Statistical Analysis Plan I5T-MC-AACH (Version 2)

Donanemab Follow-On Study: Safety, Tolerability, And Efficacy in Symptomatic Alzheimer's Disease With Validation of Remote Neuropsychological Assessments

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1. Statistical Analysis Plan: I5T-MC-AACH: Donanemab Follow-On Study: Safety, Tolerability and Efficacy in Symptomatic Alzheimer's Disease with Validation of Remote Neuropsychological Assessments

LY3002813

I5T-MC-AACH is a multicenter, randomized, open-label, Phase 2 study up to 124 weeks in approximately 200 patients with early symptomatic AD who have completed study I5T-MC-AACG.

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Protocol I5T-MC-AACH
Phase 2

SAP version 2 was approved on date provided below:

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3. Revision History

The original version of the statistical analysis plan was approved 15-Oct-2018, prior to first patient visit. Version 2 included modifications to the description of Part C analyses that incorporate data across both the feeder study and this follow-on study. Additionally, version 2 updates the feeder studies to include I5T-MC-AACC.

4. Study Objectives

Table AACH.4.1. Objectives and Endpoints

Primary Objective	Primary Endpoint
Part A To evaluate the reliability of VTC compared with on-site administered cognitive and functional measures	The intraclass correlation between VTC and on-site assessment for PAIR 1 for • ADAS-Cog$_{13}$ • ADCS-ADL • MMSE • CDR-SB
Part B To evaluate safety and tolerability of donanemab	Standard safety assessments in Part B: • Spontaneously reported AEs • Clinical laboratory tests • Vital sign and body weight measurements • 12-lead ECGs • Physical and neurological examinations MRI (ARIA and emergent radiological findings) Infusion-related reactions C-SSRS
Secondary Objectives	**Secondary Endpoints**
To assess the effect of donanemab on clinical progression in participants with symptomatic AD	Change from baseline up to Week 72 as measured in Part B by: • MMSE score • ADAS-Cog$_{13}$ score • iADRS score • ADCS-iADL score • CDR-SB
To assess the effect of donanemab on brain amyloid deposition	Change in brain amyloid plaque deposition from baseline at Week 36 of Part B as measured by florbetapir F 18 PET scan
To assess the effect of donanemab on brain region volumes	Change in volumetric MRI measures from baseline to Week 72 in Part B

To assess peripheral PK and presence of anti-donanemab antibodies	PK of donanemab in Part B. ADAs against donanemab in Part B including • treatment-emergent ADAs • neutralizing antibodies

Abbreviations: AD = Alzheimer's disease; ADA = antidrug antibody; ADAS-Cog_{13} = Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory; ADCS-iADL = Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living; AE = adverse event; ARIA = amyloid-related imaging abnormality; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; iADRS = integrated Alzheimer's Disease Rating Scale; MMSE = Mini Mental State Examination; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetics; VTC = video teleconference

5. Analysis Populations

5.1. Descriptions of Analysis Datasets

For purposes of analysis, Parts A, B, and C of the study will be analysed separately as the data for each becomes available. The table below defines subject populations which are defined primarily by participation and data creation in the applicable part of the study. When change from baseline is assessed, patients will be included in the analysis only if both a baseline and at least 1 valid post-baseline measure are available.

Population	Description
Randomized Population	Subjects from Part A randomized to receive on-site assessments first or remote assessment first.
Part A: Video Assessment	Randomized subjects that provide at least 1 pair (on-site and remote) of complete clinical assessments from Part A. Population will be scale-dependent.
Part B: Safety Population	Subjects who are dosed with donanemab during Part B.
Part C: Imaging and Clinical Follow-up	Subject who provide clinical and/or imagining data from Visit 201.

5.2. Patient Disposition

The protocol for this study makes the distinction between patient withdrawal from study and patient discontinuation of study treatment. Patient withdrawal occurs when a patient will no longer participate in the study (no longer taking study treatment and no longer being assessed). Patient discontinuation of study treatment occurs when a patient agrees to continue being assessed but will no longer take study treatments. Patient disposition summarizes the reasons for patient withdrawal from study and patient discontinuation of study treatment.

The percentage of patients withdrawing from study and discontinuing treatment across all parts of the study will be summarized.

5.3. Interim Analyses

Study AACH is an open-label study, with no study drug treatment during Parts A and C, and donanemab treatment during Part B. No interim analyses are planned for this study. Parts A, B, and C will be analysed as subjects complete those parts of the study and data becomes available. Treatment is unblinded in this study and data is available for sponsor use on a continual basis.

6. Part A Analyses

6.1. General Considerations

Statistical analyses of this study will be the responsibility of the sponsor or its designee.

Unless otherwise noted, statistical tests will be conducted at a 2-sided alpha level of 0.05 and 95% confidence intervals will be displayed as 2-sided.

No adjustments for multiple comparisons are planned.

All analyses involving calculation of ICCs will be limited to the Part A: Video Assessment population, requiring particpants to contribute complete pairs of on-site and remote clinical assessments to be included. The ICC will be calculated as 2-way mixed-effect model looking for absolute agreement across raters, with raters defined as on-site assessment and VTC assessment.

A database lock is expected to occur after all randomized participants have completed participation in Part A of the study. Analyses related to the validation of remote assessments compared to on-site assessments will be conducted. As no study drug is administered during Part A, safety analyes will be limited.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

6.2. Adjustments for Covariates

Models for each of the clinical endpoints are specified in the relevant sections below.

6.3. Handling of Dropouts or Missing Data

Because the ICC computation requires a complete on-site assessment and a complete virtual assessment, no imputation of missing values will occur in efficacy analyses for Part A. If any of the individual items for any scale are missing or unknown, the total score for that scale will be considered missing.

Whether virtual administration of the clinical assessments will result in more missing item scores relative to the on-site assessment is of interest. To address this question, the number of scale assessments with missing values for each of the clinical scales will be summarized by modality.

6.4. Baseline Demographics

Baseline demographics, clinical rating scales, disease characteristics, select concomitant medications, and imaging parameters will be summarized for the Part A: Video Assessment population.

6.5. Primary Objective

The primary objective of Part A of this study is to evaluate the reliability of VTC compared with on-site administered cognitive and functional measures. This will be assessed by estimating the intra-class correlation (ICC) and the associated 95% confidence interval for the first pair of

observations from participants and comparing the lower bound of the confidence interval to 0.70, the ICC cut-off for acceptable reliability.

Using the guidelines and notation for defining ICCs published by McGraw and Wong (1996), the ICC of primary interest for this study is a 2-way mixed model, interaction absent, with single measurements from each modality on participants, looking at absolute agreement – ICC(A,1). In the present study, the 'raters' are the two modalities by which the clinical scales are assessed, on-site and VTC. As we are interested in comparing these specific modalities, modality is considered a fixed effect.

For ADAS-Cog_{13} total score, ADCS-ADL total score, iADRS total score, CDR Sum of Boxes, and MMSE total score, individual mixed models will be fit to the data with fixed effects of modality, time effect, age, years of education, and presence/absence of anti-dementia drugs and a random effect for subject. ICCs will be estimated using the mean squares from these models and defined as:

Absolute Agreement: $ICC\ (A,1) = (MS_{subj} - MS_{error}) / (MS_{subj} + MS_{error} + 1/n(MS_{modality} - MS_{error}))$

Consistancy: $ICC\ (C,1) = (MS_{subj} - MS_{error}) / (MS_{subj} + MS_{error})$

95% Confidence intervals for these quantities will be constructed as specified in Table 7 of McGraw and Wong (1996).

Similar analyses will also be conducted for pairs 2 and 3 of each of the clinical outcomes specified above. As the number of subjects contributing additional pairs may be limited, no specific hypothesis/test is specified.

6.6. Longitudinal Assessments

To compare disease progression as measured by VTC versus on-site, an MMRM will be fit to the clinical assessment measures. Observations will be grouped by test modality (VTC and on-site). The MMRM will include terms for modality, visit, visit-by-modality interaction, age, years of education, and presence/absence of anti-dementia drugs. Visit will be considered a categorical variable. The null hypothesis is that the contrast between the VTC modality versus the on-site modality at each visit equals 0. An unstructured covariance matrix will be used to model the within-subject variance-covariance errors. If the unstructured covariance structure matrix results in a lack of convergence, the following tests will be used in sequence:

- heterogeneous Toeplitz covariance structure
- heterogeneous autoregressive covariance structure
- heterogeneous compound symmetry covariance structure
- compound symmetry covariance structure

The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

6.7. Safety Assessments

Although no study medication is given to subjects during Part A of study AACH, adverse events are routinely collected. A summary of adverse events, reported by MedDRA preferred term, will be displayed by decreasing frequency. A list of adverse events deemed serious will also be created.

7. Part B Analyses

7.1. General Considerations

All analyses will be limited to participants who received study drug and provided clinical, imaging, and/or biomarker data from Part B of AACH.

Baseline definitions are dependent on the quantity being assessed. For safety analyses, baseline will be defined as the last assessment collected prior to the first dose of donanemab, generally Visit 1 from Part B. For treatment-emergent safety analyses, only participants who have both a baseline observation and a postbaseline observation will be included in the analysis for each analyte or parameter, respectively. Where further clarification on baseline definitions is needed, the relevant subsections will specify the definitions.

7.2. Baseline Demographics

Baseline demographics, clinical rating scales, disease characteristics, select concomitant medications, and imaging parameters will be summarized for the safety population.

7.3. Concomitant Medications

Prior medications are defined as those that stop before study drug administration. Concomitant medications are defined as those being taken on or after initiation of study drug. A summary of concomitant medications will be presented as frequencies and percentages.

7.4. Extent of Exposure

Summary statistics will be provided for the total number of complete infusions received by participants during Part B of the study.

7.5. Efficacy Scales

Longitudinal assessment across scheduled visits will be summarized for Part B participants for ADAS-Cog_{13}, ADCS-iADL, iADRS Total Score, CDR Sum of Boxes, and MMSE Total Score.

7.6. Safety Analyses

The following subsections describe the summaries of safety information that will be presented for the Part B database lock. All analyses contained in the subsections below will be based on the safety population of the study.

7.6.1. Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened after the first donanemab infusion. The Medical Dictionary for Regulatory Activities (MedDRA) Lowest Level Term (LLT) will be used in the treatment-emergent computation. The version of MedDRA that will be used is the most recent version available at the time of database lock. The maximum severity for each LLT during the baseline period will be used as baseline. The treatment period will be included as post-baseline for the analysis. While unusual, it is possible to have a missing severity for events. For events with a missing severity during the

baseline period, it will be treated as "mild" in severity for determining treatment emergence. Events with a missing severity during the postbaseline period will be treated as "severe" and treatment emergence will be determined by comparing with baseline severity.

The planned summaries for adverse events (AEs) are provided in the table below.

Tables and Figures Related to Adverse Events

Analysis	Details	Analysis Set/Population
Overview of AEs	Number and percentage of participants who experienced • TEAE • SAE • death, and • discontinuation from study treatment due to an AE.	Safety Population
TEAEs by PT within SOC	Number and percentage of participants with TEAEs using MedDRA PT nested within SOC	Safety Population
SAEs by PT	The number and percentage of participants who experienced an SAE (including deaths and SAEs temporally associated or preceding deaths) using MedDRA PT	Safety Population
AEs Reported as Reason for Treatment Discontinuation by PT	Number and percentage of participants reporting an AE as the reason for discontinuing study treatment using MedDRA PT	Safety Population

Abbreviations: AE = adverse event; SAE = serious adverse event; MedDRA = Medical Dictionary for Drug Regulatory Activities; PT = preferred term; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

7.6.2. Clinical Laboratory Evaluations

Laboratory measurements will be analyzed using continuous data (change from baseline) and categorical or ordinal data (proportion of treatment-emergent abnormalities). If there are multiple records of laboratory measurements at baseline or postbaseline visit, the last record will be used. Summaries and analyses of continuous data (change from baseline) will be performed using both conventional and International System of Units (SI units).

Mean changes from baseline to scheduled post-baseline visits will be summarized for chemistry and hematology lab parameters.

The number and percentages for hematology and chemistry laboratory observations that fall outside of reference limits will be summarized. The reference limits from the performing laboratory will be used to define low and high. For a given lab parameter, a value is counted as treatment-emergent low if the minimum post-baseline value is categorized as low and the baseline value was classified as either normal or high. Similarly, a value is counted as treatment-

emergent high if the maximum post-baseline value is categorized as high and the baseline value was classified as either normal or low. All post-baseline lab assessments will be included in the analyses, whether scheduled or unscheduled.

In addition, for hepatic lab values, clinically significant changes of interest at any time are: ALT ≥3 x upper limit of normal (ULN), AST ≥3 x ULN, ALT ≥5 x ULN, ALT ≥10 x ULN, and total bilirubin ≥2 x ULN. Additionally, Hy's Law analysis will be conducted by comparing treatment groups with regard to the proportion of patients with (ALT ≥3 x ULN OR AST ≥3 x ULN) AND total bilirubin ≥2 x ULN at any time.

7.6.3. Electrocardiogram Parameters

ECG measurements will be analyzed using continuous data (change from baseline) and categorical data (proportion of treatment-emergent abnormalities).

Analysis will be done for the following ECG measurements: heart rate, PR, QT, QTc, and RR intervals and QRS duration. All analyses of QTc will be carried out using the Fridericia correction (QTcF) method. These summaries will include data from each scheduled visit at which ECG measures are performed. Mean change from baseline to each post-baseline visit at which ECG measurements are taken will be summarized.

Incidence of treatment-emergent abnormal ECGs will be assessed by comparisons at (1) anytime and (2) each post-baseline visit. Abnormal ECG criteria and criteria for abnormal QTcF prolongation are presented below:

ECG Parameter	Low Criteria	High Criteria
Heart Rate	<50 bpm	>100 bpm
PR Interval	<120 msec	≥220 msec
QRS Duration	<60 msec	≥120 msec
QTcF Interval		
Males	<330 msec	≥450 msec
Females	<340 msec	≥470 msec
Males and females		> 500 msec

Abbreviations: bpm = beats per minute; ECG = electrocardiogram; QTcF = Fridericia-corrected QT interval.

Treatment-emergent high ECG parameters (heart rate, PR interval, QRS duration, QT and QTcF intervals) are the values which are low or normal at all baseline visits and fall into the high abnormal categories post-baseline. Similarly, treatment-emergent low ECG parameters (heart rate, PR interval, QRS duration) are the values which are high or normal at all baseline visits and fall into the low abnormal categories above.

7.6.4. Vital Signs and Weight

Vitals signs and weight will be analyzed using continuous data (change from baseline) and categorical data (proportion of treatment-emergent abnormalities).

Analysis will be done for all collected vital signs and weight parameters. These summaries will include data from each scheduled visit at which vital signs are performed. Mean change from baseline to each post-baseline visit at which vital signs are taken will be summarized.

The number and percentage of participants with observations exceeding defined limits on vital signs and weight will be summarized. The measures of interest and their corresponding limits are as follows:

Vital Sign Parameter (Unit)	Postbaseline Low Criteria	Postbaseline High Criteria
Sitting systolic blood pressure (mmHg)	Absolute value ≤90 and ≥20 decrease from baseline	Absolute value ≥160 and ≥20 increase from baseline
Sitting diastolic blood pressure (mmHg)	Absolute value ≤50 and ≥10 decrease from baseline	Absolute value ≥100 and ≥10 increase from baseline
Sitting pulse (bpm)	Absolute value <50 and ≥15 decrease from baseline	Absolute value >100 and ≥15 increase from baseline
Weight	≥7% decrease	≥7% increase
Vital Sign Parameter (Unit)	**Postbaseline Criteria for Abnormality**	
Orthostatic systolic blood pressure (mmHg)	≥20 mmHg decrease in systolic blood pressure (supine to standing) (i.e., supine minus standing ≥20)	
Orthostatic diastolic blood pressure (mmHg)	≥10 mmHg decrease in diastolic blood pressure (supine to standing) (i.e., supine minus standing ≥10 mm Hg)	
Orthostatic pulse (bpm)	≥30 increase in bpm (standing to supine) (i.e., standing minus supine ≥30)	
Temperature	Absolute value ≥38.3°C and ≥1.1°C increase from baseline (Absolute value ≥101°F and ≥2°F increase from baseline)	

Abbreviation: bpm = beats per minute.

7.6.5. Columbia Suicide Severity Rating Scale (C-SSRS)

Suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent, based on the Columbia-Suicide Severity Rating Scale (C-SSRS), will be listed by patient and visit. Only patients that show suicidal ideation/behavior or self-injurious behavior without suicidal intent will be displayed (ie, if a patient answers are all 'no' for the C-SSRS, then that patient will not be displayed). However, if a patient reported any suicidal ideation/ behavior or self-injurious behavior without suicidal intent at any time point, then all their ideation and behavior will be displayed, even if not positive.

7.6.6. Immunogenicity

Subject samples will be analyzed using a 4-tiered approach. All samples will be assessed in Tier 1 (screening) for the possible presence of ADA. Samples found to produce a signal above or equal to the screening cut point will be assessed in Tier 2 to confirm specificity to LY3002813 (confirmation). Any samples confirmed as specific for anti-LY3002813 antibodies will be reported as "detected." All samples below the screening cut point (Tier 1) or not confirmed (Tier

2) will be reported as "not detected." Any "detected" sample in Tier 2 will be assessed in Tier 3 (titer assessment) and Tier 4 (neutralizing antibodies). Anti-drug antibodies titer values will be reported from Tier 3 titer assessment. Any samples above the Tier 4 assay cut point will be reported as "detected for neutralizing antibodies"; samples below the assay cut point in Tier 4 will be reported as "not detected for neutralizing antibodies."

The frequency and percentage of subjects with preexisting (baseline) ADA, ADA at any time after baseline, and treatment-emergent ADA (TE-ADA) to LY3002813 will be summarized. If no ADAs are detected at baseline, TE-ADA are defined as those with a titer 2 fold (1 dilution) greater than the minimum required dilution (MRD) of the assay (the MRD for anti-LY3002813 antibody assay is 10). For samples with ADA detected at baseline TE-ADA are defined as those with a 4-fold (2 dilutions) increase in titer compared to baseline. For subjects with TE-ADA, the distribution of maximum titers during double-blind treatment period will be described via a baseline to post-baseline shift table. The frequency of neutralizing antibodies may also be tabulated.

7.6.7. Amyloid-Related Imagine Abnormalities (ARIA)

Scheduled and unscheduled magnetic resonance imaging (MRI) will be used to present ARIA events. An overview of ARIA incidence will be presented using frequency and percentage of subjects with any ARIA (ARIA-E or ARIA-H), ARIA-E, and ARIA-H as defined by safety MRIs or TEAE cluster. ARIA-E TEAE Cluster PT are defined as amyloid-related imaging abnormality oedema/effusion, brain oedema, vasogenic cerebral oedema. ARIA-H TEAE Cluster PT are defined as amyloid-related imaging abnormality-microhaemorrhage and haemosiderin deposits, brain stem microhaemorrhage, cerebellar microhaemorrhage, cerebral hemosiderin deposit, cerebral microhaemorrhage, superficial siderosis of the central nervous system, cerebral haemorrhage.

The frequency and percentages of ARIA-E will be further broken out by asymptomatic vs. symptomatic. The frequency and percentage of subjects with ARIA-H microhemorrhage, ARIA-H superficial siderosis, and ARIA-H macrohemorrhage on safety MRI will be reported.

A table displaying the shift ARIA-H event from baseline by visit will be created based on safety MRI. ARIA-E shift table based on safety MRI will be displayed using a 5-point rating scale (mild, mild+, moderate, moderate+, severe).

7.7. Subgroup Analyses

No subgroup analyses are planned for the safety population.

8. Part C Analyses

8.1. General Considerations

Objectives for Part C of AACH will be addressed with summaries of clinical, imaging, and biomarker data. Data collected from the feeder study from which the participant came, and data from the first on-site visit from Part A will be aggregated with data from Part C to allow for display of longitudinal changes. For comparative purposes, subjects that participate in Part B will also be displayed, with their feeder study, first Part A on-site visit, and Visit 1 from Part B (pre-treatment) aggregated in a similar fashion.

Unless otherwise specified, baseline for clinical, imaging, and biomarker endpoints will be defined as the last observation prior to study drug initiation from the feeder study. When change from baseline is assessed, patients will be included in the analysis only if both a baseline and a Part C measure are available.

8.2. Adjustments for Covariates

Models for each of the clinical, imaging, and biomarker endpoints are specified in the relevant sections below.

8.3. Handling of Dropouts or Missing Data

All total and subscale scores for clinical outcomes measures will be derived from individual items. If any of the individual items are missing or unknown, every effort will be made to obtain the score for the missing item(s). Similar to Part A analyses, if any item is missing, any total or sum involving that item will be considered missing.

For fluid biomarkers, samples that were not collected for any reason as well as samples that were not quantifiable (i.e. below the limit of quantification) will be considered missing for analysis purposes.

For PET imaging, scans that were not collected for any reason as well as scans that were not quantifiable will be considered missing for analysis purposes.

8.4. Patient Demographics

Baseline characteristics will be summarized for Part C participants. Summaries will include descriptive statistics for continuous and categorical measures. Patient characteristics to be presented include:

- age
- age group: 55 to 64, 65 to 74, and 75 to 86, >86
- gender
- race
- ethnicity
- height
- body weight

- body mass index (weight (kg) / [height (m)]2)
- country
- tobacco use
- alcohol use
- years of education
- work status
- APOE4 carrier status (carrier [ε2/ε4, ε3/ε4, ε4/ε4], noncarrier [ε3/ε3, ε2/ε2, ε3/ε2])
- APOE4 genotype (ε2/ε4, ε3/ε4, ε4/ε4, no ε4)
- having 1 or more first degree relatives with AD
- AChEI and/or memantine use at baseline
- Amyloid PET

8.5. Time Between Clinical, Imaging, and Biomarker Assessments

To better understand the time between feeder study participation and collection of assessments in AACH, weeks between baseline from the feeder study and all subsequent post-baseline assessments will be summarized for the clinical, imaging, and biomarker outcomes.

8.6. Clinical Outcomes

Longitudinal assessment across the feeder study and study AACH will be summarized for Part C participants for ADAS-Cog_{13}, ADCS-iADL, iADRS Total Score, CDR Sum of Boxes, and MMSE Total Score. Change from baseline to each scheduled collection of these measures during the feeder study, to the first on-site assessment from Part A of study AACH, and to the Part C assessment of study AACH will be modelled with an analysis of covariance (ANCOVA) model with factors for baseline score, baseline age, years of education, presence/absence of anti-dementia medications (yes/no), and AACG treatment group.

For comparison purposes to an untreated participant population, change from baseline to each of the same visits will be shown for AACH subjects that participated in Part B of AACH, with the exception that the Part C assessment would be replaced by the Part B Visit 1 (prior to treatment) assessment.

Additionally, each of these outcomes will be analyzed on an annualized basis. Time from the baseline assessment to each post-baseline assessment will be determined and divided by 365 to derive a change per year value. These values will be modelled using the same ANCOVA analysis specified above.

8.7. PET Imaging Outcomes

Longitudinal assessment across the feeder study and study AACH will be summarized for Part C participants for florbetapir PET and flortaucipir PET results. Change from baseline to each scheduled collection of these measures during the feeder study and to the Part C assessment of study AACH will be modelled with an analysis of covariance (ANCOVA) model with factors for baseline PET result, baseline age, years of education, and presence/absence of anti-dementia medications (yes/no).

Additionally, each of these outcomes will be analyzed on an annualized basis. Time from the baseline assessment to each post-baseline assessment will be determined and divided by 365 to derive a change per year value. These values will be modelled using the same ANCOVA analysis specified above.

8.8. Plasma Biomarker Outcomes

Longitudinal assessment across the feeder study and study AACH will be summarized for Part C participants for Ptau-217 and neurofilament light chain (NfL) protein. Change from baseline to each scheduled collection of these measures during the feeder study and to the Part C assessment of study AACH will be modelled with an analysis of covariance (ANCOVA) model with factors for baseline value, baseline age, and AACG treatment group. For both of these biomarkers, changes on the original scale and the log-transformed scale will be displayed.

For comparison purposes to an untreated participant population, change from baseline to each of the same visits will be shown for AACH subjects that participated in Part B of AACH, with the exception that the Part C assessment would be replaced by the Part B Visit 1 (prior to treatment) assessment.

Additionally, each of these outcomes will be analyzed on an annualized basis. Time from the baseline assessment to each post-baseline assessment will be determined and divided by 365 to derive a factor to be multiplied by the observed change, resulting in a change per year value. These values will be modelled using the same ANCOVA analysis specified above.

9. References

Mcgraw, Kenneth & Wong, S.P.. (1996). Forming Inferences About Some Intraclass Correlation Coefficients. Psychological Methods. 1. 30-46. 10.1037/1082-989X.1.1.30.

10. Appendices

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