (53.7)	416 (50.4)
	Female	137 (57.6)	26 (50.0)	24 (50.0)	48 (53.9)	110 (44.7)	64 (42.1)	272 (46.3)	409 (49.6)
Ethnicity, n (%)	Hispanic or Latino	9 (3.8)	4 (7.7)	1 (2.1)	3 (3.4)	9 (3.7)	9 (5.9)	26 (4.4)	35 (4.2)
	Not Hispanic or Latino	229 (96.2)	48 (92.3)	47 (97.9)	86 (96.6)	237 (96.3)	143 (94.1)	561 (95.6)	790 (95.8)
Race, n (%)	White	216 (90.8)	48 (92.3)	46 (95.8)	7 (82.0)	222 (90.2)	141 (92.8)	530 (90.3)	746 (90.4)
	Black or African American	5 (2.1)	2 (3.8)	1 (2.1)	4 (4.5)	4 (1.6)	4 (2.6)	15 (2.6)	20 (2.4)
	Chinese	1 (<1.0)	0	0	0	0	0	0	1 (<1.0)
	Japanese	10 (4.2)	1 (1.9)	0	6 (6.7)	12 (4.9)	5 (3.3)	24 (4.1)	34 (4.1)
	Other Asian	5 (2.1)	1 (1.9)	1 (2.1)	3 (3.4)	5 (2.0)	2 (1.3)	12 (2.0)	17 (2.1)
	Other	1 (<1.0)	0	0	3 (3.4)	3 (1.2)	0	6 (1.0)	7 (<1.0)
Region, n (%)	North America	195 (81.9)	47 (90.4)	41 (85.4)	70 (78.7)	215 (87.4)	135 (88.8)	508 (86.5)	703 (85.2)
	Western Europe	28 (11.8)	4 (7.7)	6 (12.5)	7 (7.9)	15 (6.1)	10 (6.6)	42 (7.2)	70 (8.5)
	Asia	15 (6.3)	1 (1.9)	1 (2.1)	12 (13.5)	16 (6.5)	7 (4.6)	37 (6.3)	52 (6.3)
CDR-Global, n (%)	0.5	200 (84.0)	44 (84.6)	40 (83.3)	77 (86.5)	210 (85.4)	133 (87.5)	504 (85.9)	704 (85.3)
	1	38 (16.0)	8 (15.4)	8 (16.7)	12 (13.5)	13 (14.6)	19 (12.5)	83 (14.1)	121 (14.7)
APOE4 carrier status, n (%)	Carrier	169 (7.0)	38 (73.1)	37 (77.1)	81 (91.0)	218 (88.6)	46 (30.3)	420 (71.6)	589 (71.4)
	Heterozygous	129 (54.2)	33 (63.5)	26 (54.2)	67 (75.3)	160 (65.0)	38 (25.0)	324 (55.2)	453 (54.9)
	Homozygous	40 (16.8)	5 (9.6)	11 (22.9)	14 (15.7)	58 (23.6)	8 (5.3)	96 (16.4)	136 (16.5)
	Non-carrier	69 (29.0)	14 (26.9)	11 (22.9)	8 (9.0)	28 (11.4)	106 (69.7)	167 (28.4)	236 (28.6)
Disease stage, n (%)	MCI due to AD	154 (64.7)	34 (65.4)	33 (68.8)	52 (58.4)	166 (67.5)	90 (59.2)	375 (63.9)	529 (64.1)
	Mild AD	84 (35.3)	18 (34.6)	15 (31.3)	37 (41.6)	80 (32.5)	62 (40.8)	212 (36.1)	296 (35.9)
AChEIs and/or memantine at Baseline, n (%)	No	110 (46.2)	24 (46.2)	23 (47.9)	33 (37.1)	115 (46.7)	73 (48.0)	268 (45.7)	378 (45.8)
	Yes	128 (53.8)	28 (53.8)	25 (52.1)	56 (62.9)	131 (53.3)	79 (52.0)	319 (54.3)	447 (54.2)
Number of years of	n	237	52	48	89	245	152	586	823

Table 6: Patient demographics for patients in the Study 201 Core used in the full dataset analysis

Category		Placebo (PBO) (N=238)	Lecanemab					Total (N=587)	Combine d Total (N=825)
			2.5 mg/kg Biweekly (LEC2.5- BW) (N=52)	5 mg/kg Monthly (LEC5- M) (N=48)	5 mg/kg Biweekl y (LEC5- BW) (N=89)	10 mg/kg Monthly (LEC10- M) (N=246)	10 mg/kg Biweekly (LEC10- BW) (N=152)		
disease since	Mean (SD)	2.38 (1.659)	2.27 (1.705)	2.08 (1.235)	2.16 (1.242)	2.20 (1.551)	2.22 (1.491)	2.19 (1.479)	2.25 (1.534)
Diagnosis	Median	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
	Min, max	1.0, 11.0	1.0, 7.0	1.0, 6.0	1.0, 6.0	1.0, 12.0	1.0, 9.0	1.0, 12.0	1.0, 12.0
Age at diagnosis (years)	n	237	52	48	89	245	152	586	823
	Mean (SD)	70.32 (8.740)	69.75 (8.364)	69.94 (7.575)	70.09 (7.442)	70.71 (7.526)	72.03 (8.855)	70.81 (7.971)	70.67 (8.197)
	Median	70.00	70.00	71.00	71.00	71.00	73.00	71.00	71.00
	Min, max	50.0, 90.0	49.0, 86.0	54.0, 84.0	52.0, 87.0	52.0, 90.0	51.0, 89.0	49.0, 90.0	49.0, 90.0
Age at onset of symptoms (years)	n	238	52	48	89	246	152	587	825
	Mean (SD)	68.00 (8.880)	67.35 (8.220)	67.13 (7.601)	67.93 (7.513)	68.48 (7.815)	69.95 (9.057)	68.57 (8.156)	68.40 (8.370)
	Median	68.00	68.00	67.50	69.00	69.00	71.00	69.00	69.00
	Min, max	46.0, 88.0	47.0, 83.0	51.0, 82.0	50.0, 87.0	45.0, 89.0	47.0, 87.0	45.0, 89.0	45.0, 89.0

AChEIs = acetylcholinesterase inhibitor; AD = Alzheimer's disease; *APOE4* = apolipoprotein E4; CDR = Clinical Dementia Rating; MCI = mild cognitive impairment. Age was calculated at date of informed consent. Percentages are based on total number of subjects with non-missing values in relevant treatment group.

[337] There was a notable protocol amendment during the course of the study related to a safety observation for apolipoprotein E4 (ApoE4) gene carriers receiving the highest dose (10 mg/kg biweekly) of lecanemab. Emerging data from the study just prior to the 350 subject interim analysis indicated that ApoE4 positive homozygous individuals on the highest dose of lecanemab had the highest risk of developing symptomatic amyloid-related imaging abnormalities-edema/effusion (ARIA-E). Following comprehensive data review, one regulatory authority requested that ApoE4 carriers (homozygous and heterozygous; approximately 70% of the overall subject population) no longer be administered the 10 mg/kg biweekly dose of lecanemab going forward, and this approach was adopted for all subsequent randomizations. At the same time, a request was also made to discontinue from study drug administration, without exception, all ApoE4 carriers (homozygous and heterozygous) who were randomized to the 10 mg/kg biweekly dose and were on study for less than 6 months.

- Efficacy Assessments

[338] Primary efficacy of BAN2401 was assessed via Bayesian analysis, by comparing to placebo, the change from Baseline at 12 months on ADCOMS, a composite clinical score representing a new approach to the analysis of selected items (12 total) from 3 fully validated and well-established clinical tools, including CDR (all 6 items), ADAS-Cog14 (4 items), and MMSE (2 items).

[339] The key secondary efficacy of BAN2401 was assessed using mixed model repeated measures (MMRM) analysis, by comparing to placebo at 18 months as follows: brain amyloid pathophysiology as measured by PET; clinical status on ADCOMS, CDR-SB, and ADAS-Cog14; CSF biomarkers (including Aβ[1-42], t-tau, and p-tau); information from measurements of potential novel emerging CSF biomarkers at 18 months [e.g., neurogranin

and neurofilament light chain (NfL, also measured in plasma)]; and total hippocampal volume as measured by vMRI.

[340] The secondary efficacy was assessed using MMRM analyses at 12 months using brain amyloid pathophysiology by PET, clinical status on ADCOMS, CDR-SB, and ADAS-Cog14, and CSF biomarkers (including A β [1-42], t-tau, and p-tau); information from measurements of potential novel emerging CSF biomarkers at 12 months [e.g., neurogranin, and NfL (also measured in plasma)]; and total hippocampal atrophy by vMRI at 6 and 12 months, and left and right hippocampus, whole brain, and total ventricular volume by vMRI at 6, 12, and 18 months.

[341] Exploratory efficacy was evaluated by clinical status on ADCOMS, CDR-SB, and ADAS-Cog14 at other time points, as well as MMSE and FAQ. A summary of the clinical outcomes is listed in table 10.

- Amyloid PET and CSF A β (1-42)

[342] Amyloid PET imaging or CSF A β (1-42) assessment was used to confirm that all subjects with EAD have amyloid deposition in the brain. This criterion allowed for the definition of subjects with MCI due to AD – intermediate likelihood and confirmed amyloid pathology in mild Alzheimer’s disease dementia subjects.

[343] Amyloid PET or CSF A β (1-42) assessment was required at Baseline during the Prerandomization Phase for all subjects to qualify for study inclusion per the protocol, and subjects who consented to participate in the imaging subgroup received amyloid PET imaging at 12 and 18 months of treatment. Duration of the PET scan and its timing relative to injection of the imaging agent were as per the imaging agent manufacturer's guidance. As the imaging agent, florbetapir and flutemetamol were used, however, most of the subjects who had amyloid PET scan used florbetapir. Data are included for those subjects who received florbetapir as the imaging agent.

[344] Amyloid plaque load identified by PET imaging uptake was determined via 2 separate methodologies: visual read and standard uptake value ratio (SUVr) using a cortical composite versus a reference region.

Sampling of blood for Exploratory Plasma Biomarkers

[345] Blood was collected from subjects at Baseline during the Prerandomization Phase prior to amyloid PET assessment and at 12 and 18 months of treatment to evaluate potential novel biomarkers of AD. A summary of the biomarker results is listed in Table 8.

Open-Label Extension Phase (Study 201 OLE)

[346] The ongoing Extension Phase is conducted in accordance with the protocol outlined as below.

[347] The Open-Label Extension (OLE) Phase was initiated following the Core Study to allow subjects to receive open-label BAN2401 10 mg/kg biweekly. All subjects who are continuing on in the Extension Phase and who have completed at least 18 months of treatment in the Extension Phase may take part in an optional dosing regimen substudy to evaluate the effects on safety, PK exposure, biomarker, and clinical efficacy of alternate dosing regimens for maintenance dosing of BAN2401. Subjects may choose to enter this substudy at any study visit according to their prior biweekly schedule of assessments. Subjects who choose to participate in this substudy will be randomized to 1 of 2 intravenous dosing regimens; either BAN2401 10 mg/kg once every 4 weeks (Q4W) or BAN2401 10 mg/kg once every 3 months (Q3M). All subjects will continue participation in the Extension Phase for up to 60 months (5 years), until the drug is commercially available in the country

where the subject resides, or until the benefit to risk ratio from treatment with BAN2401 is no longer considered favorable, whichever comes first. Any subject who completed study treatment (Visit 42 [Week 79] of the Core Study) and fulfills the Extension Phase inclusion and exclusion criteria had the option to participate. Subjects who previously completed the Core Study (through the Follow-Up Visit, Visit 43) at any time before implementation of the Extension Phase, and/or fulfill the Extension Phase inclusion and exclusion criteria, were eligible to participate. Subjects who discontinued the Core Study were eligible to participate in the Extension Phase, provided they met the inclusion and exclusion criteria for the Extension Phase. No subjects entered the OLE Phase immediately after the Core Study completed, and for all subjects there was a gap of at least 9 months between the last dose in the Core Study and the first dose in the OLE Phase. No treatment was given, and no data were collected during this gap period.

[348] All subjects in the ongoing extension phase have received and will continue to receive the BAN2401 10 mg/kg biweekly dose (or Q4W or Q3M, if enrolled in the dosing regimen substudy), including subjects who are confirmed *APOE4* positive (hetero- or homozygous). All infusions take place in the clinic; however, if approved by the Sponsor and allowable and conducted according to country and local guidelines, subjects are offered the option of home infusions for approved visits. Home infusions are being implemented as a result of the Coronavirus Disease 2019 (COVID-19) pandemic to allow subjects who cannot visit clinical sites for various reasons to continue receiving treatment. Home infusions are allowed per Sponsor approval according to country and local guidelines during the COVID-19 pandemic and following its resolution, where permitted. The Follow-up Visit in the Extension Phase takes place 3 months after the last dose of study drug. Subjects may discontinue from study drug for any reason. Subjects who discontinue the study drug are requested to undertake the Early Termination Visit (within 7 days after the last dose of study drug) and the Follow-up Visit (3 months after the last dose of study drug). Table 7 is a summary of the patient demographics for patients in the OLE Phase used in the full dataset analysis.

Table 7: Summary of the patient demographics for patients in the OLE Phase used in the full dataset analysis

Category	Lecanemab 10 mg/kg biweekly (N = 180) n (%)
Age (year) ^a	
N	180
Mean (SD)	74.0 (7.69)
Median	74.0
Min, Max	52, 87
Sex, n (%)	
Male	93 (51.7)
Female	87 (48.3)
Race, n (%)	
White	148 (82.2)
Black or African American	2 (1.1)
Asian	30 (16.7)
Japanese	21 (11.7)
Chinese	1 (0.6)
South Korean	8 (4.4)
Ethnicity, n (%)	
Hispanic or Latino	1 (0.6)
Not Hispanic or Latino	179 (99.4)
Region, n (%)	
North America	139 (77.2)
Europe	12 (6.7)
Asia Pacific	29 (16.1)
APOE4 Status, n (%)	
Positive	125 (69.4)
Heterozygous	97 (53.9)
Homozygous	28 (15.6)
Negative	55 (30.6)
Concurrent approved symptomatic AD treatment at OLE Baseline, n (%)	
Yes	122 (67.8)
No	58 (32.2)
Clinical Subgroup at Core Baseline, n (%)	
MCI due to AD	110 (61.1)
Mild AD dementia	70 (38.9)

Table 8: Summary of biomarker results from Study 201 Core.

Biomarker Endpoints	BAN2401 10 mg/kg biweekly	Placebo
Amyloid Beta PET Composite SUVR	N=44	N=98
Mean baseline	1.373	1.402
Adjusted mean change from baseline at Week 53 Difference from placebo	-0.266 -0.257 (p<0.001)	-0.009
Adjusted mean change from baseline at Week 79 Difference from placebo	-0.306 -0.310 (p<0.001)	0.004
Amyloid Beta PET Centiloid	N=44	N=98
Mean baseline	78.02	84.75
Adjusted mean change from baseline at Week 53 Difference from placebo	-62.827 -60.673 (p<0.001)	-2.154
Adjusted mean change from baseline at Week 79 Difference from placebo	-72.495 -73.499 (p<0.001)	1.004
Conversion to Amyloid Negative (visual read)	N=44	N=99
% Amyloid negative at Week 53	65.1%	11.5%
% Amyloid negative at Week 79	81.1%	21.6%
Plasma Aβ42/40	N=43	N=88
Mean baseline	0.0842	0.0855
Adjusted mean change from baseline at Week 53 Difference from placebo	0.0049 0.0048 (p=0.0029)	0.0000
Adjusted mean change from baseline at Week 79 Difference from placebo	0.0075 0.0054 (p=0.0036)	0.0021
Plasma p-tau181 (pg/mL)	N=84	N=179
Mean baseline	4.6474	4.435
Adjusted mean change from baseline at Week 53 Difference from placebo	-1.2054 -1.2718 (p<0.0001)	0.0664
Adjusted mean change from baseline at Week 79 Difference from placebo	-1.1127 -1.1960 (p<0.0001)	0.0832
CSF p-tau181 (pg/mL)	N=12	N=24
Adjusted mean change from baseline at Week 53 Difference from placebo	-9.732 -12.990 (p=0.078)	3.258
Adjusted mean change from baseline at Week 79 Difference from placebo	-10.880 -12.315 (p=0.044)	1.436

N is the number of patients with baseline value.

Table 9: Summary of biomarker results of OLE Phase

Biomarker Endpoints	BAN2401 10 mg/kg biweekly*
Amyloid Beta PET Composite SUVR	N=22
Mean OLE baseline	1.370
Adjusted mean change from baseline at Week 13	-0.088 (p<0.001)
Adjusted mean change from baseline at Week 27	-0.157 (p<0.001)
Adjusted mean change from baseline at Week 53	-0.232 (p<0.001)
Amyloid Beta PET Centiloid	N=22
Mean OLE baseline	77.20
Adjusted mean change from baseline at Week 13	-18.347 (p=0.022)
Adjusted mean change from baseline at Week 27	-40.921 (p<0.001)
Adjusted mean change from baseline at Week 53	-56.328 (p<0.001)
Conversion to Amyloid Negative (visual read)	N=17
% Amyloid negative at Week 13	42.9%
% Amyloid negative at Week 27	75.0%
% Amyloid negative at Week 53	83.3%
Plasma Aβ42/40	N=32
Mean OLE baseline	0.0857
Mean change from baseline at Week 13	0.0028
Mean change from baseline at Week 27	0.0044
Mean change from baseline at Week 53	0.0097
Plasma p-tau181 (pg/mL)	N=27
Mean OLE baseline	5.272
Mean change from baseline at Week 13	0.089
Mean change from baseline at Week 27	-0.921
Mean change from baseline at Week 53	-1.596

* Patients who were randomized to placebo in the double-blind, placebo-controlled period of Study 201 Core and received 10 mg/kg biweekly in the Open-Label Extension

Table 10: Summary results of clinical outcomes in Study 201 Core.

Clinical Endpoints	BAN2401 10 mg/kg biweekly	Placebo
ADCOMS	N=152	N=238
Mean baseline	0.373	0.370
Adjusted mean change from baseline at Week 53 Difference from placebo	0.085 -0.046 (p=0.027)	0.131
Adjusted mean change from baseline at Week 79 Difference from placebo	0.136 -0.057 (p=0.034)	0.193
CDR-SB	N=152	N=238
Mean baseline	2.97	2.89
Adjusted mean change from baseline at Week 53 Difference from placebo	0.568 -0.344 (p=0.077)	0.911
Adjusted mean change from baseline at Week 79 Difference from placebo	1.102 -0.396 (p=0.125)	1.499
ADAS-Cog 14	N=152	N=237
Mean baseline	22.06	22.56
Adjusted mean change from baseline at Week 53 Difference from placebo	1.481 -1.361 (p=0.073)	2.842
Adjusted mean change from baseline at Week 79 Difference from placebo	2.588 -2.313 (p=0.017)	4.902

N is the number of patients with baseline value.

All p-values are nominal.

- Efficacy Assessment

[350] ADCOMS: This composite clinical score represents a new approach to the analysis of selected items (12 total) from 3 fully validated and well-established clinical tools, including the MMSE, the CDR, and the ADAS-Cog. The data from 4 studies, including the Alzheimer's Disease Neuroimaging Initiative (ADNI) (MCI subset), ADCS-008, E2020-A001-412 and E2020-E033-415 have been used in a statistically validated model aimed at optimizing sensitivity to disease progression over time in the MCI population. The MMSE, the CDR, and the ADAS-Cog will each be administered to subjects using standard methods, and results will be used to calculate the ADCOMS.

- Amyloid PET

[351] All subjects who underwent amyloid PET for inclusion in the Core Study received a baseline amyloid PET scan before dosing in the Extension Phase. The baseline amyloid PET scan had to be conducted with the same imaging tracer that was used for inclusion at the baseline visit for the Core Study. In addition, qualified subjects located in the US and Japan had the option to participate in the longitudinal PET substudy. Florbetapir was used in the US and flutemetamol was used in Japan for longitudinal amyloid PET analysis. At Extension Screening Visits, subjects who consented to the longitudinal imaging substudy were stratified

into 2 cohorts based on their treatment allocation during the Core Study. Cohort 1 amyloid PET assessments are performed at baseline (Extension Screening Visit), Visit 50 (Extension Week 13), Extension Phase Visit 70 [Extension Week 53], and continue annually; Cohort 2 amyloid PET assessments are performed at baseline (Extension Screening Visit), Visit 57 (Extension Week 27), at Extension Phase Visit 70 [Extension Week 53], and continue annually. In Japan, those who consented to the longitudinal imaging substudy only underwent amyloid PET at Extension Phase Visit 70 [Extension Week 53], and continue annually.

- Sampling of blood for Exploratory Plasma Biomarkers

[352] Blood was collected from subjects at baseline (Extension Screening Visit), Extension Phase Visit 50 [Extension Week 13], Extension Phase Visit 57 [Extension Week 27], Extension Phase Visit 70 [Extension Week 53], Extension Phase Visit 83 [Extension Week 79], Extension Phase Visit 96 [Extension Week 105], Extension Phase Visit 109 [Extension Week 131], Extension Phase Visit 122 [Extension Week 157], Extension Phase Visit 135 [Extension Week 183], Extension Phase Visit 148 [Extension Week 209], Extension Phase Visit 161 [Extension Week 235], Extension Phase Visit 174 [Extension Week 261], and early termination visit.

[353] In the dosing regimen substudy, subjects will undertake a baseline plasma blood draw upon entry to the substudy and will attend site visits every 4 weeks, regardless of dosing regimen for the 1st year of the dosing regimen substudy. Blood will be drawn at each dosing regimen substudy visit for plasma biomarker monitoring to assess that baseline levels (at substudy entry) are maintained over the course of treatment at each dosing regimen. The sponsor will assess the plasma biomarker responses periodically, and if an optimal regimen is established, that regimen will be administered to all subjects in the substudy. For those subjects who are also enrolled in the optional longitudinal PET substudy, a dosing regimen substudy baseline amyloid PET assessment should be conducted before substudy Visit 1 (Week 1), unless it has been conducted within 3 months of the dosing regimen substudy Visit 1. A summary of the biomarker results is listed in Table 9.

2. P-tau181 (Core)

[354] Plasma P-tau181 was evaluated from 558 subjects (PBO: n=177, LEC2.5-BW: n=36, LEC5-M: n=38, LEC5-BW: n=70, LEC10-M: n=153, LEC10-BW: n=84). Plasma ptau181 was measured using the Quanterix™ Simoa® Advantage V2 assay. Lecanemab showed a statistically significant response at all dose levels except LEC2.5-BW in the MMRM analyses of plasma p-tau181 at 18 months, with $P < 0.0001$ for the top two doses. The least square mean changes from Baseline in plasma p-tau181 at 18 months are presented in **Fig.1**.

[355] CSF p-tau181 in the LEC10-BW group (Table 15) showed a significant reduction relative to placebo at 12 and 18 months. Lecanemab-mediated effects on p-tau181 suggests that targeting amyloid may influence the downstream neurodegenerative processes associated with AD.

Table 15: Summary of CSF Biomarker p-tau181 - Study 201 Core (PD Analysis Set)

Parameter Statistic	Placebo (N=14)	Lecanemab 10 mg/kg biweekly (N=12)
p-tau181 (pg/mL)		
n	12	10
Least Square Mean at 12 Months	3.258	-9.732
LS Mean Difference: Active - Placebo		-12.990
p-value		0.078
n	19	10
Least Square Mean at 18 Months	1.436	-10.880
LS Mean Difference: Active - Placebo		-12.315
p-value		0.044

CSF = cerebrospinal fluid, LS = least squares, PD = pharmacodynamics.
Source: Study 201 Core CSR, Table 14.2.3.1.5c.

3. Correlation Between Amyloid PET and Plasma P-Tau181 (Core)

[356] Longitudinal changes in amyloid levels are mirrored by changes in plasma p-tau181 levels during the Core Study. An increased treatment effect in amyloid brain clearance as measured by amyloid PET SUVR was associated with increased treatment effect on p-tau181 levels (**Fig. 2**; Pearson correlation coefficient = 0.840). A significant correlation between reduction in amyloid level and reduction in plasma p-tau181 at the individual subject level was observed during the Core Study (**Fig. 3**; Spearman correlation coefficient = 0.342, $P = 0.000$). An updated analysis with the PD analysis dataset of the correlation between reduction in amyloid level and reduction in plasma p-tau181 at the individual subject level is presented in **Fig. 14**.

4. Plasma P-Tau181 and Clinical Efficacy (Core)

[357] Population-level correlation between the lecanemab effect on plasma p-tau181 levels and the lecanemab effect on clinical endpoints at dose level was calculated based on the subset of subjects who had post-Baseline assessments for both endpoints (p-tau181 levels and clinical endpoints). An increased treatment effect in brain amyloid clearance as measured by changes in p-tau181 levels was associated with increased treatment effect on CDR-SB (**Fig. 4**, Pearson correlation coefficient = 0.463), ADCOMS (**Fig. 5**, Pearson correlation coefficient = 0.284), and ADAS-Cog14 (**Fig. 6**, Pearson correlation coefficient = 0.327).

5. P-Tau181 (Open Label Extension (OLE))

[358] In the OLE Phase, both newly treated Core Study placebo subjects and re-treated LEC10-BW and LEC10-M subjects showed a decrease in plasma p-tau181 following treatment with LEC10-BW (**Fig. 7**), which, without being bound by theory, is likely associated with lecanemab clearing newly generated amyloid including protofibrils even after amyloid plaque removal. The largest decrease in plasma p-tau181 is seen in the newly treated Core Placebo group, the group which had the largest PET SUVR reduction from OLE Baseline, with a statistically significant reduction ($P < 0.001$) seen as early as 3 months (Week

13 Visit, amyloid reduction of 0.09 SUVR) and amyloid reduction of 0.16 ($p < 0.001$) SUVR at Week 27,, and which was maintained through to the 24 month visit in the OLE.

6. Correlation Between Amyloid PET and Plasma P-Tau 181 (OLE)

[359] The correlations observed in the OLE replicate those seen in the Core. There is a strong correlation between change from OLE Baseline in plasma p-tau181 level and change from OLE Baseline in amyloid PET SUVR ($r = -0.743$, $P = 0.022$) (**Fig. 8**).

7. Correlations Between Amyloid PET SUVR, Plasma A β 42/40, and Plasma P-Tau181 from Study 201 Core, Gap Period, and OLE

[360] Treatment with lecanemab reduced amyloid PET SUVR and this reduction was correlated with statistically significant increase in plasma A β 42/40 ratio and decrease in plasma p-tau181 in the Study 201 Core. Similar relationships were noted in the OLE Phase.

[361] During the 24-month average Gap Period, while subjects were off treatment, a gradual decrease in plasma A β 42/40 ratio was observed, with slight increases in plasma p-tau181 and amyloid levels (amyloid accumulation) as measured using PET SUVR observed over the same period. In the OLE Phase, treatment with LEC10-BW resulted in rapid reduction in amyloid plaque, which correlated with corresponding increase in plasma A β 42/40 and decrease in p-tau181. See **Fig. 9**.

CDR-SB

[362] The pattern of individual subject-level changes with LEC10-BW in Study 201 Core showed a decrease in amyloid PET SUVR and slower progression on CDR-SB, while placebo subjects showed an increase in amyloid PET SUVR and fast progression on CDR-SB (**Fig. 15**). During the Gap Period, while some treatment effect was maintained for lecanemab-treated subjects, all Core Study treatment groups showed overall progression in CDR-SB with a small general increase in amyloid PET SUVR. In the OLE Phase, Core placebo subjects showed a similar pattern to those who were treated with LEC10-BW in Study 201 Core, where decreases in amyloid PET SUVR were generally accompanied by slower progression on CDR-SB.

[363] The pattern of individual subject-level changes with LEC10-BW in plasma A β 42/40 ratio versus CDR-SB in the Study 201 Core, Gap Period, and OLE Phase were inverse to that observed for amyloid PET SUVR (**Fig. 15**).

[364] The pattern of individual subject-level changes with LEC10-BW in plasma p-tau181 versus CDR-SB in the Study 201 Core, Gap Period, and OLE Phase were similar to that observed for amyloid PET (**Fig. 15**) and showed a strong dose-dependent and statistically significant reduction in subjects treated with LEC10-BW. Plasma p-tau181 levels showed significant correlations with amyloid PET SUVR and plasma A β 42/40 ratio, and reductions in plasma p-tau181 were associated with slowing of clinical decline.

ADCOMS

[365] The pattern of individual subject-level changes with LEC10-BW in plasma p-tau181 (**Fig. 16**) versus ADCOMS in the Study 201 Core, Gap Period, and OLE Phase were similar to that observed for CDR-SB.

ADAS-Cog14

[366] The pattern of individual subject-level changes with LEC10-BW in plasma p-tau181 (**Fig. 17**) versus ADAS-Cog14 in the Study 201 Core, Gap Period, and OLE Phase were similar to that observed for ADCOMS and CDR-SB.

8. Effects of Dosing and Dosing Frequency (Including Modeling)

Methods:

[367] From the PK model previously developed with PK data from earlier studies, including CORE and OLE, and Bayesian predictions of PK parameters for each subject were made, using the NONMEM POSTHOC function. For Bayesian predictions of PK parameters for each subject, final PK model with old dataset was used. These predicted parameters were used to generate individually predicted PK profile, which were then incorporated into the analyses datasets to be used in the subsequent analyses.

PK/PD Model for Plasma p-tau181

[368] Absolute plasma p-tau181 measurements over time ($R(t)$) were related to model-predicted lecanemab serum concentration at the time of the assessment. A high plasma p-tau181 is indicative of elevated amyloid in the brain, therefore treatment aimed toward reducing brain amyloid is expected to decrease the plasma p-tau181. The relationship between the lecanemab concentration and the p-tau181 change time course was described by an indirect response model with the lecanemab concentration as a linear function decreasing the plasma p-tau181 formation rate, as indicated in **Fig. 10**.

[369] The equation for p-tau181 PK/PD model is presented below:

$$\frac{dR}{dt} = K_{in} \cdot [1 - SLOPE \cdot Conc] - R(t) \cdot K_{out}$$

$$K_{in} = Baseline \cdot K_{out}$$

[370] Estimated parameters included baseline plasma p-tau181, indirect response parameters (K_{in} and K_{out}) and slope of drug effect (SLOPE). E_{max} function was also explored. Inter-individual variability was estimated for the baseline and SLOPE. Residual variability was modeled using proportional model.

[371] This model was applied to pooled data from lecanemab treatment arms in Study 201 Core and OLE with placebo arm in Study 201 Core. Estimation of model parameters was performed using FOCEI.

[372] Covariate analysis was performed for the effect of APOE4 carrier status, sex, AD diagnosis (MCI or mild AD), ADA and neutralizing ADA (NAb) at subject level on baseline, K_{out} and SLOPE, age and body weight on baseline and SLOPE and baseline p-tau181 on SLOPE. If the ADA sample was positive, an NAb assay was performed. In the categorical covariate analysis of NAb status at subject level, ADA(+)/NAb(+) was assigned as NAb positive, and ADA(+)/NAb(-) or samples with missing NAb category (NAb assay was not performed) were assigned as NAb negative. One subject (ID=195) had ADA(-) but NAb(+) result, and this subject was assigned as NAb positive.

Relationship between Plasma p-tau181 and Amyloid PET or Clinical Efficacy Endpoints

[373] Bayesian predictions of PD parameters for each subject were made, using the NONMEM POSTHOC function using the developed PK/PD for p-tau181. These predicted parameters were used to generate individually predicted plasma p-tau181 concentration profile, which was then incorporated into the datasets for relationship between p-tau181 and amyloid PET or clinical efficacy endpoints to be used in the subsequent analyses.

Model for Relationship between Plasma p-tau181 and Amyloid PET SUVR

[374] Change from baseline (CFB) of PET SUVR (*CFB SUVR*) was related to model-predicted CFB of plasma p-tau181 (*CFB PTAU*) at the time of the assessment. The relationship between the CFB of plasma p-tau181 and CFB of PET SUVR was described by a direct response sigmoidal E_{max} model as indicated in the following equation:

$$CFB\ SUVR = INT + \frac{E_{max} \cdot CFB\ PTAU^{Hill}}{E50^{Hill} + CFB\ PTAU^{Hill}}$$

[375] Estimated parameters included intercept (INT), maximum drug effect (E_{max}), CFB of plasma p-tau181 resulting in half of the maximum drug effect ($E50$) and Hill coefficient (Hill). Linear function was also tested. Inter-individual variability as proportional model was estimated for the parameters. Residual variability was modeled using an additive model.

[376] This model was applied to data from Study 201 Core and OLE. Estimation of model parameters was performed using FOCEI.

Model for Relationship between Plasma p-tau181 and Amyloid PET SUVR - Predicted Changes During Maintenance Period

[377] The relationship between the CFB of plasma p-tau181 (*CFB PTAU*) and CFB of SUVR was described by a direct response sigmoidal E_{max} model as indicated in the following equation:

$$CFB\ SUVR = (0.593 \cdot CFB\ PTAU^{0.555}) / (1.59^{0.555} + CFB\ PTAU^{0.555})$$

[378] **Fig. 13** demonstrates the model predicted CFB in SUVR with increasing CFB in plasma p-tau181. Model predicted mean decrease from baseline in plasma p-tau181 is 0.765 pg/mL for a dosing regimen of 10 mg/kg bi-weekly for 18 months. Assuming that baseline SUVR is 1.4, 0.765 pg/mL decrease in plasma p-tau181 from baseline can attain 0.237-unit reduction in SUVR from baseline to reach an amyloid negativity for PET SUVR (<1.17) as measured using florbetapir (Fleisher, et al., 2011).

Model for Relationship between Plasma p-tau181 and Amyloid PET SUVR Clinical Efficacy Endpoint

[379] To explore the relationship between CFB of plasma p-tau181 and clinical efficacy endpoints (CDR-SB, ADCOMS and ADAS-Cog), model predicted CFB of plasma p-tau181 was also evaluated as a predictor of the efficacy endpoints (referred to as the plasma p-tau181–efficacy model), as indicated in **Fig. 11**.

[380] Absolute clinical efficacy endpoint score (*EFF*) over time was related to model-predicted CFB of plasma p-tau181 at the time of the assessment. The relationship between the CFB of the p-tau181 and clinical efficacy endpoint time course was described by a model

correlating decrease from baseline of the plasma p-tau181 with slower disease progression. The equation for plasma p-tau181–efficacy is presented below:

$$EFF = INT + SLP \cdot (1 - KPTAU \cdot CFB) \cdot Time$$

[381] Estimated parameters included baseline clinical score (*INT*), the effect of change from baseline of plasma p-tau181 on the disease progression (*KPTAU*) and disease progression rate (*SLP*). Inter-individual variability was estimated for all parameters. Residual variability was modeled using combined proportional and additive model.

[382] This model was applied to data from Study 201 Core (placebo and lecanemab treatment arms). Estimation of model parameters was performed using FOCEI.

[383] For PK/PD analysis of plasma p-tau181, all subjects receiving lecanemab with serum PK information or receiving placebo in Study 201 Core and who had baseline and at least one post-dose p-tau181 assessment were included. Subjects treated with lecanemab 10 mg/kg bi-weekly in OLE and who had baseline and post-dose p-tau181 assessment were also included.

[384] For plasma p-tau181-amyloid PET SUVR modeling, subjects receiving lecanemab or placebo in Study 201 Core and OLE and who had baseline and at least one post-dose p-tau181 assessment as well as baseline and at least one post-dose PET SUVR value were included. Subjects receiving lecanemab in Study 201 Core and who did not have a Core baseline value of PET SUVR were excluded because CFB could not be calculated.

[385] For plasma p-tau181-efficacy modeling, subjects receiving lecanemab or placebo in Study 201 Core and who had baseline and at least one post-dose p-tau181 assessment baseline and at least one post-dose CDR-SB, ADCOMS and ADAS-cog value were included.

[386] Population mean plasma p-tau181-time profiles were simulated for the following dosing regimens, based on the estimates from the final PK/PD model.

[387] 10 mg/kg bi-weekly for 42 months.

[388] 10 mg/kg bi-weekly for 18 months, followed by 24 months treatment discontinuation.

[389] 10 mg/kg bi-weekly for 18 months, followed by 10 mg/kg monthly for 24 months.

[390] 10 mg/kg bi-weekly for 18 months, followed by 10 mg/kg every 3 months for 24 months.

Results:

[391] **Fig. 18** summarizes the model-predicted, dose-dependent decrease in SUVR and p-tau181 and increase in Aβ42/40 ratio following 18 months treatment with lecanemab at 10 mg/kg biweekly or 10 mg/kg monthly.

[392] As depicted in **Fig. 12**, when treatment at 10 mg/kg bi-weekly is continued beyond 18 months, plasma p-tau181 level is predicted to continue decreasing further, whereas once treatment is discontinued after 18 months plasma p-tau181 level is predicted to start to increase slowly. A maintenance dose of 10 mg/kg monthly is predicted to maintain plasma p-tau181 level at a level achieved following 18 months of treatment at 10 mg/kg bi-weekly.

[393] For alternative dosing regimens at 10 mg/kg bi-weekly with a monthly maintenance dose of 10 mg/kg for 18 months, the plasma p-tau181 level is predicted to be maintained at a relatively constant level for a duration of 2 years of treatment. However, for a dosing regimen of 10 mg/kg bi-weekly for 18 months followed by a maintenance dose of 10 mg/kg every 3 months for 2 years, the plasma p-tau181 level starts to increase gradually,

slightly at a lower rate compared to that following treatment discontinuation after 18 months of treatment at 10 mg/kg.

[394] Modeling data in **Fig. 19** illustrates that when treatment at 10 mg/kg biweekly is continued beyond 18 months, amyloid PET SUVR is predicted to continue declining to the lower bound of SUVR = 1.0, whereas once treatment is discontinued after 18 months, amyloid PET SUVR is predicted to start increasing slowly and take over 15 years for amyloid to reaccumulate to baseline levels prior to treatment initiation with lecanemab. Plasma A β 42/40 ratio and p-tau181 is predicted to take approximately 6 - 8 years for both biomarkers to reach a plateau by continuous lecanemab dosing at 10 mg/kg biweekly, or to return to baseline levels after the treatment discontinuation.

Conclusions:

PK/PD analysis for Plasma p-tau181

[395] For plasma p-tau181 PK/PD analysis, data from 562 subjects receiving lecanemab or placebo in Study 201 Core and OLE were included in the analysis (PD Analysis Set).

[396] Absolute plasma p-tau181 measurements over time were related to model-predicted lecanemab serum concentration at the time of the assessment. A high plasma p-tau181 is indicative of elevated amyloid in the brain, therefore treatment aimed toward reducing brain amyloid is expected to decrease the plasma p-tau181. The relationship between the lecanemab concentration and the p-tau181 change time course was best described by an indirect response model with the lecanemab concentration as a linear function decreasing the plasma p-tau181 formation rate. The half-life of plasma p-tau181 is estimated to be approximately 1.5 years which is comparable to that for plasma A β 42/40 ratio (approximately 1.9 years) but shorter than the half-life of PET SUVR (approximately 4 years). This suggests that p-tau181 would return to pretreatment levels after 4-5 half-lives, e.g., 6-7.5 years. This supports the finding that plasma p-tau181 and plasma A β 42/40 ratio may be earlier indicators of brain amyloid accumulation assessed by PET.

[397] Covariate analysis was performed for the effect of body weight, age, APOE4 carrier status, sex, AD diagnosis (MCI or mild AD), ADA and neutralizing ADA at subject level and baseline p-tau181. Except for a small effect of body weight on baseline plasma p-tau181, no other covariates examined (ADA and NAb status at subject level, APOE4 carrier status, sex, AD diagnosis on baseline, K_{out} and slope, and age and weight on baseline and slope, and baseline plasma p-tau181 value on slope) were identified to be significant. For a 50 kg subject (5th percentile of dataset), baseline plasma p-tau181 is 11.7% higher, and for a 96 kg subject (95th percentile of dataset), baseline plasma p-tau181 is 8.2% lower than a typical 72 kg subject (median body weight of dataset).

[398] The final plasma p-tau181 PK/PD model was implemented for simulations to explore the effects of dosing regimens on plasma p-tau181 reduction. Simulations showed that following 18 months of treatment 10 mg/kg bi-weekly dosing results in a larger and faster decrease in plasma p-tau181 with time compared to 10 mg/kg monthly dosing.

Conclusions from the PK/PD analysis for p-tau181 are:

[399] The relationship between serum lecanemab concentration and plasma p-tau181 time course in Study 201 Core and OLE was well characterized by an indirect response model with lecanemab exposure as a linear function decreasing plasma p-tau181. All key model parameters were estimated with good precision (%RSE < 25%).

[400] Except for a small effect of body weight on baseline plasma p-tau181, no other covariates examined (ADA and NAb status at subject level, *APOE4* carrier status, sex, AD diagnosis on baseline, K_{out} and slope, age and weight on baseline and slope, and baseline plasma p-tau181 value on slope) were identified to be significant. The effect of body weight on baseline p-tau181 is minimal and of no clinical relevance.

[401] Simulations showed that following 18 months of treatment, 10 mg/kg bi-weekly dosing results in a larger and faster decrease in plasma p-tau181 with time compared to 10 mg/kg monthly dosing.

[402] Simulations suggest that a maintenance dose of 10 mg/kg monthly is predicted to maintain plasma p-tau181 at a level achieved following 18 months of treatment at 10 mg/kg bi-weekly.

Relationship between Plasma p-tau181 and Amyloid PET SUVR

[403] For plasma p-tau181-amyloid PET SUVR modeling, data from 329 subjects receiving lecanemab or placebo in Study 201 Core and OLE were included in the analysis. Final exposure-p-tau181 model was used to generate ad-hoc model-imputed typical individual p-tau181 profiles for 21 subjects without p-tau181 observations based on the individual covariates and the final covariate model.

[404] To explore if p-tau181 is a predictor of PET SUVR, the relationship between the CFB of plasma p-tau181 and CFB of SUVR was subjected to nonlinear mixed effects modeling. The relationship between the CFB of plasma p-tau181 and CFB of PET SUVR was well described by a direct sigmoidal E_{max} model with the CFB of plasma p-tau181 increasing the CFB of SUVR. All key model parameters were estimated with good precision (%RSE <21%). Decrease in plasma p-tau181 was a significant predictor of PET SUVR reduction ($P < 0.001$).

[405] Model-predicted mean decrease from baseline in plasma p-tau181 is 0.765 pg/mL for a dosing regimen of LEC10-BW for 18 months. Assuming that baseline SUVR is 1.4, 0.765 pg/mL decrease in plasma p-tau181 from baseline can attain 0.237-unit reduction in SUVR from baseline to reach brain amyloid negativity for PET SUVR (<1.17) as measured using florbetapir.

[406] None of the covariates examined (age, body weight, *APOE4* carrier status, sex, AD diagnosis, ADA and NAb at subject level and baseline plasma p-tau181 value) were identified to be significant on the relationship between plasma p-tau181 and brain amyloid PET SUVR.

[407] Covariate analysis was performed for the effect of age, weight, *APOE4* carrier status, sex, AD diagnosis (MCI or mild AD), ADA and neutralizing ADA at subject level and baseline p-tau181. However, none of these covariates were found to have a significant effect on the relationship between plasma p-tau181 and PET SUVR.

Conclusions from the Analysis for Relationship between Plasma p-tau181 and Amyloid PET SUVR:

[408] Plasma p-tau181 was a significant predictor ($p < 0.001$) of SUVR reduction. The relationship between the CFB of plasma p-tau181 and CFB of SUVR was well described by a direct sigmoidal E_{max} model with the CFB of plasma p-tau181 increasing the CFB of SUVR. All key model parameters were estimated with good precision (%RSE < 21%).

[409] None of the covariates examined (age, weight, *APOE4* carrier status, sex, AD diagnosis, ADA, neutralizing ADA at subject level and baseline plasma p-tau181 value) were

identified to be significant on the relationship between plasma p-tau181 and amyloid PET SUVR.

[410] Model predicted mean decrease from baseline in plasma p-tau181 is 0.765 pg/mL for a dosing regimen of 10 mg/kg bi-weekly for 18 months. Assuming that baseline SUVR is 1.4, 0.765 pg/mL decrease in plasma p-tau181 from baseline can attain 0.237-unit reduction in SUVR from baseline to reach an amyloid negativity for PET SUVR (<1.17) as measured using florbetapir.

Relationship between Plasma p-tau181 and Clinical Efficacy Endpoints

[411] Relationships between the increase of plasma p-tau181 and key clinical endpoints (CDR-SB, ADCOMS and ADAS-Cog) were explored based on data from 829 subjects (828 subjects for ADAS-Cog) in Study 201 Core. As there were p-tau181 observations for 562 subjects in the p-tau181-efficacy dataset, the final exposure-p-tau181 model was used to generate ad-hoc model-imputed typical individual p-tau181 profiles for 267 subjects without p-tau181 observations based on the individual covariates and the final covariate model.

[412] To explore if p-tau181 is a predictor of slowing cognitive decline, relationships for change from baseline (CFB) of plasma p-tau181 versus CFB of clinical endpoints over 18 months of treatment with different dosing regimen of lecanemab or placebo were subjected to nonlinear mixed effects modeling. Absolute clinical efficacy endpoint score over time was related to model-predicted CFB of plasma p-tau181 at the time of the assessment. The relationship between the CFB of the p-tau181 and clinical efficacy endpoint time course was described by a model correlating decrease from baseline of the plasma p-tau181 with slowing of cognitive decline. In all models examined IIV on CDR-SB baseline was modeled using proportional model whereas IIV on disease progression rate (SLP) and rate constant for the effect of change of plasma p-tau181 was evaluated using additive model. Residual variability was modeled using combined additive and proportional models. For CDR-SB, ADCOMS and ADAS-Cog, decrease in plasma p-tau181 from baseline over a treatment period of 18 months was a significant predictor of slowing cognitive decline.

[413] In each analysis, univariate analysis was performed for the effect of ADA and neutralizing ADA (NAb) at subject level, APOE4 carrier status, sex, and AD diagnosis (MCI or mild AD), age and body weight on CDR-SB baseline, disease progression rate and rate constant for the effect of change of plasma p-tau181. For CDR-SB there were significant effects of mild AD dementia on baseline CDR-SB and effect of concomitant acetylcholine esterase inhibitors (AChEI) on progression rate. Baseline CDR-SB is 70% higher in subjects with mild AD than in subjects with MCI due to AD and progression rate was 65% in subjects receiving concomitant AChEI. For ADCOMS there were significant effects of mild AD dementia and concomitant AChEI on baseline ADCOMS and effect of concomitant AChEI on progression rate. Baseline ADCOMS is 60% higher in subjects with mild AD than in subjects with MCI due to AD and 9% higher with concomitant AChEI and progression rate is 43% higher with concomitant AChEI. For ADAS-Cog there were significant effects of mild AD dementia and body weight on baseline ADAS-Cog and effects of mild AD dementia, concomitant AChEI and age on progression rate. Baseline ADAS-Cog and progression rate are 30% and 53% higher, respectively, in subjects with mild AD than in subjects with MCI due to AD and progression rate is 137% higher with concomitant AChEI. Baseline ADAS-Cog declines with an exponent of 0.248 with body weight whereas disease progression decreases with an exponent of 2.41 with age. For a typical 50 kg subject (5th percentile of dataset), baseline ADAS-Cog is 9.7% higher, and for a typical 98 kg subject (95th percentile of dataset), baseline ADAS-Cog is 7.0% lower than a typical 73 kg subject (median body

weight of dataset). In addition, younger age was associated with faster rate of progression of ADAS-Cog. A typical 56-year-old subject (5th percentile of dataset) had an 84.6% faster, and an typical 85-year-old subject (95th percentile of dataset) had a 49.1 % slower rate compared to a typical 72-year-old subject [median age of dataset]).

[414] The plasma p-tau181–CDR-SB/ADCOMS/ADAS-Cog models showed that greater reduction of plasma p-tau181 was a significant predictor ($P < 0.001$) of slowing of cognitive decline as measured by CDR-SB, ADCOMS and ADAS-Cog. Model predicted disease progression rates for CDR-SB, ADCOMS and ADAS-Cog were reduced by 5.90%, 4.26% and 5.82%, respectively, for every 0.2 pg/mL reduction from baseline in plasma p-tau181. The model predicted reduction from baseline in plasma p-tau181 over 18 months of 10 mg/kg bi-weekly was 0.765 pg/mL; the model predicts corresponding reduction of progression rates in CDR-SB, ADCOMS and ADAS-Cog of 22.6%, 16.3% and 22.3%, respectively.

Conclusions from the Analyses for Relationship between Plasma p-tau181 and Clinical Efficacy Endpoints:

[415] The relationship between the CFB of p-tau181 and each clinical efficacy endpoint time course was best described by a model that associates the greater change from baseline of plasma p-tau181 with slowing of cognitive decline. For each efficacy endpoint analysis, key model parameters were estimated with good precision (%RSE < 30%).

[416] For CDR-SB, ADCOMS and ADAS-Cog, decrease in plasma p-tau181 from baseline over a treatment period of 18 months was a significant predictor ($p < 0.001$) of slowing cognitive decline.

[417] Model predicted disease progression rates in CDR-SB, ADCOMS and ADAS-Cog were reduced by 5.90%, 4.26% and 5.82%, respectively, for every 0.2 pg/mL reduction from baseline in plasma p-tau181.

[418] For lecanemab 10 mg/kg bi-weekly, the model predicted reduction from baseline in plasma p-tau181 over 18 months of 10 mg/kg bi-weekly was 0.765 pg/mL; the corresponding model predicted reduction of progression rates in CDR-SB, ADCOMS and ADAS-Cog were 22.6%, 16.3% and 22.3%, respectively.

Abbreviation used in the examples

A β	amyloid beta
A β (1-42)	amyloid beta monomer from amino acid 1 to 42
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale - Cognitive Subscale
ADCOMS	Alzheimer's Disease Composite Score
ADNI	Alzheimer's Disease Neuroimaging Initiative
APOE	Apolipoprotein E
APOE4	apolipoprotein ϵ 4 variant
ARIA	amyloid-related imaging abnormalities
ARIA-E	amyloid related imaging abnormality edema/effusion
ARIA-H	amyloid related imaging abnormality hemorrhage
BAN2401	a humanized IgG1 monoclonal antibody
BQL	Below Quantifiable Limit
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating – Sum of Boxes
COVID-19	Coronavirus Disease 2019
CSF	cerebrospinal fluid
EAD	early Alzheimer's Disease
FAQ	Functional Assessment Questionnaire
FOCEI	First order conditional estimation with interaction
IV	intravenous
LC-MS/MS	liquid chromatography – tandem mass spectrometry
MCI	mild cognitive impairment
MMRM	mixed-effects model with repeated measures
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
NIA-AA	National Institute of Aging-Alzheimer's Association
NONMEM	Nonlinear mixed effects model
OLE	open-label extension
PET	positron emission tomography
PD	pharmacodynamics
p-tau	phospho-tau
RAR	response adaptive randomization
SE	standard error
SUVr	standard uptake value ratio
t _{1/2}	terminal elimination half-life

t-tau

total tau

vMRI

volumetric magnetic resonance imaging

CLAIMS

1. A method of treating Alzheimer's disease (AD) in a subject having or suspected of having AD, comprising:

- a. measuring or having measured a level of p-tau181 in a blood sample obtained from the subject; and
- b. if the subject has a level of p-tau181 above a threshold, administering a treatment comprising a therapeutically effective dose of an anti-amyloid β (A β) protofibril antibody to the subject,

wherein the anti-A β protofibril antibody comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 7 and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 8.

2. The method of claim 1, further comprising:

- a. measuring a second level of p-tau181 in a second blood sample obtained from the subject after the first sampling; and
- b. if the subject has a level of p-tau181 above a threshold, administering a second therapeutically effective dose comprising the same amount of the anti-A β protofibril antibody as in the first dose to the subject.

3. The method of claim 1, further comprising:

- a. measuring a second level of p-tau181 in a second blood sample obtained from the subject after the first sampling; and
- b. if the subject has a level of p-tau181 at or below a threshold, administering a second therapeutically effective dose comprising the same amount or lower of the anti-A β protofibril antibody as in the first dose to the subject.

4. A method of selecting a subject for treatment with an anti-amyloid β (A β) protofibril antibody, comprising

- a. measuring or having measured a p-tau181 level in a blood sample obtained from the subject; and
- b. selecting the subject for treatment with an anti-amyloid β (A β) protofibril antibody if the level is above a threshold value.

5. A method of monitoring treatment efficacy in a subject having or suspected of having AD, comprising:

administering to the subject a dose of an anti-A β protofibril antibody;

measuring or having measured a post-dose level of p-tau181 in a blood sample obtained from the subject; and

comparing the post-dose level of the blood sample to a blood sample obtained from the subject prior to the administration of the first dose of the anti-A β protofibril

antibody or to a control level, wherein the treatment is considered effective if the post-dose level is lower than the level prior to the first dose or the control level.

6. A method of detecting a decrease in a brain A β level, comprising:
 - measuring or having measured a first level of p-tau181 in a first blood sample obtained from a subject prior to administration of an anti-A β protofibril antibody;
 - administering to the subject a dose of the anti-A β protofibril antibody;
 - measuring or having measured a second level of p-tau181 in a second blood sample obtained from the subject after administration of the anti-A β protofibril antibody;
 - comparing the first and second levels,
wherein a second level that is lower than the first level indicates a decrease of brain amyloid β in the subject.
7. The method of any one of claims 1-6, wherein the level of p-tau181 is measured without a brain amyloid measurement by PET.
8. The method of any one of claims 1-6, further comprising measuring brain amyloid level in the subject before and/or after treatment.
9. The method of claim 8, wherein a reduction in the PET SUVR value indicates a reduction in brain amyloid level.
10. The method of any one of claims 1-9, wherein the subject has Alzheimer's disease.
11. The method of any one of claims 1-9, wherein the subject has early Alzheimer's disease.
12. The method of any one of claims 1-9, wherein the subject has pre-Alzheimer's disease (pre-AD).
13. The method of any one of claims 1-9, wherein the subject has Alzheimer's disease, Down's Syndrome, chronic traumatic encephalopathy, cerebral amyloid angiopathy, Lewy Body Dementia, or another brain disease or conditions with A β peptide-containing soluble and/or insoluble A β aggregates.
14. The method of any one of claims 1-9, wherein the subject has been diagnosed with
 - a. mild cognitive impairment due to Alzheimer's disease - intermediate likelihood and/or has been diagnosed as having mild Alzheimer's disease dementia.;
 - b. mild cognitive impairment due to Alzheimer's disease - intermediate likelihood by National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria;
 - c. mild cognitive impairment due to Alzheimer's disease - intermediate likelihood by a CDR global score of 0.5 and a Memory Box score of 0.5 or greater before treatment;

- d. mild cognitive impairment due to Alzheimer's disease - intermediate likelihood by a history of subjective memory decline with gradual onset and slow progression over the last 1 year before treatment;
 - e. mild Alzheimer's disease dementia by the NIA-AA core clinical criteria for probable Alzheimer's disease dementia; or
 - f. mild Alzheimer's disease dementia by a CDR score of 0.5 to 1.0 and a Memory Box score of 0.5 or greater before treatment.
15. The method of any one of claims 1-14, wherein the subject is amyloid-positive prior to administration.
16. The method of any one of claims 1-15, wherein the subject has at least one copy of the ApoE4 gene.
17. The method of any one of claims 1-16, wherein the p-tau181 is measured using an LC MS/MS platform.
18. The method of claim 3 or claim 6, wherein if the second level is lower than the first level, the subject is indicated as converted from amyloid-positive to amyloid-negative, or wherein treatment is discontinued if it does not result in a level below a threshold.
19. The method of any one of claims 1-18, wherein the anti-A β protofibril antibody is administered as an intravenous infusion at a therapeutically effective dose of 10 mg/kg relative to the weight of the subject.
20. The method of claim 19, wherein the therapeutically effective dose is administered every 2 weeks.
21. The method of claim 20, wherein the frequency of administration is reduced after 18 months of treatment.
22. The method of claim 20 or 21, wherein the therapeutically effective dose is reduced after 18 months of treatment.
23. The method of claim 20, wherein the frequency of administration is reduced, after a subject exhibits a level of p-tau181 in a blood sample at or below a threshold.
24. The method of claim 20 or 23, wherein the therapeutically effective dose is reduced after a subject exhibits a level of p-tau181 in a blood sample at or below a threshold.
25. The method of any one of claims 1-18, wherein the anti-A β protofibril antibody is administered subcutaneously at a therapeutically effective dose of 720 mg.
26. The method of claim 25, wherein the therapeutically effective dose is administered weekly.
27. The method of claim 26, wherein the frequency of administration is reduced after 18 months of treatment.

28. The method of claim 26 or 27, wherein the therapeutically effective dose is reduced after 18 months of treatment.
29. The method of claim 26, wherein the frequency of administration is reduced after a subject exhibits a level of p-tau181 in a blood sample at or below a threshold.
30. The method of claim 26 or 29, wherein the therapeutically effective dose is reduced after a subject exhibits a level of p-tau181 in a blood sample at or below a threshold.
31. The method of any one of claims 21-30, wherein the reduced therapeutically effective dose and/or frequency is increased if a subject exhibits a level of p-tau181 in a blood sample above a threshold.
32. The method of any one of claims 1-31, wherein the anti-A β protofibril antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 9 and a light chain comprising an amino acid sequence of SEQ ID NO: 10.
33. The method of any one of claims 1-32, wherein the subject is sequentially or simultaneously administered at least one additional AD medication.
34. The method of any one of claims 1-33, wherein the method results in:
- a. a reduction or a slowing of increase of cerebrospinal fluid biomarkers; and/or
 - b. a reduction or a slowing of increase of plasma or serum biomarkers;
- as compared to before treatment.
35. The method of any one of claims 1-34, wherein the treatment
- a. delays clinical decline as determined by ADCOMS;
 - b. delays clinical decline as determined by ADAS MCI-ADL;
 - c. delays clinical decline as determined by modified iADRS;
 - d. delays clinical decline as measured by a CDR-SB; or
 - e. delays clinical decline as measured by an ADAS-Cog.
36. The method of any one of claims 1-35, wherein the method further comprises monitoring for ARIA.
37. The method of any one of the claims 1-36, wherein the method does not require a titration step prior to administering to the subject a first therapeutically effective dose of the anti-A β protofibril antibody.
38. A method of treating pre-Alzheimer's disease (pre-AD) in a subject, comprising
- a. measuring or having measured a level of p-tau181 in a blood sample obtained from the subject; and
 - b. if the subject has a level of p-tau181 above a threshold, administering a treatment comprising a therapeutically effective dose of an anti-amyloid β (A β) protofibril antibody to the subject,

wherein the anti-A β protofibril antibody comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 7 and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 8.

39. The method of claim 38, wherein the subject is switched to a maintenance dosing regimen at or before 18 months of treatment, e.g., when the level of p-tau181 is at or below a threshold.

40. The method of claim 38 or 39, wherein the subject has intermediate brain amyloid.

41. A method of treating Alzheimer's disease (AD) in a subject having or suspected of having AD, comprising:

- a. measuring or having measured a first level of phosphorylated tau181 (p-tau181) in a first blood sample obtained from the subject;
- b. administering a treatment dosing regimen comprising a therapeutically effective dose of an anti-amyloid β (A β) protofibril antibody to the subject having a level of p-tau181 above a threshold; and
- c. determining that a subsequent level of p-tau181 in a blood sample from the patient is at or below a threshold and switching to a maintenance dosing regimen,

wherein the anti-A β protofibril antibody comprises a heavy chain variable region comprising an amino acid sequence of SEQ ID NO: 7 and a light chain variable region comprising an amino acid sequence of SEQ ID NO: 8.

42. The method of claim 41, wherein the switch to a maintenance dose occurs after at least 6 months following the start of the treatment dosing regimen.

43. The method of claim 41 or 42, wherein the treatment dosing regimen comprises administering the anti-A β protofibril antibody as an intravenous infusion at a therapeutically effective dose of 10 mg/kg relative to the weight of the subject every two weeks.

44. The method of any one of claims 41-43, wherein the treatment dosing regimen comprises administering the anti-A β protofibril antibody subcutaneously at a therapeutically effective dose of 720 mg weekly.

45. The method of any one of claims 41-44, wherein the maintenance dosing regimen comprises an intravenous infusion at a therapeutically effective dose of 10 mg/kg relative to the weight of the subject every two weeks.

46. The method of any one of claims 41-44, wherein the maintenance dosing regimen comprises administering the anti-A β protofibril antibody subcutaneously at a therapeutically effective dose of 720 mg biweekly or at a weekly dose of 360 mg.

47. The method of any one of claims 41-46, wherein a decrease in p-tau181 is detected in a blood sample from the subject before switching to a maintenance dose.

48. The method of any one of claims 41-47, wherein a brain amyloid negativity as measured by PET SUVR is detected in the subject before switching to a maintenance dose.

49. The method of any one of claims 41-48, wherein the maintenance dose is administered at a dose and/or frequency selected to maintain
- a. a level of p-tau181 in a blood sample from the patient at or below a threshold;
and/or
 - b. a florbetapir PET SUVR level at or below 1.17.