Janssen Research & Development

Statistical Analysis Plan

A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study With a Long-Term Extension Treatment Period to Assess the Efficacy and Safety of JNJ-63733657, an Anti-tau Monoclonal Antibody, in Participants with Early Alzheimer's Disease

Protocol 63733657ALZ2002; Phase 2

JNJ-63733657

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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VERSION HISTORY

Please refer to Table 1 for the version history of this document.

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
5	19Sep2025	Section 1.1: updated the Exploratory Objectives and Endpoints to align with the current protocol version	To align with protocol
		Section 1.2.2: clarified blinding in LTE	Clarification
		Section 4: specified Analysis Set details regarding participants from site US10099 and for the participants who were plasma ptau271 positive who were randomized although they did not meet the tau PET eligibility criteria	Specification of analysis details
		Section 5.1.1: clarified details for the end of the Double-blind analysis period and the start of the LTE analysis period	Clarification
		Section 5.1.3: added a subgroup of interest	Specification of analysis details
		Section 5.1.4: updated data handling rules for APOE data and to prioritize the APOE proteotype	Specification of analysis details

SAP Version	Approval Date	Change	Rationale
		result over the DNA-based APOE genotype for analysis purposes; added data handling rules for fluid biomarkers	
		Section 5.2: specified the event time for the Time to termination of study participation	Specification of analysis details
		Section 5.3.1: clarified the data handling rules for derivation of the iADRS total score	Clarification
		Sections 5.3.3.1, 5.4.1.3, 5.4.2.3, and 5.7.3.1.2: specified that an MMRM model with an additional baseline-by-visit term may be explored	Specification of analysis details
		Section 5.3.3.3.2: removed the 20% of randomized participants requirement for sensitivity analyses; clarified sensitivity analysis details; added sensitivity analyses for participants with previous exposure to anti-amyloid AD treatment; added sensitivity analyses for participants who were plasma ptau217 positive who were randomized although they did not meet the tau PET eligibility criteria	Specification of analysis details
		Section 5.3.3.4.1: updated the covariance matrix structure specifications for polynomial regression	Specification of analysis details
		Section 5.3.3.4.2: updated analysis details in case assumptions are violated	Specification of analysis details
		Section 5.3.3.4.3: updated analysis details for the time variable	Specification of analysis details
		Section 5.4.2.3: added frequency tables for the time to event analysis	Specification of analysis details
		Section 5.4.2.4: clarified time points to be included in supplementary analyses of secondary endpoints; indicated that correlations may be explored with scatterplots and/or with Pearson/Spearman correlation coefficients	Clarification
		Section 5.3.3: specified additional data handling rules and calculations	Specification of analysis details
		Section 5.6.3.1: specified the censoring time for time to event analyses of safety data	Specification of analysis details

SAP Version	Approval Date	Change	Rationale
		Section 5.6.3.3: updated the criteria for abnormal QTc values and criteria for interpretation of ECGs	Correction
		Section 5.6.3.5: clarified analysis definitions	Clarification
		Section 5.7.3.1: specified ROIs for tau PET analyses	Specification of analysis details
		Section 5.7.3.1.1: specified ROIs for tau PET analyses	Specification of analysis details
		Section 5.7.3.1.2: clarified the rules for inclusion of the baseline score in the model; specified transformation of the values may be applied if needed; specified ROIs; updated sensitivity analysis specifications	Specification of analysis details
		Section 5.7.3.1.3: clarified the rules for inclusion of the baseline score in the model; specified transformation of the values may be applied if needed	Specification of analysis details
		Section 5.7.4: added reference to a separate Pharmacometric Plan; indicated that correlations may be explored with scatterplots and/or with Pearson/Spearman correlation coefficients	Specification of analysis details
		Section 5.7.5, 5.7.6, 5.7.7, 5.7.8, 5.7.9 and 5.7.10: specified handing of intercurrent events	Specification of analysis details
		Section 5.7.8: specified the bilateral measures will be included in analyses	Specification of analysis details
		Sections 5.7.10 and 5.7.12: indicated that correlations may be explored with scatterplots and/or with Pearson/Spearman correlation coefficients	Specification of analysis details
		Section 6.2: added baseline characteristics for summary	Specification of analysis details
		Section 6.3: updated protocol deviations details	Specification of analysis details
		Section 6.4: clarified definition of concomitant medications	Clarification
		Section 6.4.1: clarified summary of AChEIs	Clarification
		Section 6.5: specified summary of data for past and ongoing occurrences separately	Specification of analysis details
		Section 6.7: updated title of section and added data handling details and calculations of scores for eCOA data	Specification of analysis details
		Throughout: minor grammatical, formatting, or spelling changes	Correction

SAP Version	Approval Date	Change	Rationale
4	20Apr2025	Section 1: added clarification that the term "iADRS" refers to the iADRS-MCI	Clarification
		Section 1.1: specified the timepoints for secondary and exploratory objectives	Clarification
		Section 1.1: added TEAEs of special interest	To summarize specific AEs that could be related to treatment and align with Protocol Amendment 5
		Section 1.2.1: added information about LTE treatment period	To align with Protocol Amendments 6 and 7
		Section 1.2.2: added information about the LTE treatment period and clarifications to distinguish between the DB and LTE treatment periods	To align with Protocol Amendments 6 and 7
		Section 4: added clarification to specify the DB treatment period	To align with Protocol Amendments 6 and 7
		Section 4: added definitions for PK analysis set and Immunogenicity analysis set	To support PK and Immunogenicity analyses
		Section 5.1.1: added details to distinguish between the DB and LTE treatment periods	To align with Protocol Amendments 6 and 7
		Section 5.1.2: combined hematology and chemistry visit windows with those of exposure and vital signs to align with current protocol SoA	To align with Protocol Amendment 5
		Section 5.1.3: added subgroups of interest and specified endpoints in scope of subgroup analyses	Specification of analysis details
		Section 5.1.4: added section to describe data handling rules	Specification of analysis details
		Section 5.2: specified summaries for the DB period through week 104 and after week 104	To align with Protocol Amendments 6 and 7
		Section 5.2: added Kaplan-Meier summary of time to termination of study participation in the DB period	Specification of analysis details
		Section 5.3: added the endpoint of CDR-SB to the hierarchy for multiple comparison adjustment	To ensure study-wide strong control of Type 1 error and support interpretation of the results
		Section 5.3.1, 5.4.1.1.2 and 5.4.1.6: added clarification of the items in the ADCS-ADL-MCI used for analyses	Clarification
		Sections 5.3.2 and 5.3.4.2: added clarification regarding concomitant symptomatic non-disease-modifying AD therapies	Clarification
		Section 5.3.3.1: specified that the MMRM in the primary analysis method will include visits	Specification of analysis details

SAP Version	Approval Date	Change	Rationale
		through Week 104, added the definition of percent slowing, and specified supplementary analyses including visits up to and after Week 104	
		Section 5.3.3.3.1: added another version of the sensitivity analysis using the Delta Method	To support interpretation of results
		Section 5.3.3.3.2: clarified endpoints to be included for each of the sensitivity analyses	Clarification
		Section 5.3.3.4.1 specified that the polynomial regression analysis will include visits up to a maximum of Week 156	Specification of analysis details; data after that visit are expected to be sparse given the current study design
		Section 5.3.3.4.2: added analysis details for time-saved analyses	Specification of analysis details
		Section 5.3.3.4.3: specified that the natural cubic splines model will include visits up to Week 156.	Specification of analysis details; data after that visit are expected to be sparse given the current study design
		Section 5.3.4.2: added clarifications and a sensitivity analysis	Specification of analysis details
		Section 5.3.4.3: clarified that the analysis may be performed and specified data handing strategy for other ICEs.	Specification of analysis details
		Section 5.3.5: specified that the strategy for handling ICEs for subgroup analyses will be the same as for the primary estimand, that redundant terms will be dropped from the model in those cases where the subgroup of interest is overlapping with the general model, that visits up to and including Week 104 will be included in the model, and that additional analyses will be performed separately for each of the baseline tau PET subgroups.	Specification of analysis details
		Section 5.4.1.3: specified that the MMRM will include visits through Week 104, added the definition of percent slowing, and specified a supplementary analysis including visits up to and after Week 104	Specification of analysis details
		Sections 5.4.1 and 5.4.1.4: added the endpoint of CDR-SB to the hierarchy for multiple comparison adjustment at the end of the procedure outlined in the previous SAP version (i.e, after the ADCS-ADL-MCI)	To ensure study-wide strong control of Type 1 error and support interpretation of the results

SAP Version	Approval Date	Change	Rationale
		Section 5.4.1.6: added supplementary analysis of the ADCS-ADL-MCI total score based on all 23 scored items	Specification of analysis details
		Section 5.4.2: changed title from Supportive Secondary Endpoints to Other Secondary Endpoints	Clarification
		Section 5.4.2.1.2: added definitions for the CDR Cognition score and CDR Function score	Specification of analysis details
		Section 5.4.2.3: specified that the MMRM will include visits through Week 88 for RBANS scores and through Week 104 for other scales, added definition of percent slowing, and specified supplementary analyses including additional visits	Specification of analysis details
		Section 5.4.2.3: for the CDR-GS analysis, specified an additional analysis defining the event time as the first of 2 consecutive visits demonstrating worsening from baseline	Specification of analysis details
		Section 5.4.2.4: added various supplementary analyses and clarifying details for secondary efficacy endpoints	Specification of analysis details
		Sections 5.5.1, 5.5.2, and 5.5.3: added MMRM analysis and subgroup analyses for exploratory endpoints	Specification of analysis details
		Section 5.6: specified that risk differences and corresponding 95% confidence intervals may be presented for safety findings	Specification of analysis details
		Section 5.6.1: added Kaplan-Meier summary of time to permanent discontinuation of DB study intervention	Specification of analysis details
		Section 5.6.2: added clarifications to distinguish between the DB and LTE treatment periods; added various summaries of TEAEs; added definitions of AESIs; added summaries for TEAEs and TE SAEs with onset during the first 104 weeks of the DB analysis period; and added summary of the HAC outcomes	Specification of analysis details
		Section 5.6.3.1: specified analysis approaches regarding inclusion of central laboratory and/or local lab data; clarified summaries by analysis visit window; added	Specification of analysis details

SAP Version	Approval Date	Change	Rationale
		summaries of data during the first 104 weeks of the DB analysis period; and added various summaries of liver enzyme data	
		Sections 5.6.3.2 and 5.6.3.3: clarified summaries by analysis visit window	Specification of analysis details
		Section 5.6.3.6: added summaries of data by APOE subgroups	Specification of analysis details
		Section 5.7.1: added details for the summary of PK data	Specification of additional analyses
		Section 5.7.2.1 corrected definition for treatment-boosted antibodies to JNJ-63733657	Correction
		Section 5.7.2.2: added summaries for participants with and without TE liver enzyme elevations	Specification of analysis details
		Section 5.7.3: removed redundant details present in subsequent sections	Clarification
		Section 5.7.3.1: clarified tau PET methods of assessing tau spread and specified ROIs of interest and specification of data handling rules for Week 104 tau PET performed after start of LTE	Clarification and specification of analysis details
		Section 5.7.3.1.1: clarified tau PET endpoints	Clarification
		Section 5.7.3.1.2: added tau PET ROIs, clarified analysis details, added definition of percent slowing, and added sensitivity analysis	Specification of analysis details
		Section 5.7.3.1.3: clarified subgroup analysis details	Specification of analysis details
		Sections 5.7.5 and 5.7.8: added MMRM analyses	Specification of analysis details
		Section 5.7.6: Section added to distinguish neurodegeneration fluid biomarkers from other biomarkers and add MMRM analyses	Clarification and specification of analysis details
		Section 5.7.7: added MMRM analyses and summary of amyloid positivity	Specification of analysis details
		Section 5.7.9: clarified details of biomarkers to be analyzed and added MMRM analyses	Clarification and specification of analysis details
		Section 5.7.10: clarified types of biomarkers and summaries of data	Clarification
		Section 5.7.11: added summary of APOE cross-assay comparison	Specification of analysis details
		Section 6.2: added summaries by subgroups of interest	Specification of analysis details

SAP Version	Approval Date	Change	Rationale
		Section 6.3: updated list of deviations	Specification of analysis details
		Section 6.4: removed redundant information	Clarification
		Section 6.4.1: added clarifications to definitions of types of medications	Clarification
		Section 6.4.2: added definition and summaries of disease-modifying AD therapies	Clarification and specification of analysis details
		Section 6.5: renamed and added liver imaging assessments listing	Specification of analysis details
		Section 6.6: added criteria	Specification of analysis details
		Section 6.8: added CAA AE search terms	Specification of analysis details
		Throughout: minor grammatical, formatting, or spelling changes	Correction
3	14Aug2023	Section 1.2.2: updated reference for the operational plans	Clarification
		Section 5.1: to specify data handling rules for eCOA values of -99 or -999 which will be considered as missing for analysis	Clarification
		Section 5.1.1: clarification to the definition of double-blind analysis period and post-treatment analysis period.	Clarification
		Section 5.1.2: clarification of visit window assignment rules	Clarification
		Section 5.1.2: correction to the visit 19 window in tables 7, 8, and 11	Correction
		Section 5.1.3: added BDNF subgroup	Specification of additional analyses
		Section 5.3.1: clarification to the data handling rules of iADRS components not administered on the same day.	Clarification
		Section 5.3.3.1, 5.3.3.4.1, 5.3.4.1, 5.4.2.3: Clarified observations included or excluded from analysis.	Clarification
		Section 5.3.3.1, 5.3.5, 5.4.1.3, 5.4.2.3, 5.7.3.1.2, and 5.7.3.1.3: specified the method for approximating the denominator degrees of freedom and specified that the robust variance estimator will be used if a structured covariance matrix is used due to convergence issues.	Clarification
		Section 5.3.3.3: moved “Sensitivity Analyses for Missing Data” to Section 5.3.3.3.1	Clarification
		Section 5.3.3.3.2: added section for additional sensitivity analyses	Specification of additional analyses

SAP Version	Approval Date	Change	Rationale
		Section 5.3.3.4.1: renumbered from 5.3.3.4 and specified that the robust variance estimator will be used.	Clarification
		Section 5.3.3.4.2: added time-saved analysis as a supplementary analysis	Specification of additional analyses
		Section 5.3.3.4.3: added natural cubic splines analysis as a supplementary analysis	Specification of additional analyses
		Section 5.3.4.1: clarified that data after the start of LTE would not be included	Clarification
		Section 5.3.4.2: clarified that "on study treatment" includes data until the end of the double-blind analysis period	Clarification
		Section 5.3.4.2: added a graph for the model-adjusted means and SEs	Specification of additional analyses
		Section 5.3.4.3: added details for the Balanced Estimand analysis plans	Specification of analysis details
		Section 5.4.1.6: added time-saved and NCS analyses for the 2 key secondary endpoints as supplementary analyses	Specification of additional analyses
		Section 5.4.2.4: added time-saved and NCS analyses for the CDR-SB and RBANS total scale score as supplementary analyses	Specification of additional analyses
		Section 5.6.3.6: clarified the names of the MRI safety-related observations to be summarized	Clarification
		Section 5.7.3.1: revised the wording for New Tau Composite to New Tau Volume	Clarification
		Section 5.7.3.1.1: added tau PET measures to the estimand statement	Clarification and specification of additional analyses
		Section 5.7.3.1.2: added clarification for the baseline factors to be included in the model	Clarification
		Section 5.7.3.1.2: revised the wording for New Tau Composite to New Tau Volume and added measures of New Tau Volume in Braak ROIs 2, 3 and 4	Clarification and specification of additional analyses
		Section 5.7.3.1.2: clarified which endpoint would be considered for model diagnostics and sensitivity analyses for tau PET	Clarification
		Section 6.4: added summary of disease-modifying AD therapy	Clarification

SAP Version	Approval Date	Change	Rationale
2	05May2023	Section 1: Clarified that the document is relevant to the double-blind placebo-controlled period and that data for a long-term extension will be out of scope and described in a separate SAP	Clarification
		Section 1.1: Specification of the primary and key secondary endpoint time point, ie, Week 104 (which was previously unspecified and deferred to SAP)	To incorporate changes to statistical methods
		Section 1.1: Removed definitions of abbreviations from below the table and added them to Appendix 1 List of Abbreviations	To align with updated style guidelines
		Section 1.2.1: Clarification was provided for the study population details. The planned number of subjects in the trial was increased from 420 to 480. The duration of the study in relation to the availability of the long-term extension was updated.	To align with Protocol Amendment 3
		Section 3: Sample size and power were updated.	Sample size and power were re-evaluated due to the change of the primary analysis method from polynomial regression to MMRM and due to the anticipated increase in dropout rate.
		Section 5.1.1: Removed week 128 as a potential endpoint visit and clarified that the endpoint visit is Week 104 for efficacy analyses.	To incorporate changes to statistical methods and align with Protocol Amendment 3.
		Section 5.1.2: Added a rule for analysis visit selection for handling ADAS-Cog13 and RBANS assessments.	To ensure the analysis visit selection for these endpoints will use the same form as baseline.
		Section 5.1.2: Corrections to Time Interval days	Correction.
		Section 5.2 Added summary of participant dispositions through Week 104	To facilitate interpretation of efficacy results for which the endpoint is at Week 104
		Section 5.3.1: Modified the calculation method for the primary efficacy endpoint to no longer exclude the dressing item from the ADCS-ADL-MCI score	To incorporate changes to statistical methods and align with Protocol Amendment 3.
		Section 5.3.2: Clarified the endpoint at Week 104 is during the double-blind placebo-controlled period, clarified the AD medications of memantine and acetylcholinesterase	Clarification

SAP Version	Approval Date	Change	Rationale
		inhibitors as "symptomatic non-disease-modifying" instead of "standard of care".	
		Section 5.3.2: Modified the strategy for the intercurrent event of treatment discontinuation	To incorporate changes to statistical methods and align with Protocol Amendment 3.
		Section 5.3.3.1: Clarified which observations will be included and excluded from the primary analysis	To incorporate changes to statistical methods and align with Protocol Amendment 3.
		Section 5.3.3.1: Changed the primary analysis method from polynomial regression to MMRM and specified model details.	To incorporate changes to statistical methods and align with Protocol Amendment 3.
		Section 5.3.3.2: Changed the method from polynomial regression to MMRM	To incorporate changes to statistical methods
		Section 5.3.3.3: Clarified the assumption for the primary analysis hypothetical strategy for treatment discontinuations	Clarification
		Section 5.3.3.3: Removed code specification that could be used to perform analyses	Remove unnecessary information
		Section 5.3.3.3: Changed the method from polynomial regression to MMRM	To incorporate changes to statistical methods
		Section 5.3.3.4: Changed the supplementary analysis of the primary efficacy endpoint from MMRM to polynomial regression	To incorporate changes to statistical methods
		Section 5.3.4.1: Renamed the Treatment Policy Strategy estimand to "Supplementary Estimand 1" and added details to clarify which intercurrent events will be handled with treatment policy strategy, and which with hypothetical strategy.	To incorporate changes to statistical methods
		Section 5.3.4.2: Clarified the details for handling intercurrent events for the slope analysis with while-on-treatment strategy	To incorporate changes to statistical methods
		Section 5.3.4.3: removed the alternate iADRS score calculation.	To incorporate changes to statistical methods and align with Protocol Amendment 3.
		Section 5.3.4.3: added the Balanced Estimand as a supplementary estimand	To incorporate changes to statistical methods
		Section 5.4.1.1.2: removed plans for removing the dressing item when used as part of the iADRS	To incorporate changes to statistical methods and align with Protocol Amendment 3.
		Section 5.4.1.3: changed the analysis method for the key secondary efficacy endpoints from polynomial regression to	To incorporate changes to statistical methods and align with Protocol Amendment 3.

SAP Version	Approval Date	Change	Rationale
		MMRM and specified model details	
		Section 5.4.1.4: updated the footnote to change the analysis method for the key secondary efficacy endpoints from polynomial regression to MMRM	To incorporate changes to statistical methods and align with Protocol Amendment 3.
		Section 5.4.1.6: changed the supplementary analyses for the key secondary efficacy endpoints from MMRM to polynomial regression	To incorporate changes to statistical methods.
		Section 5.4.2.3: clarified handling of intercurrent events and details for variables in the model for supportive secondary efficacy endpoints	To incorporate changes to statistical methods.
		Section 5.4.2.4: changed the sensitivity analysis of the CDR-SB versus iADRS and ADCS-ADL-MCI versus the Amsterdam IADL from polynomial regression to MMRM	To incorporate changes to statistical methods.
		Section 5.7.2: added details for immunogenicity analyses planned	To incorporate changes to statistical methods.
		Section 5.7.3.1: specified the region of interest for the New Tau Composite as the neocortex	Clarification
		Section 5.7.11: Added exploration of the relationship between baseline MRI vascular findings and clinical and cognitive measures of decline	To incorporate changes to statistical methods.
		Section 6.1: added terms to the list of abbreviations	Clarification
		Section 6.2: added summary of the screening GDS-30 score to the list of demographic and baseline variables to be summarized	To incorporate changes to statistical methods.
		Section 6.3: added missing baseline RBANS total score to the list of protocol deviations to be summarized	To incorporate changes to statistical methods.
		Section 6.4.1: added a summary of the timing of participants starting AChEI and/or memantine during the study	To incorporate changes to statistical methods.
		Section 6.7. Appendix 7: Section was added with details for how item scores and total scores are calculated for the ADAS-Cog13 and ADCS-ADL-MCI which are the 2 scales comprising the primary efficacy endpoint measure of iADRS.	Clarification

SAP Version	Approval Date	Change	Rationale
		Throughout the document: Removed the "standard of care" when referring to memantine and/or acetylcholinesterase inhibitors	Clarification.
		Throughout the document: Minor changes in text were made	To correct errors.
1	08 September 2022	Not Applicable	Initial version sent to regulatory agencies

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all planned analyses of the double-blind, placebo-controlled period for study 63733657ALZ2002.

Data for a long-term extension will be out of scope for the analyses described in this SAP. Analysis methods for a long-term extension would be described in a separate SAP.

Throughout this document, the term "iADRS" refers to the integrated AD Rating Scale for Mild Cognitive Impairment (iADRS-MCI) in this study.

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of JNJ-63733657 versus placebo on clinical decline as measured by the iADRS, a composite of cognition and function	• Change from baseline on the iADRS total score at Week 104
Key Secondary – Cognition and Function	
• To evaluate the effect of JNJ-63733657 versus placebo on cognitive decline as measured by the ADAS-Cog13	• Change from baseline on the ADAS-Cog13 total score at Week 104
• To evaluate changes in functional status between participants treated with JNJ-63733657 or placebo as measured by the ADCS-ADL-MCI	• Change from baseline on the ADCS-ADL-MCI total score at Week 104
Secondary – Cognition and Function	
• To evaluate the effect of JNJ-63733657 compared with placebo on cognitive decline, as measured by the RBANS Total Scale Index Score	• Change from baseline on the RBANS Total Scale Index Score at Week 88
• To evaluate the effect of JNJ-63733657 compared with placebo as measured by the 5 RBANS indices and 12 subtests comprising the RBANS	• Change from baseline in each of the 5 individual RBANS indices and each of the 12 subtests comprising the RBANS at Week 88
• To evaluate the effect of JNJ-63733657 on clinical progression compared with placebo as measured by the CDR-SB	• Change from baseline on the CDR-SB at Week 104

Objectives	Endpoints
• To evaluate changes in neuropsychiatric/behavioral status between participants treated with JNJ-63733657 or placebo as measured by the NPI	• Change from baseline in NPI at Week 104
• To evaluate the effect of JNJ-63733657 compared with placebo on proportion of participants progressing from CDR-GS 0 to 0.5 or higher, 0.5 to 1 or higher, or 1 to 2 or higher, from baseline to post-baseline	• Progression from CDR-GS 0 to 0.5 or higher, 0.5 to 1 or higher, or 1 to 2 or higher, from baseline to post-baseline through Week 104
Secondary – Biomarkers, Pharmacokinetics, Immunogenicity	
• To evaluate the effect of JNJ-63733657 on the accumulation and/or propagation of tau pathology compared with placebo, as measured by tau PET	• Change from baseline in brain tau burden, as measured by tau PET at Week 104
• To evaluate the effect of JNJ-63733657 on levels of total, free, and bound p217+tau fragments in CSF	• Change from baseline in CSF concentrations of total, free, and bound p217+tau fragments at Week 104
• To evaluate the peripheral and central exposure (PK) of JNJ-63733657 following chronic treatment	• CSF and serum concentrations of JNJ-63733657 at time points per the protocol SoA
• To evaluate the immunogenicity (presence of ADA in serum) of JNJ-63733657 following chronic treatment	• ADA in serum at time points per the protocol SoA
Secondary – Safety Outcomes	
To investigate the safety and tolerability of JNJ-63733657 in participants with Early AD, as assessed by AEs, SAEs, early discontinuations due to AEs, ECGs, laboratory evaluations, physical and neurological examinations, vital signs, and C-SSRS. In addition, brain MRI is included for safety evaluation	• Nature, frequency, severity, and timing of AEs, discontinuations due to AEs, treatment-emergent AESIs, and SAEs • Evaluation of other safety parameters, as measured by: - 12-lead ECGs (performed in triplicate) - Laboratory evaluations, including hematology, chemistry, and urinalysis - Complete physical and neurological examination - Vital signs including supine and standing systolic and diastolic blood pressure and pulse, temperature, and weight - Brain MRI - Assessment of suicidality with C-SSRS.

Objectives	Endpoints
Exploratory	
• To evaluate changes in functional status between participants treated with JNJ-63733657 versus placebo as measured by the Amsterdam IADL	• Change from baseline on the Amsterdam IADL at Week 104
• To evaluate changes in quality of life between participants treated with JNJ-63733657 versus placebo as measured by the QOL-AD	• Change from baseline on the QOL-AD at Week 104
• To evaluate the relationship between dose and PK of JNJ-63733657 on clinical efficacy, safety, and biomarker assessments	• Correlation of JNJ-63733657 dose and serum and CSF levels with efficacy, safety and biomarkers
• To evaluate the relationship between tau PET burden and CSF and plasma phosphorylated tau (p181tau and p217+tau) levels	• Correlation/concordance of baseline and change from baseline in CSF and plasma concentrations of p181tau and p217+tau and tau PET
• To evaluate the relationship between CSF and plasma amyloid levels	• Correlation/concordance between CSF Aβ and plasma Aβ at baseline and change from baseline
• To evaluate the effect of JNJ-63733657 on changes in brain volume as measured by volumetric MRI	• Change from baseline during the Double-blind Treatment Period in hippocampal, whole brain, and ventricular volume using MRI
• To explore the effects of JNJ-63733657 on markers of Aβ pathophysiology and downstream markers of neuronal injury, neurodegeneration, and inflammation in CSF and/or plasma/serum compared with placebo	• Change from baseline during the Double-blind Treatment Period in markers of Aβ pathophysiology, neuronal injury, neurodegeneration or inflammation as measured in CSF and/or plasma/serum
• To explore the potential relationship of biomarkers of tau and neurodegeneration (e.g., CSF p-tau, t-tau, NfL, neurogranin, tau PET, volumetric MRI) with change in clinical decline	• Correlation between baseline and change from baseline in biomarkers of tau and neurodegeneration (e.g., CSF p-tau, t-tau, NfL, neurogranin, tau PET, volumetric MRI) and change from baseline in clinical decline (e.g., CDR-SB, iADRS, RBANS, ADAS-Cog13)
• To evaluate differences in resource utilization (caregiver time, hospitalizations, changes in housing, etc) between participants treated with JNJ-63733657 or placebo as measured by RUD-Lite	• Change from baseline during the Double-blind Treatment Period in resource utilization (eg, caregiver time, hospitalizations, changes in housing) on RUD-Lite

1.2. Study Design

1.2.1. Study Design Overview

This is a global, multicenter, double-blind, placebo-controlled, randomized, parallel-group study, with an active treatment, dose-blinded long-term extension (LTE) treatment period, assessing the ability of JNJ-63733657 to slow clinical decline (cognitive and functional) in participants with Early AD, as well as its safety and tolerability. In addition, effects of JNJ-63733657 on accumulation of tau, as measured by tau PET, will be evaluated. Additional efficacy, safety, biomarker, pharmacokinetic, immunogenicity, and health outcomes data will be obtained in the LTE treatment period.

Early AD is defined by having an abnormal cognitive performance (Clinical Dementia Rating – Global Score [CDR-GS]=0.5 with memory box score ≥0.5 in the absence of any other evidence of brain disease explaining the cognitive deficit),[1] with only mild impairment in daily activities, as well as a biomarker pattern indicative of amyloid and tau pathology:

- Elevated tau (T+) within a pre-specified range for eligibility, defined first in plasma as determined by the central laboratory and specified in a separate Laboratory Manual. Sites will be notified of eligibility status and will not receive assay results.
- Eligible plasma T+ participants will undergo a tau PET scan to confirm T+ status. Scans will be reviewed centrally by a qualified reader for evidence of pathologic tau that meets the prespecified eligibility criteria outlined in a separate Imaging Charter. Participants with inadequate (ie, too little) or widespread (ie, too much) tau, as defined in the Imaging Manual/Charter, will be excluded. Sites will be notified of eligibility and will not receive results.

For all enrolled participants, the study will consist of:

- a 90-day (13 weeks) screening period (can be extended up to 120 days with prior approval from medical monitor on a case-by-case basis; if necessary, may be further extended up to 180 days with prior approval from medical monitor on a case-by-case basis),
- a Double-blind Treatment Period with a variable duration (maximum of 4.5 years, see below),
- An optional LTE Treatment Period with a variable duration (see below); and
- a Follow-up Period with a duration of13 weeks), with visits approximately 30, 60, and 90 days after the last dose of study intervention, unless otherwise specified in the protocol or the participant will be transitioning to commercially available JNJ-63733657 (if applicable) within 1 month of last dose of study intervention.

This will be an outpatient study. The Double-blind Treatment Period will be of variable duration, continuing until all participants have had the opportunity to complete the Week 104 visit of the Double-blind Treatment Period. The maximum treatment duration in the Double-blind Treatment Period for a participant is 232 weeks (4.5 years).

After the LTE Treatment Period becomes available at the clinical site, all participants receiving double-blind study intervention (including participants with temporary interruption of study

intervention, eg, due to ALT>1.5xULN or AST≥3xULN) and those in the Double-blind Treatment Period without study intervention who have completed the Week 104 visit will be discontinued from the Double-blind Treatment Period to either enter the LTE Treatment Period (if eligible) or proceed to the Follow-up Period to complete the safety follow-up visits (for participants not entering in the LTE Treatment Period).

The timing and availability of the LTE Treatment Period at a clinical site will vary. Therefore, if a participant has completed the Week 104 visit prior to the LTE Treatment Period becoming available at the clinical site, then the participant must remain in the Double-blind Treatment Period receiving double-blind study intervention until after the LTE Treatment Period becomes available, at which time the participant will be discontinued from the Double-blind Treatment Period to either enter the LTE Treatment Period or proceed to the Follow-up Period to complete the safety follow-up visits.

The LTE Treatment Period will be of variable duration, continuing until one of the following criteria are met (whichever comes first):

- Until 2 years after marketing authorization for the indication in a participant's respective country/territory or until JNJ-63733657 becomes commercially available; or
- JNJ-63733657 can be provided to the participant via another access mechanism (eg, Post-Trial Access Program, if available); or
- The participant no longer benefits from further treatment (based on the investigator's clinical judgment) or withdraws consent (or shows behavioral dissent); or
- The sponsor terminates clinical development of JNJ-63733657 for AD.

Each participant in the study will have a designated study partner who will accompany the participant to study visits. The primary role of the study partner will be as informant.

1.2.2. Randomization and Blinding

Randomization

Central randomization will be implemented in this study. In the Double-blind Treatment Period, participants will be randomly assigned to 1 of 3 intervention groups (1 of 2 dosages of JNJ-63733657 (1000 or 3000 mg) or placebo) at a ratio of 1:1:1 based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be stratified by geographic region (North America, Europe, Australia, and Japan) and baseline tau burden on tau PET (low versus high, as described in the Imaging Charter). The RTSM system (eg, IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the RTSM system (eg, IWRS) and will then give the relevant participant details to uniquely identify the participant.

In the LTE Treatment Period, all LTE participants will receive active (JNJ-63733657) treatment. At the time of entry into the LTE Treatment Period, the RTSM system (eg, IWRS) will assign treatment for the LTE Treatment Period as follows:

- Participants receiving JNJ-63733657 (1000 mg, 3000 mg) in the Double-blind Treatment Period will continue to receive the same treatment and dose during the LTE Treatment Period. For statistical analysis purposes, these participants are referred to as "Early Start" participants.
- Participants receiving placebo treatment in the Double-blind Treatment Period will be rerandomized in a 1:1 ratio to receive either JNJ-63733657 1000 mg or 3000 mg. For statistical analysis purposes, these participants are referred to as "Delayed Start" participants.

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the RTSM system (eg, IWRS), which has the functionality to allow the investigator to break the blind for an individual participant.

Under normal circumstances, the blind should not be broken by investigators or sites until all participants have completed the study and the database is finalized and locked. Otherwise, the blind should be broken only if a specific emergency treatment or course of action would be dictated by knowing the treatment status of the participant. If possible, the investigator should attempt to contact the sponsor or its designee first to discuss the particular situation before breaking the blind. Participants who have had their intervention assignment unblinded should continue to return for scheduled evaluations.

Data that may potentially unblind the intervention assignment (eg, study intervention serum and CSF concentrations, anti-JNJ-63733657 antibodies, study intervention preparation/accountability data, intervention allocation, biomarker, or other specific laboratory data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. If an interim analysis or other analysis (e.g, Primary Double-blind Analysis, End of Double-blind Analysis) is specified, the randomization codes and, if required, the translation of randomization codes into intervention and control groups will be disclosed to those authorized and only for those participants included in the specified analysis.

An external, independent Statistical Support Group (SSG) will perform the safety monitoring analyses and the interim analyses and will communicate the results to the IDMC who will make recommendations to the Sponsor Committee based on the rules defined in the IDMC Charter, Safety SAP and/or the IA SAP, as appropriate. For IDMC safety monitoring, the level of unblinding on the outputs will be partial, i.e., the treatment groups will be masked, and will be

presented as Treatment A, Treatment B, etc. The identity of the masked treatment groups will be provided in a separate document to those authorized per the IDMC Charter and only for those participants included in the IDMC safety monitoring review. For the IAs, if conducted, unblinded data will be presented to the IDMC, and only for those participants included in the IA.

Operational plans for safety monitoring and IA#1 (EDMS-RIM-1097319) and for IA#2 (EDMS-RIM-1108594) will be in place to ensure that the results of the interim analyses do not influence the conduct of the study, investigators, or participants.

2. STATISTICAL HYPOTHESES FOR TRIAL OBJECTIVES

Primary Hypothesis: Participants treated with JNJ-63733657 will show slower clinical decline on iADRS, a composite of cognition and function, as compared with participants receiving placebo.

3. SAMPLE SIZE JUSTIFICATION

The standardized treatment effect sizes that correspond to 35% slowing of clinical decline with JNJ-63733657 treatment versus placebo over time are shown in Table 2. For example, the standardized treatment group difference at Week 104 (24 months) is assumed to be 0.38 on the iADRS. A sample size of 480 participants, 160 participants per treatment arm, provides approximately 87% power of determining successful slowing of clinical decline relative to the control arm at the Week 104 [24 months] time point, at a 2-sided Type 1 error rate of 5%. This assumes an initial 7.5% annual dropout rate, and an anticipated higher (13%) annual dropout rate after an approved disease-modifying AD therapy becomes available at different times in different regions, and an accrual rate of 20 participants per month.

Table 2: Standardized Treatment Effect Sizes Corresponding to 35% Slowing of Clinical Decline with JNJ-63733657 Treatment Versus Placebo in Standardized Units Over Time

Endpoint	6 months	12 months	18 months	24 months	30 months	36 months	42 months	48 months
iADRS	0.09	0.27	0.32	0.38	0.42	0.44	0.49	0.55

iADRS=integrated Alzheimer's Disease Rating Scale

Prior to the completion of enrollment, and prior to the database lock of the first IA, the study sample size may be adjusted based on the midcourse study information (eg, variance estimate, dropout rate) and external data.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Analysis Sets	Description
Screened	All participants who sign the ICF
Randomized	The randomized analysis set includes all participants who were randomized to an intervention group for the DB Treatment Period of the study.
Full Analysis Set (FAS)	The full analysis set (FAS) includes all randomized participants who received at least 1 dose of DB study intervention.

Analysis Sets	Description
Safety	The safety analysis set includes all randomized participants who received at least 1 dose of DB study intervention.
PK analysis set	The PK analysis set includes all randomized participants who received at least 1 complete dose of JNJ-63733657 in the DB Treatment Period of the study and have at least 1 valid post-dose blood sample drawn for PK analysis.
Immunogenicity analysis set	The Immunogenicity analysis set includes all randomized participants who received at least 1 dose (partial or complete) of JNJ-63733657 in the DB Treatment Period of the study and have at least 1 valid post-dose serum sample evaluable for antibodies to JNJ-63733657.

Participants from site US10099 (15 screen-failed and 1 randomized) will be included in the Screened and Randomized Analysis Sets, but the randomized participant from this site will be excluded from the Full Analysis Set, Safety Analysis Set, PK Analysis Set, and the Immunogenicity Analysis Set due to a site GCP compliance issue. Data for the randomized participant from this site will be presented in listings, and sensitivity analyses for the primary endpoint will be provided.

Eleven participants who were plasma ptau217 positive (i.e., met Inclusion Criteria #3) who were randomized although they did not meet the tau PET eligibility criteria (Inclusion Criteria #4) due to an error in Z-score calculation by the tau PET vendor will be included in analysis sets.

5. STATISTICAL ANALYSES

5.1. General Considerations

5.1.1. Study Days and Analysis Periods

Study Day 1 for a randomized participant refers to the first study intervention dose date, which is also the reference start date. All assessments at all visits will be assigned a day relative to this date.

Study day or relative day for a visit is defined as:

- Visit date - (date of Study Day 1) +1, if visit date is ≥ date of Day 1
- Visit date - date of Day 1, if visit date < date of Day 1

There is no 'Day 0'.

Study Days <1 will be considered in the Screening analysis period.

“Baseline” for RBANS should only consider the RBANS Form A version in the selection of baseline and should be prior to the first dose of study intervention. However, if no observation for RBANS Form A is available prior to the first dose and the RBANS Form A was observed at a

post-randomization visit prior to receiving the 2nd study intervention dose, the value at the first post-randomization visit will be used as the baseline value.

"Baseline" for ADAS-Cog13 should only consider the Visit 6 value since it uses the same word list (Word List 1) as being used at Week 104 which is the endpoint visit for the efficacy analyses. Visit 6 scales are to be completed prior to the first dose of study intervention. However, if there is no observation for Visit 6 available prior to the first dose of study intervention and the Visit 6 ADAS-Cog13 is administered post-randomization prior to receiving the 2nd dose of study intervention, then this value will be used as the analysis baseline value.

Similarly, for other scales, if there is no observation available prior to the first dose of study intervention, but an observation is available for the participant after the first dose and prior to receiving the 2nd dose, then that value will be used as the baseline value.

For all other measures, "Baseline" is defined as the last observation prior to or on the date of the first study intervention dose for the participant. Thus "Baseline" could be a value on the first day of the Double-blind analysis period, or a value during the Screening period.

The Double-blind analysis period start is defined as the date of first dose of study intervention (Study Day 1).

The LTE analysis period start date/time is defined as the date/time of first dose of LTE study intervention.

The Double-blind analysis period end is defined as the minimum of the following: date of last dose of Double-blind study intervention + 90 days; or LTE start date, if applicable. Because End of Double-blind analysis Period assessments may occur on the same day as the LTE start date, if observations on the LTE analysis period start day are collected on the Double-blind analysis period end date as defined above, they will be included in the Double-blind analysis period.

Since participants may have study visits after discontinuing Double-blind study intervention, the Post-Double-blind treatment analysis period start is defined as the Double-blind analysis period end + 1 for participants who discontinue Double-blind study intervention and have a study visit and/or trial completion/discontinuation date after the Double-blind analysis period end.

For participants with non-missing Post-Double-blind treatment analysis start, the Post-Double-blind treatment analysis period end is defined as the maximum of the date of last visit and trial completion/discontinuation (if not entering the LTE) or the LTE start date, if applicable.

For visit dates and other data (e.g., AE or concomitant medication start dates, etc.) after the date of the last dose of Double-blind study intervention (study intervention end date), an analysis day will be defined relative to the study intervention end date as Visit (or observation) date – study intervention end date + 1.

The reference end date for participants who have completed/discontinued from the study is the earlier of (i) the maximum of the Double-blind analysis period end and the Post-Double-blind

treatment analysis period end, or (ii) the data cut-off date. For participants who are ongoing, the reference end date is the data cut-off date.

5.1.2. Visit Windows

As participants do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. Listed below are the visit windows and the target days for each visit. The reference day is Study Day 1 and will apply to all visits before or after the study intervention end date. If a participant has 2 or more actual visits in 1 visit window, the visit closest to the target day will be used as the protocol visit for that visit window. The other additional visit(s) will not be used in the efficacy endpoint summaries or analyses, but they can be used for determination of clinically important safety endpoints. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used. The following exception is noted for efficacy scales/questionnaires RBANS (all postbaseline visits) and ADAS-Cog13 (Week 52 and 104, the timepoint for IA#1 and IA#2, respectively), where a scheduled visit will take precedence over an unscheduled visit if both exist within the same visit window time interval, because the scheduled visit uses the same form (RBANS) and word list (ADAS-Cog13) as baseline.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point. Listed below (Table 3) are the visit windows and the target days for each visit for exposure, vital signs, hematology and chemistry.

Table 3 Visit Windows for Exposure, Vital Signs, Hematology and Chemistry

Scheduled Visit Number	Time period (label on output)	Time Interval (Day*)	Target Time Point (Day*)
6	Baseline	≤ 1	1
7	Week 4	2 to 43	29
8	Week 8	44 to 71	57
9	Week 12	72 to 99	85
10	Week 16	100 to 127	113
11	Week 20	128 to 155	141
12	Week 24	156 to 183	169
13	Week 28	184 to 211	197
14	Week 32	212 to 239	225
15	Week 36	240 to 267	253
16	Week 40	268 to 295	281
17	Week 44	296 to 323	309
18	Week 48	324 to 351	337
19	Week 52	352 to 379	365
20	Week 56	380 to 407	393
21	Week 60	408 to 435	421
22	Week 64	436 to 463	449
23	Week 68	464 to 491	477
24	Week 72	492 to 519	505
25	Week 76	520 to 547	533
26	Week 80	548 to 575	561
27	Week 84	576 to 603	589
28	Week 88	604 to 631	617
29	Week 92	632 to 659	645
30	Week 96	660 to 687	673

31	Week 100	688 to 715	701
32	Week 104	716 to 743	729
33	Week 108	744 to 771	757
34	Week 112	772 to 799	785
35	Week 116	800 to 827	813
36	Week 120	828 to 855	841
37	Week 124	856 to 883	869
38	Week 128	884 to 911	897
39	Week 132	912 to 939	925
40	Week 136	940 to 967	953
41	Week 140	968 to 995	981
42	Week 144	996 to 1023	1009
43	Week 148	1024 to 1051	1037
44	Week 152	1052 to 1079	1065
45	Week 156	1080 to 1107	1093
46	Week 160	1108 to 1135	1121
47	Week 164	1136 to 1163	1149
48	Week 168	1164 to 1191	1177
49	Week 172	1192 to 1219	1205
50	Week 176	1220 to 1247	1233
51	Week 180	1248 to 1275	1261
52	Week 184	1276 to 1303	1289
53	Week 188	1304 to 1331	1317
54	Week 192	1332 to 1359	1345
55	Week 196	1360 to 1387	1373
56	Week 200	1388 to 1415	1401
57	Week 204	1416 to 1443	1429
58	Week 208	1444 to 1471	1457
59	Week 212	1472 to 1499	1485
60	Week 216	1500 to 1527	1513
61	Week 220	1528 to 1555	1541
62	Week 224	1556 to 1583	1569
63	Week 228	1584 to 1611	1597
64	Week 232	1612 to 9999	1625

*Relative to Study Day 1

Listed below (Table 4) are the visit windows and the target days for each visit for physical examinations and neurological examinations.

Table 4: Visit Windows for Physical Examinations and Neurological Examinations

Scheduled Visit Number	Time period (label on output)	Time Interval (Day*)	Target Time Point (Day*)
6	Baseline	≤ 1	1
12	Week 24	2 to 267	169
19	Week 52	268 to 449	365
25	Week 76	450 to 631	533
32	Week 104	632 to 813	729
38	Week 128	814 to 995	897
45	Week 156	996 to 1275	1093
58	Week 208	1276 to 1541	1457
64	Week 232	1542 to 9999	1625

*Relative to Study Day 1

Listed below (Table 5) are the visit windows and the target days for ADAS-Cog13, CDR, ADCS ADL-MCI, NPI, RUD-Lite, and Amsterdam IADL.

Table 5: Visit Windows for ADAS-Cog13, CDR, ADCS ADL-MCI, NPI, RUD-Lite, and Amsterdam IADL

Scheduled Visit Number	Time period (label on output)	Time Interval (Day*)	Target Time Point (Day*)
6	Baseline	≤ 1	1
12	Week 24	2 to 267	169
19	Week 52	268 to 449	365
25	Week 76	450 to 631	533
32	Week 104	632 to 813	729
38	Week 128	814 to 995	897
45	Week 156	996 to 1177	1093
51	Week 180	1178 to 1359	1261
58	Week 208	1360 to 1541	1457
64	Week 232	1542 to 9999	1625

*Relative to Study Day 1

Listed below (Table 6) are the visit windows and the target days for RBANS.

Table 6: Visit Windows for RBANS

Scheduled Visit Number	Time period (label on output)	Time Interval (Day*)	Target Time Point (Day*)
5	Baseline	≤ 1	N/A
9	Week 12	2 to 169	85
15	Week 36	170 to 351	253
22	Week 64	352 to 533	449
28	Week 88	534 to 715	617
35	Week 116	716 to 897	813
41	Week 140	898 to 1079	981
48	Week 168	1080 to 1261	1177
54	Week 192	1262 to 1443	1345
61	Week 220	1444 to 9999	1541

*Relative to Study Day 1

Listed below (Table 7) are the visit windows and the target days for Weight, C-SSRS, Urinalysis and Blood Samples (Pharmacodynamics and Biomarkers).

Table 7: Visit Windows for Weight, C-SSRS, Urinalysis and Blood Samples (Pharmacodynamics and Biomarkers)

Scheduled Visit Number	Time period (label on output)	Time Interval (Day*)	Target Time Point (Day*)
2/6	Baseline	≤ 1	≤ 1
9	Week 12	2 to 126	85
12	Week 24	127 to 210	169
15	Week 36	211 to 308	253
19	Week 52	309 to 449	365

25	Week 76	450 to 631	533
32	Week 104	632 to 813	729
38	Week 128	814 to 995	897
45	Week 156	996 to 1177	1093
51	Week 180	1178 to 1359	1261
58	Week 208	1360 to 1541	1457
64	Week 232	1542 to 9999	1625

*Relative to Study Day 1

Listed below (Table 8) are the visit windows and the target days for ECG collections.

Table 8: Visit Windows for ECG

Scheduled Visit Number	Time period (label on output)	Time Interval (Day*)	Target Time Point (Day*)
6	Baseline	≤ 1	1
7	Week 4	2 to 43	29
8	Week 8	44 to 71	57
9	Week 12	72 to 127	85
12	Week 24	128 to 210	169
15	Week 36	211 to 308	253
19	Week 52	309 to 449	365
25	Week 76	450 to 631	533
32	Week 104	632 to 813	729
38	Week 128	814 to 995	897
45	Week 156	996 to 1177	1093
51	Week 180	1178 to 1359	1261
58	Week 208	1360 to 1541	1457
64	Week 232	1542 to 9999	1625

*Relative to Study Day 1

Listed below (Table 9) are the visit windows and the target days for QOL-AD, tau PET and CSF.

Table 9: Visit Windows for QOL-AD, tau PET and CSF

Scheduled Visit Number	Time period (label on output)	Time Interval (Day*)	Target Time Point (Day*)
4/5/6	Baseline	≤ 1	N/A
19	Week 52	2 to 547	365
32	Week 104	548 to 911	729
45	Week 156	912 to 1275	1093
58	Week 208	1276 to 9999	1457

*Relative to Study Day 1

Listed below (Table 10) are the visit windows and the target days for MRI.

Table 10: Visit Windows for MRI

Scheduled Visit Number	Time period (label on output)	Time Interval (Day*)	Target Time Point (Day*)
3	Baseline	≤ 1	N/A
12	Week 24	2 to 267	169
19	Week 52	268 to 449	365

25	Week 76	450 to 631	533
32	Week 104	632 to 813	729
38	Week 128	814 to 995	897
45	Week 156	996 to 1177	1093
51	Week 180	1178 to 1359	1261
58	Week 208	1360 to 1541	1457
64	Week 232	1542 to 9999	1625

*Relative to Study Day 1

Listed below (Table 11) are the visit windows and the target days for Blood Samples (Pharmacokinetics/Immunogenicity).

Table 11: Visit Windows for Blood Samples (Pharmacokinetics/Immunogenicity)

Scheduled Visit Number	Time period (label on output)	Time Interval (Day*)	Target Time Point (Day*)
2/6	Baseline	≤ 1	N/A
7	Week 4	2 to 43	29
8	Week 8	44 to 71	57
9	Week 12	72 to 99	85
10	Week 16	100 to 127	113
11	Week 20	128 to 155	141
12	Week 24	156 to 210	169
15	Week 36	211 to 308	253
19	Week 52	309 to 449	365
25	Week 76	450 to 631	533
32	Week 104	632 to 813	729
38	Week 128	814 to 995	897
45	Week 156	996 to 1177	1093
51	Week 180	1178 to 1359	1261
58	Week 208	1360 to 1541	1457
64	Week 232	1542 to 9999	1625

*Relative to Study Day 1

5.1.3. Definition of Subgroups

Subgroup analyses will be performed for the primary endpoint, change from baseline in the iADRS total score, the key secondary efficacy endpoints (change from baseline in the ADAS-Cog13 total score and change from baseline in the ADCS-ADL-MCI total score), the secondary efficacy endpoint of change from baseline in CDR-SB, and for the tau PET endpoints (e.g, change in tau PET SUVR assessed over the Tau Naïve Composite ROI). For other secondary endpoints, subgroup analyses will be conducted for subgroups as specified in their respective sections.

- Sex
- Race (White, Black, Asian, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Other/Not reported)
- Age Group (<65 years, 65-74 years, ≥75 years)
- Education Level (less than high school or at least some high school or greater)

- Geographic Region: North America (Canada and United States), Europe (includes Belgium, France, Netherlands, United Kingdom, Spain, Sweden), Australia, and Japan
- Country (Australia, Belgium, Canada, France, Japan, Netherlands, Spain, Sweden, United Kingdom, United States)
- Baseline iADRS total score (≤/> median)
- Use of memantine and/or acetylcholinesterase inhibitors (AChEI) at baseline (Y/N)
- Stop, add or change memantine and/or AChEI at any time during the DB Analysis Period up to and including Week 104 (Y/N)
- Baseline tau burden (within the intermediate tau range) on tau PET (Low, High, based on the randomization stratum)
- Baseline tau burden on tau PET (terciles, defined based on the Braak 4 SUVR uptake z-score which was used to assign the participant to the tau burden randomization stratum)
- APOE ε4 carrier status (Y, N)
- APOE ε4 genotype (non-carrier, heterozygous carrier, homozygous carrier, as determined by genotyping or proteotyping methodology described in Section 5.1.4)
- Baseline plasma p217+tau level (terciles)
- Clinical diagnosis (Prodromal AD, Mild AD Dementia)
- Number of missed doses of DB study intervention prior to Week 104 of the DB Analysis Period (<3 doses, 3-6 or >6)
- Maximum number of consecutive missed doses of DB study intervention prior to Week 104 of the DB Analysis Period (<3, >=3)
- Uninterrupted exposure to DB study intervention since baseline (At least 76 weeks, less than 76 weeks)
- Uninterrupted exposure to DB study intervention since baseline (At least 52 weeks, less than 52 weeks)
- Treatment-emergent anti-drug antibodies to JNJ-63733657 at any time during the DB Analysis Period up to and including Week 104 (with, without)
- Treatment-emergent neutralizing antibodies to JNJ-63733657 at any time during the DB Analysis Period up to and including Week 104 (with, without)
- Presence of microhemorrhages at baseline based on Safety MRI (with, without)
- Baseline brain-derived neurotrophic factor (BDNF) Val66Met group, if data available: (Met66 carriers, Val66 homozygotes)
- Braak stage by tau PET at screening, if data available

5.1.4. Data Handling Rules

Electronic clinical outcomes assessments (eCOA) values of -99 or -999 indicate a score that was not evaluable and will be considered as a missing value in analyses.

APOE data will be available from 2 sources: DNA-based APOE genotype data from LabCorp, and APOE proteotype data from C2N (Precivity-APOE LC-MS assay). For the APOE ε4 carrier status factor in statistical models and for subgroup analyses by APOE ε4 carrier status and by APOE ε4 allele status (referred to as genotype), the APOE proteotype result will be used, and if not available, the result from the DNA-based APOE genotype will be used. APOE results may be based on samples taken during any phase, including screening, DB, or LTE. If there are multiple results within a given source type for a participant (e.g, multiple proteotype results), the most recent one will be used.

Fluid biomarker results reported as "<LLOQ" will use the LLOQ/2 in analyses, results reported as ">ULOQ" will use 110% of the ULOQ in analyses; otherwise, values will be analyzed as reported. For phosphorylated pau protein measures, bound is calculated as maximum(0, total – free), to avoid negative values which would be due to variability of the assay.

5.2. Participant Dispositions

The number of participants in the following disposition categories will be summarized throughout the study by intervention group and overall. The entire DB phase will be summarized, with additional summaries through Week 104, and after Week 104, where applicable.

- Participants randomized
- Participants who received at least one dose of study intervention
- Participants who completed study intervention (per Protocol Amendment 6 or later)
- Participants who discontinued study intervention
- Reasons for discontinuation of study intervention
- Participants who continued study visits after discontinuing study intervention
- Participants who discontinued study visits
- Reasons for discontinuation of study visits

Listings of participants will be provided for the following categories:

- Participants who discontinued study intervention
- Participants who terminated study prematurely
- Participants who were unblinded during the study period
- Participants who were randomized yet did not receive study intervention.

Time to termination of study participation of the DB Analysis Period will be presented graphically using Kaplan-Meier methods. The DB Analysis Period end date will be used as the event time.

5.3. Primary Endpoint Analysis

Efficacy analyses will be performed on the FAS. The multiplicity, with regard to testing multiple doses of JNJ-63733657 (1000 mg versus placebo and 3000 mg versus placebo), and multiple endpoints, i.e, for the primary analysis efficacy endpoint (iADRS), the 2 key secondary efficacy endpoints (ADAS-Cog13 and ADCS-ADL-MCI), and the secondary endpoint CDR-SB, will be controlled by a Hochberg sequential gatekeeping test procedure using a family-wise error rate of 2 sided 0.05 as described in Section 5.4.1.4.

5.3.1. Definition of Endpoint

The primary efficacy endpoint is the iADRS total score change from baseline to Week 104.

The iADRS is a composite measure of cognition and function. The iADRS score used in this study is derived according to Wessels et al (2015)[9] as a combination of ADAS-Cog13 (score 0 to 85, higher scores indicate worse cognitive performance) and the ADCS-ADL-MCI score based on the standard 18 items (0 to 53, lower scores indicate worse daily function). Therefore, the iADRS score is calculated as [-1(ADAS-Cog13 score)+85] + ADCS-ADL-MCI score. The ADAS-Cog13 score and the ADCS-ADL-MCI score should be obtained from the same visit, but if they are not, they must be no more than 28 days apart in the same window (see Section 5.1.2 Visit Windows)

for iADRS calculation, otherwise it is considered missing. The 28 days is used because it is the recall period for ADCS-ADL-MCI, and functional impairment related to cognitive impairment is not expected to meaningfully change in this amount of time. If either or both of the 2 scores are missing, the iADRS score will be missing. The iADRS score ranges from 0 to 138 with lower scores indicating worse performance.

5.3.2. Estimand

The primary estimand, the main clinical quantity of interest to be estimated in this study, is defined by the following 5 components:

- **Population:** Early AD participants with pathological brain tau [T+]
- **Endpoint:** Change from baseline in iADRS total score at Week 104 during the double-blind placebo-controlled period.
- **Treatment:** JNJ-63733657 (1000 mg, 3000 mg) versus placebo. Current symptomatic non-disease-modifying AD medications (memantine and acetylcholinesterase inhibitors) are permitted as described in the protocol.
- **Intercurrent Events (ICE) and Corresponding Strategy:**

ICE	Strategy
Treatment Discontinuation, with or without a switch to an alternative disease-modifying AD therapy	Hypothetical Strategy, as if participants adhere to the study treatment and do not switch to an alternative disease-modifying AD treatment.
Adding, changing, or stopping concomitant symptomatic non-disease-modifying AD therapies	Treatment policy strategy, targeting the effect of the study treatment regardless of the occurrence of this ICE.

- **Population Level Summary:** The difference in means between each dose and placebo for the primary endpoint at Week 104 of the double-blind placebo-controlled period.

Current symptomatic non-disease-modifying AD medications (memantine and acetylcholinesterase inhibitors) are permitted in this study as described in the protocol Sections 5.2 (Exclusion Criteria) and 6.8 (Concomitant Therapies). Participants are not required to be taking these medications at study entry. The study population includes MCI participants in geographies where these therapies are not approved and available for MCI. It is likely that up to 40% of enrolled

participants will not be taking one of these medications at baseline but, due to the long study duration, may progress to mild dementia and become eligible for symptomatic AD treatment. In addition, modifications (e.g., start, stop, or change dose) to symptomatic AD treatments may be necessary during study participant due to the long duration. A treatment policy strategy is proposed in the primary estimand for the ICEs related to symptomatic non-disease-modifying AD therapies. However, these therapies may acutely affect cognition and potentially confound any disease modifying effects. Due to this reason, a supplementary estimand employing a while-on-treatment strategy for all ICEs was added to capture a treatment effect while treatment is being taken as directed by the protocol, see Section 5.3.4.2.

5.3.3. Analysis Methods for the Primary Estimand

5.3.3.1. Primary Analysis

Under the primary estimand, which applies a hypothetical strategy for the ICE of treatment discontinuation, only the changes from baseline occurring prior to the end of the double-blind analysis period for participants with the ICE of treatment discontinuation will be included in the primary analysis. Study treatment must be discontinued prior to the addition of any alternative disease-modifying AD therapy. Observations after the occurrence of the ICE of the addition of any alternative disease-modifying AD therapy will not be included in the primary analysis. Observations after the start of the LTE, if applicable, are not included in the primary analysis. The primary analysis will be an MMRM analysis including analysis visits through Week 104. The dependent variable will be the change from baseline in the iADRS total score. The model will include baseline iADRS total score, age and baseline tau burden on tau PET (defined as the Braak 4 SUVR uptake z-score which was used to assign the participant to the tau burden randomization stratum, a continuous variable) as covariates, and treatment, geographic region, sex, APOE ε4 carrier status (Y/N), education level (less than high school or at least some high school or greater), use of memantine and/or AChEI at baseline (Y/N), visit, and visit-by-treatment interaction as fixed effects. An unstructured covariance matrix structure will be utilized to account for correlation among observations within participants. In case of convergence problems, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1) with separate subject random effect. The Kenward-Roger method will be used for approximating the denominator degrees of freedom. If a structured covariance matrix is used due to convergence issues, the robust variance estimator, commonly referred to as the “sandwich” estimator, will be used to address the potential impact of covariance matrix misspecification on the estimation and testing of treatment effect. The treatment effect at Week 104 will be estimated using the difference in LS means and separate contrasts will be obtained for each dose level versus placebo. Point estimates and 95% confidence intervals (2-sided) will be provided for the treatment differences versus placebo at each time point. Percent slowing for each dose level compared to placebo at each time point will be calculated as the LS mean of the treatment difference versus placebo in change from baseline, divided by the absolute value of the LS estimate of mean change from baseline in the placebo group, times 100.

Plots of the LS means and SE for each treatment over time will be presented. Descriptive statistics for the iADRS total score and the change from baseline will be provided for each timepoint. An MMRM including visits up to and after analysis visit Week 104 may also be presented as a supplementary analysis. An MMRM model with an additional baseline-by-visit term may be explored.

The number and percentage of participants with post-intercurrent event observations at each visit will be summarized.

5.3.3.2. Model Diagnostics

The normality and equal variance assumptions underlying the primary MMRM will be assessed graphically for the change from baseline in the iADRS total score at Week 104. Residuals from the models will be plotted against the predicted values and a QQ plot of the residuals versus the expected quantiles of the standard normal distribution will be presented.

5.3.3.3. Sensitivity Analyses

5.3.3.3.1. Sensitivity Analyses for Missing Data

The robustness of the primary analysis with respect to deviations from the assumptions pertaining to data that is missing or not deemed relevant after ICEs and thus excluded under the hypothetical strategy will be evaluated with the sensitivity analyses described below. Additional sensitivity analyses may be performed as needed.

Delta Method

The key assumption in the primary analysis is that missing data arise from a Missing at Random (MAR) mechanism. This assumption is aligned with the estimand and the hypothetical strategy for treatment discontinuations. A delta adjustment multiple imputation method will be used for a sensitivity analysis for stress-testing the MAR assumption. This type of method is regarded to be an informative sensitivity analysis in clinical trials (2010 National Research Council report on missing data[3] and T Permutt[4]). It is assumed in this method that efficacy scores worsen after study treatment discontinuation. This method will employ the following 3 steps:

Step 1 – Multiple Imputation (MI)

Note: Most missing data will be a result of participants dropping out of the study and having observations at every scheduled visit up to the point they dropped but no observations thereafter. This is a monotone missing data pattern. Some participants may have 'intermediate missing' data between non-missing observations. This is a non-monotone missing data pattern. MAR is assumed for intermediate missing data.

If there are participants with a non-monotone missing data pattern, datasets with only monotone missing data patterns will be created first by imputing the intermediate missing values using the MCMC (Markov Chain Monte Carlo) method. 500 imputations will be performed to create 500 unique datasets which now have monotone missing data pattern.

If all participants have a monotone missing data pattern (either directly from the study or created by the previous step), the MAR-based multiple imputation with the regression option will be used to impute missing values.

Step 2 – Delta Adjustments

The imputed values will be adjusted by adding δ_P to the imputed values for participants randomized to placebo and adding δ_A to the imputed values for participants randomized to an active JNJ-63733657 arm. Delta-adjusted fully imputed datasets will be generated for different combinations of δ_P and δ_A values as defined below:

- $\delta_P = 0$ and $\delta_A = 0\ to\ -\Delta_1^*$ in increments of 1 (active-only adjustment analysis)
- $\delta_P = \delta_A = 0\ to\ -\Delta_2^*$ in increments of 1 (all arms adjustment analysis).

For iADRS endpoint, subtracting values results in lower (worse) scores. Δ_1^* and Δ_2^* represent the adjustments leading to the 'tipping point', or the smallest delta adjustments values at which conclusions change from *favorable to drug* (i.e. statistically significant: 2-sided p-value < 0.05) to *unfavorable* (fail to reject the null hypothesis of no treatment difference).

Step 3 – Analysis and Pooling

For each (δ_P, δ_A) combination:

- The same MMRM as described for the primary efficacy analysis will be performed for each set of the 500 adjusted fully imputed datasets; and
- Multiple imputation using Rubin's methodology[26] will be applied to the MMRM results from the imputed datasets to produce final inferences.

Between-group comparisons to placebo at Week 104 (e.g. 2-sided p-values, point estimates for treatment difference) will be displayed graphically for each considered (δ_P, δ_A) combination, up to the 'tipping point' adjustment.

The delta adjustment MI method as described above will be applied to all missing data under the hypothetical strategy (where efficacy scores after the ICE are considered missing). In addition, another version of these methods will be applied to missing data under hypothetical strategy except for those caused by discontinuations not related to study intervention including Lost to Follow-Up, Withdrawal by Subject, or Other.

Copy Reference Method

Another sensitivity analysis, utilizing "Copy Reference" multiple imputation, will also be performed to impute missing data in the JNJ-63733657-treated groups after the last observed value for participants who experienced an ICE (where efficacy scores after the ICE are considered missing).

Step 1 – Multiple Imputation (MI)

In this analysis, missing not at random (MNAR) is assumed for monotone missing data in the JNJ-63733657 groups after the last observed value for participants who experienced an ICE. MAR is assumed for the placebo group. For this method, the model-expected mean for imputations is derived as if the participant had always been a member of the placebo group. Insofar as a JNJ-63733657-group participant's observed values are better (or worse) than those of participants in the placebo group, the mean for imputations for that participant at the imputed visit will tend to be better (or worse) than those observed for the placebo group at the imputed visit.

Step 2 – Analysis and Pooling

- The same MMRM as described for the primary efficacy analysis will be performed for each set of the 500 adjusted fully imputed datasets; and
- Multiple imputation will be applied to the MMRM results from the imputed datasets to produce final inferences.

5.3.3.3.2. Other Sensitivity Analyses

The number and percentage of participants whose study partner changed during the study after the baseline visit up to and including the Week 104 analysis visit will be summarized. Subgroup analyses of the primary endpoint, the key functional secondary endpoint, (ADCS-ADL-MCI), and secondary or exploratory endpoints where the study partner participates (e.g., CDR-SB, Amsterdam IADL score) will be performed (with and without study partner change).

Similarly, the number and percentage of participants whose electronic clinical outcomes assessment (eCOA) rater at Week 104 (Week 88 for RBANS) was different from the rater at baseline, as well as the number whose rater was different at any time up to and including the Week 104 analysis visit (Week 88 for RBANS) compared to the baseline rater, for the ADAS-Cog13, the RBANS total scale score, or the CDR-SB will be summarized. Subgroup analyses of the primary endpoint (iADRS) and for the ADAS-Cog13, CDR-SB, and RBANS Total Scale endpoints will be performed (with and without eCOA rater change at any time up to and including the Week 104 analysis visit [Week 88 for RBANS]).

The number and percentage of participants with previous (exclude known placebo) exposure to anti-amyloid AD treatment (including investigational drugs in AD trials) will be summarized. Subgroup analyses of primary efficacy (iADRS), key secondary (ADAS-Cog13 and ADCS-ADL-MCI), and other secondary efficacy endpoints (CDR-SB, tau naïve composite ROI SUVR, and Cerebral Cortex ROI SUVR) will be performed for participants without previous exposure (with and without previous exposure).

The analysis methods for the above will be performed as described in Section 5.3.5 Subgroup Analyses.

Sensitivity analyses of the primary efficacy (iADRS), key secondary (ADAS-Cog13 and ADCS-ADL-MCI), and other secondary efficacy endpoints (CDR-SB, tau naïve composite ROI SUVR, and Cerebral Cortex ROI SUVR) will be performed where the participants who were plasma

ptau217 positive (i.e., met Inclusion Criteria #3) who were randomized although they did not meet the tau PET eligibility criteria (Inclusion Criteria #4) due to an error in Z-score calculation by the tau PET vendor will be excluded.

5.3.3.4. Supplementary Analyses

5.3.3.4.1. Polynomial Regression

The double-blind treatment period for the Phase 2 study will be of variable duration, where some participants will receive double-blind treatment for longer than 104 weeks. The variable double-blind observation period in this study allows for better modeling the clinical trajectories over time, and therefore better estimating differences due to treatment effects. Polynomial regression utilizes a smoothing effect taking into consideration timepoints before and after the timepoint of interest while taking advantage of the common close study design and is expected to provide more power than MMRM. Given the length of the study and the uncertainty around the rate of disease progression, a polynomial regression is planned in order to utilize as much data as possible (through Week 156) to have better understanding of the treatment effect of JNJ-63733657.

Under the primary estimand, which applies a hypothetical strategy for the ICE of treatment discontinuation, only the changes from baseline occurring prior to the end of the double-blind analysis period for participants with the ICE of treatment discontinuation will be included in this analysis. Study treatment must be discontinued prior to the addition of any alternative disease-modifying AD therapy. Observations after the occurrence of the ICE of the addition of any alternative disease-modifying AD therapy will not be included in this analysis. Observations after the start of the LTE, if applicable, are not included in this analysis. This supplementary analysis will be based on a mixed effects polynomial regression model of order 3 with respect to time as a continuous variable interacting with treatment group. The dependent variable is the change from baseline in the iADRS total score and the model adjusts for the following variables (the same variables included in the primary analysis MMRM): geographic region, baseline tau burden on tau PET (defined as the Braak 4 SUVR uptake z-score which was used to assign the participant to the tau burden randomization stratum, a continuous variable), baseline iADRS total score, age, sex, APOE ε4 carrier status (Y/N), education level (less than high school or at least some high school or greater), use of memantine and/or AChEI at baseline (Y/N). An unstructured covariance matrix structure will be utilized to account for correlation among observations within participants. In case of convergence problems, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1) with separate subject random effect. The Kenward-Roger method will be used for approximating the denominator degrees of freedom. If a structured covariance matrix is used due to convergence issues, the robust variance estimator, commonly referred to as the "sandwich" estimator, will be used to address the potential impact of covariance matrix misspecification on the estimation and testing of treatment effect. Comparison of each JNJ-63733657 dose versus placebo will be performed using the appropriate contrast at Week 104.

The basic mathematical form of the model is as follows, where changes from baseline in the iADRS total scores at each follow-up visit, Y_{ij}, for each participant i, $i = 1, \ldots, N$ at post-

baseline time points, $t_{ij,}$ for j = 24, 52, 76, …., 156 weeks. The three-category treatments are represented in the regression equation by introducing two dummy regressors: D_{1i}=1 if JNJ-63733657 1,000 mg and 0 otherwise and D_{2i}=1 if JNJ 63733657 3,000 mg and 0 otherwise. The model includes two dummy variables of the treatment group, a continuous variable of the disease progression time, and treatment-by-time interactions as fixed effects:

$$\begin{aligned} Y_{ij} = \beta_0 + \beta_1 D_{1i} + \beta_2 D_{2i} + \beta_3 t_{ij} + \beta_4 t_{ij}^2 + \beta_5 t_{ij}^3 + \\ (\beta_6 D_{1i} + \beta_7 D_{2i}) t_{ij} + (\beta_8 D_{1i} + \beta_9 D_{2i}) t_{ij}^2 + \\ (\beta_{10} D_{1i} + \beta_{11} D_{2i}) t_{ij}^3 + \varepsilon_{ij,} \end{aligned} \quad (1)$$

where $\boldsymbol{\varepsilon}_{ij}$ denotes the residual term. The baseline covariates would be included as well but are not listed here for simplicity.

Comparison of each JNJ-63733657 dose versus placebo will be performed using the appropriate contrast at each timepoint. The contrasts are made at a single time point but are interpreted with respect to the trajectory over time. The contrasts for each treatment group versus placebo, and the LS means for each treatment group at each timepoint will be presented.

Plots of the LS means and SE for each treatment over time will be presented.

5.3.3.4.2. Time-Saved Analysis

Treatment effects on the time scale will be estimated using two methods, Time Component Test[20] (TCT) and Progression Models for Repeated Measures[21] (PMRM) which are described below. A key assumption in both methods is that the change in clinical endpoints is monotone over time. Both methods also use placebo trajectory as the reference and further assume that the range of the trajectory in the treatment arm is within the range of the reference trajectory. If the assumptions are violated, the data will be assessed to evaluate if excluding a time point may mitigate the violation and if it is reasonable to exclude that time point. The parameters for time-specific and common acceleration factors along with their confidence intervals will be estimated from both models. For example: an estimate acceleration factor of 0.8 would represent a cumulative 20% change at visit j and if j is 24 months, time saved will be 0.2 * 24 = 4.8 months. The analysis will be conducted for each active treatment arm independently using R. Analyses will be conducted using timepoints (analysis visits) through Week 104 (the same timepoints included in the primary MMRM analysis). Separate analyses including timepoints through Week 156 may be conducted.

Time Component Test: Least squares mean estimates over time for the two treatment arms (placebo and active) from the primary analysis of MMRM will be used to interpolate between time points using Natural Cubic Splines. The interpolated trajectory for the two arms will be mapped to each other on a time scale via an acceleration factor. Estimation of time-specific acceleration factors only requires the population level summary measures from the MMRM analysis. The common acceleration factor methodology additionally requires an assumption of proportional change over time. A test to verify this assumption of proportionality will be performed. Time saved

at specific time points using time-specific acceleration factor and time saved using a common acceleration factor will be presented along with their confidence intervals[20,22].

PMRM: The placebo group is modeled as a continuous-time extension model and its relationship to the mean values in the treatment group is described as a function with a parameter vector that maps to the study visits which is estimated using non-linear modeling. The time-PMRM model assumes that the mean outcome of the treatment group at a given visit can be described as the mean outcome of the placebo group at another time point. With an assumption of proportional change over time, a common parameter to define change across all time points can be modeled. Both time-specific and proportional change results will be presented. The parameters from the model will represent an effect of time[21, 23].

5.3.3.4.3. Natural Cubic Splines Analysis

Natural cubic splines[25] will be used to model change from baseline in iADRS as the dependent variable using analysis visits through Week 156. Continuous visit timepoints, treatment group and their interaction will be included as independent variables. Other covariates that will be included in the model are: baseline iADRS score, age, baseline tau burden on tau PET (continuous), geographic region, sex, APOE e4 carrier status (Y/N), education level (less than high school or at least some high school or greater) and use of memantine and/or AChEI at baseline (Y/N). The time variable (the month component of "study day divided by 30") will be used to create basis functions using ns() function from the splines package in R using a single knot at the default location of 50th percentile of time values of the DB analysis period to control flexibility of the spline. A random intercept model will be specified with an unstructured covariance matrix structure to account for correlation among observations within participants. In case of convergence problems, alternative variance-covariance structures will be tried. The treatment effect at Week 104 with its 95% confidence interval will be estimated from the model.

5.3.4. Analysis Methods for Supplementary Estimands

5.3.4.1. Supplementary Estimand 1

A supplementary estimand, utilizing the treatment policy strategy for handling the ICEs of discontinuation of randomized study treatment without a switch to an alternative disease-modifying AD therapy and the ICE of adding, changing, or stopping concomitant symptomatic non-disease-modifying AD therapies, will be utilized to inform the design of subsequent trials. This estimand is defined the same as the primary estimand, except for this estimand, data pre- and post- ICEs leading to changes in treatment, such as premature discontinuation of the randomized treatment without a switch to alternative disease-modifying AD therapies, are included. For the ICE of discontinuation of randomized study treatment with a switch to an alternative disease-modifying AD therapy, a hypothetical strategy will be applied. Thus, data after switching to an alternative disease-modifying AD therapy would not be included (deemed missing for analysis). If the participant enters the LTE, data after this date would not be included. Otherwise, the same analysis methods as for the primary estimand described in Section 5.3.3.1 will be applied. Sensitivity analyses outlined in Section 5.3.3.3 will also be performed.

5.3.4.2. Slope Analysis with While-on-Treatment Strategy

In order to provide a clinically meaningful measurement of the slowing of disease progression, a supplementary estimand utilizing the while-on-treatment policy for handling ICEs, comparing the slopes between treatment groups, will be presented. This supplementary estimand is defined by the following 5 components:

- **Population:** Early AD participants with pathological brain tau [T+].
- **Endpoint:** The slope of the change from baseline in iADRS total score while on study treatment (i.e, until the end of the double-blind analysis period).
- **Treatment:** JNJ-63733657 (1000 mg, 3000 mg) versus placebo. Current symptomatic non-disease-modifying AD medications (memantine and acetylcholinesterase inhibitors) are permitted.
- **Intercurrent Events (ICE) and Corresponding Strategy:**

ICE	Strategy
Treatment Discontinuation with or without a switch to an alternative disease-modifying AD therapy	While-on-Treatment Strategy, as reflected in the endpoint definition
Adding, changing, or stopping concomitant symptomatic non-disease-modifying AD therapies	While-on-Treatment Strategy, as reflected in the endpoint definition

- **Population Level Summary:** The difference in slopes.

Current symptomatic non-disease-modifying AD medications (memantine and acetylcholinesterase inhibitors) are permitted in this study as described in the protocol Sections 5.2 (Exclusion Criteria) and 6.8 (Concomitant Therapies). Participants are not required to be taking these medications at study entry. Modifications (e.g., start, stop, or change dose) to symptomatic AD treatments may be necessary during study participant due to the long duration. Under this supplementary estimand, values after the end of the DB analysis period for participants with the ICE of discontinuation of assigned study treatment (with or without a switch to an alternative disease-modifying AD therapy) and after addition, change, or stopping of concomitant symptomatic non-disease-modifying AD therapies will not be included in the calculation of the endpoint. Study treatment must be discontinued prior to the addition of any alternative disease-

modifying AD therapy. Observations after the occurrence of the ICE of the addition of any alternative disease-modifying AD therapy will not be included.

A mixed effect model treating time as a continuous variable (the numeric week corresponding to the analysis visit) will be computed for the change from baseline in iADRS total score while on treatment. The model will include fixed effects of time, treatment group and time-by-treatment interaction, as well as a random slope (for time) and intercept. Additionally, fixed-effects of the following covariates will be included: baseline iADRS total score, baseline tau burden on tau PET (continuous), and age as a covariates, and factors for geographic region, sex, APOE ε4 carrier status (Y/N), education level (less than high school or at least some high school or greater), and use of memantine and/or AChEI at baseline (Y/N). The difference in slopes and 2-sided 95% CIs will be obtained for each treatment group (1000 mg and 3000 mg) vs placebo.

Sensitivity analyses may be performed where analysis visits up to Week 104 are included.

5.3.4.3. Balanced Estimand

An additional supplementary analysis (addressing a "balanced" estimand[16]) may be performed in case of imbalance occurrence (e.g., 10% or more difference between groups) of the ICE of treatment discontinuation with switching to an alternative disease-modifying AD therapy to enable estimation of the treatment effect if switching had been balanced across treatment groups; this analysis will include the outcome data collected after switching. Data for other ICEs would be handled with the same approach as for the primary estimand.

The analysis will be performed as follows. The analysis will be performed for each dose of JNJ-63733657 separately.

Let:

TRT_i = indicator denoting randomized treatment assignment of participant i (1 = JNJ-63733657, 0 = placebo or 0 = JNJ63733657, 1 = placebo)

S_i = indicator denoting whether or not participant i switched to alternative disease-modifying AD treatment (1 = switched, 0 = did not switch)

$Y_{i,52}$ = IADRS change from baseline at Week 52 for participant i

$Y_{i,104}$ = IADRS change from baseline at Week 104 for participant i

M_i = indicator denoting whether or not alternative disease-modifying AD treatment is available for participant i to switch to during FU. (1 = available, 0 = not available)

ρ = pre-specified sensitivity parameter $\in [0.8,1)$

NOTE: Switching to alternative disease-modifying AD treatment on or prior to Week 52 is considered a dropout for the purposes of applying the estimator defined below. Steps 1-5 are to be applied to the subset of participants who have not dropped out before Week 104 (and therefore those who have not switched to alternative disease-modifying AD treatment on or prior to Week 52). Additionally, steps 1-4 are to be applied to the further subset of those participants for whom alternative disease-modifying AD treatment is available to switch to during FU ($M_i = 1$).

Step 1: Within the subset of participants with $M_i = 1$, calculate the proportion of participants with $TRT_i = 1$, i.e.,

$$\hat{\pi} = \frac{\sum_{\{i:M_i=1\}} TRT_i M_i}{\sum_{\{i:M_i=1\}} M_i}.$$

Step 2:

a.) Within the subset of participants with $TRT_i = 1$ & $M_i = 1$, regress S_i on $Y_{i,52}$, i.e., fit the following logistic regression model for the probability of switching:

$$logit\ P\left(S_i = 1 \middle| TRT_i = 1, M_i = 1, Y_{i,52}\right) = \omega_0 + \omega_1 Y_{52}$$

b.) Obtain the predicted probabilities for all participants with $M_i = 1$ using the fitted logistic regression model in Step 2(a) as:

$$\widehat{pp}_i \equiv \hat{P}\left(S_i = 1 \middle| Y_{i,52}, M_i = 1\right) = \begin{cases} expit\left(\hat{\omega}_0 + \hat{\omega}_1 Y_{i,52}\right), \text{ if participant } i \text{ has } TRT_i = 1 \text{ (and } M_i = 1) \\ 0 \quad\quad\quad\

$$W_{i,M_i=1} =$$

$$\begin{cases} \frac{expit(\hat{\lambda}+\rho\,\hat{\omega}_1 Y_{i,52})}{expit(\hat{\omega}_0+\hat{\omega}_1 Y_{i,52})}, \text{ for participants who switch } (S_i = 1) \text{ (and } M_i = 1) \\ \frac{1-expit(\hat{\lambda}+\rho\,\hat{\omega}_1 Y_{i,52})}{1-expit(\hat{\omega}_0+\hat{\omega}_1 Y_{i,52})}, \text{ for participants who do not switch } (S_i = 0) (\text{and } M_i = 1) \end{cases}$$

Step 5:

a.) Calculate the proportion of participants in the treatment arm for whom alternative disease-modifying AD treatment is available after Week 52, i.e.,

$$\hat{\xi} = \frac{\sum_{i=1}^{N} TRT_i M_i}{\sum_{i=1}^{N} TRT_i}.$$

b.) Estimate $\mu_1 = E\left[Y^{1S^0}\right]$ and $\mu_0 = E[Y^0]$ as follows:

$$\hat{\mu}_1 = \hat{\xi}\left[\frac{\sum_{i=1}^{N} Y_{i,104}\, TRT_i\, W_i\, M_i}{\sum_{i=1}^{N} TRT_i\, W_i\, M_i}\right] + \left(1-\hat{\xi}\right)\left[\frac{\sum_{i=1}^{N} Y_{i,104}\, TRT_i\, (1-M_i)}{\sum_{i=1}^{N} TRT_i\, (1-M_i)}\right]$$

and

$$\hat{\mu}_0 = \frac{\sum_{i=1}^{N} Y_{i,104}\, (1-TRT_i)}{\sum_{i=1}^{N} (1-TRT_i)}$$

c.) Estimate $\mu = \mu_1 - \mu_0$ as $\hat{\mu} = \hat{\mu}_1 - \hat{\mu}_0$. The variance of $\hat{\mu}$ can be obtained using non-parametric bootstrap.

5.3.5. Subgroup Analyses

Subgroup analyses for each subgroup listed in Section 5.1.3 will be performed. The strategy for handling ICEs will be the same as for the primary estimand. An MMRM model will be used to analyze the iADRS change from baseline as the dependent variable, with factors for treatment (placebo, JNJ-63733657 1000 mg or JNJ-63733657 3000 mg), geographic region, sex, APOE ε4 carrier status (Y/N), education level (less than high school or at least some high school or greater), use of memantine and/or acetylcholinesterase inhibitors (AChEI) at baseline (Y/N), visit and treatment-by-visit interaction, subgroup, treatment-by-subgroup and treatment-by-visit-by-subgroup interaction terms as fixed effects. Age, baseline tau burden on tau PET and baseline iADRS score will be included as continuous covariates and an unstructured covariance matrix structure will be utilized to account for correlation among observations within participants. In case of convergence problems, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1) with separate subject random effect. The Kenward-Roger method will be used for approximating the denominator degrees of freedom. If a structured covariance

matrix is used due to convergence issues, a robust variance estimator, commonly referred to as the "sandwich" estimator, will be used to address the potential impact of covariance matrix misspecification on the estimation and testing of treatment effect. The between-treatment difference of the change from baseline at each time point at each level of the subgroup variable, and its 95% confidence interval (2-sided), will be estimated from the model with a linear contrast. Estimates and 95% confidence intervals will be displayed with forest plots. Redundant terms will be dropped from the model in those cases where the subgroup of interest overlaps with the general model. For example, baseline iADRS total score (as a continuous covariate) will not be included in the model when the dichotomized baseline iADRS total score is included in the model, and baseline tau burden on tau PET (as a continuous covariate) will not be included in the model when the dichotomized baseline tau PET score or the terciles of baseline tau PET score are subgroup terms included in the model. Consistent with the estimand for the primary analysis, which applies a hypothetical strategy for treatment discontinuation, only the measurements occurring prior to the end of the DB analysis period including analysis visits through Week 104 will be included in the subgroup analyses.

Forest plots will be provided displaying analysis results for each subgroup listed in Section 5.1.3. In addition, analyses using the model described in Section 5.3.3.1 will be performed separately for each of the baseline tau PET subgroups.

5.4. Secondary Endpoints Analysis

5.4.1. Key Secondary Endpoints

Key secondary efficacy analyses will be performed on the FAS. The multiplicity, with regard to testing multiple doses of JNJ-63733657 (1000 mg versus placebo and 3000 mg versus placebo) and multiple endpoints, i.e, for the primary analysis efficacy endpoint (iADRS), for the 2 key secondary efficacy endpoints (ADAS-Cog13 and ADCS-ADL-MCI), and for the secondary efficacy endpoint CDR-SB, will be controlled by a Hochberg sequential gatekeeping test procedure using a family-wise error rate of 2 sided 0.05 as described in Section 5.4.1.4.

5.4.1.1. Definition of Endpoints

The key secondary efficacy endpoints are measured by the ADAS-Cog13 (cognition) and the ADCS-ADL-MCI (function). These are the 2 components of the iADRS which is the measure used for the primary efficacy endpoint. The CDR-SB is defined in Section 5.4.2.1.2.

5.4.1.1.1. Alzheimer's Disease Assessment Scale Cognitive subscale 13-item version

The ADAS-Cog is a rater administered instrument that was designed to assess the severity of dysfunction in cognition characteristic of persons with AD.[17,18] The ADAS-Cog11 consists of 11 tasks measuring the disturbances of memory, language, praxis, attention, and other cognitive abilities, which are often referred to as the core symptoms of AD.[19]

The modified ADAS-Cog13 item scale includes all original ADAS Cog items with the addition of a number cancellation task and a delayed free recall task, for a total of 85 points, with higher scores

indicative of worse cognitive performance. Item scores are recorded on an electronic device which will provide the total score. Additional details are provided in Appendix 7.

5.4.1.1.2. Alzheimer's Disease Cooperative Study Activities of Daily Living for Mild Cognitive Impairment (ADCS-ADL-MCI)

The ADCS-ADL-MCI is a functional measure based on information provided by the study partner (informant) that describes the performance of patients in several ADLs. The ADCS-ADL-MCI scale version used in this study comprises 24 items of which 18 items are used for the standard analysis.[7,8] Total score ranges from 0 to 53 with higher scores indicating less impairment. Item scores are recorded on an electronic device which will provide the total scores. Additional details are provided in Appendix 7. The analysis of ADCS-ADL-MCI as a key secondary endpoint will use the original total score including all 18 items (ranging from 0 to 53). A supplementary analysis utilizing the full 24 items (23 of which are scored, and item 24 is useful for interpreting the scale results) will also be performed with total score ranging from 0 to 69.

5.4.1.2. Estimands

The estimands for the key secondary endpoints of cognition and function are defined in the same way as the primary endpoint (see Section 5.3.2), except for the endpoints, which are the change from baseline on the ADAS-Cog13 total score and the ADCS-ADL-MCI total score.

5.4.1.3. Analysis Methods

The analysis for each of the 2 key secondary efficacy endpoints will be an MMRM including analysis visits through Week 104, similar to the primary endpoint. The dependent variable will be the change from baseline in the key secondary efficacy scale. The model adjusts for the following variables: baseline score for the scale, age, and baseline tau burden on tau PET (defined as the Braak 4 SUVR uptake z-score which was used to assign the participant to the tau burden randomization stratum, a continuous variable) as covariates, and treatment group, geographic region, sex, APOE ε4 carrier status (Y/N), education level (less than high school or at least some high school or greater), use of memantine and/or AChEI at randomization (Y/N), visit, and visit-by-treatment interaction as fixed effects. An unstructured covariance matrix structure will be utilized to account for correlation among observations within participants. In case of convergence problems, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1) with separate subject random effect. The Kenward-Roger method will be used for approximating the denominator degrees of freedom. If a structured covariance matrix is used due to convergence issues, the robust variance estimator, commonly referred to as the "sandwich" estimator, will be used to address the potential impact of covariance matrix misspecification on the estimation and testing of treatment effect. The treatment effect at Week 104 will be estimated using the difference in LS means and separate contrasts will be obtained for each dose level versus placebo. Point estimates and 95% confidence intervals (2-sided) will be provided for the treatment differences at each time point. For ADAS-Cog13 total score, percent slowing for each dose level compared to placebo at each time point will be calculated as -(LS mean of the treatment difference versus placebo in change from baseline), divided by the absolute value of the LS estimate of mean

change from baseline in the placebo group, times 100. For ADCS-ADL-MCI total score, percent slowing for each dose level compared to placebo at each time point will be calculated as the LS mean of the treatment difference versus placebo in change from baseline, divided by the absolute value of the LS estimate of mean change from baseline in the placebo group, times 100.

Descriptive statistics for each of the 2 key secondary efficacy endpoints and the change from baseline will be provided for each timepoint. An MMRM including analysis visits up to and after Week 104 may also be presented as a supplementary analysis. An MMRM model with an additional baseline-by-visit term may be explored.

5.4.1.4. Multiple Comparison Adjustment

Statistical adjustment will be made to account for multiplicity due to multiple dose comparisons for the primary endpoint, the 2 key secondary endpoints (Sections 5.3 and 5.4.1), and the secondary endpoint CDR-SB (Section 5.4.2.1.2). To strongly control Type I error across the primary and the 2 key secondary efficacy endpoints (change in iADRS total score, change in ADAS-Cog13 total score, and change in ADCS-ADL-MCI total score) and the secondary endpoint of change in CDR-SB, and across the 2 JNJ-63733657 dose-placebo comparisons, a Hochberg sequential gatekeeping test procedure[13] will be applied between families of hypotheses corresponding to the endpoints, and between the two dose-placebo comparisons within each family, at the 2-sided family-wise error rate of 0.05. The 2 dose-placebo comparisons corresponding to each efficacy endpoint are considered as a family of hypotheses. The approach is illustrated in Figure 1 below.

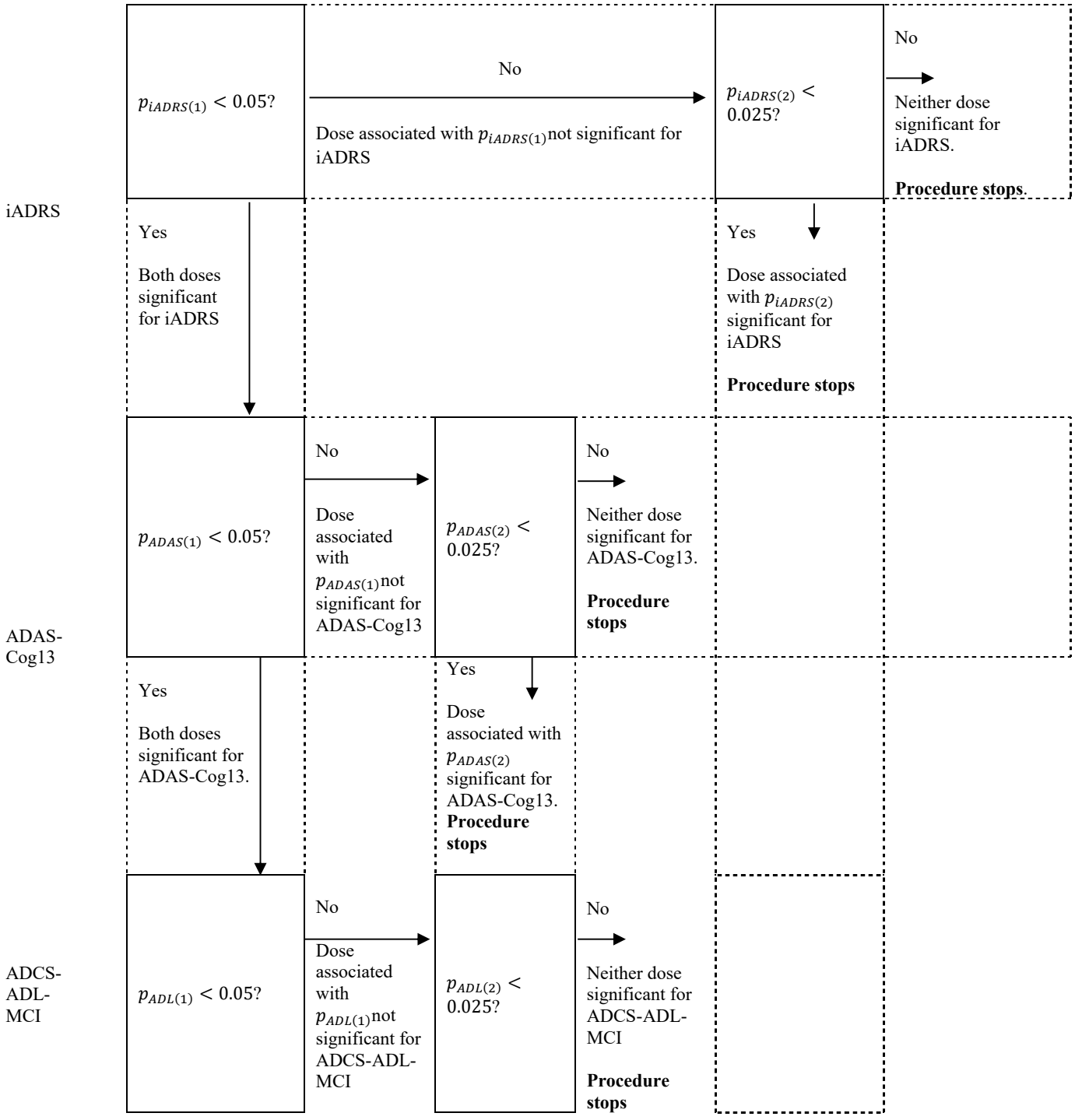
Testing will start with the primary endpoint and will proceed to other endpoints along the sequence only if both JNJ-63733657 dose-placebo comparisons are significant at a pre-specified level of significance.

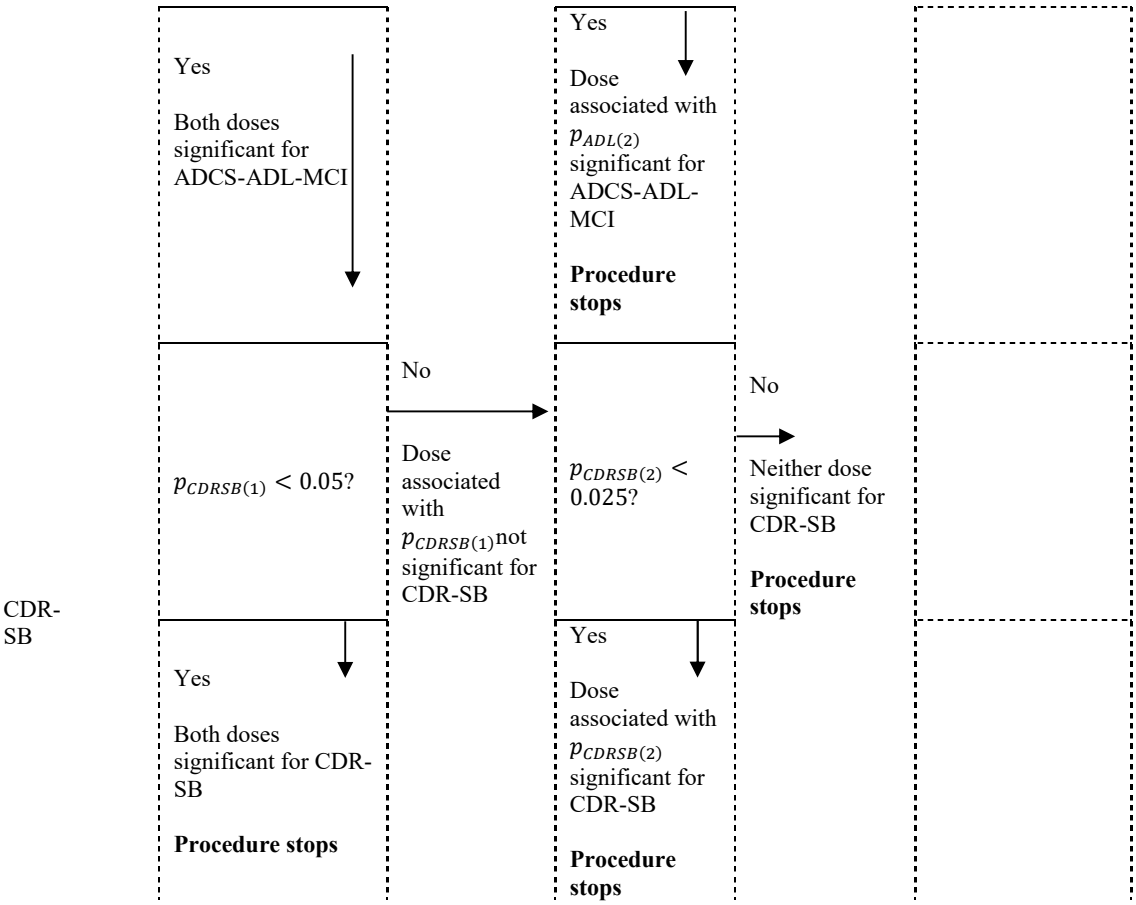
First, the JNJ-63733657 dose groups will be compared with placebo on the primary efficacy endpoint using a Hochberg procedure with a 2-sided $\alpha = 0.05$. If both dose groups are superior to placebo for the primary efficacy endpoint (change in iADRS total score), both dose groups will be compared with placebo on the first key secondary efficacy endpoint (change in ADAS-Cog 13 total score) using the Hochberg procedure with a 2-sided $\alpha=0.05$. Then, if both dose groups are superior to placebo for the first key secondary efficacy endpoint, both dose groups will be compared with placebo on the second key secondary efficacy endpoint (change in ADCS-ADL-MCI total score) using the Hochberg procedure with a 2-sided $\alpha=0.05$. Then, if both dose groups are superior to placebo for the second key secondary efficacy endpoint, both dose groups will be compared with placebo on the change in CDR-SB using the Hochberg procedure with a 2-sided $\alpha=0.05$.

If only 1 dose group or neither dose group is superior to placebo on the primary efficacy endpoint, the procedure will stop and the comparisons of each JNJ-63733657 dose group to placebo for each of the 2 key secondary endpoints and the CDR-SB endpoint will also be ruled not statistically significant. Likewise, if only 1 dose group or neither dose group is superior to placebo on a subsequent secondary efficacy endpoint, the procedure will stop and the comparison of each JNJ-

63733657 dose group to placebo for the remaining secondary endpoints will also be ruled not statistically significant.

Figure 1: Hochberg Sequential Gatekeeping Multiple Comparison Procedure





Key:

$p_{iADRS(1)}$, $p_{iADRS(2)}$: P-values of each JNJ-63733657 dose versus placebo comparison of change from baseline in iADRS at Week 104 (from MMRM analysis), ranked in descending order (i.e, $P_{(1)}$ represents the larger p-value and $P_{(2)}$ represents the smaller p-value.

$p_{ADAS(1)}$, $p_{ADAS(2)}$: P-values of each JNJ-63733657 dose versus placebo comparison of change from baseline in ADAS-Cog13 at Week 104 (from MMRM analysis), ranked in descending order.

$p_{ADL(1)}$, $p_{ADL(2)}$: P-values of each JNJ-63733657 dose versus placebo comparison of change from baseline in ADCS-ADL-MCI at Week 104 (from MMRM analysis), ranked in descending order.

$p_{CDRSB(1)}$, $p_{CDRSB(2)}$: P-values of each JNJ-63733657 dose versus placebo comparison of change from baseline in CDR-SB at Week 104 (from MMRM analysis), ranked in descending order.

5.4.1.5. Sensitivity Analyses

Sensitivity analyses similar to those described in Section 5.3.3.3 will be performed to stress-test the robustness of the analyses of the 2 key secondary endpoints to deviations from the assumptions pertaining to data that is deemed missing under the hypothetical treatment strategy for handling ICEs.

5.4.1.6. Supplementary Analyses

A polynomial regression analysis will be performed for each of the 2 key secondary efficacy endpoints. The model for the polynomial regression will be similar to the one used for the supplementary analysis of the iADRS total score change from baseline described in Section 5.3.3.4.1, replacing the iADRS total score change from baseline dependent variable and the covariate of the iADRS baseline score with the respective values for the key secondary endpoint.

Comparison of each JNJ-63733657 dose versus placebo will be performed using the appropriate contrast. Plots of the LS means and SE for each treatment over time will be presented.

In addition, time-saved analyses similar to those described for the iADRS total score in Section 5.3.3.4.2, an NCS analysis as outlined in Section 5.3.3.4.3, and subgroup analyses as outlined in Section 5.3.5 will be performed for each of the 2 key secondary efficacy endpoints.

An MMRM analysis will be performed for the change from baseline in the ADCS-ADL-MCI (Plus Additional Items) total score (based on all 23 scored items) as described in Section 5.4.1.3. Descriptive statistics will be provided for each individual item by treatment group at each time point.

5.4.2. Other Secondary Endpoints

5.4.2.1. Definition of Endpoints

5.4.2.1.1. Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

The RBANS is an approximately 20- to 30-minute battery developed for cognitive assessment, detection, and characterization of dementia as well as neuropsychological screening for younger patients.[5] The RBANS includes 12 subtests that are divided into 5 RBANS indices:

1. Immediate Memory – List Learning and Story Memory
2. Visuospatial/Constructional – Figure Copy and Line Orientation
3. Language – Picture Naming and Semantic Fluency
4. Attention – Digit Span and Coding
5. Delayed Memory – List Recall, List Recognition, Story Recall, and Figure Recall

Index scores are expressed as an age-adjusted standard score with a normal mean of 100 and an SD of 15. The Sum of Index Scores is the sum of the 5 index scores, and the Sum of Index Scores is converted to an RBANS Total Scale Index Score via a mapping table. The RBANS Total Scale Index Score is a norm-based t-score, based on a distribution with a mean of 100 and an SD of 15. Item scores are recorded on an electronic device which will provide the total scores.

5.4.2.1.2. Clinical Dementia Rating (CDR)

The CDR[6] is a subjectively rated outcome measure that serves as a global clinical staging instrument that includes 3 cognitive and 3 functional ratings, including: 1) memory, 2) orientation, 3) judgment and problem solving, 4) involvement in community affairs, 5) home and hobbies, and 6) personal care based on the CDR interview. The CDR has been used as a global clinical staging measure in a number of AD trials. The CDR is scored 2 ways yielding a global CDR score (CDR-GS, derived from an algorithm developed by the Knight Alzheimer Disease Research Center at Washington University School of Medicine in St. Louis, Missouri, US, and including categorical scoring of 0, 0.5, 1, 2, and 3), as well as CDR-Sum of Boxes (CDR-SB, the continuous sum of 6 domains, up to a total score of 18, with higher scores representing worse disease state).

Item scores are recorded on an electronic device which will provide the total scores. The CDR Cognition score will be calculated as the sum of the CDR Memory, Orientation, and Judgment and Problem-Solving box scores. The CDR Function score will be calculated as the sum of the CDR Community Affairs, Home and Hobbies, and Personal Care box scores.

5.4.2.1.3. Neuropsychiatric Inventory (NPI)

The NPI is a measure of psychobehavioral disturbances,[10] assessing the frequency and severity of disturbances in 12 domains, based on a caregiver interview. For each domain, there is also an assessment of caregiver burden. Frequency for each domain is rated on a 4-point scale (from 1=rarely to 4=very often) and severity on a 3-point scale (from 1=mild to 3=severe), with the score for each domain being the product of the frequency and severity scores, such that each domain is scored from 1 to 12. The NPI total score is the sum of the 12 domain scores, ranging from 0 (best) to 144 (worst). Caregiver distress, based on the response to the question "how emotionally distressing do you find this behavior?", is rated on a 6-point scale (from 0=not at all to 5=very severely or extremely), with the total score for caregiver distress ranging from 0 (best) to 60 (worst). Item scores are recorded on an electronic device which will provide the total scores.

5.4.2.2. Estimands

The estimands for the following secondary endpoints are defined in the same way as the primary endpoint, except for the endpoints and population level summary:

- **Endpoints and Population Level Summary:**

Endpoint	Population Level Summary
Change from baseline on the RBANS Total Scale Index Score	The difference in means between each dose and placebo at Week 88.
Change from baseline in each of the 5 individual RBANS indices and each of the 12 subtests comprising the RBANS	The difference in means between each dose and placebo at Week 88.
Change from baseline on the CDR-SB	The difference in means between each dose and placebo at Week 104.
Progression in CDR-GS from 0 to 0.5 or higher, 0.5 to 1 or higher, or from 1 to 2 or higher, from baseline to post-baseline	The difference in proportions between each dose and placebo at Week 104.
Change from baseline on the NPI total score	The difference in means between each dose and placebo at Week 104.

5.4.2.3. Analysis Methods

The analysis population includes all randomized participants who receive at least 1 dose of study intervention. Under this estimand, which applies a hypothetical strategy for treatment discontinuation, only the measurements occurring prior to the end of the double-blind analysis period for participants with the ICE of treatment discontinuation will be included in the analysis. Study treatment must be discontinued prior to the addition of any alternative disease-modifying

AD therapy. Observations after the occurrence of the ICE of the addition of any alternative disease-modifying AD therapy will not be included in the analysis. Observations after the start of the LTE, if applicable, are not included. The analysis for each of the continuous secondary efficacy endpoints of cognition and function will be based on an MMRM, similar to the primary endpoint, including analysis visits through Week 88 for RBANS, and through Week 104 for other scales. The dependent variable will be the change from baseline in the secondary efficacy scale. The model adjusts for the following variables: baseline score for the scale, age, and baseline tau burden on tau PET (defined as the Braak 4 SUVR uptake z-score which was used to assign the participant to the tau burden randomization stratum, a continuous variable) as covariates, and sex, APOE ε4 carrier status (Y/N), education level (less than high school or at least some high school or greater), use of memantine and/or AChEI at randomization (Y/N), visit, and visit-by-treatment interaction as fixed effects. An unstructured covariance matrix structure will be utilized to account for correlation among observations within participants. In case of convergence problems, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1) with separate subject random effect. The Kenward-Roger method will be used for approximating the denominator degrees of freedom. If a structured covariance matrix is used due to convergence issues, the robust variance estimator, commonly referred to as the "sandwich" estimator, will be used to address the potential impact of covariance matrix misspecification on the estimation and testing of treatment effect. Point estimates and 95% confidence intervals (2-sided) will be provided for the treatment differences for each dose level versus placebo at each timepoint. For RBANS scores, percent slowing for each dose level compared to placebo at each time point will be calculated as the LS mean of the treatment difference versus placebo in change from baseline, divided by the absolute value of the LS estimate of mean change from baseline in the placebo group, times 100. For CDR-SB and NPI scores, percent slowing for each dose level compared to placebo at each time point will be calculated as -(LS mean of the treatment difference versus placebo in change from baseline), divided by the absolute value of the LS estimate of mean change from baseline in the placebo group, times 100.

Descriptive statistics for each of the continuous secondary efficacy endpoints and the change from baseline will be provided for each timepoint. An MMRM including visits up to and after Week 88 for RBANS and up to and after Week 104 for other scales may also be presented as a supplementary analysis. An MMRM model with an additional baseline-by-visit term may be explored.

The proportion of participants progressing from CDR-GS 0 to 0.5 or higher, 0.5 to 1 or higher, or 1 to 2 or higher, from baseline to post-baseline, will be analyzed using frequency tables and survival analysis methods. The distribution of the time to an event will be displayed with Kaplan-Meier curves, and the Kaplan-Meier curves will be used to estimate the percentage of participants converting at the Week 104 analysis visit timepoint. The conversion time for a participant who converted is the first postbaseline timepoint when the CDR assessment was recorded as progressing from 0 at baseline to 0.5 or higher postbaseline, or from 0.5 at baseline to 1 or higher postbaseline, or from 1 at baseline to 2 or higher postbaseline. The last CDR analysis visit assessment date up to and including Week 104 analysis visit date is used as the censoring time for

a participant who discontinued prior to converting. Participants who completed Week 104 or later without converting will use the last CDR assessment up to and including the Week 104 analysis visit date as the censoring time. Under this estimand, which applies a hypothetical strategy for treatment discontinuation, only the measurements occurring prior to the end of the DB analysis period will be included in the analysis. Study treatment must be discontinued prior to the addition of any alternative disease-modifying AD therapy. Observations after the occurrence of the intercurrent event of the addition of any alternative disease-modifying AD therapy will not be included in the analysis. Observations after the start of the LTE, if applicable, are not included in the analysis. Cox proportional hazards regression models will be used with treatment group, geographic region, and baseline tau burden on tau PET (continuous variable), baseline score, age, sex, APOE ε4 carrier status (Y/N), education level (less than high school or at least some high school or greater) and use of memantine and/or AChEI at baseline (Y/N) as independent variables. The hazard ratio and 95% CIs (2-sided) for the hazard ratios will be provided. An additional analysis where the event is defined as worsening from baseline seen at 2 consecutive postbaseline analysis visits, where event time is the first of the 2 visits, will be performed as a sensitivity analysis.

5.4.2.4. Supplementary Analyses of Secondary Endpoints

The following supplementary analyses will be performed to provide additional insight to the treatment effect and to the sensitivity of the instruments to detect disease progression. They will utilize the same strategy as their respective main estimands with regard to handling ICEs.

An analysis of change from baseline in the CDR Cognition score and change from baseline in the CDR Function score will be performed using an MMRM similar to the primary endpoint. Descriptive statistics will be provided.

For the CDR-SB and RBANS total scale score, time-saved analyses will be performed similar to those described in Section 5.3.3.4.2, and an NCS analysis (through Week 156 for CDR-SB and through Week 140 for RBANS) will be performed as outlined in Section 5.3.3.4.3.

For the change from baseline to Week 104 in CDR-SB, subgroup analyses using the model similar to the one outlined in Section 5.3.5 will also be performed.

For the change from baseline to Week 88 in the RBANS total scale score and the 5 indices, subgroup analyses by age group and by tau burden subgroups will be performed using the model similar to the one described in Section 5.3.5.

The Kaplan-Meier estimates of time to CDR-GS progression will be evaluated for the tau burden subgroups. In addition, subgroup analyses for the tau burden subgroups will be performed using the Cox proportional hazards regression model as described above with the addition of the subgroup and treatment-by-subgroup interaction effects added to the model and removing redundant continuous baseline tau burden term from the model.

A multivariate analysis, namely the O-Brien test, for the change from baseline in the iADRS total score [at the Week 104 timepoint], the change from baseline in the ADAS-Cog13 total score [at

the Week 104 timepoint], the change from baseline in the ADCS-ADL-MCI score [at the Week 104 timepoint], the change from baseline in the RBANS Total Scale [at the Week 88 time point], the change from baseline in the Amsterdam IADL total score [at the Week 104 timepoint], and the change from baseline in CDR-SB [at the Week 104 time point] will be conducted to evaluate the consistency of results for the primary endpoint across other endpoints. For each outcome variable, after excluding missing values, the outcome score will be assigned a rank, where a higher rank is better (improvement) and a lower rank indicates worsening. The ranks will be assigned ignoring the treatment group. Next, the ranks for each outcome variable will be summed for each participant to obtain the O'Brien Score. The O'Brien test p-value and a Radar Plot will be provided. In addition, analyses will be performed separately for each of the baseline tau PET subgroups.

The correlations between baseline and changes from baseline in measures of clinical, cognitive and/or functional measures will be explored graphically with scatterplots and/or with Pearson/Spearman correlation coefficients.

The sensitivity of the CDR-SB versus the iADRS, the standard ADCS-ADL-MCI versus the Amsterdam IADL, and the ADCS-ADL-MCI (Plus Additional Items) versus the Amsterdam IADL to detect disease progression will be further investigated by calculating signal-to-noise ratio (SNR) as per Wessels et al (2015)[9]. Bootstrapping, a general resampling procedure for estimating the distributions of statistics based on independent observations, will be used to sample the original dataset with replacement to generate 500 new data sets of the same size as the original data set. MMRM analyses will be conducted to estimate the least squares (LS) mean change from baseline (and standard deviation [SD]) up to Visit 104 timepoint. The MMRM will follow that used for the primary endpoint analysis (see Section 5.3.3.1). Because these scales have differences in total points and point differences relative to decline, direct comparisons of the LS mean change of the scales are not informative. The SNR will be computed as the least squares mean change from baseline divided by the SD for the placebo group. The 95% CI (2-sided) of each estimated SNR will be determined by the 2.5th and 97.5th percentiles of these 500 SNRs. An alternative approach of deriving bootstrap-based CI (reverse percentile/ "basic bootstrap")[27] may be explored. A higher SNR represents greater change detected by the scale, corrected for variability. The median SNR and 95% CIs for each of these scales will be displayed in a forest plot. The SNR will also be computed using the difference between each active JNJ-63733657 dose versus placebo (LS mean and SD) at Week 104 to investigate the sensitivity of these instruments to detect treatment effect.

The probability of not progressing on the CDR-SB from baseline to each post-baseline analysis visit through Week 104 will be evaluated. Participants will be classified as "not progressing" if their CDR-SB change from baseline is less than or equal to 0, which will be calculated as a binary outcome at each analysis visit. A generalized linear mixed model will be applied to assess the difference in probability of "not progressing" by treatment group, with the binary "not progressing" status (Yes or No) as the dependent variable with a binary distribution option, with fixed effects of baseline CDR-SB score, age, baseline tau burden on tau PET (continuous variable), treatment, geographic region, sex, APOE ε4 carrier status (Y/N), education level (less than high school or at least some high school or greater), use of memantine and/or AChEI at baseline (Y/N), visit, and visit-by-treatment interaction. Visit will be considered a categorical variable. An

unstructured covariance matrix structure will be utilized to account for correlation among observations within participants. In case of convergence problems, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1) with separate subject random effect. If a structured covariance matrix is used due to convergence issues, the robust variance estimator, commonly referred to as the "sandwich" estimator, will be used to address the potential impact of covariance matrix misspecification on the estimation and testing of treatment effect. The probability of "not progressing" will be presented for each time point by treatment group. The difference in probability of "not progressing" at each time point will be evaluated for each dose level versus placebo with 95% CI.

The time to substantial decline as measured by the CDR-SB[24] will be analyzed using survival analysis methods. Substantial decline is defined as 1 point or more increase in CDR-SB from baseline. The event time for a participant is the first postbaseline timepoint where the criteria are met. The last CDR analysis visit assessment date up to and including Week 104 visit date is used as the censoring time for a participant who discontinued prior to observing the event. Participants who completed Week 104 or later without converting will use the last CDR analysis visit assessment date up to and including Week 104 analysis visit date as the censoring time. Under this estimand, which applies a hypothetical strategy for treatment discontinuation, only the measurements occurring prior to the end of the DB analysis period will be included. Study treatment must be discontinued prior to the addition of any alternative disease-modifying AD therapy. Observations after the addition of any alternative disease-modifying AD therapy will not be included in the analysis. Observations after the start of the LTE, if applicable, will not be included in the analysis. Cox proportional hazards regression models will be used with treatment group, geographic region, and baseline tau burden on tau PET (continuous variable), baseline score, age, sex, APOE ε4 carrier status (Y/N), education level (less than high school or at least some high school or greater) and use of memantine and/or AChEI at baseline (Y/N) as independent variables. The hazard ratio and 95% CIs (2-sided) for the hazard ratios will be provided. An additional analysis where the event is defined as worsening from baseline seen at 2 consecutive analysis visits, where event time is the first of the 2 visits, will be performed as a sensitivity analysis.

The Kaplan-Meier estimates of CDR-SB time to substantial decline will be evaluated for the tau burden subgroups. In addition, subgroup analyses for the tau burden subgroups will be performed using the Cox proportional hazards regression model as described above with the addition of the subgroup and treatment-by-subgroup interaction effects added to the model and removing redundant continuous baseline tau burden term from the model.

5.5. Exploratory Endpoints Analysis

5.5.1. Amsterdam Instrumental Activities of Daily Living Questionnaire (IADL)

The Amsterdam IADL is a computerized questionnaire aimed at measuring difficulties with complex daily activities. It is completed by the study partner of the participant, and unlike the ADCS-ADL MCI, it scores only IADLs the participant actually performs.

The Amsterdam IADL questionnaire consists of 70 items and for each item difficulty is rated on a 5-point scale. To optimize individual differences in premorbid IADL activities, items are tailored to individual responses. If the patient had not performed the main activity, more detailed items on that activity are skipped.

The total score is calculated using an item response theory method of scoring. Item response theory assumes that ordered-categorical item responses represent an underlying construct. In this case, the construct is IADL functioning, ranging from disability to ability. The total score is normally distributed (mean = 50, standard deviation = 10), with higher scores indicating better functioning[11]. The total score is calculated by VU University Medical Center, Amsterdam, The Netherlands[11].

An analysis of change from baseline in the Amsterdam IADL total score will be performed using an MMRM similar to the primary endpoint. Subgroup analyses by geographic region and for tau burden subgroups will be performed using the model similar to the primary endpoint as described in Section 5.3.5.

Actual values and changes from baseline on the Amsterdam IADL total score will be summarized with descriptive statistics by intervention group at each assessment time point. A further summary by geographic region will be provided.

5.5.2. Quality of Life in Alzheimer's Disease (QOL-AD)

The QOL-AD is a 13-item questionnaire, administered in interview format to individuals with dementia.[12] The interview is carried out with the participant and study partner separately. The questions in both participant and study partner versions are the same and concern different aspects of quality of life rated on a 4-point scale (from 1=poor to 4=excellent). The total score is the sum of all 13 items. Item scores are recorded on an electronic device which will provide the total scores.

An analysis of change from baseline in the QOL-AD total score will be performed using an MMRM similar to the primary endpoint, for the participant and study partner separately.

Actual values and changes from baseline on the QOL-AD total score will be summarized with descriptive statistics by intervention group at each assessment time point, for the participant and study partner separately.

5.5.3. Resource Utilization in Dementia Lite (RUD-Lite)

The Resource Utilization in Dementia Lite (RUD-Lite) is administered at time points indicated on the SoA in the protocol to assess the healthcare resource utilization of participants and their study

partners, and to determine the level of formal and informal care attributable to AD. It assesses time spent assisting participants with basic (dressing, bathing, etc) and instrumental ADLs (shopping, cooking, etc). The RUD-Lite results can be used for calculating cost offsets and cost-effectiveness modeling.

The RUD-Lite is a questionnaire rather than an assessment scale, and, as such, it is not 'scored'. Instead, individual questions of the participant component provide resource use information. It includes both participant and caregiver components.

For any accommodation changes, the "current type of accommodation" reported at postbaseline visits will be compared to the last available accommodation type (i.e. the most recent previous RUD lite assessment with accommodation-type documented). This could be the baseline RUD-lite or a post-baseline prior visit with a documented change. Normalization of data to a 30-day period may be computed for items measuring occurrences since the last assessment.

An analysis of change from baseline in the RUD-Lite caregiver time will be performed using an MMRM similar to the primary endpoint.

Actual values and changes from baseline in numeric measurements of resource utilization (eg, caregiver time, hospitalizations, changes in housing) on RUD-Lite will be summarized with descriptive statistics by intervention group at each assessment time point. Categorical variables will be summarized by intervention group using frequency counts and percentages at each assessment time point.

5.6. Safety Analyses

All safety analyses will be based on the Safety Analysis Set, unless otherwise specified.

For all continuous safety variables, descriptive statistics by intervention group will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by intervention group using frequency counts and percentages. Risk differences for select safety variables may be included in analyses for exploratory purposes; corresponding 95% confidence intervals may also presented but not adjusted for multiplicity.

5.6.1. Extent of Exposure

The number and percentage of participants who receive study intervention will be summarized.

Descriptive statistics for duration of study intervention will be summarized. Participant-years of intervention are calculated as days of intervention/365.25. Participant-years will be presented by intervention group.

Duration of intervention will be summarized in the following duration categories: <24 weeks, 24 – <52 weeks, 52 - <76 weeks, 76 - <104 weeks, 104 - <128 weeks, 128 - <156 weeks, 156 - <180 weeks, and >=180 weeks for each study intervention and presented graphically in a histogram.

Cumulative duration of intervention will be summarized for the same categories as indicated for duration of intervention.

Study intervention duration is defined as (date of last dose of study intervention – date of first dose of study intervention) + 1.

The number of participants who did not receive the complete infusion of study intervention will be tabulated by study visit.

Time to permanent discontinuation of DB study intervention will be presented graphically using Kaplan-Meier methods.

5.6.2. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of DB study intervention through the day of last dose plus 90 days, prior to the first administration of LTE study intervention, if applicable, is considered to be a treatment emergent AE (TEAE) for the DB analysis period. If the AE starts on the day of the initial administration of DB study intervention, and either AE start time or time of administration are missing, then the event will be assumed to be a TEAE for the DB analysis period. For participants not entering the LTE, if the AE start date is recorded as partially or completely missing, then the AE will be considered to be a TEAE for the DB analysis period unless it is known to be prior to the first administration of DB study intervention or more than 90 days after the last dose based on partial start date or resolution date. All reported TEAEs will be included in the analysis. For each TEAE, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group. Participants who stop study intervention but continue in the study may have AEs after study intervention cessation. These will be reported as post cessation adverse events (PCAEs) and are defined as any AE that begins >90 days after stopping study intervention.

Summary tables will be provided for treatment-emergent adverse events:

- AEs
- AEs with incidence>= 5% in any treatment group
- Serious AEs (SAEs)
- AEs leading to death
- AEs leading to discontinuation of study intervention
- AEs by severity
- AEs by relationship (study treatment, study procedure, MK-6240 (tau PET tracer), or not related)
- AEs leading to dose interruption or reduction of infusion rate of study intervention
- AEs from the MedDRA Haematopoietic cytopenias (SMQ) (Broad + Narrow Scope)

- AEs from the MedDRA Ischaemic CNS vascular conditions (SMQ) (Narrow Scope)
- AEs from the MedDRA Ischaemic CNS vascular conditions with outcome of death (SMQ) (Narrow Scope)
- AEs from the MedDRA Haemorrhagic CNS vascular conditions (SMQ) (Narrow Scope)
- AEs from the MedDRA Haemorrhagic CNS vascular conditions with outcome of death (SMQ) (Narrow Scope)
- Cerebral Amyloid Angiopathy (CAA) Neuroimaging AEs (based on a pre-defined list of preferred terms listed in Appendix 8)
- AEs of Special Interest (AESI)
    - Hepatobiliary disorders/liver enzyme abnormality related AEs, from the MedDRA Drug related hepatic disorders – comprehensive search SMQ (Broad + Narrow Scope).
    - Infusion-related reactions (excluding local infusion site reactions [eg, bruising, pain, extravasation], defined as AEs occurring on the same day as a study intervention dose with either a preferred term of "Infusion related reaction" or indicated on the AE eCRF as AESI of "Infusion Reaction").
        - Symptom severity of TE Infusion Reactions will be summarized.

Summary tables will also be provided for TEAEs and TE SAEs with onset during the first 104 weeks of the DB analysis period, where a cutoff of study day 743 will be applied to those who participated in the DB analysis period beyond this cutoff.

Summary tables will be provided for the following types of PCAEs:

- All PCAEs
- PC SAEs
- PC AEs leading to death.

In addition to the summary tables, listings will be provided for participants who:

- Had AEs
- Had SAEs (treatment-emergent and non-treatment-emergent)
- Had AEs considered related to study treatment by the investigator
- Had AEs leading to discontinuation of study intervention
- Had severe AEs
- Had AEs leading to death
- Had AEs from the MedDRA searches listed above
- Had AESIs
- Had AEs after switching to an alternative disease-modifying AD therapy (eg, aducanumab, donanemab, or lecanemab).

A Hepatic Adjudication Committee will perform an independent, blinded assessment and adjudication of individual hepatic cases reported in study 63733657ALZ2002 meeting Case Definition criteria to determine the likelihood (e.g., probable, possible, unlikely, insufficient information) that the cases represent drug-induced liver injury (DILI) due to blinded study intervention (JNJ-63733657 or placebo), as outlined in a separate Hepatic Adjudication Committee Charter (EDMS-RIM-1223365). This outcome will be tabulated by treatment group.

5.6.3. Additional Safety Assessments

5.6.3.1. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the participants included in the safety analysis set. Summaries may be presented using 2 approaches: one including central laboratory data only, and one including both central laboratory data and local laboratory data.

Descriptive statistics and graphical displays will be presented for all numeric chemistry, hematology, and urinalysis laboratory tests at scheduled time points. A boxplot of values at each scheduled time point will be provided. The plots will include reference lines for the lower and upper limit of the normal range (LLN and ULN). If a test has more than one LLN, the largest among the LLN values for that test for that time point will be presented on the plot. If a test has more than one ULN, the smallest among ULN values for that test for that time point will be presented on the plot. Summary statistics for the values will be annotated beneath each box plot.

Change from baseline to each scheduled time point based on analysis visit will be summarized by intervention group. A boxplot of change from baseline to each scheduled time point will be provided.

An abnormality (based on the laboratory normal range) or a potentially clinically significant (PCS) value (based on criteria defined in Appendix 6) will be attributed to the baseline and postbaseline values. Summaries of abnormalities and PCS values over time will consider all observations during the analysis visit window (not just the one closest to the target day).

Postbaseline abnormalities and PCS values will be compared with their corresponding baseline result:

- If the postbaseline value is above the upper limit and the baseline value is below the upper limit (eg, Normal or Low), then the postbaseline abnormality will be considered treatment-emergent (TE). The same applies to the postbaseline value being below the lower limit with the baseline value being above the lower limit (eg, Normal or High).
- If the baseline value is missing, a postbaseline abnormality will always be considered as TE.

The number and percentage of participants with TE abnormal laboratory values and/or TE PCS values will be presented by intervention group over time. The number and percentage of participants experiencing a TE abnormal laboratory value and/or TE PCS value at any time during the intervention period will be summarized for each laboratory parameter by intervention group. Summaries of TE abnormal laboratory values will be presented separately to summaries of TE

PCS values. A listing of PCS laboratory values will be provided. Summaries will also be provided for TE abnormal laboratory values and/or TE PCS values occurring during the first 104 weeks of the DB analysis period, where a cutoff of study day 743 will be applied to those who participated in the DB analysis period beyond this cutoff.

The PCS laboratory criteria are provided in Appendix 6.

Shift tables will be provided summarizing the shift in laboratory values from baseline to the maximum value during the DB period, as well as to the minimum value, with respect to normal ranges (low, normal, high).

Summaries for time to first TE ALT or AST elevation ≥ 3xULN, and eDISH plots will be presented. The Double-blind analysis period end date will be used as the censoring time for a participant who did not have the event.

The number and percentage of participants meeting the below liver enzymes criteria during the DB analysis period will be presented by intervention group:

- Alanine Aminotransferase (ALT)
  - >5x the upper limit of normal (ULN),
  - >=3x ULN to <=5x ULN,
  - >ULN to <3x ULN
- Aspartate Aminotransferase (AST)
  - >5x ULN,
  - >=3x ULN to <=5x ULN,
  - >ULN to <3x ULN
- Gamma Glutamyl Transferase (GGT)
  - >5x ULN,
  - >3x ULN to <=5x ULN,
  - >ULN to <=3x ULN
- Alkaline Phosphatase (ALP)
  - >5x ULN,
  - >2x ULN to <=5x ULN,
  - >ULN to <=2x ULN
- Total Bilirubin (TBL)
  - >2x ULN
  - >ULN to <=2x ULN
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >=3xULN and (either TBL >2xULN or INR >1.5)
- ALT or AST >= 3x ULN
- ALT > 1.5x ULN
- ALT or AST >ULN.

Additional summaries of liver enzyme elevations will be presented for subgroups of participants whose ALT and AST <= ULN in Pre-Day 1 Dose Period versus those who had at least 1 ALT or AST > ULN in the Pre-Day 1 Dose Period.

A listing of participants meeting elevated liver enzyme criteria (ALT>=3xULN, AST>=3xULN, TBL>2xULN, or INR>1.5 at any visit in the screening, baseline, or DB period) will be presented. A listing of participants meeting the Hy's Law criteria of ALT or AST >=3xULN and (either TBL >2xULN or INR >1.5) will also be presented.

5.6.3.2. Vital Signs and Physical Examination Findings

Box plots of continuous vital signs values (temperature, weight, pulse, systolic blood pressure, diastolic blood pressure, and Body Mass Index (BMI)) and changes from baseline at each scheduled time point for each position will be provided. BMI will be calculated as weight (kg)/(height (m))^2, at each time point that body weight is measured. The height measurement collected at the screening visit will be used in the calculation.

Change from baseline will be summarized at scheduled time points. Descriptive statistics will be presented.

Abnormality criteria (based on criteria defined below) will be applied to baseline and postbaseline values. For baseline values, increase or decrease criteria are not applied.

Postbaseline values will be considered TE if they meet both value and change criteria in the table below. A postbaseline PCS change in weight meeting the criteria in Table 12 will be considered TE regardless of the baseline value.

For criteria that do not include an increase or decrease from baseline:

- TE will be concluded if the postbaseline value is above the high PCS criteria and the baseline value is below the high PCS criteria (eg, Normal or Low). The same applies to the postbaseline value being below the lower limit with the baseline value being above the low PCS criteria (eg, Normal or High).
- If the baseline value is missing, a postbaseline abnormality will always be considered as TE.

Incidence of TE PCS vital signs at any time during intervention, as defined in Table 12, will be summarized for participants who had a baseline assessment and at least 1 postbaseline assessment for that vital sign. Incidence of TE PCS vital signs will also be summarized over time by intervention group. Summaries of abnormalities and PCS values over time will consider all observations during the analysis visit window (not just the one closest to the target day). A listing of participants with TE PCS vital signs will be presented.

Table 12: PCS Vital Signs

Vital Sign	Criteria for Low PCS Values	Criteria for High PCS Values
Temperature (C)	<35	>38
Weight (kg)	Decrease of ≥10% relative to baseline	Increase of ≥10% relative to baseline
Pulse (bpm)	< 45	>120
Systolic BP (mmHg)	< 90	>180

Diastolic BP (mmHg)	< 50	>105

Orthostatic hypotension is defined as an absolute decrease in systolic (>20 mm Hg) or diastolic (>10 mm Hg) blood pressure after standing for 1 to 3 minutes relative to supine position with an increase in pulse rate of >15 beats per minute, as shown in Table 13 below. The number and percentage of participants who experience TE orthostatic hypotension (TE defined as not being present at baseline) will be tabulated for each scheduled time point. Also presented by intervention group and parameter will be the number and percentage of participants experiencing TE orthostatic hypotension at any time during the DB analysis period.

Table 13: Abnormal Limits for Orthostatic Hypotension Parameters (Changes in Vital Signs in Standing Relative to Supine Position)

Vital Sign	Outside of normal limit if difference (standing minus supine)
(1) Pulse (bpm)	> 15 bpm
(2a) Systolic blood pressure (mm Hg) (SBP)	< -20 mm Hg
(2b) Diastolic blood pressure (mm Hg) (DBP)	< -10 mm Hg

Note: Orthostatic hypotension requires that conditions (1) and [(2a) or (2b)] are met.

For participants who are unable to stand and have the vital signs measured in a sitting or supine position instead of the standing position, the difference between standing and supine values will remain missing.

5.6.3.3. Electrocardiogram

12-lead ECGs will be performed in triplicate at visits indicated in the protocol Schedule of Assessments at approximately 1-minute intervals, at approximately the same time of day and pre-dose.

The ECG parameters that will be analyzed are heart rate, PR interval, RR interval, QRS interval, QT interval, and corrected QT (QTc) interval using the following correction methods: Bazett's formula (QTcB), Fridericia's formula (QTcF), and Linear formula (QTcL).

Bazett's formula: QTcB (msec) = QT (msec) / (RR (msec)/1000)$^{1/2}$; if RR is missing, use QT (msec) * (HR(bpm)/60)$^{1/2}$;

Fridericia's formula: QTcF (msec) = QT (msec) / (RR (msec)/1000)$^{1/3}$; if RR is missing, use QT (msec) * (HR(bpm)/60)$^{1/3}$;

Linear regression formula: QTcL (msec) = QT (msec) + 0.154(1000-RR (msec)); if RR is missing, use QT (msec) + 154 * (1 - 60/HR(bpm)).

QTcB and QTcF will be provided by the central ECG vendor and not recalculated. QTcL will be calculated by statistical programming using the formula above. The analysis value for each parameter on a given date will be the average of the values obtained from the triplicate ECGs.

Descriptive statistics and box plots of the ECG parameter values and changes from baseline at each scheduled time point will be provided.

The number and percentage of participants with QTc interval will be summarized for the maximum post-baseline value and at each scheduled time point. The number and percentage of participants with QTc interval increases from baseline to the maximum postbaseline value will be summarized. Refer to the Table 14 below for summary categories.

Table 14: Criteria for Abnormal QTc Values and Changes from Baseline

QTc value (msec)	≤450 for male, ≤470 for female
	>450 – ≤480 for male, >470 – ≤480 for female
	>480 – ≤500
	>500
QTc change from baseline	≤30
	>30 – ≤60
	> 60

Abnormality criteria (based on criteria defined below) will be applied to baseline and postbaseline values.

Postbaseline abnormalities will be compared with their corresponding baseline result:

- TE will be concluded if the postbaseline value is above the high PCS criteria and the baseline value is below the high PCS criteria (eg, Normal or Low). The same applies to the postbaseline value being below the low PCS criteria with the baseline value being above the low PCS criteria (eg, Normal or High).
- If the baseline value is missing, a postbaseline abnormality will always be considered as TE.

The number and percentage of participants with TE PCS ECG values as shown in Table 15 will be presented by intervention group over time. Summaries of abnormalities and PCS values over time will consider all observations during the analysis visit window (not just the one closest to the target day). Also presented by intervention group and ECG parameter will be the number and percentage of participants experiencing TE PCS ECG values at any time during the intervention period.

Table 15: PCS Values for ECG

Parameter	Criteria for Low PCS Values	Criteria for High PCS Values
HR (bpm)	< 45	> 120
PR (msec)	< 120	> 200
RR (msec)	< 600	> 1200
QRS (msec)	< 70	> 120

A listing of PCS ECG abnormalities will also be provided.

The interpretation of the ECGs as determined by a qualified physician (investigator or qualified designee) will be displayed by the number and percentage of participants meeting the normality criteria (not evaluable; normal; abnormal). The interpretation will be summarized over time.

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

The Columbia Suicide Severity Rating Scale (C-SSRS) is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed in the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment[2]. It is a semi structured clinician-administered questionnaire designed to solicit the occurrence, severity, and frequency of suicide-related ideation and behaviors during the assessment period. Using the C-SSRS, potentially suicide-related events will be categorized at each time point using the following scores:

Suicidal Ideation (1-5)
1: Wish to be Dead
2: Non-specific Active Suicidal Thoughts
3: Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
4: Active Suicidal Ideation with Some Intent to Act, without Specific Plan
5: Active Suicidal Ideation with Specific Plan and Intent

Suicidal Behavior (6-10)
6: Preparatory Acts or Behavior
7: Aborted Attempt
8: Interrupted Attempt
9: Actual Attempt (non-fatal)
10: Completed Suicide

If no events qualify for a score of 1 to 10, a score of 0 will be assigned (0="no event that can be assessed on the basis of C-SSRS"). Higher scores indicate greater severity. A participant with an event of non-suicidal self-injurious behavior only will not be considered as having suicidal ideation or behavior, therefore a score of 0 will be assigned. However, an additional score of 11 will be assigned to summarize any participants with an event of non-suicidal self-injurious behavior.

Shifts from baseline to the maximum postbaseline score pertaining to suicidal ideation or suicidal behavior (i.e, scores 0 to 10) will be summarized by study intervention for the Double-blind analysis period.

The maximum score (of scores 0 to 10) assigned for each participant will be grouped into one of three broad categories: No suicidal ideation or behavior (0), Suicidal ideation (1-5), Suicidal behavior (6-10). Shifts from baseline to the maximum postbaseline category will be summarized by study intervention for the Double-blind analysis period.

A frequency distribution of the C-SSRS scores for the 11 categories (0 to 10) will be provided by study intervention at each time point. In addition, the number and proportion of participants with non-suicidal self-injurious behavior (a score of 11) will be provided by study intervention at each time point.

A listing of participants with TE suicidal ideation or behavior will be provided.

5.6.3.5. Neurological Examination

A neurological examination will be performed at visits indicated in the protocol Schedule of Assessments. The neurological examination includes an evaluation of mental status, cranial nerves, motor ability (including strength, tone, and involuntary movements), coordination (including finger-to-nose, gait, and postural reflexes), and sensation (including proprioception, cold, light touch, and deep tendon reflexes). The number and percentage of participants with abnormal findings in the Double-blind analysis period who had either missing or normal assessment at baseline will be summarized by finding and by intervention group.

5.6.3.6. Brain Magnetic Resonance Imaging (MRI)

MRI safety-related observations from the central imaging vendor including vasogenic edema (e.g, presence, severity), cerebral microhemorrhages (e.g, presence, number), cerebral superficial siderosis and other findings will be summarized.

Descriptive statistics will also be presented by APOE ε4 carrier status subgroup and by APOE ε4 genotype.

5.7. Other Analyses

5.7.1. Pharmacokinetic Analyses

Pharmacokinetics (PK) secondary endpoints include CSF and serum concentrations of JNJ-63733657 at time points per the SoA.

PK analyses will be performed on the PK analysis set, defined as participants who have received at least 1 dose of JNJ-63733657 and have at least 1 valid blood sample drawn for PK analysis.

Participants will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study intervention; missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation).

Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics.

For each intervention group, descriptive statistics, including sample size, arithmetic mean, SD, percent coefficient of variation, median, minimum, and maximum will be calculated for serum and CSF concentrations of JNJ-63733657 at each sampling time point in the DB analysis period. Additional summaries will be provided to explore the relationship between concentrations of JNJ-63733657 and hepatic safety.

Further details of populational PKPD and exposure response analyses will be described in a separate plan (EDMS-RIM-1660645).

5.7.2. Immunogenicity

The immunogenicity endpoints listed as secondary endpoints for this study include antibodies to JNJ-63733657 (ADAs), including neutralizing antibodies, at time points per the SoA.

Participants evaluable for immunogenicity are defined as having at least 1 dose of JNJ-63733657 and at least 1 post-baseline ADA time point collected for anti- JNJ-63733657 antibody detection.

"Sample ADA status" and sample titer as well as the cumulative "participant ADA status" and peak titer through the visit will be coded and provided by the bioanalytical group.

5.7.2.1. Participant ADA Classification

Participants with treatment-emergent antibodies to JNJ-63733657 include participants with treatment-induced antibodies to JNJ-63733657 and treatment-boosted antibodies to JNJ-63733657.

Participants with treatment-induced antibodies to JNJ-63733657 have a negative ADA sample prior to JNJ-63733657 administration and at least one post-treatment sample positive for ADA.

Participants with treatment-boosted antibodies to JNJ-63733657 have a positive ADA sample prior to JNJ-63733657 administration and at least one post-treatment sample positive for ADA with titer at least 4-fold higher than the titer of the baseline sample.

If titer remains the same after intervention or if ADA titer reduces or ADA disappears, the participant is classified as "treatment-emergent ADA negative". Participants that are unavailable for treatment-emergent ADA following intervention will be classified as "participants with baseline samples only", i.e, no appropriate sample is available after intervention.

5.7.2.2. Immunogenicity Analyses

The summary and analysis of antibodies to JNJ-63733657 will be based on the observed data; therefore, no imputation of missing data will be performed. Note: participant status is through each visit, thus, participant status and peak titers may change as the study progresses over time. Therefore, the "subject ADA status" at a visit represents the cumulative ADA status through that visit. For example, for the interim analyses, datasets through the IA cutoff will have participant level status (e.g, negative) but at the final double-blind phase visit, they may have developed ADA and the participant status becomes "treatment-emergent ADA positive" from the interim to the final database lock of the double-blind phase. Peak titers can also change (increase) if a higher titer occurs after an interim database lock.

The summary of participants with baseline positive samples is taken from the sample status at baseline. There is no participant level status at baseline.

The incidence of antibodies to JNJ-63733657 (evaluable, treatment-emergent ADA positive, treatment-emergent ADA negative) status will be summarized by treatment group. In addition, the incidence of anti-JNJ-63733657 antibodies will be summarized separately for participants with

and without treatment-emergent liver enzyme elevations ≥3xULN. Summaries of AESIs (e.g, infusion-related reactions) may also be presented by ADA and/or NAb status.

The incidence of neutralizing antibodies (NAbs) to JNJ-63733657 will be summarized for participants who are positive for antibodies to JNJ-63733657 and have samples evaluable for NAbs.

Listings of participants with samples positive for antibodies to JNJ-63733657 at baseline will be provided. In addition, listings of participants who are classified as positive for treatment-emergent antibodies to JNJ-63733657, and listings of participants who discontinue the study by treatment-emergent antibodies to JNJ-63733657 status (positive or negative) may be provided.

Descriptive statistics (N, mean, SD, median, range, and IQ range) of PK serum JNJ-63733657 concentrations (value) over time by treatment-emergent antibodies to JNJ-63733657 status (positive or negative) may be assessed. Graphical representation of median PK concentration by antibody status may be presented.

5.7.2.3. Other Immunogenicity Analyses

The following analysis may be conducted if there is a sufficient number (e.g., ≥20) of participants who are treatment-emergent ADA positive.

Treatment-induced Onset (data summarized will be exclusive to baseline negative participants)

Days from first administration of study intervention to the date of first instance of treatment-induced ADA (positive for treatment-induced antibody) will be summarized.

Number of days until first instance of treatment-induced ADA = (First date for positive antibody - Date of first administration of study intervention+1).

Participants with no treatment-induced ADA (negative for treatment-induced antibody) will be censored on the last date participant was known to have last blood samples to assess immunogenicity.

Survival techniques will be used to estimate the median time to treatment-induced ADA. The Kaplan-Meier plot of onset of treatment-induced ADA will be presented.

Additional immunogenicity analyses may be specified in a separate populational PKPD and exposure response analysis plan (EDMS-RIM-1660645).

5.7.3. Biomarkers

5.7.3.1. Tau PET

For the tau PET analyses, there are several regions of interest (ROI) over which treatment effects on tau tangles are assessed. These regions include anatomically defined ROIs (such as cerebral cortex, specific brain regions and Braak regions) and subject-specific ROIs (such connectivity-based ROIs and tau naïve ROI).

Two measures are designed to assess tau spread will be evaluated: the change in SUVR in the tau naïve ROI and the spatial progression of tauopathy (SPOT). These parameters were developed to measure tau spread, as JNJ-63733657 is hypothesized to interfere with tau seed spread. Using these spread measures, the quantification process of the tau PET brain scans will account for individual differences in tau PET burden at baseline. For the tau naïve ROI method, the change in Standardized Uptake Value Ratio (SUVR) is assessed over regions without evidence of tau burden at baseline (i.e. within 1 standard deviation of a cognitively normal amyloid negative reference population). The use of tau naive ROI to assess spread is motivated by the hypothesis that the presence of neurofibrillary tangles at baseline indicates the tau seed has already spread to this region potentially making the treatment less effective there. In the SPOT method, the extent of spread of tau will be quantified by measuring the difference in volume of elevated tau PET burden (defined as exceeding an SUVR threshold of 1.2) in the cerebral cortex ROI at follow up versus that at baseline.

Anatomically defined ROIs including the cerebral cortex, specific brain regions (e.g. meta temporal, mesial temporal, inferior temporal, temporal, frontal, parietal, occipital lobes) and individual Braak regions will be evaluated.

Alternate methods combining functional connectivity defined ROIs will also be explored with the goal of identifying regions most sensitive for showing treatment effect (Connection Rank ROI)[14,15].

Week 104 observations after the start of the LTE but before the 2nd administration of LTE study medication will be included in the DB analysis period. Otherwise, observations after the start of the LTE are not included.

5.7.3.1.1. Estimand

The tau PET estimand is defined in the same way as the primary endpoint estimand except for the endpoint. One endpoint is change in tau PET SUVR assessed over the Tau Naïve Composite ROI.

Other measures include change in tau PET SUVR over anatomical ROIs (including cerebral cortex, specific brain regions [e.g. meta temporal, medial temporal, inferior temporal, temporal, frontal, parietal and occipital lobes], and individual Braak regions), each of 4 Connection Rank ROIs, and the SPOT parameter over the cerebral cortex ROI at Week 104.

5.7.3.1.2. Analysis Methods

An MMRM analysis will be performed on change in tau PET SUVR at analysis visits through Week 104 assessed in regions without evidence of tau burden at baseline, as measured by tau PET (e.g, Tau Naïve Composite ROI), with treatment (placebo, JNJ-63733657 1000 mg or JNJ-63733657 3000 mg), geographic region, sex, and APOE ε4 carrier status (Y/N), visit, and treatment-by-visit interaction as fixed effects. Age, the baseline value of the dependent variable, and baseline tau burden on tau PET (defined as the Braak 4 SUVR uptake z-score which was used to assign the participant to the tau burden randomization stratum, a continuous variable) will be included continuous covariates. An unstructured covariance matrix structure will be utilized to

account for correlation among observations within participants. In case of convergence problems, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1) with separate subject random effect. The Kenward-Roger method will be used for approximating the denominator degrees of freedom. If a structured covariance matrix is used due to convergence issues, the robust variance estimator, commonly referred to as the "sandwich" estimator, will be used to address the potential impact of covariance matrix misspecification on the estimation and testing of treatment effect. The treatment effects will be estimated using the difference in least square (LS) means and separate contrasts will be obtained for each dose level (1000 mg and 3000 mg) vs placebo at each time point. Point estimates and 2-sided 95% CIs will be provided for the treatment differences at each time point. Note, for the Braak 4 SUVR endpoint, the Braak 4 SUVR uptake z-score at randomization will not be included in the model. Transformation of the values (such as log) of the outcome variable may be applied if needed to fit the normality assumption of the model. An MMRM model with an additional baseline-by-visit term may be explored.

Percent slowing for each dose level compared to placebo at each time point will be calculated as -(LS estimate of the treatment difference versus placebo in change from baseline), divided by the absolute value of the LS estimate of mean change from baseline in the placebo group, times 100.

Similarly, change in tau PET SUVR over the cerebral cortex; each of the specific brain regions (meta temporal, mesial temporal, inferior temporal, temporal, frontal, parietal and occipital lobes); each of the 6 Braak ROIs; each of 4 regions (Q1, Q2, Q3, and Q4) grouped based on their level of functional connectedness to the tau PET epicenter at baseline (Connection Rank ROI); and SPOT change in volume over the cortex ROI from baseline at Week 104 analysis visit will be assessed using the MMRM model above.

Actual values and changes from baseline will be summarized with descriptive statistics by intervention group at each assessment time point.

A sensitivity analysis (MMRM at analysis visits through Week 104) will be performed for change in SUVR over the Tau Naïve Composite ROI excluding all observations after the start of LTE.

5.7.3.1.3. Subgroup Analyses

Subgroup analyses for selected subgroups listed in Section 5.1.3 will be performed.

An MMRM model will be used for subgroup analyses of the tau PET endpoints, e.g, change in SUVR at Week 104 analysis visit assessed in regions without evidence of tau burden at baseline (Tau Naïve Composite ROI), as measured by tau PET. The model will include factors for treatment (placebo, JNJ-63733657 1000 mg or JNJ-63733657 3000 mg), geographic region, sex, APOE ε4 carrier status (Y/N), visit and treatment-by-visit interaction, subgroup, treatment-by-subgroup interaction, and treatment-by-visit-by-subgroup interaction terms as fixed effects. Age, baseline for the endpoint variable, and baseline tau burden on tau PET will be included as continuous covariates and an unstructured covariance matrix structure will be utilized to account for correlation among observations within participants. Baseline tau burden on tau PET (Braak 4

SUVR uptake z-score, as a continuous covariate) will not be included in the model when the dichotomized baseline tau PET score or the terciles of baseline tau PET score are included in the model. In case of convergence problems, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1) with separate subject random effect. The Kenward-Roger method will be used for approximating the denominator degrees of freedom. If a structured covariance matrix is used due to convergence issues, the robust variance estimator, commonly referred to as the "sandwich" estimator, will be used to address the potential impact of covariance matrix misspecification on the estimation and testing of treatment effect. The between-treatment difference of the change from baseline at each time point at each level of the subgroup variable, and its 95% confidence interval (2-sided), will be estimated from the model with a linear contrast. Estimates and 95% confidence intervals will be displayed with forest plots. Note, for the Braak 4 SUVR endpoint, the Braak 4 SUVR uptake z-score at randomization will not be included in the model. Transformation of the values (such as log) of the outcome variable may be applied if needed to fit the normality assumption of the model.

5.7.4. Pharmacokinetic/Pharmacodynamic Relationships

An exploratory objective of this study will be to evaluate the relationship between dose and PK of JNJ-63733657 on fluid biomarker and imaging biomarker (eg, tau PET) assessments.

Correlation of JNJ-63733657 dose and serum and CSF levels with efficacy, safety and biomarker findings of note will be explored graphically with scatterplots and/or with Pearson/Spearman correlation coefficients.

For continuous efficacy, safety and biomarker endpoints, descriptive statistics may be presented to assess the relationship between PD and quartiles of PK JNJ-63733657 concentration, if data permits. Additional details will be provided in a separate populational PKPD and exposure response analysis plan (EDMS-RIM-1660645).

5.7.5. Tau PET and Tau Protein Relationships

To evaluate the relationship between tau PET burden and CSF and plasma phosphorylated tau levels, including correlation/concordance of baseline concentrations of CSF p181tau and t-tau, and CSF and plasma p217+tau (total, free, and bound), and change from baseline in CSF concentrations of p181tau, t-tau and p217+tau with tau PET, which will be explored graphically with scatterplots and/or with Pearson/Spearman correlation coefficients. Intercurrent events will be handled in the same way as for the primary endpoint estimand.

Actual values and changes from baseline will be summarized with descriptive statistics by intervention group at each assessment time point. Changes from baseline may also be analyzed using an MMRM as described in Section 5.7.3.1.2.

5.7.6. Neurodegeneration Fluid Biomarkers

Neurogranin will be measured in CSF longitudinally. Neurofilament light chain (NfL) and GFAP will be measured in plasma and CSF longitudinally. Intercurrent events will be handled in the same

way as for the primary endpoint estimand. Actual values, changes from baseline, and percent changes from baseline will be summarized with descriptive statistics by intervention group at each assessment time point, for each specimen type separately. Changes from baseline may also be analyzed using an MMRM as described in Section 5.7.3.1.2.

5.7.7. Aβ Fragments

The effects of JNJ-63733657 on markers of Aβ pathophysiology (eg, $A\beta_{1-42}$, $A\beta_{1-40}$, and $A\beta_{42/40}$) in the CSF will be assessed at the time points indicated on the SoA in the protocol.

Actual values, changes from baseline, and percent changes from baseline will be summarized with descriptive statistics by intervention group at each assessment time point. Intercurrent events will be handled in the same way as for the primary endpoint estimand. Changes from baseline may also be analyzed using an MMRM as described in Section 5.7.3.1.2.

The proportion of participants that were highly likely to be A+ at screening based on a plasma p217+tau assay-specific threshold for specificity will be summarized by treatment group.

5.7.8. Brain Volume

Changes in brain volume as measured by volumetric MRI will be measured at the time points indicated on the SoA in the protocol.

Volumes and volume changes from baseline in bilateral hippocampal, whole brain, and ventricular volume will be summarized with descriptive statistics by intervention group at each assessment time point. An appropriate correction for intracranial volume will be applied. Intercurrent events will be handled in the same way as for the primary endpoint estimand. Changes from baseline may also be analyzed using an MMRM as described in Section 5.7.3.1.2.

5.7.9. Other Biomarkers

Other CSF and plasma biomarkers may be assessed, including downstream markers of neuronal injury, neurodegeneration, and inflammation (eg, chitinase-3-like protein 1 [YKL40], soluble triggering receptor expressed on myeloid cells 2 [TREM2]). In addition, other biomarkers associated with AD may be explored, including blood-based biomarkers for tau pathology and unbiased proteomics.

Actual values, changes from baseline, and percent changes from baseline will be summarized with descriptive statistics by intervention group at each assessment time point, for each specimen type separately. Intercurrent events will be handled in the same way as for the primary endpoint estimand. Changes from baseline may also be analyzed using an MMRM as described in Section 5.7.3.1.2.

5.7.10. Relationships Between Biomarkers and Measures of Clinical Decline

The correlation between baseline and/or change from baseline in markers of tau, neuronal injury, neuroinflammation, and neurodegeneration (e.g, CSF and/or plasma p181tau, p217+tau, t-tau, NfL, neurogranin, GFAP, tau PET, volumetric MRI) and change from baseline in clinical decline

(e.g, CDR-SB, iADRS) or cognitive scores (e.g, ADAS-Cog13) will be explored graphically with scatterplots and/or with Pearson/Spearman correlation coefficients. Intercurrent events will be handled in the same way as for the primary endpoint estimand.

These data will be used to validate models (linear, non-linear, and/or others based on external observational data) linking changes in tau PET to clinical and cognitive decline, with the aim of establishing tau PET as a surrogate biomarker.

5.7.11. Pharmacogenomic Analyses

DNA samples will be analyzed for APOE type. The number and percentage of participants by APOE type will be tabulated. In addition, cross-tabulations per APOE type will compare the APOE genotype and APOE proteotype determined by DNA-based assay and Precivity-APOE assay, respectively.

DNA sample analysis will also allow for the possible evaluation of genetic factors that may influence the PK, PD, safety, or tolerability of JNJ-63733657 and pathways related to AD/tauopathy. These analyses will be described in a separate Pharmacogenomics Plan.

5.7.12. Other Analyses

The correlation between baseline MRI measures of vascular disease and change from baseline in clinical decline (e.g, CDR-SB and iADRS) or cognitive scores (e.g, RBANS and ADAS-Cog13) will be explored graphically with scatterplots and/or with Pearson/Spearman correlation coefficients.

5.8. Interim Analyses

A separate IA SAP provides the details of the interim analyses which may be performed.

An Independent Data Monitoring Committee (IDMC) will monitor unblinded safety data on an ongoing basis (as defined in the IDMC Charter) to ensure the continuing safety of the participants enrolled in the study. A separate IDMC Safety SAP provides the details of the safety analyses to be performed for the IDMC and a charter defines data flow and decision-making process. In addition, the committee will review interim analyses as described in a separate IA SAP. After the reviews, the IDMC will make recommendations to a sponsor committee separate from the study team based on the rules and details as provided in the IDMC charter.

The IDMC consists of 4 medical experts in AD including 1 biomarker expert, and 1 statistician. The IDMC responsibilities, authorities, and procedures are documented in its charter.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

A+	elevated brain amyloid
Aβ	amyloid beta
AChEI	acetyl-cholinesterase-inhibitor
AD	Alzheimer's disease
ADA	anti-drug antibody
ADAS-Cog	Alzheimer's Disease Assessment Scale Cognitive subscale
ADAS-Cog13	Alzheimer's Disease Assessment Scale Cognitive subscale 13-item version
ADCS-ADL-MCI	Alzheimer's Disease Cooperative Study Activities of Daily Living for Mild Cognitive Impairment
ADL	Activities of Daily Living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APOE	apolipoprotein E
AST	aspartate aminotransferase
ATC	anatomic and therapeutic class
BDNF	brain-derived neurotrophic factor
BMI	body mass index
BP	blood pressure
CAA	cerebral amyloid angiopathy
CDR	Clinical Dementia Rating
CDR-GS	Clinical Dementia Rating – Global Score
CDR-SB	Clinical Dementia Rating – sum of boxes
CI	confidence interval
CSF	cerebrospinal fluid
CNS	central nervous system
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
DMI	Delayed Memory Index
DPS	data presentation specifications
ECG	electrocardiogram
eCOA	electronic clinical outcomes assessment
eCRF	electronic case report form
FAS	full analysis set
FDA	Food and Drug Administration
GDS-30	30-item Geriatric Depression Scale
GFAP	glial fibrillary acidic protein
GGT	gamma-glutamyl transferase
IA	interim analysis
IADL	Instrumental Activities of Daily Living
iADRS	Integrated Alzheimer's Disease Rating Scale
ICE	intercurrent event
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
INR	international normalized ratio
IV	intravenous(ly)
IWRS	interactive web response system
LLN	lower limit of the normal range
LLOQ	lower limit of quantification
LTE	long-term extension
MAR	missing at random
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities

MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
NAb	neutralizing antibodies
NCS	natural cubic splines
NfL	neurofilament light chain
NFT	neurofibrillary tangles
NPI	Neuropsychiatric Inventory
PC AE	post cessation adverse event
PD	pharmacodynamic(s)
PET	positron emission tomography
PK	pharmacokinetic(s)
p-tau	phosphorylated tau
QOL-AD	Quality of Life in Alzheimer's Disease
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
QTcL	QT interval corrected using the Framingham linear regression formula
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
ROI	region of interest
RTSM	Randomization and Trial Supply Management
RUD-Lite	Resource Utilization in Dementia Lite
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SoA	schedule of activities
SPOT	spatial progression of tauopathy
SSG	statistical support group
TBL	total bilirubin
TE	treatment emergent
TE AE	treatment emergent adverse event
TREM2	triggering receptor expressed on myeloid cells 2
t-tau	total tau
ULN	upper limit of the normal range
ULOQ	upper limit of quantification
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
YKL40	chitinase-3-like protein 1

6.2. Appendix 2 Demographics and Baseline Characteristics

The number of participants in each analysis set will be summarized and listed by intervention group, combined active intervention group, and overall.

Table 16 presents a list of the demographic variables and baseline disease characteristics that will be summarized by intervention group and overall for the All Randomized and Full Analysis Sets. Demographics will also be summarized by geographic region, by baseline tau burden on tau PET and by clinical diagnosis using the Full Analysis Set.

Table 16: Demographic and Baseline Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
Baseline iADRS-MCI Total Score	
Baseline ADAS-Cog13 Score	
Baseline ADCS-ADL-MCI Score	
Screening RBANS DMI Score	
Baseline RBANS Total Scale	
Baseline CDR-SB	
Baseline NPI Total Score	
Screening GDS-30 Score	
Baseline Braak 4 SUVR Z-Score	
Categorical Variables:	**Summary Type**
Age (<65 years, 65-74 years, ≥75 years)	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female, undifferentiated)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
Education Level (Did not complete secondary school or less than high school, Some secondary or high school education, High school or secondary school degree complete, Associate's or technical degree complete, College or baccalaureate degree complete, Doctoral or post graduate education, More than high school, Unknown) Education Level (derived): Less than high school (derived by combining the categories of "Did not complete secondary school or less than high school", "Some secondary or high school education" and "Unknown") At least some high school or greater (derived by combining the remaining categories)	
BMI: underweight <18.5 kg/m^2 normal 18.5-<25 kg/m^2 overweight 25-<30 kg/m^2 obese ≥30 kg/m^2	
Geographic Region: North America (Canada and United States) Europe (Belgium, France, Netherlands, United Kingdom, Spain, Sweden) Australia Japan	

Clinical Diagnosis (Prodromal AD, Mild AD dementia (Early AD))	
Screening GDS-30 Score (0-9, 10-12, >12)	
Baseline tau Burden on tau PET (Low, High)	
Screening CDR-GS	
Baseline CDR-GS	
Screening RBANS DMI (≤85, >85)	
Use of AChEI and/or memantine at baseline (Yes, No)	
APOE ε4 Carrier Status (Yes, No)	
APOE ε4 Genotype (Homozygous Carrier, Heterozygous Carrier, Non-Carrier)	

[a] If multiple race categories are indicated, the Race is recorded as 'Multiple'

A summary of the demographics data for Study Partners will also be presented. Study Partner age, sex, education level, relationship to participant, living with participant (Y/N) and number of hours spent with the participant per week will be summarized by intervention group and overall for the Full Analysis Set.

6.3. Appendix 3 Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be summarized by category.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose of study medication
- Other
  - Study medication not administered according to IPPI
  - Missing Baseline ADAS Cog13 total score
  - Missing Baseline ADCS-ADL-MCI total score
  - Missing Baseline RBANS total score
  - Other

In addition, if applicable, any COVID-19-related protocol deviations (major and/or minor) will be summarized by category.

6.4. Appendix 4 Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study intervention during the DB analysis period, including those that started before and continue on after the first dose of study intervention, and those that started during the DB analysis period.

Summaries of concomitant medications will be presented by ATC term and intervention group. The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 concomitant medication.

Prior medications will be summarized by ATC term and intervention group.

6.4.1. Concomitant use of AChEI and memantine

AChEI and/or memantine (i.e, non-disease-modifying medications) are defined as medications coded as any of the following:

If the coded term contains any of the following text strings: [“Memantine”, “Donepezil”, “Galantamine”, “Rivastigmine”] or the class is “ANTICHOLINESTERASES” then the medication will be considered.

For participants who were taking AChEIs and/or memantine at baseline (used on the day of first dose of study intervention, including those that started before and continue on after the first dose of study intervention), the following will be presented:

- Number of participants stopping and not re-starting these medications during the study

For participants who were not taking AChEIs and/or memantine at baseline, the following will be presented:

- Number of participants starting AChEIs and/or memantine during the study, and a graphical and/or tabular presentation of the timing of starting these relative to baseline

Finally, the number of participants who started AChEIs and/or memantine at each Double-Blind Analysis Visit will be presented.

6.4.2. Alternative Disease-modifying AD Therapy

Alternative disease-modifying AD therapies are defined as any of the following:

If either the reported name or the coded term of the concomitant medication contains any of the following text strings: [“aducanumab”, “donanemab”, or “lecanemab”].

The number of participants starting alternative disease-modifying AD therapies during the study will be presented by ATC term and intervention group.

6.5. Appendix 5 Medical History, Pre-planned Surgeries/Procedures, and Other Procedures

The verbatim terms used in the CRF by investigators to identify medical history diseases or conditions will be coded using MedDRA. For each disease/condition, the number and percentage of participants with at least 1 past occurrence and with at least 1 ongoing occurrence of the disease or condition will be summarized by intervention group and overall. Past and ongoing occurrences will be summarized separately by body system and coded term.

A listing of pre-planned surgeries or procedures including the specific surgery/procedure, indication, the planned date of the surgery/procedure, and the study day of the planned surgery/procedure will be provided.

A listing of liver imaging assessments performed during the study will be provided.

6.6. Appendix 6 Potentially Clinically Significant Criteria for Laboratory Tests

Test	Criteria for Low PCS Values	Criteria for High PCS Values
Hematology		
WBC Leukocytes (x10E9/L)	<3	>16
Eosinophils (x10E9/L)	NA	> 0.6
Lymphocytes (x10E9/L)	<0.6	NA
Monocytes (x10E9/L)	NA	> 1.0
Neutrophils, Segmented (x10E9/L)	<1.5	> 8.0
Reticulocytes (fraction of 1)	<0.006	>0.025
Platelets (x10E9/L)	< 75	> 700
Hematocrit (fraction)	<0.3	> 0.5 females, > 0.55 males
Hemoglobin (g/L)	value <100 or change from baseline <= - 20	>165 females, >185 males
MCV (fL)	< 75	>105
Chemistry		
Serum Albumin (g/L)	< 30	NA
Alkaline Phosphatase (U/L)	NA	> 3 ULN
ALT (U/L)	NA	>= 3 ULN
AST (U/L)	NA	>= 3 ULN
Bicarbonate (mmol/L)	< 17	> 32
Bilirubin (umol/L)	NA	> 3 ULN
BUN (mmol/L)	NA	> 1.5 ULN
Calcium (mmol/L)	< 2.0	> 2.7
Chloride (mmol/L)	< 94	> 112
Creatine Kinase (U/L)	NA	> 1.5 ULN
Creatinine (umol/L)	NA	> 1.5 ULN
GGT (U/L)	NA	> 3 ULN
Glucose (mmol/L)	< 2.2	> 16.7
Phosphate (mmol/L)	< 0.7	> 1.7
Potassium (mmol/L)	< 3	> 5.5
Protein (g/L)	< 40	> 120
Sodium (mmol/L)	< 130	> 150
Urate (umol/L)	NA	> 500
Urinalysis		
pH	< 4	> 8
Specific Gravity	NA	> 1.035

6.7. Appendix 7 Additional Scoring Information for eCOA Endpoints

For the scales, item scores are recorded on an electronic clinical outcomes assessment (eCOA) device which will provide the total scores. Additional data handling rules are described below.

ADAS-Cog13

For the ADAS-Cog13, a score is calculated for each item. For the items of Word Recall, Delayed Word Recall, Commands, Constructional Praxis, Ideational Praxis, Naming, Orienting, Word Recognition, and Number Cancellation, if the reason it was not done was "Cognitive Reasons", the item score is given the maximum (worst) possible score. Otherwise, the item score is missing (-99). If performed, the Delayed Word Recall score is computed as the sum of the words not correctly recalled.

When calculating the ADAS-Cog13 total score, if any of the individual items have a score of missing (-99), then the total score is missing (-999). If there are no item scores missing, then the ADAS-Cog13 total score is the sum of the item scores.

ADCS-ADL-MCI

For the ADCS-ADL-MCI, all items must be answered with "yes", "no", or "don't know". No items can be skipped. If the item response is "yes" there is an additional question for which the response translates into an item score where higher scores indicate better functioning. If the response is "no" or "don't know" it proceeds to the next question (essentially giving a score of 0 for that item).

The ADCS-ADL-MCI total score is the sum of the scores for each item. The number of "don't know" responses is also provided.

For example, if there are many responses of "no" or "don't know", the ADCS-ADL-MCI total score will be low. Lower scores indicate worse functioning.

RBANS

For the RBANS, the Total Scale, the 5 Index scores, and 10 of the subtest scores are computed by the vendor. For the List Learning and Story Memory subtests, scores are computed as the sum of the item scores when all items for that subtest are present. Subtest scores are not computed if any items are missing (no imputation).

6.8. Appendix 8 Adverse Event Search Terms

Cerebral Amyloid Angiopathy (CAA) Preferred Terms:

Amyloid related imaging abnormalities
Amyloid related imaging abnormality-microhaemorrhages and haemosiderin deposits
Amyloid related imaging abnormality-oedema/effusion
Brain oedema
Brain stem microhaemorrhage
Cerebellar microhaemorrhage
Cerebral amyloid angiopathy
Cerebral haemosiderin deposition
Cerebral microhaemorrhage
Superficial siderosis of central nervous system
Thalamic microhaemorrhage
Vasogenic cerebral oedema

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