Janssen Research & Development *

Clinical Protocol

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

Version: Amendment 8

JNJ-63733657

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United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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DOCUMENT HISTORY	
Document	**Date**
Amendment 8	24 July 2025
Amendment 7	24 January 2025
Amendment 6	19 April 2024
Amendment 5	13 December 2023
Amendment 4	12 October 2023
Amendment 3	25 April 2023
Amendment 2	28 March 2022
Amendment 1	3 September 2021
Original Protocol	22 April 2020

Amendment 8 (24 July 2025)

Overall Rationale for the Amendment: To incorporate information about the new JNJ-63733657 drug product that will be used in the LTE Treatment Period.

The changes made to the clinical protocol 63733657ALZ2002 as part of Protocol Amendment 8 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.8 Appendix 8: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
1.1. Synopsis; 1.3.5. SoA - LTE Treatment Period, Continued - Year 2 (Through LTE Week 104); 4.1. Overall Design; 4.2. Scientific Rationale for Study Design; 6.1. Study Interventions Administered; 6.3. Measures to Minimize Bias: Randomization and Blinding	Incorporated information in the text and as a footnote to the SoA about the new JNJ-63733657 drug product (1000 mg/vial, 175 mg/mL) and the timing for the assignment of the new JNJ-63733657 drug product (1000 mg/vial, 175 mg/mL) through the RTSM system.	To provide information about the introduction of the new, unblinded JNJ-63733657 drug product (1000 mg/vial, 175 mg/mL) and details of the formulation and the timing for the assignment of the new JNJ-63733657 drug product (1000 mg/vial, 175 mg/mL) through the RTSM system.
1.1. Synopsis; 6.4. Study Intervention Compliance	Added text noting that the medical monitor should be contacted if a participant has missed/held 3 consecutive doses of study intervention.	To ensure the site is in contact with the medical monitor to discuss the status of the participant.
1.1. Synopsis; 3. Objectives and Endpoints; 8.9.3.2. Aβ Fragments; 8.9.3.3. Other Biomarkers	Modified the language regarding which biomarkers will be assessed.	To provide flexibility in the specific biomarkers that will be assessed.
2.2. Background	New information on Study 63733657EDI1003.	To provide updates on Study 63733657EDI1003 following database lock.
1.1. Synopsis; 6.1. Study Interventions Administered	Updated the color of the investigational product from ‘clear, mostly colorless liquids’ to ‘clear to slightly yellow solutions’ when referring to the 500 mg/vial, 50 mg/mL and matching placebo and ‘clear to yellow solution’	To reflect the color of the investigational products used in the study.

Section Number and Name	Description of Change	Brief Rationale
	when referring to the 1000 mg/vial, 175 mg/mL.	
6.1. Study Interventions Administered	Added placebo and doses for JNJ-63733657.	Clarification
1.1. Synopsis; 4.1. Overall Design; 4.2. Scientific Rationale for Study Design; 6.3. Measure to Minimize Bias: Randomization and Blinding	Clarified that while the Sponsor will be unblinded to the double-blind treatment assignment after the Double-blind Treatment Period is completed, clinical sites and participants will continue to remain blinded to double-blind treatment assignment for all participants.	Clarify that clinical sites and participants will remain blinded to double-blind treatment assignment to minimize any impact on the planned LTE analyses.
1.1. Synopsis; 4.1. Overall Design; 4.2. Scientific Rationale for Study Design; 8.8. Genetics	Modified text detailing that APOE will only be assessed through DNA analysis to indicate that determination of APOE status could be through either plasma or DNA analysis.	Clarification
3.2. Long-Term Extension Treatment Period; 9.3.2. Safety Analyses	Added an objective and endpoint to compare the safety of the 500 mg/vial, 50 mg/mL and 1000 mg/vial, 175 mg/mL product along with a definition of the associated time periods.	To assess any differences in safety due to the change in investigational product.
4.2. Scientific Rationale for Study Design	Replacement of ‘at least’ with ‘approximately’ for the timing of the lumbar puncture.	To clarify the timing of the lumbar puncture
10.2. Appendix 2: Clinical Laboratory Tests; 10.7.1. Hepatitis Event Assessments – Level 1	Added “IgG” to the existing “HBcAb IgM” testing following confirmation from central laboratory that total HBcAb testing includes both IgG and IgM antibodies. Specified that IgG is the Hepatitis C antibody being tested.	Clarification.
10.4.1. Adverse Event Definitions and Classifications	Removed “Refer to Appendix 7, Table 5 (Hepatic Adverse Event Definitions and Report Requirements) from AESIs section.	Clarification since the AESI category will capture more than AEs reported per Appendix 7 as the entire SMQ will be used.
10.4.5. Procedures	Added that the list of AESIs would be defined in the SAP.	Clarification.
Throughout the protocol	Minor grammatical changes were made.	Minor errors were noted.

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1. PROTOCOL SUMMARY

1.1. Synopsis

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

DESCRIPTION OF COMPOUND

JNJ-63733657 is being developed by Janssen Research & Development for the treatment of Alzheimer's Disease (AD), namely the prevention or slowing of clinical (cognitive and functional) decline. JNJ-63733657 is a humanized IgG1/κ monoclonal anti-tau antibody. JNJ-63733657 binds with high affinity to paired helical filament (PHF) tau, consisting of p-tau, and binds very weakly to non-p-tau. Specifically, JNJ-63733657 binds to p-tau at the phosphorylation site "p217+tau". JNJ-63733657 has demonstrated reduction of tau seeding in both an in vitro cellular depletion study and an in vivo preclinical animal model following peripheral injection.

This Phase 2 study for JNJ-63733657 will assess the possible slowing of clinical (cognitive and functional) decline seen in prodromal AD and mild AD dementia (Early AD). In addition, effects of JNJ-63733657 on the accumulation of tau, as measured by tau PET, will also be explored.

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.
Secondary	
• KEY: 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.
• KEY: To evaluate changes in functional status between participants treated with JNJ-63733657 versus placebo as measured by the ADCS-ADL-MCI.	• Change from baseline on the ADCS-ADL-MCI total score at Week 104.

HYPOTHESIS

JNJ-63733657 binds to p-tau, and it is hypothesized that it will decrease tau spread and thereby slow clinical decline as measured by the iADRS, a composite of cognition and function, as compared with participants receiving placebo.

OVERALL DESIGN

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 (cognitive and functional) decline 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 (PK), immunogenicity, and health outcomes data will be obtained in the LTE Treatment Period.

For all enrolled participants, the study will consist of:

- a 90-day (13 weeks) screening period (may be extended up to 120 days with prior approval from the 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 of 13 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). The Primary Double-blind Analysis will be performed when the last participant completes the Week 104 visit of the Double-blind Treatment Period (including participants who discontinue treatment but continue in the Double-blind Treatment Period and provide off-treatment data) or withdraws prior to the Week 104 visit of the Double-blind Treatment Period. The End of Double-blind Analysis will be performed when all participants have completed at least the Week 104 visit of the Double-blind Treatment Period, or are discontinued from the Double-blind Treatment Period and are not continuing into the LTE Treatment Period, and have completed the Follow-up Period (90 days after last dose of study intervention).

After the LTE Treatment Period becomes available at the clinical site, all participants receiving double-blind study intervention (includes 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 of the Double-blind Treatment Period 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 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 being available at the clinical site, 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 (as specified in the SoA). A study partner can be a relative or friend indicated by the participant, who is at least 18 years old, or a legal adult, who may or may not live with the participant, who has at least 10 hours of contact with the participant each week, and who is available for face-to-face contact with the study site staff at each visit requiring study partner attendance. For visits not requiring study partner attendance, if someone other than the study partner (ie, a different legal adult) accompanies the participant to the visit, the study partner must be available for telephone contact by the study site. As participants in this study have mild cognitive impairment or mild dementia (ie, CDR-GS=0.5), and should be capable of providing informed consent at the time of study entry, the primary role of the study partner will be as informant. As judged by the investigator, study partners should have adequate literacy to participate and be judged to have high likelihood of completing the study with the participant. Prior to study assessments, study partners will receive oral and written information about the study and will sign a Study Partner ICF.

After giving initial written informed consent, participants will be screened over a period of up to 90 days to assess their eligibility for the study according to the inclusion and exclusion criteria. To allow for treatment of transient conditions, laboratory retesting, scheduling of MRI and tau PET, and/or operational delays, the Screening Period of 90 days may be extended up to 120 days with prior approval from the 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.

Participants who progress to more advanced clinical stages of AD during the study should be assessed for understanding of potential risks/benefits of participation by the investigator and may continue in the study at the discretion of the investigator.

In the Double-blind Treatment Period, eligible participants will be assigned randomly (central randomization) to 1 of 3 treatment groups: 1 of 2 dosages of JNJ-63733657 (1000 or 3000 mg) or placebo at a ratio of 1:1:1. Following randomization using the RTSM system (eg, IWRS), participants will enter a Double-blind Treatment Period of variable duration (maximum of 4.5 years).

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.

The assigned LTE dose (1000 mg or 3000 mg) for a participant will be unblinded to the Sponsor after the Double-blind Treatment Period is completed but initially will remain blinded to the clinical sites and participants. At each participant's LTE Visit 18 (LTE Week 68), or later if required (eg, pending IRB/Ethics Committee approvals), the RTSM system (eg, IWRS) will begin assigning the new JNJ-63733657 drug product (1000 mg/vial, 175 mg/mL). At this time, the participant's assigned JNJ-63733657 dose in the LTE Treatment Period will be unblinded and the 1000 mg/vial, 175 mg/mL product will continue to be used for the remainder of the LTE Treatment Period.

After the Double-blind Treatment Period is completed, the Sponsor will be unblinded to the double-blind treatment assignment. To minimize any impact on the planned LTE analyses, clinical sites and participants will continue to remain blinded to double-blind treatment assignment for all participants.

The study intervention (JNJ-63733657 or placebo) will be administered IV every 4 weeks; infusions will take place at a constant rate over approximately 60 minutes, followed by an IV flush, as described in the

IPPI. The infusion duration may be increased if issues of tolerability are encountered. Infusions are to be monitored by the principal investigator/designated study staff in a designated hospital/clinic setting.

The dose levels of JNJ-63733657 selected for this study are in the dose range expected to reduce CSF p217+tau from baseline by approximately 93% at a dose of 1000 mg and approximately 98% at a dose of 3000 mg, based on the analyses of the single ascending dose/multiple ascending dose study (63733657EDI1001).

The following key measures/assessments will be performed during the study:

- Cognitive performance will be assessed by the ADAS-Cog13 and the RBANS™.
- Functional status will be assessed by the ADCS-ADL-MCI and the Amsterdam IADL Questionnaire.
- Global clinical assessment of cognition and function and clinical dementia status will be assessed by completion of the CDR and calculation of the CDR-SB and CDR-GS, respectively.
- The frequency and severity of psychobehavioral disturbances will be assessed by the NPI.
- Tau PET imaging will assess propagation/accumulation of tau pathology.
- Peripheral and central PK, immunogenicity (eg, anti-drug antibodies), and peripheral and central pharmacodynamic (PD) parameters (total, free, and bound p217+tau) of JNJ-63733657 via blood and CSF collection.
- Safety and tolerability assessments will include AEs, vital signs, electrocardiograms (ECGs), physical and neurological examinations, laboratory evaluations, suicidality risks (C-SSRS), and brain MRI (eg, brain volume).

A mandatory pharmacogenomic (DNA) blood sample will be collected from all participants at the start of the Double-blind Treatment Period. This sample will be used for APOE genotyping. DNA samples may also be further analyzed for additional genetic factors that may influence PK, PD, immunogenicity, safety, and/or tolerability of JNJ-63733657, or that may relate to AD pathways or other neurodegenerative diseases, if it is hypothesized that this may help with the interpretation of the clinical data. Determination of APOE status may be through plasma or DNA analysis.

Missing data in clinical trials can lead to problems that undermine the scientific credibility of causal conclusions. The most common reason for missing data is participants who discontinue the assigned treatment because of AEs, lack of efficacy, or inconvenience. In order to reduce missing data in this study, if a participant discontinues double-blind study intervention for reasons other than withdrawal of consent (or behavioral dissent) for participation in the study prior to completion of the Double-blind Treatment Period, the participant should complete the remaining scheduled visits/study procedures (without study intervention administration) per the SoA through Week 104 of the Double-blind Treatment Period. If full participation in study procedures is considered too burdensome, the focus should be on collecting primary and secondary clinical outcome measures (ADAS-Cog13, CDR-SB, RBANS, ADCS-ADL-MCI), tau PET, PK, and clinical laboratory safety tests (particularly in those with abnormal results at the time of discontinuation of study intervention), and reducing other assessments. If a participant remains in the Double-blind Treatment Period without study intervention administration, then PK and monthly clinical laboratory safety tests would need to continue throughout 90 days after the last dose of study intervention or longer if clinically indicated (eg, to follow up an SAE until resolution).

If a participant discontinues the double-blind study intervention (for reasons other than withdrawal of consent [or behavioral dissent]) prior to the completion of the Double-blind Treatment Period and declines to further participate in the Double-blind Treatment Period assessments without study intervention administration, the participant will have an ET/End of DB visit performed as soon as possible after the last dose of study intervention. The participant will then return to the site for safety follow-up visits approximately 30, 60, and 90 days after the last dose of study intervention.

If a participant discontinues the LTE Treatment Period (for reasons other than withdrawal of consent [or behavioral dissent]), the participant will have an End of LTE Treatment Period visit performed as soon as possible after the last dose of study intervention. The participant will then return to the site for safety follow-up visits performed approximately 30, 60, and 90 days after the last dose of study intervention, unless the participant is receiving a dose of the commercially available product within 30 days of the last dose of study intervention.

NUMBER OF PARTICIPANTS

This study will enroll approximately 480 participants with prodromal AD or mild AD dementia (Early AD), approximately 160 participants per treatment group in the Double-blind Treatment Period.

INTERVENTION GROUPS AND DURATION

JNJ-63733657 drug product (500 mg/vial, 50 mg/mL and 1000 mg/vial, 175 mg/mL) and matching placebo (for 500 mg/vial, 50 mg/mL product only) are supplied as a final vialed product that must be stored refrigerated at 2°C to 8°C and be protected from light as described on the label. The drug product and placebo should be prepared as per the label and/or IPPI. Drug product and placebo for IV administration must be administered with in-line filtration. JNJ-63733657 500 mg/vial, 50 mg/mL and matching placebo appear as clear to slightly yellow solutions; JNJ-63733657 1000 mg/vial, 175 mg/mL appears as a clear to yellow solution.

Predose ALT and AST results must be reviewed prior to each study intervention administration. Dosing is not permitted for any participant with treatment-emergent predose ALT>1.5xULN or AST ≥3xULN (tested within 14 days prior to dosing). Retesting once is allowed if ALT>1.5xULN but <3xULN.

The study intervention will be administered under the supervision of the investigator or his/her designee in a designated hospital/clinic setting. A physician must be immediately available at the site at all times during the administration of study intervention. A single dose of JNJ-63733657 or placebo will be administered by IV infusion at a constant rate to each participant in the arm via a separate line using an administration set with a filter, as described in the IPPI. Consult the medical monitor if there are any questions or concerns regarding administration of the study intervention in the arm. The infusion duration will be approximately 60 minutes, followed by an IV flush, and may be increased if tolerability issues are encountered.

If a participant has missed/held 3 consecutive doses of study intervention during the LTE Treatment Period, the medical monitor should be contacted to discuss the current status of the participant.

EFFICACY EVALUATIONS

The primary efficacy endpoint is change from baseline on the iADRS at Week 104. The iADRS is a combination of the ADAS-Cog13 and the ADCS-ADL-MCI and is therefore a cognitive/functional composite. The ADAS-Cog is a rater-administered instrument that was designed to assess the severity of dysfunction in cognition characteristics of persons with AD. 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. The modified ADAS-Cog 13-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. The ADCS-ADL-MCI is an instrument used to track early changes in function such as the ability to perform high-level ADL. The scale is administered to the study partner (informant) by a site rater.

PHARMACOKINETIC EVALUATIONS

Venous blood samples (and CSF samples for those participants opting for lumbar puncture) will be used to evaluate the PK of JNJ-63733657.

The relationship between dose and PK of JNJ-63733657 on clinical efficacy, safety, and biomarker assessments is an exploratory objective of the study.

IMMUNOGENICITY EVALUATIONS

Antibodies to JNJ-63733657 (anti-drug antibodies), including neutralizing antibodies, will be evaluated. The impact of anti-drug antibodies on safety, efficacy, PK, and PD will be evaluated.

BIOMARKER EVALUATIONS

PET imaging for pathological tau will be performed. A single tau imaging radiotracer (MK-6240) will be used in all tau PET scans conducted during the Screening Period, Double-blind Treatment Period, and the LTE Treatment Period of the study. MK-6240 is not an authorized medicinal product in the European Union. Tracer retention in different brain regions (described in a separate Imaging Manual) will be determined.

Changes from baseline in volumetric assessments (including hippocampal [right and left], whole brain, and ventricular volume) of MRI brain will be performed. An appropriate correction for intercranial volume will be applied.

Changes from baseline in concentrations of the exploratory biomarkers in CSF and/or plasma/serum (including but not limited to total tau, p181tau, p217+tau, Aβ fragments, downstream markers of neuronal injury, neurodegeneration, and inflammation) may be measured.

PHARMACOGENOMIC (DNA) EVALUATIONS

A mandatory pharmacogenomic blood sample (DNA) will be collected. The goal of the pharmacogenomic component is to collect DNA to allow for the possible evaluation of genetic factors that may influence the PK, PD, immunogenicity, safety, or tolerability of JNJ-63733657 and pathways related to AD/tauopathy. Determination of APOE status may be through plasma or DNA analysis.

SAFETY EVALUATIONS

Safety evaluations will include collection and monitoring of treatment-emergent AEs, SAEs, AESI, 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.

STATISTICAL METHODS

The sample size for the primary objective was calculated to detect a 35% slowing of clinical decline of JNJ-63733657 versus placebo over time. A sample size of 480 participants, 160 per treatment arm in the Double-blind Treatment Period, provides approximately 87% power of determining successful slowing of clinical decline relative to the control arm (at the Week 104 time point), at a 2-sided Type 1 error rate of 5%. This sample size assumes an initial 7.5% annual dropout rate, an anticipated higher (13%) annual dropout rate after an approved disease-modifying therapy for AD becomes available at different times in different regions, and an accrual rate of 20 participants per month.

The primary efficacy endpoint is the iADRS change from baseline at Week 104. The primary analysis for the Double-blind Treatment Period will be performed on the full efficacy analysis set (FAS) which is defined as all randomized participants who receive at least 1 dose of study intervention in the Double-blind Treatment Period. The primary analysis method will be MMRM. The model will include age, baseline tau burden on tau PET (as a continuous variable), and iADRS baseline score 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 standard of care medications (acetylcholinesterase inhibitors [AChEIs] and/or memantine) 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 treatment effects 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.

The key secondary efficacy endpoints of cognition and function, respectively, are the change from baseline in the ADAS-Cog13 score at Week 104 and the change from baseline in the ADCS-ADL-MCI total score at Week 104, which are the 2 scales used to compose the primary efficacy endpoint of iADRS. The analysis method for each of the 2 key secondary efficacy endpoints will be MMRM, similar to the primary endpoint.

Statistical adjustment will be made to account for multiplicity due to multiple dose comparisons for the primary endpoint and the key secondary endpoints using a sequential gatekeeping test procedure.

Each of the other secondary continuous cognitive and functional endpoints will be analyzed using similar models to those used for the primary analysis. The proportion of participants progressing 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 postbaseline, will be summarized and 95% confidence intervals for the difference in proportions between each JNJ-63733657 dose and placebo will be provided.

Efficacy analyses for the LTE Treatment Period will be performed on the LTE FAS, which is defined as all participants who have received at least 1 dose of study intervention in the LTE Treatment Period and have completed at least one assessment of cognitive, functional, or clinical scales in the LTE Treatment Period, using descriptive statistics. Summaries of efficacy data for the LTE FAS will include the LTE Treatment Period, and, as appropriate, the combined Double-blind and LTE Treatment Periods, to summarize changes over time. Additional analyses may be performed for the FAS including the Double-blind Treatment Period and any data available in the LTE Treatment Period. For each of the cognitive, functional, and clinical scales, changes during the LTE Treatment Period (LTE Weeks 12, 36, and 64 for RBANS and Amsterdam IADL; LTE Weeks 24 and 52 for all other scales) compared to the double-blind baseline will be estimated with point estimates and 95% confidence intervals from an MMRM model, comparing the Early Start JNJ-63733657 1000 mg group with the Delayed Start JNJ-63733657 1000 mg group, and the Early Start JNJ-63733657 3000 mg group with the Delayed Start JNJ-63733657 3000 mg group. Change from baseline at each time point through the end of the LTE Treatment Period will be summarized as well. 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 the double-blind baseline through the first 1 year of the LTE Treatment Period, will be summarized using survival analysis methods and 95% confidence intervals for the difference in proportions between the Early Start JNJ-63733657 1000 mg group and the Delayed Start JNJ-63733657 1000 mg group and between the Early Start JNJ-63733657 3000 mg group and the Delayed Start JNJ-63733657 3000 mg group. 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 the double-blind baseline at each time point through the end of the LTE Treatment Period will be summarized as well. Analyses will take into consideration the varying amount of exposure to study intervention in the double-blind period prior to entering the LTE. Further details will be provided in the LTE SAP.

All safety analyses for the Double-blind Treatment Period will be performed on the Safety Analysis Set, defined as all randomized participants who receive at least 1 dose of double-blind study intervention. Safety analyses for the LTE Treatment Period will be performed on the LTE Safety Analysis Set, defined as all participants who have received at least 1 dose of study intervention in the LTE Treatment Period. Baseline will be defined as the most recent observation on or before the initial administration of study intervention in the respective period (double-blind or LTE). Further details will be provided in the respective SAPs.

For participants not participating in the LTE Treatment Period, any AE occurring at or after the initial administration of study intervention through the day of last dose in the Double-blind Treatment Period plus

90 days (during the safety Follow-up Period, if applicable) is considered to be treatment-emergent in the Double-blind Treatment Period. For participants participating in the LTE Treatment Period, any AE occurring at or after the initial administration of study intervention in the LTE Treatment Period through the day of last dose in the LTE Treatment Period plus 90 days is considered to be treatment-emergent in the LTE Treatment Period. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by treatment group.

Summaries, listings, datasets, or participant narratives may be provided for those participants who die, discontinue intervention due to an AE, experience a severe AE or an SAE, experience a treatment-emergent AESI (eg, hepatobiliary disorders/liver enzyme abnormality related AEs, infusion-related reactions) or meet other criteria, as needed.

Laboratory data will be summarized by type of laboratory test. Reference ranges and predefined thresholds will be used. Mean and mean change from baseline, with 95% confidence intervals will be calculated for all laboratory analytes at each scheduled time point. Frequency tabulations of the laboratory results above or below predefined thresholds will be provided. A listing of participants with any laboratory results outside the reference ranges will be provided. A listing of participants with above or below predefined thresholds will also be provided.

The ECG data will be summarized by ECG parameter. Mean and mean change from baseline, with 95% confidence intervals will be calculated. Frequency tabulations of the abnormalities will be presented. The ECG variables that will be analyzed are heart rate, PR interval, QRS duration, QT interval, QTcB, QTcF, and QTcL. All clinically relevant abnormalities in ECG waveform that are changes from the baseline readings will be reported (eg, changes in T-wave morphology or the occurrence of U-waves).

Vital signs including supine and standing pulse and blood pressure (systolic and diastolic) and temperature will be summarized over time, using descriptive statistics and/or graphically. Orthostatic changes will be assessed. The percentage of participants with values above or below predefined thresholds will be summarized.

A frequency distribution of C-SSRS scores at each scheduled time point by treatment will be provided. Shifts from the baseline visit to the most severe/maximum score during the Treatment Period will be summarized by treatment.

MRI observations will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point.

1.2. Schema

Figure 1: Schematic Overview of the Study

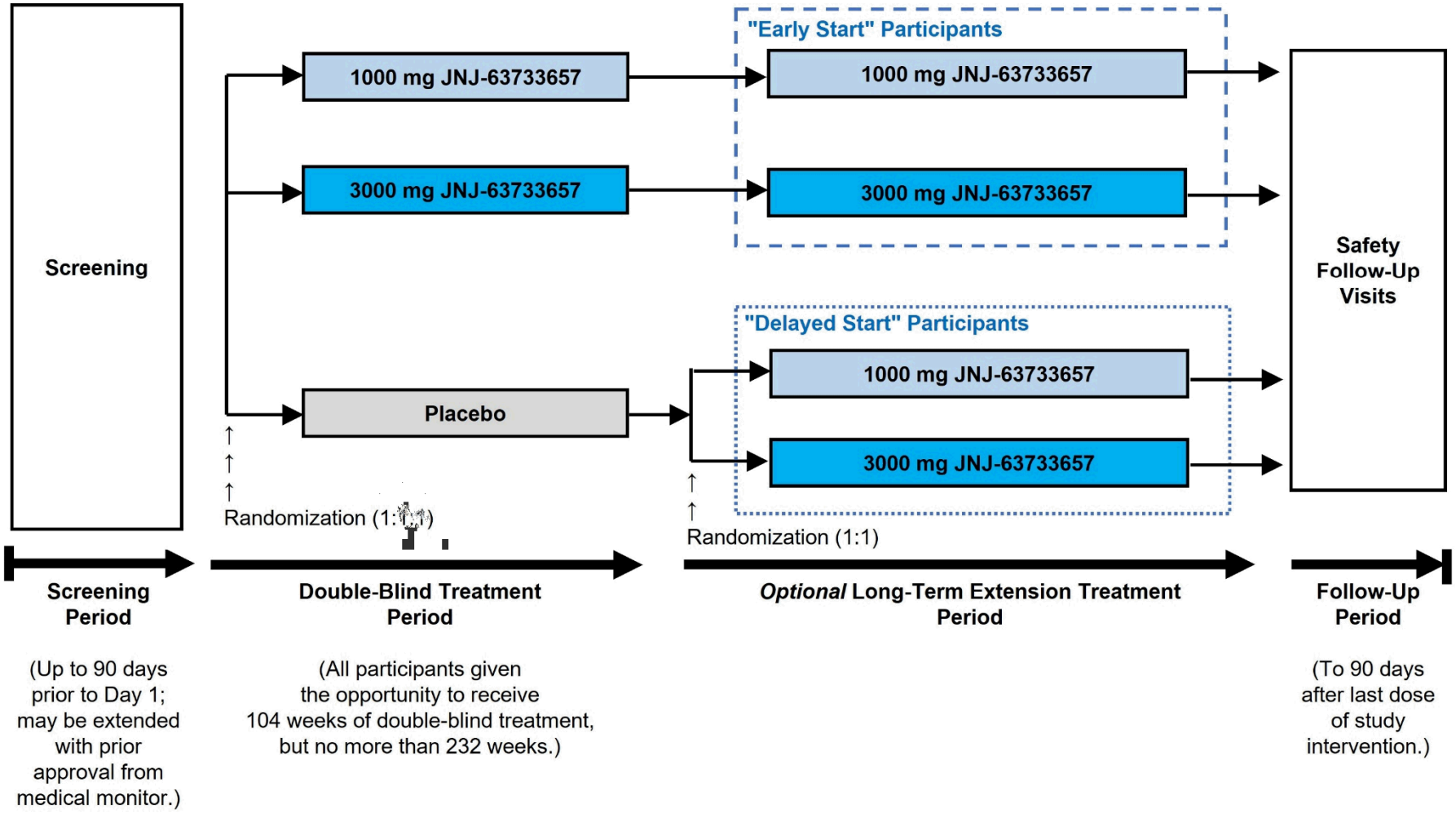
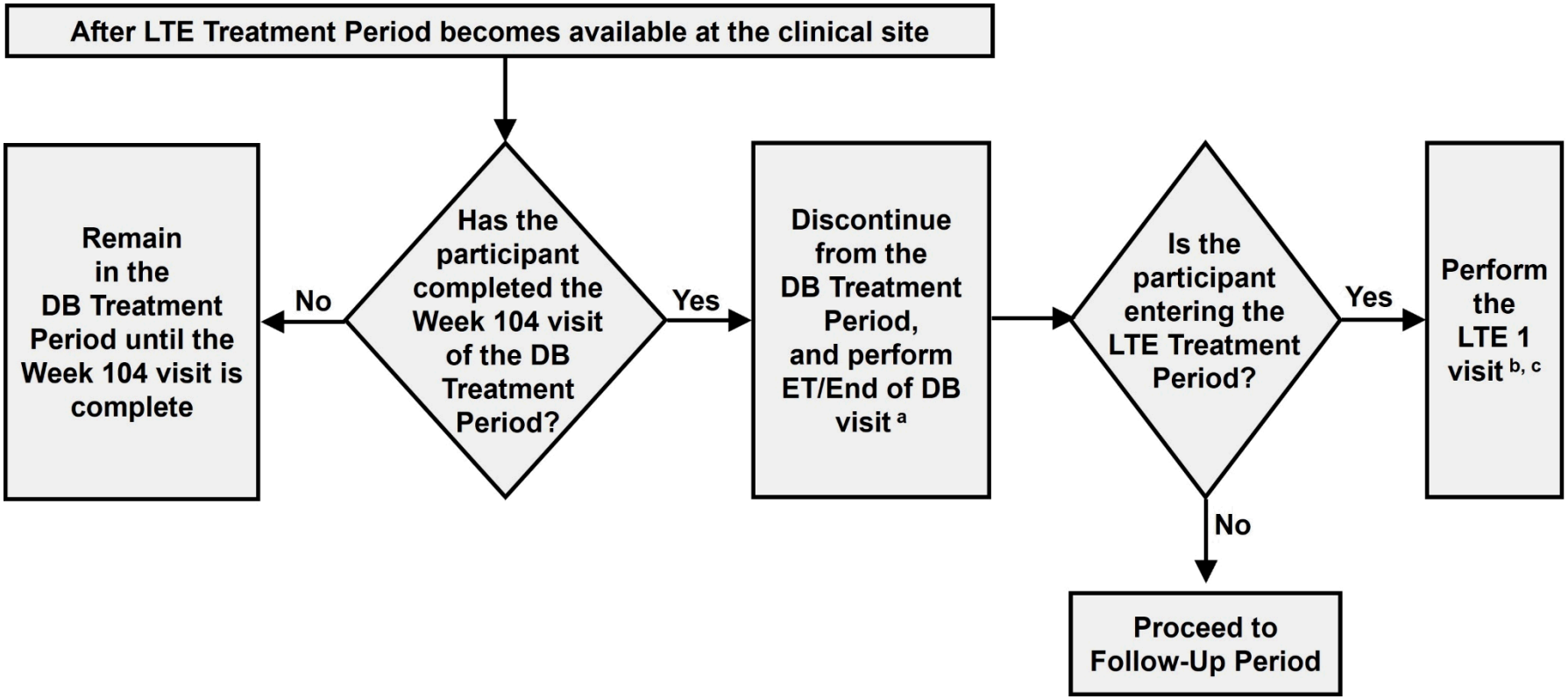


Figure 2: Transition From Double-blind Treatment Period to LTE Treatment Period



[a] The ET/End of DB visit must be completed prior to proceeding to either the LTE Treatment Period (if eligible) or the Follow-up Period.
[b] After completing the ET/End of DB visit, the LTE 1 visit can occur on the same day if sufficient time has elapsed between the last administration of study intervention in the Double-blind Treatment Period. A minimum of 4 weeks (±7 days) is required between the last dose of study intervention in the Double-blind Treatment Period and the first dose of study intervention at Week 0 (LTE 1).
[c] Refer to the Schedule of Activities for guidance regarding which study procedures do not have to be repeated if previously performed within the specified timeframe.

1.3. Schedule of Activities (SoA)

1.3.1. Schedule of Activities - Screening

Period	Screening[a, b]				
	I: Cognitive Status	II: General Health	III: MRI	IV: Tau Status	V: Baseline RBANS (required)/ Lumbar Puncture (optional)[c]
Visit Number	1	2	3[d]	4[d]	5
Period	Day -90 to Day -1				
Screening/Administrative					
Informed consent[e]	X				
Demographics	X				
Medical history	X[f]				
Review of inclusion/exclusion criteria	X				
Prestudy therapy	X				
Preplanned surgery/procedure(s)	X				
Safety Evaluations					
Physical examination	X[g]				
Neurological examination	X[g]				
Height	X[g]				
Weight	X[g]				
Vital signs (supine and standing BP, pulse)	X[g]				
12-lead ECG (in triplicate)	X[g]				
Temperature (tympanic)	X[g]				
Clinical Laboratory Tests					
Hematology, chemistry[h]	X				
Thyroid stimulating hormone (TSH)	X				
Coagulation (PT, PTT, INR)[i]	X				
Serology (HIV; if applicable, HBsAg and HCV)	X				
Urinalysis	X				
Urine drug screen	X				
Alcohol breath test	X				
Clinical Scales					
C-SSRS (baseline)	X[g]				
CDR	X				
GDS-30	X				
Hachinski Ischemic Scale	X[g,j]				

Period	Screening[a, b]				
	I: Cognitive Status	II: General Health	III: MRI	IV: Tau Status	V: Baseline RBANS (required)/ Lumbar Puncture (optional)[c]
Visit Number	1	2	3[d]	4[d]	5
Period	Day -90 to Day -1				
Cognitive Measures					
RBANS[k]	X				X
ADAS-Cog13[l]		X			
Imaging					
Tau PET				X[m]	
MRI			X[n]		
Pharmacodynamics and Biomarkers					
Blood collection for biomarker status	X				
CSF sample collection (optional)[o]					X
Ongoing Participant Review					
Concomitant therapy	X	X	X[p]	X[p]	X
Adverse events	X	X	X[p]	X[p]	X

a. The ADAS-Cog13 and RBANS assessments should have at least 7 days separating each visit that includes these assessments to ensure adequate time between the cognitive measures. (Screening visits are not to be combined but flexibility for conducting some study procedures at different visits is provided).

b. Unless otherwise noted in the SoA, the clinical scales/cognitive measures involving the participant should be conducted/completed before any other study procedures to prevent adversely influencing participant performance. Guidance regarding modifications to study procedures due to a natural disaster/major disruption/pandemic are described in Appendix 6.

c. The MRI and tau PET results confirming participant eligibility are required prior to performing Step 5. Step 5 is required for all participants; however, the lumbar puncture procedure is optional.

d. Visit to clinical site is not required (visit to imaging center only). There will be a telephone contact with the participant/study partner to collect information regarding AEs and concomitant therapies.

e. Including consent from study partner. Must be signed before first study-related activity. There is a separate consent for optional lumbar puncture procedure and collection of CSF, which can be signed at any screening visit but must be signed prior to performing the lumbar puncture procedure.

f. This medical history assessment includes cognitive history.

g. Procedure can be performed as part of Screening Step II if preferred by the clinical site.

h. Chemistry in fasting condition when feasible. Includes vitamin B12 and folic acid. Refer to Appendix 2 for more information regarding Clinical Laboratory Tests.

i. Only for participants who opt to undergo lumbar puncture. Results of PT, PTT, INR, and platelet count should be reviewed prior to lumbar puncture to confirm it is safe to proceed with lumbar puncture.

j. HIS requires data from other screening procedures (general medical history, neurologic exam) to complete, therefore these procedures should be performed at the same visit as the HIS.

k. The RBANS performed at Step I will be used to assess concordance with CDR from Step I (CDR-GS of 0.5). The baseline RBANS assessment is performed at Step 5 and should be completed 7 to 14 days prior to Day 1 (ie, Visit 6). The RBANS should not be performed within 7 days of the ADAS-Cog13 to avoid confounding cognitive performance (eg, confusion in word list recall).

l. The ADAS-Cog13 performed at Step II is to assess for and mitigate practice effects. The ADAS-Cog13 should not be performed within 7 days of the RBANS to avoid confounding cognitive performance (eg, confusion in word list recall).
m. Plasma p217+tau and MRI results confirming participant eligibility are required prior to performing tau PET.
n. The screening MRI can be performed after Step II is completed, there is no required minimum amount of time between Step II and Step III.
o. CSF sample by single lumbar puncture is for sites/participants participating in optional lumbar puncture. If lumbar puncture is done on the same day as cognitive or other assessments, the lumbar puncture should be performed last.
p. Collected via telephone contact.

1.3.2. Schedule of Activities - Double-blind Treatment Period

Period	Double-blind Treatment Period[a,b,c,d]																				
Week	0 Day 1	4[e,f]/ 8[e,f]	12[e]	16[e,f]/ 20[e,f]	24	28[e,f]/ 32[e,f]	36[e]	40[e,f]/ 44[e,f]/ 48[e,f]	52	56[e,f]/ 60[e,f]	64[e]	68[e,f]/ 72[e,f]	76	80[e,f]/ 84[e,f]	88[e]	92[e,f]/ 96[e,f]/ 100[e,f]	104	108[e,f]/ 112[e,f]	116[e]	120[e,f]/ 124[e,f]	128
Visit Window (Days ±)		7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Visit Number	6	7/ 8	9	10/ 11	12	13/ 14	15	16/ 17/ 18	19	20/ 21	22	23/ 24	25	26/ 27	28	29/ 30/ 31	32	33/ 34	35	36/ 37	38
Study Intervention																					
Randomization[g]	X																				
Administer study intervention (IV)[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Evaluations																					
Physical examination[i]	X				X				X				X				X				X
Neurological examination[i]	X				X				X				X				X				X
Weight			X		X		X		X				X				X				X
Vital signs (supine and standing BP, pulse)[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (triplicate)[i,j]	X	X	X		X		X		X				X				X				X
Temperature (tympanic)[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests																					
Hematology, chemistry[i,k,l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CRP[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
INR[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[i]	X		X		X		X		X				X				X				X
Alcohol breath test[i]	X																				
Clinical Scales																					
C-SSRS (since last visit)[i]	X		X		X		X		X[m]				X				X[m]				X
ADCS-ADL-MCI[i]	X				X				X[m]				X				X[m]				X
Amsterdam IADL[i]	X				X				X[m]				X				X[m]				X
CDR[i]	X				X				X[m]				X				X[m]				X
NPI[i]	X				X				X[m]				X				X[m]				X
RUD-Lite[i]	X				X				X[m]				X				X[m]				X
QOL-AD[i]	X								X[m]								X[m]				
Cognitive Measures																					
RBANS[i]			X				X				X				X				X		
ADAS-Cog13[i]	X				X				X[m]				X				X[m]				X

Period	Double-blind Treatment Period[a,b,c,d]																				
Week	0 Day 1	4[e,f]/ 8[e,f]	12[e]	16[e,f]/ 20[e,f]	24	28[e,f]/ 32[e,f]	36[e]	40[e,f]/ 44[e,f]/ 48[e,f]	52	56[e,f]/ 60[e,f]	64[e]	68[e,f]/ 72[e,f]	76	80[e,f]/ 84[e,f]	88[e]	92[e,f]/ 96[e,f]/ 100[e,f]	104	108[e,f]/ 112[e,f]	116[e]	120[e,f]/ 124[e,f]	128
Visit Window (Days ±)		7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Visit Number	6	7/ 8	9	10/ 11	12	13/ 14	15	16/ 17/ 18	19	20/ 21	22	23/ 24	25	26/ 27	28	29/ 30/ 31	32	33/ 34	35	36/ 37	38
Imaging																					
Tau PET									X[n]								X[n]				
MRI[o]					X				X				X				X				X
PK and Immunogenicity																					
Blood sample collection	X[i]	X[i]	X[i]	X[p]	X[i]		X[i]		X[i]				X[i]				X[i]				X[i]
CSF sample collection[q]									X								X				
PD and Biomarkers																					
Blood sample collection[i]	X		X		X		X		X				X				X				X
CSF sample collection[q]									X								X				
Pharmacogenomics (DNA)																					
Blood sample collection[r]	X																				
Ongoing Participant Review																					
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. Visits which include MRI, PET, predose clinical laboratory safety tests (hematology, chemistry, CRP, INR), and/or dose administration allow flexibility regarding when these study procedures can be performed for a visit (refer to footnotes below).

b. Study procedures should be performed at the study site (not remotely) unless otherwise specified in the protocol. Guidance regarding modifications to study procedures due to a natural disaster/major disruption/pandemic are described in Appendix 6.

c. The Double-blind Treatment Period will be of variable duration, continuing until all participants have had the opportunity to receive double-blind treatment for 104 weeks. The maximum treatment duration 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 (includes 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 of the Double-blind Treatment Period 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 the LTE Treatment Period).

d. In order to reduce missing data in this study, if a participant discontinues double-blind study intervention for reasons other than withdrawal of consent (or behavioral dissent) for participation in the study prior to completion of the Double-blind Treatment Period, the participant should complete the remaining scheduled visits/study procedures (without study intervention dosing) through Week 104 of the Double-blind Treatment Period. If full participation in study procedures is considered too burdensome, then the focus should be on collecting primary and secondary clinical outcome measures (ADAS-Cog13, CDR-SB, RBANS, ADCS-ADL-MCI), tau PET, PK, and clinical laboratory safety tests (particularly in those with abnormal results at the time of discontinuation of study intervention), and reducing other assessments.

e. It is preferred the study partner accompany the participant to these visits even though no study partner assessments are planned. However, if the study partner is unable to attend, then another individual (who is at least 18 years old or a legal adult) may accompany the participant. In such cases, the study

partner must be available for a telephone contact with the site (within the permitted visit window) to collect information regarding AEs and concomitant therapies.

f. If it is determined that a participant will not be administered study intervention at this visit (eg, due to predose ALT>1.5xULN or AST ≥3xULN), then this visit may be done remotely and only AEs and concomitant therapies should be recorded. Other missed assessments (eg, blood sample collection) should be performed at the next clinic visit.

g. Randomization may occur after all screening procedures are complete and up to Day 1 (baseline). All inclusion and exclusion criteria should be reviewed; it must be verified that the participant meets all inclusion and no exclusion criteria.

h. The study intervention should not be administered until review of predose ALT and AST results. Dosing is not permitted for any participant with treatment-emergent predose ALT>1.5xULN or AST ≥3xULN. Study intervention will be administered under the supervision of the investigator or his/her designee in a designated hospital/clinic setting. If predose ALT and AST values are not available on the day of the clinic visit, dosing may occur on a separate day (within 14 days of the predose ALT and AST). In this case, predose vital signs, and recording of AEs and concomitant medications must be repeated on the same day of dosing. A physician must be immediately available at the site at all times during the administration of study intervention. A single dose of JNJ-63733657 or placebo will be administered at a constant rate over approximately 60 minutes, followed by an IV flush, as described in the IPPI. The infusion duration may be increased if issues of tolerability are encountered.

i. Predose. "Predose" for hematology, chemistry, CRP, and INR is defined as within 14 days of the study intervention administration visit to allow participants to have tests performed prior to the scheduled visit, if preferred. If testing is performed prior to the visit day, the study partner is not required to accompany the participant to the location of blood collection. All other predose assessments are to be performed on the day of the regular visit, unless otherwise specified per protocol. If a participant continues in the double-blind period without treatment, they will continue monthly laboratory tests for 90 days after the last dose (or longer if clinically indicated per investigator discretion).

j. ECGs performed predose in triplicate at approximately 1-minute intervals, at approximately the same time of day.

k. Predose ALT and AST results must be reviewed prior to each study intervention administration. Dosing is not permitted for any participant with treatment-emergent predose ALT>1.5xULN or AST ≥3xULN (tested within 14 days prior to dosing). Refer to Appendix 7 for hepatic safety monitoring assessments, including stopping criteria and guidance regarding the management of abnormal hepatic chemistry results.

l. Chemistry in fasting condition when feasible. Includes fractionated bilirubin (if available). Refer to Appendix 2 for more information regarding Clinical Laboratory Tests.

m. Prior to lumbar puncture, if participating in optional lumbar puncture.

n. The window for tau PET scan at this visit is ±14 days.

o. If MRI is done on the same day as cognitive or other assessments (except lumbar puncture), the MRI should be performed last, prior to administration of study intervention. If not performed on the same day, the MRI should be performed within 7 days prior to the visit (ie, -7 day visit window). At visits that include both MRI and lumbar puncture, the MRI should be performed prior to lumbar puncture to minimize any impact of the lumbar puncture procedure on the MRI data.

p. Week 16 visit only. At this visit, blood (8.5 mL) should be drawn for assessment of drug concentration within 10 minutes of the completion of infusion from the contralateral arm. Exact start and end times of infusion and sampling time should be recorded.

q. CSF sample by single lumbar puncture for participants who opt for lumbar puncture. If lumbar puncture is done on the same day as cognitive or other assessments, the lumbar puncture should be performed last, prior to administration of study intervention. If not performed on the same day, the lumbar puncture should be performed within 7 days prior to the visit (ie, -7 day visit window). At visits that include both MRI and lumbar puncture, the MRI should be performed prior to lumbar puncture to minimize any impact of the lumbar puncture procedure on the MRI data.

r. The pharmacogenomic (DNA) sample should be collected at the specified time point. However, if necessary, it may be collected at a later time point without constituting a protocol deviation. Tests on this sample will include APOE genotyping.

1.3.3. Schedule of Activities - Double-blind Treatment Period, Continued

Period	Double-blind Treatment Period[a,s,t,u]																
Week	132[b,c]/ 136[b,c]	140[b]	144[b,c]/ 148[b,c]/ 152[b,c]	156	160[b,c]/ 164[b,c]	168[b]	172[b,c]/ 176[b,c]	180	184[b,c]/ 188[b,c]	192[b]	196[b,c]/ 200[b,c]/ 204[b,c]	208	212[b,c]/ 216[b,c]	220[b]	224[b,c]/ 228[b,c]	232	
Visit Window (Days ±)	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Visit Number	39/ 40	41	42/ 43/ 44	45	46/ 47	48	49/ 50	51	52/ 53	54	55/ 56/ 57	58	59/ 60	61	62/ 63	64	ET/ End of DB
Study Intervention																	
Administer study intervention (IV)[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety Evaluations																	
Physical examination[e]				X								X				X	X[n]
Neurological examination[e]				X								X				X	X[n]
Height																	X[n]
Weight				X				X				X				X	X[n]
Vital signs (supine and standing BP, pulse)[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (triplicate)[e,f]				X				X				X				X	X[l]
Temperature (tympanic)[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests																	
Hematology, chemistry[e,g,h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[m]
CRP[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[m]
INR[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[m]
Urinalysis[e]				X				X				X				X	X[m]
Clinical Scales																	
C-SSRS (since last visit)[e]				X				X				X[i]				X	X[i,n]
ADCS-ADL-MCI[e]				X				X				X[i]				X	X[i,o]
Amsterdam IADL[e]				X				X				X[i]				X	X[i,o]
CDR[e]				X				X				X[i]				X	X[i,o]
NPI[e]				X				X				X[i]				X	X[i,o]
RUD-Lite[e]				X				X				X[i]				X	X[i,o]
QOL-AD[e]				X								X[i]					
Cognitive Measures																	
RBANS[e]		X				X				X				X			X[i,o]
ADAS-Cog13[e]				X				X				X[i]				X	X[i,o]

Period	Double-blind Treatment Period[a,s,t,u]																
Week	132[b,c]/ 136[b,c]	140[b]	144[b,c]/ 148[b,c]/ 152[b,c]	156	160[b,c]/ 164[b,c]	168[b]	172[b,c]/ 176[b,c]	180	184[b,c]/ 188[b,c]	192[b]	196[b,c]/ 200[b,c]/ 204[b,c]	208	212[b,c]/ 216[b,c]	220[b]	224[b,c]/ 228[b,c]	232	
Visit Window (Days ±)	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Visit Number	39/ 40	41	42/ 43/ 44	45	46/ 47	48	49/ 50	51	52/ 53	54	55/ 56/ 57	58	59/ 60	61	62/ 63	64	ET/ End of DB
Imaging																	
Tau PET				X[k]								X[k]					X[q]
MRI[j]				X				X				X				X	X[p]
PK and Immunogenicity																	
Blood sample collection				X[e]				X[e]				X[e]				X[e]	X[n]
CSF sample collection[r]												X					X[q]
PD and Biomarkers																	
Blood sample collection				X[e]				X[e]				X[e]				X[e]	X[n]
CSF sample collection[r]												X					X[q]
Ongoing Participant Review																	
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. In order to reduce missing data in this study, if a participant discontinues double-blind study intervention for reasons other than withdrawal of consent (or behavioral dissent) for participation in the study prior to completion of the Double-blind Treatment Period, the participant should complete the remaining scheduled visits/study procedures (without study intervention dosing) through Week 104 of the Double-blind Treatment Period. If full participation in study procedures is considered too burdensome, then the focus should be on collecting primary and secondary clinical outcome measures (ADAS-Cog13, CDR-SB, RBANS, ADCS-ADL-MCI), tau PET, PK, and clinical laboratory safety tests (particularly in those with abnormal results at the time of discontinuation of study intervention), and reducing other assessments.

b. It is preferred the study partner accompany the participant to these visits even though no study partner assessments are planned. However, if the study partner is unable to attend, then another individual (who is at least 18 years old or a legal adult) may accompany the participant. In such cases, the study partner must be available for a telephone contact with the site (within the permitted visit window) to collect information regarding AEs and concomitant therapies.

c. If it is determined that a participant will not be administered study intervention at this visit (eg, due to predose ALT>1.5xULN or AST≥3xULN), then this visit may be done remotely and only AEs and concomitant therapies should be recorded. Other missed assessments (eg, blood sample collection) should be performed at the next clinic visit.

d. The study intervention should not be administered until review of predose ALT and AST results. Dosing is not permitted for any participant with treatment-emergent predose ALT>1.5xULN or AST≥3xULN. Study intervention will be administered under the supervision of the investigator or his/her designee in a designated hospital/clinic setting. If predose ALT and AST values are not available on the day of the clinic visit, dosing may occur on a separate day (within 14 days of the predose ALT and AST). In this case, predose vital signs, and recording of AEs and concomitant medications must be repeated on the same day of dosing. A physician must be immediately available at the site at all times during the administration of study intervention. A single dose of JNJ-63733657 or placebo will be administered at a constant rate over approximately 60 minutes, followed by an IV flush, as described in the IPPI. The infusion duration may be increased if issues of tolerability are encountered.

e. Predose. "Predose" for hematology, chemistry, CRP, and INR is defined as within 14 days of the study intervention administration visit to allow participants to have tests performed prior to the scheduled visit, if preferred. If testing is performed prior to the visit day, the study partner is not required to accompany the participant to the location of blood collection. All other predose assessments are to be performed on the day of the regular visit, unless otherwise specified per protocol. If a participant continues in the double-blind period without treatment, they will continue monthly laboratory tests for 90 days after the last dose (or longer if clinically indicated per investigator discretion).
f. ECGs performed predose in triplicate at approximately 1-minute intervals, at approximately the same time of day.
g. Chemistry in fasting condition when feasible. Includes fractionated bilirubin (if available). Refer to Appendix 2 for more information regarding Clinical Laboratory Tests.
h. Predose ALT and AST results must be reviewed prior to each study intervention administration. Dosing is not permitted for any participant with treatment-emergent predose ALT>1.5xULN or AST≥3xULN (tested within 14 days prior to dosing). Refer to Appendix 7 for hepatic safety monitoring assessments, including stopping criteria and guidance regarding the management of abnormal hepatic chemistry results.
i. Prior to lumbar puncture, if participating in optional lumbar puncture.
j. If MRI is done on the same day as cognitive or other assessments (except lumbar puncture), the MRI should be performed last, prior to the administration of study intervention. If not performed on the same day, the MRI should be performed within 7 days prior to the visit (ie, -7 day visit window). At visits that include both MRI and lumbar puncture, the MRI should be performed prior to lumbar puncture to minimize any impact of the lumbar puncture procedure on the MRI data.
k. The window for tau PET scan at this visit is ±14 days.
l. If not performed within the previous 7 days.
m. If not performed within the previous 14 days.
n. If not performed within the previous 4 weeks.
o. If not performed within the previous 12 weeks. The RBANS and the ADAS-Cog13 should never be administered on the same day. Sites should perform whichever cognitive assessment was not performed at the participant's previous visit, to maintain the alternating pattern of cognitive assessments. If a participant will enter the LTE Treatment Period, and if the ET/End of DB visit will occur on the same day as the LTE 1 visit, then the RBANS should not be performed (because the LTE 1 visit requires the ADAS-Cog13 assessment).
p. If not performed within the previous 24 weeks. If a participant will not enter the LTE Treatment Period, then an MRI is only required if not performed within the last 24 weeks. If a participant will enter the LTE Treatment Period, then an MRI scan can be performed at the ET/End of DB visit to meet the requirement for the LTE 1 visit (ie, the MRI scan must be performed within 4 weeks of the LTE 1 visit).
q. If not performed within the previous 52 weeks. If a participant will enter the LTE Treatment Period, then a tau PET scan can be performed at the ET/End of DB visit to meet the requirement for the LTE 1 visit; refer to LTE Visit 1 requirements in Section 1.3.4.
r. CSF sample by single lumbar puncture for participants who opt for lumbar puncture. If lumbar puncture is done on the same day as cognitive or other assessments, the lumbar puncture should be performed last, prior to the administration of study intervention. If not performed on the same day, the lumbar puncture should be performed within 7 days prior to the visit (ie, -7 day visit window). At visits that include both MRI and lumbar puncture, the MRI should be performed prior to lumbar puncture to minimize any impact of the lumbar puncture procedure on the MRI data.
s. Study procedures should be performed at the study site (not remotely) unless otherwise specified in the protocol. Guidance regarding modifications to study procedures due to a natural disaster/major disruption/pandemic are described in Appendix 6.
t. Visits which include MRI, PET, predose clinical laboratory safety tests (hematology, chemistry, CRP, INR), and/or dose administration allow flexibility regarding when these study procedures can be performed for a visit (refer to footnotes above).
u. The Double-blind Treatment Period will be of variable duration, continuing until all participants have had the opportunity to receive double-blind treatment for 104 weeks. The maximum treatment duration 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 (includes 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 of

the Double-blind Treatment Period 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 the LTE Treatment Period).

1.3.4. Schedule of Activities - Long-Term Extension Treatment Period - Year 1 (LTE Week 0 to LTE Week 52)

Period	Long-Term Extension Treatment Period [q,u]													
Week	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Visit Number	LTE 1[a]	LTE 2[r,s]	LTE 3[r,s]	LTE 4	LTE 5[r,s]	LTE 6[r,s]	LTE 7	LTE 8[r,s]	LTE 9[r,s]	LTE 10	LTE 11[r,s]	LTE 12[r,s]	LTE 13[r,s]	LTE 14
Visit Window (Days ±)		7	7	7	7	7	7	7	7	7	7	7	7	7
Study Intervention														
Randomization	X													
Administer study intervention (IV)[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Evaluations														
Physical examination[c]	X[k]						X							X
Neurological examination[c]	X[k]						X							X
Weight	X[k]			X			X			X				X
Vital signs (supine and standing BP, pulse)[c]	X[t]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (triplicate)[c,o]	X[i]	X	X	X			X			X				X
Temperature (tympanic)[c]	X[t]	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests														
Hematology, chemistry[c,d,e]	X[j]	X	X	X	X	X	X	X	X	X	X	X	X	X
CRP[c]	X[j]	X	X	X	X	X	X	X	X	X	X	X	X	X
INR[c]	X[j]	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[c]	X[j]			X			X			X				X
Clinical Scales														
C-SSRS (since last visit)[c]	X[f,k]			X			X			X				X[f]
ADCS-ADL-MCI[c]	X[f,l]						X							X[f]
Amsterdam IADL[c]	X[f,l]			X						X				
CDR[c]	X[f,l]						X							X[f]
NPI[c]	X[f,l]						X							X[f]
RUD-Lite[c]	X[f,l]						X							X[f]
QOL-AD[c]	X[f,l]													X[f]
Cognitive Measures														
RBANS[c]				X						X				
ADAS-Cog13[c]	X[f,l]						X							X[f]
Imaging														
Tau PET	X[m]													X[h]
MRI[g]	X[k]						X							X

Period	Long-Term Extension Treatment Period [q,u]													
Week	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Visit Number	LTE 1[a]	LTE 2[r,s]	LTE 3[r,s]	LTE 4	LTE 5[r,s]	LTE 6[r,s]	LTE 7	LTE 8[r,s]	LTE 9[r,s]	LTE 10	LTE 11[r,s]	LTE 12[r,s]	LTE 13[r,s]	LTE 14
Visit Window (Days ±)		7	7	7	7	7	7	7	7	7	7	7	7	7
PK and Immunogenicity														
Blood sample collection[c]	X[k]			X			X			X				X
CSF sample collection[p]	X[n]													X
PD and Biomarkers														
Blood sample collection[c]	X[k]			X			X			X				X
CSF sample collection[p]	X[n]													X
Ongoing Participant Review														
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. For participants eligible for the LTE, after completing the ET/End of DB visit, the LTE 1 visit may be performed on the same day if sufficient time (a minimum of 4 weeks ±7 days) has elapsed between the last dose of study intervention in the Double-blind Treatment Period and first dose of study intervention scheduled for LTE 1. A participant who enters the LTE on the same day as the ET/End of DB visit will receive the first dose of study intervention in the LTE Treatment Period at Week 0 (LTE 1). If the LTE 1 visit is performed on the same day or shortly after the ET/End of DB visit, then some LTE 1 visit assessments may not need to be repeated; see relevant footnotes in this SoA.

b. The study intervention should not be administered until review of predose ALT and AST results. Dosing is not permitted for any participant with treatment-emergent predose ALT>1.5xULN or AST≥3xULN. Study intervention will be administered under the supervision of the investigator or his/her designee in a designated hospital/clinic setting. If predose ALT and AST values are not available on the day of the clinic visit, dosing may occur on a separate day (within 14 days of the predose ALT and AST). In this case, predose vital signs, and recording of AEs and concomitant medications must be repeated on the same day of dosing. A physician must be immediately available at the site at all times during the administration of study intervention. A single dose of JNJ-63733657 will be administered at a constant rate over approximately 60 minutes, followed by an IV flush, as described in the IPPI. The infusion duration may be increased if issues of tolerability are encountered.

c. Predose. "Predose" for hematology, chemistry, CRP, and INR is defined as within 14 days of the study intervention administration visit to allow participants to have tests performed prior to the scheduled visit, if preferred. If testing is performed prior to the visit day, the study partner is not required to accompany the participant to the location of blood collection. All other predose assessments are to be performed on the day of the regular visit, unless otherwise specified per protocol.

d. Chemistry in fasting condition when feasible. Includes fractionated bilirubin (if available). Refer to Appendix 2 for more information regarding Clinical Laboratory Tests.

e. Predose ALT and AST results must be reviewed prior to each study intervention administration. Dosing is not permitted for any participant with treatment-emergent predose ALT>1.5xULN or AST≥3xULN (tested within 14 days prior to dosing). Refer to Appendix 7 for hepatic safety monitoring assessments, including stopping criteria and guidance regarding the management of abnormal hepatic chemistry results.

f. Prior to lumbar puncture, if participating in optional lumbar puncture.

g. If MRI is done on the same day as cognitive or other assessments (except lumbar puncture), the MRI should be performed last, prior to the administration of study intervention. If not performed on the same day, the MRI should be performed within 7 days prior to the visit (ie, -7 day visit window). At visits that include both MRI and lumbar puncture, the MRI should be performed prior to lumbar puncture to minimize any impact of the lumbar puncture procedure on the MRI data.

h. The window for tau PET scan at this visit is ±4 weeks. If the tau PET cannot be scheduled within this timeframe (eg, due to operational challenges), then tau PET window may be extended only with medical monitor approval.
i. If not performed within the previous 7 days.
j. If not performed within the previous 14 days.
k. If not performed within the previous 4 weeks.
l. If not performed within the previous 12 weeks.
m. If not performed within the previous 24 weeks. If tau PET is required, then it can be performed within 24 weeks prior to the LTE 1 visit, and it should be performed before the first administration of study intervention in the LTE Treatment Period. If the tau PET cannot be scheduled within this timeframe (eg, due to operational challenges), then tau PET window may be extended to no more than 4 weeks after the LTE 1 visit (ie, prior to LTE 2 visit) only with medical monitor approval.
n. If not performed within the previous 52 weeks.
o. ECGs performed predose in triplicate at approximately 1-minute intervals, at approximately the same time of day.
p. CSF sample by single lumbar puncture for participants who opt for lumbar puncture. If lumbar puncture is done on the same day as cognitive or other assessments, the lumbar puncture should be performed last, prior to the administration of study intervention. If not performed on the same day, the lumbar puncture should be performed within 7 days prior to the visit (ie, -7 day visit window). At visits that include both MRI and lumbar puncture, the MRI should be performed prior to lumbar puncture to minimize any impact of the lumbar puncture procedure on the MRI data.
q. Study procedures should be performed at the study site (not remotely) unless otherwise specified in the protocol. Guidance regarding modifications to study procedures due to a natural disaster/major disruption/pandemic are described in Appendix 6.
r. It is preferred the study partner accompany the participant to these visits even though no study partner assessments are planned. However, if the study partner is unable to attend, then another individual (who is at least 18 years old or a legal adult) may accompany the participant. In such cases, the study partner must be available for a telephone contact with the site (within the permitted visit window) to collect information regarding AEs and concomitant therapies.
s. If it is determined that a participant will not be administered study intervention at this visit (eg, due to predose ALT>1.5xULN or AST≥3xULN), then this visit may be done remotely and only AEs and concomitant therapies should be recorded. Other missed assessments (eg, blood sample collection) should be performed at the next clinic visit.
t. If not performed within the same day. (Vital signs and temperature do not have to be performed at LTE 1 if already performed on the same day as part of ET/End of DB visit.)
u. Visits which include MRI, PET, predose clinical laboratory safety tests (hematology, chemistry, CRP, INR), and/or dose administration allow flexibility regarding when these study procedures can be performed for a visit (refer to footnotes above).

1.3.5. Schedule of Activities - Long-Term Extension Treatment Period, Continued - Year 2 (Through LTE Week 104)

Period	Long-Term Extension Treatment Period[k,m]												
Week	56	60	64	68	72	76	80	84	88	92	96	100	104
Visit Number	LTE 15[i,j]	LTE 16[i,j]	LTE 17	LTE 18[i,j]	LTE 19[i,j]	LTE 20	LTE 21[i,j]	LTE 22[i,j]	LTE 23	LTE 24[i,j]	LTE 25[i,j]	LTE 26[i,j]	LTE 27
Visit Window (Days ±)	7	7	7	7	7	7	7	7	7	7	7	7	7
Study Intervention													
JNJ-63733657 drug product changed from 500 mg/vial, 50 mg/mL to 1000 mg/vial, 175 mg/mL				X[n]									
Administer study intervention (IV)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Evaluations													
Physical examination[b]						X							X
Neurological examination[b]						X							X
Weight						X							X
Vital signs (supine and standing BP, pulse)[b]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (triplicate)[b,h]						X							X
Temperature (tympanic)[b]	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests													
Hematology, chemistry[b,c,d]	X	X	X	X	X	X	X	X	X	X	X	X	X
CRP[b]	X	X	X	X	X	X	X	X	X	X	X	X	X
INR[b]	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[b]						X							X
Clinical Scales													
C-SSRS (since last visit)[b]						X							X[e]
ADCS-ADL-MCI[b]						X							X[e]
Amsterdam IADL[b]			X						X				
CDR[b]						X							X[e]
NPI[b]						X							X[e]
RUD-Lite[b]						X							X[e]
QOL-AD[b]													X[e]
Cognitive Measures													
RBANS[b]			X						X				
ADAS-Cog13[b]						X							X[e]
Imaging													
Tau PET													X[f]
MRI[g]						X							X
PK and Immunogenicity													

Period	Long-Term Extension Treatment Period[k,m]												
Week	56	60	64	68	72	76	80	84	88	92	96	100	104
Visit Number	LTE 15[i,j]	LTE 16[i,j]	LTE 17	LTE 18[i,j]	LTE 19[i,j]	LTE 20	LTE 21[i,j]	LTE 22[i,j]	LTE 23	LTE 24[i,j]	LTE 25[i,j]	LTE 26[i,j]	LTE 27
Visit Window (Days ±)	7	7	7	7	7	7	7	7	7	7	7	7	7
Blood sample collection[b]						X							X
CSF sample collection[l]													X
PD and Biomarkers													
Blood sample collection[b]						X							X
CSF sample collection[l]													X
Ongoing Participant Review													
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X

a. The study intervention should not be administered until review of predose ALT and AST results. Dosing is not permitted for any participant with treatment-emergent predose ALT>1.5xULN or AST≥3xULN. Study intervention will be administered under the supervision of the investigator or his/her designee in a designated hospital/clinic setting. If predose ALT and AST values are not available on the day of the clinic visit, dosing may occur on a separate day (within 14 days of the predose ALT and AST). In this case, predose vital signs, and recording of AEs and concomitant medications must be repeated on the same day of dosing. A physician must be immediately available at the site at all times during the administration of study intervention. A single dose of JNJ-63733657 will be administered at a constant rate over approximately 60 minutes, followed by an IV flush, as described in the IPPI. The infusion duration may be increased if issues of tolerability are encountered.

b. Predose. "Predose" for hematology, chemistry, CRP, and INR is defined as within 14 days of the study intervention administration visit to allow participants to have tests performed prior to the scheduled visit, if preferred. If testing is performed prior to the visit day, the study partner is not required to accompany the participant to the location of blood collection. All other predose assessments are to be performed on the day of the regular visit, unless otherwise specified per protocol.

c. Chemistry in fasting condition when feasible. Includes fractionated bilirubin (if available). Refer to Appendix 2 for more information regarding Clinical Laboratory Tests.

d. Predose ALT and AST results must be reviewed prior to each study intervention administration. Dosing is not permitted for any participant with treatment-emergent predose ALT>1.5xULN or AST≥3xULN (tested within 14 days prior to dosing). Refer to Appendix 7 for hepatic safety monitoring assessments, including stopping criteria and guidance regarding the management of abnormal hepatic chemistry results.

e. Prior to lumbar puncture, if participating in optional lumbar puncture.

f. The window for tau PET scan at this visit is ±4 weeks. If the tau PET cannot be scheduled within this timeframe (eg, due to operational challenges), then tau PET window may be extended only with medical monitor approval.

g. If MRI is done on the same day as cognitive or other assessments (except lumbar puncture), the MRI should be performed last, prior to administration of study intervention. If not performed on the same day, the MRI should be performed within 7 days prior to the visit (ie, -7 day visit window). At visits that include both MRI and lumbar puncture, the MRI should be performed prior to lumbar puncture to minimize any impact of the lumbar puncture procedure on the MRI data.

h. ECGs performed predose in triplicate at approximately 1-minute intervals, at approximately the same time of day.

i. It is preferred the study partner accompany the participant to these visits even though no study partner assessments are planned. However, if the study partner is unable to attend, then another individual (who is at least 18 years old or a legal adult) may accompany the participant. In such cases, the study partner must be available for a telephone contact with the site (within the permitted visit window) to collect information regarding AEs and concomitant therapies.

j. If it is determined that a participant will not be administered study intervention at this visit (eg, due to predose ALT>1.5xULN or AST≥3xULN), then this visit may be done remotely and only AEs and concomitant therapies should be recorded. Other missed assessments (eg, blood sample collection) should be performed at the next clinic visit.
k. Study procedures should be performed at the study site (not remotely) unless otherwise specified in the protocol. Guidance regarding modifications to study procedures due to a natural disaster/major disruption/pandemic are described in Appendix 6.
l. CSF sample by single lumbar puncture for participants who opt for lumbar puncture. If lumbar puncture is done on the same day as cognitive or other assessments, the lumbar puncture should be performed last prior to the administration of study intervention. If not performed on the same day, the lumbar puncture should be performed within 7 days prior to the visit (ie, -7 day visit window). At visits that include both MRI and lumbar puncture, the MRI should be performed prior to lumbar puncture to minimize any impact of the lumbar puncture procedure on the MRI data.
m. Visits which include MRI, PET, predose clinical laboratory safety tests (hematology, chemistry, CRP, INR), and/or dose administration allow flexibility regarding when these study procedures can be performed for a visit (refer to footnotes above).
n. At each participant's LTE Visit 18 (LTE Week 68), or later if required (eg, pending IRB/Ethics Committee approvals), the RTSM system (eg, IWRS) will begin assigning the new JNJ-63733657 drug product (1000 mg/vial, 175 mg/mL). At this time, the participant's assigned JNJ-63733657 dose in the LTE Treatment Period will be unblinded and the 1000 mg/vial, 175 mg/mL product will continue to be used for the remainder of the LTE Treatment Period.

1.3.6. Schedule of Activities - Long-Term Extension Treatment Period, Continued - Year 3 (Through LTE Week 156)

Period	Long-Term Extension Treatment Period [k,m]												
Week	108	112	116	120	124	128	132	136	140	144	148	152	156
Visit Number	LTE 28[i,j]	LTE 29[i,j]	LTE 30	LTE 31[i,j]	LTE 32[i,j]	LTE 33	LTE 34[i,j]	LTE 35[i,j]	LTE 36	LTE 37[i,j]	LTE 38[i,j]	LTE 39[i,j]	LTE 40
Visit Window (Days ±)	7	7	7	7	7	7	7	7	7	7	7	7	7
Study Intervention													
Administer study intervention (IV)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Evaluations													
Physical examination[b]						X							X
Neurological examination[b]						X							X
Weight						X							X
Vital signs (supine and standing BP, pulse)[b]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (triplicate)[b,h]						X							X
Temperature (tympanic)[b]	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests													
Hematology, chemistry[b, c, d]	X	X	X	X	X	X	X	X	X	X	X	X	X
CRP[b]	X	X	X	X	X	X	X	X	X	X	X	X	X
INR[b]	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[b]						X							X
Clinical Scales													
C-SSRS (since last visit)[b]						X							X[e]
ADCS-ADL-MCI[b]						X							X[e]
Amsterdam IADL[b]			X						X				
CDR[b]						X							X[e]
NPI[b]						X							X[e]
RUD-Lite[b]						X							X[e]
QOL-AD[b]													X[e]
Cognitive Measures													
RBANS[b]			X						X				
ADAS-Cog13[b]						X							X[e]
Imaging													
Tau PET													X[f]
MRI[g]						X							X
PK and Immunogenicity													
Blood sample collection[b]						X							X
CSF sample collection[l]													X

Period	Long-Term Extension Treatment Period [k,m]												
Week	108	112	116	120	124	128	132	136	140	144	148	152	156
Visit Number	LTE 28[i,j]	LTE 29[i,j]	LTE 30	LTE 31[i,j]	LTE 32[i,j]	LTE 33	LTE 34[i,j]	LTE 35[i,j]	LTE 36	LTE 37[i,j]	LTE 38[i,j]	LTE 39[i,j]	LTE 40
Visit Window (Days ±)	7	7	7	7	7	7	7	7	7	7	7	7	7
PD and Biomarkers													
Blood sample collection[b]						X							X
CSF sample collection[l]													X
Ongoing Participant Review													
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X

a. The study intervention should not be administered until review of predose ALT and AST results. Dosing is not permitted for any participant with treatment-emergent predose ALT>1.5xULN or AST≥3xULN. Study intervention will be administered under the supervision of the investigator or his/her designee in a designated hospital/clinic setting. If predose ALT and AST values are not available on the day of the clinic visit, dosing may occur on a separate day (within 14 days of the predose ALT and AST). In this case, predose vital signs, and recording of AEs and concomitant medications must be repeated on the same day of dosing. A physician must be immediately available at the site at all times during the administration of study intervention. A single dose of JNJ-63733657 will be administered at a constant rate over approximately 60 minutes, followed by an IV flush, as described in the IPPI. The infusion duration may be increased if issues of tolerability are encountered.

b. Predose. "Predose" for hematology, chemistry, CRP, and INR is defined as within 14 days of the study intervention administration visit to allow participants to have tests performed prior to the scheduled visit, if preferred. If testing is performed prior to the visit day, the study partner is not required to accompany the participant to the location of blood collection. All other predose assessments are to be performed on the day of the regular visit, unless otherwise specified per protocol.

c. Chemistry in fasting condition when feasible. Includes fractionated bilirubin (if available). Refer to Appendix 2 for more information regarding Clinical Laboratory Tests.

d. Predose ALT and AST results must be reviewed prior to each study intervention administration. Dosing is not permitted for any participant with treatment-emergent predose ALT>1.5xULN or AST≥3xULN (tested within 14 days prior to dosing). Refer to Appendix 7 for hepatic safety monitoring assessments, including stopping criteria and guidance regarding the management of abnormal hepatic chemistry results.

e. Prior to lumbar puncture, if participating in optional lumbar puncture.

f. The window for tau PET scan at this visit is ±4 weeks. If the tau PET cannot be scheduled within this timeframe (eg, due to operational challenges), then tau PET window may be extended only with medical monitor approval.

g. If MRI is done on the same day as cognitive or other assessments (except lumbar puncture), then the MRI should be performed last prior to administration of study intervention. If not performed on the same day, then MRI should be performed within 7 days prior to the visit (ie, -7 day visit window). At visits that include both MRI and lumbar puncture, the MRI should be performed prior to lumbar puncture to minimize any impact of the lumbar puncture procedure on the MRI data.

h. ECGs performed predose in triplicate at approximately 1-minute intervals, at approximately the same time of day.

i. It is preferred the study partner accompany the participant to these visits even though no study partner assessments are planned. However, if the study partner is unable to attend, then another individual (who is at least 18 years old or a legal adult) may accompany the participant. In such cases, the study partner must be available for a telephone contact with the site (within the permitted visit window) to collect information regarding AEs and concomitant therapies.

j. If it is determined that a participant will not be administered study intervention at this visit (eg, due to predose ALT>1.5xULN or AST≥3xULN), then this visit may be done remotely and only AEs and concomitant therapies should be recorded. Other missed assessments (eg, blood sample collection) should be performed at the next clinic visit.
k. Study procedures should be performed at the study site (not remotely) unless otherwise specified in the protocol. Guidance regarding modifications to study procedures due to a natural disaster/major disruption/pandemic are described in Appendix 6.
l. CSF sample by single lumbar puncture for participants who opt for lumbar puncture. If lumbar puncture is done on the same day as cognitive or other assessments, the lumbar puncture should be performed last prior to the administration of study intervention. If not performed on the same day, the lumbar puncture should be performed within 7 days prior to the visit (ie, -7 day visit window). At visits that include both MRI and lumbar puncture, the MRI should be performed prior to lumbar puncture to minimize any impact of the lumbar puncture procedure on the MRI data.
m. Visits which include MRI, PET, predose clinical laboratory safety tests (hematology, chemistry, CRP, INR), and/or dose administration allow flexibility regarding when these study procedures can be performed for a visit (refer to footnotes above).

1.3.7. Schedule of Activities - Long-Term Extension Treatment Period, Continued - Year 4 Through End of Study

Period	Long-Term Extension Treatment Period [q,t]			
Week	160, 164, 168, 172, etc	180, 204, 228, 252, etc	208, 260, 312, 364, etc	End of LTE Treatment Period[a]
Visit Number	LTE 41,[o,p] LTE 42,[o,p] LTE 43,[o,p] LTE 44,[o,p] etc	LTE 46,[o] LTE 52,[o] LTE 58,[o] LTE 64,[o] etc	LTE 53, LTE 66, LTE 79, LTE 92, etc	
Frequency	Every 4 Weeks	Every 24 Weeks	Every 52 Weeks	
Visit Window (Days ±)	7	7	7	
Study Intervention				
Administer study intervention (IV)[b]	X			
Safety Evaluations				
Physical examination[c]		X		X[s]
Neurological examination[c]		X		X[s]
Weight		X		X[s]
Vital signs (supine and standing BP, pulse)[c]	X			X
12-lead ECG (triplicate)[c,n]			X	X[s]
Temperature (tympanic)[c]	X			X
Clinical Laboratory Tests				
Hematology, chemistry[c, d, e]	X			X[s]
CRP[c]	X			
INR[c]	X			
Urinalysis[c]		X		X[s]
Clinical Scales				
C-SSRS (since last visit)[c]			X[f]	X[f, s]
ADCS-ADL-MCI[c]			X[f]	X[f, g]
Amsterdam IADL[c]			X[f, l]	X[f, g]
CDR[c]			X[f]	X[f, g]
NPI[c]			X[f]	X[f, g]
RUD-Lite[c]			X[f]	X[f, g]
QOL-AD[c]			X[f]	X[f, g]
Cognitive Measures				
RBANS[c]			X[f,m]	X[f, g]
ADAS-Cog13[c]			X[f]	X[f, g]
Imaging				
Tau PET[i]			X[l]	X[h]
MRI[j]			X[l]	X[h]

Period	Long-Term Extension Treatment Period [q,t]			
Week	160, 164, 168, 172, etc	180, 204, 228, 252, etc	208, 260, 312, 364, etc	End of LTE Treatment Period[a]
Visit Number	LTE 41,[o,p] LTE 42,[o,p] LTE 43,[o,p] LTE 44,[o,p] etc	LTE 46,[o] LTE 52,[o] LTE 58,[o] LTE 64,[o] etc	LTE 53, LTE 66, LTE 79, LTE 92, etc	
Frequency	Every 4 Weeks	Every 24 Weeks	Every 52 Weeks	
Visit Window (Days ±)	7	7	7	
PK and Immunogenicity				
Blood sample collection[c]			X	X[s]
CSF sample collection[r]			X[l]	X[k]
PD and Biomarkers				
Blood sample collection[c]			X	X[s]
CSF sample collection[r]			X[l]	X[k]
Ongoing Participant Review				
Concomitant therapy	X			X
Adverse events	X			X

a. Performed as close as possible to the last dose of study intervention.
b. The study intervention should not be administered until review of predose ALT and AST results. Dosing is not permitted for any participant with treatment-emergent predose ALT>1.5xULN or AST≥3xULN. Study intervention will be administered under the supervision of the investigator or his/her designee in a designated hospital/clinic setting. If predose ALT and AST values are not available on the day of the clinic visit, dosing may occur on a separate day (within 14 days of the predose ALT and AST). In this case, predose vital signs, and recording of AEs and concomitant medications must be repeated on the same day of dosing. A physician must be immediately available at the site at all times during the administration of study intervention. A single dose of JNJ-63733657 will be administered at a constant rate over approximately 60 minutes, followed by an IV flush, as described in the IPPI. The infusion duration may be increased if issues of tolerability are encountered.
c. Predose. "Predose" for hematology, chemistry, CRP, and INR is defined as within 14 days of the study intervention administration visit to allow participants to have tests performed prior to the scheduled visit, if preferred. If testing is performed prior to the visit day, the study partner is not required to accompany the participant to the location of blood collection. All other predose assessments are to be performed on the day of the regular visit, unless otherwise specified per protocol.
d. Chemistry in fasting condition when feasible. Includes fractionated bilirubin (if available). Refer to Appendix 2 for more information regarding Clinical Laboratory Tests.
e. Predose ALT and AST results must be reviewed prior to each study intervention administration. Dosing is not permitted for any participant with treatment-emergent predose ALT>1.5xULN or AST≥3xULN (tested within 14 days prior to dosing). Refer to Appendix 7 for hepatic safety monitoring assessments, including stopping criteria and guidance regarding the management of abnormal hepatic chemistry results.
f. Prior to lumbar puncture, if participating in optional lumbar puncture.
g. If not done in past 24 weeks.
h. If not done in past 52 weeks.
i. The window for tau PET scan at this visit is ±4 weeks. If the tau PET cannot be scheduled within this timeframe (eg, due to operational challenges), then tau PET window may be extended only with medical monitor approval.
j. If MRI is done on the same day as cognitive or other assessments (except lumbar puncture), the MRI should be performed last, prior to administration of study intervention. If not performed on the same day, the MRI should be performed within 7 days prior to the visit (ie, -7 day visit window). At visits that

include both MRI and lumbar puncture, the MRI should be performed prior to lumbar puncture to minimize any impact of the lumbar puncture procedure on the MRI data.

k. If not done in past 104 weeks.
l. Collected at Year 5 and Year 7. Not collected at Year 4 or Year 6.
m. The RBANS is only conducted at Years 6 and 8 (ie, not every 52 weeks). The RBANS and ADAS-Cog13 cannot be performed at the same visit. Therefore, at Years 5 and 7, the RBANS is performed 3 months after the ADAS-Cog13 (ie, in Years 6 and 8, respectively).
n. ECGs performed predose in triplicate at approximately 1-minute intervals, at approximately the same time of day.
o. For visits with no study partner assessments planned: It is preferred the study partner accompany the participant to these visits even though no study partner assessments are planned. However, if the study partner is unable to attend, then another individual (who is at least 18 years old or a legal adult) may accompany the participant to these visits. In such cases, the study partner must be available for a telephone contact with the site (within the permitted visit window) to collect information regarding AEs and concomitant therapies.
p. For visits with no clinical scales or cognitive measures assessments planned: If it is determined that a participant will not be administered study intervention at this visit (eg, due to predose ALT>1.5xULN or AST≥3xULN), then this visit may be done remotely and only AEs and concomitant therapies should be recorded. Other missed assessments (eg, blood sample collection) should be performed at the next clinic visit.
q. Study procedures should be performed at the study site (not remotely) unless otherwise specified in the protocol. Guidance regarding modifications to study procedures due to a natural disaster/major disruption/pandemic are described in Appendix 6.
r. CSF sample by single lumbar puncture for participants who opt for lumbar puncture. If lumbar puncture is done on the same day as cognitive or other assessments, the lumbar puncture should be performed last prior to the administration of study intervention. If not performed on the same day, the lumbar puncture should be performed within 7 days prior to the visit (ie, -7 day visit window). At visits that include both MRI and lumbar puncture, the MRI should be performed prior to lumbar puncture to minimize any impact of the lumbar puncture procedure on the MRI data.
s. If not done in past 4 weeks.
t. Visits which include MRI, PET, predose clinical laboratory safety tests (hematology, chemistry, CRP, INR), and/or dose administration allow flexibility regarding when these study procedures can be performed for a visit (refer to footnotes above).

1.3.8. Schedule of Activities - Follow-up Period

Follow-up Period [e,f]			
Days After Last Dose of Study Intervention	**30 Days**	**60 Days**	**90 Days**
Visit Number	**Follow-up Visit 1[a]**	**Follow-up Visit 2[a]**	**Follow-up Visit 3[a]**
Visit Window (Days ±)	**7**	**7**	**7**
Safety Evaluations			
Physical examination			X
Neurological examination			X
Weight			X
Vital signs (supine and standing BP, pulse)	X	X	X
12-lead ECG (triplicate)[b]			X
Temperature (tympanic)	X	X	X
Clinical Laboratory Tests			
Hematology, chemistry[c]	X	X	X
CRP	X	X	X
INR	X	X	X
Urinalysis			X
Clinical Scales			
C-SSRS (since last visit)			X
Immunogenicity			
Blood sample collection			X[d]
Ongoing Participant Review			
Concomitant therapy	X	X	X
Adverse events	X	X	X

a. Safety follow-up visits are not required for participants who discontinue double-blind study intervention but remain in the Double-blind Treatment Period and continue to perform study visits (without study intervention administration) for at least 90 days after the last dose of study intervention. If a participant discontinues the LTE Treatment Period and will receive a dose of the commercially available product within 30 days, follow-up visits are not required.
b. ECGs performed in triplicate at approximately 1-minute intervals, at approximately the same time of day.
c. Chemistry in fasting condition when feasible. Includes fractionated bilirubin (if available). Refer to Appendix 2 for more information regarding Clinical Laboratory Tests.
d. For immunogenicity only.
e. Study procedures should be performed at the study site (not remotely) unless otherwise specified in the protocol. Guidance regarding modifications to study procedures due to a natural disaster/major disruption/pandemic are described in Appendix 6.
f. It is preferred the study partner accompany the participant to these visits even though no study partner assessments are planned. However, if the study partner is unable to attend, then another individual (who is at least 18 years old or a legal adult) may accompany the participant. In such cases, the study partner must be available for a telephone contact with the site (within the permitted visit window) to collect information regarding AEs and concomitant therapies.

2. INTRODUCTION

AD is a fatal neurodegenerative disease that is manifested by progressive cognitive deficits including memory loss followed by loss of independent function as well as neuropsychiatric symptoms such as apathy, depression, anxiety, agitation and psychosis. Worldwide, it is estimated that 50 million people are living with AD (Alzheimer's Association 2022a), and AD is the 6th leading cause of death in the United States (Alzheimer's Association 2022b). There are limited disease-modifying therapies for AD, and the prevalence of AD is estimated to grow to 76 million worldwide by 2030 (Alzheimer's Association 2022a). Age is the greatest risk factor for AD and with the increasing number of elderly in the global population, AD is a major medical and economic concern.

Extracellular amyloid plaques and intracellular tau tangles are pathological hallmarks of AD. According to the amyloid cascade hypothesis (Selkoe 2016), Aβ accelerates tau aggregation and propagation, leading to inflammation and ultimately synaptic and neuronal loss, and progressing clinically to dementia. Current standard of care therapies for AD treat the symptoms of the disease and include AChEIs and/or memantine to slow cognitive impairment, as well as treatments to control the behavioral problems frequently associated with AD, such as antidepressants or antipsychotics.

Prevention of Aβ and tau accumulation and aggregation are being explored as potentially disease-modifying AD treatments. In recent years, many amyloid targeting therapies have failed in late stage clinical trials (Doody 2013; Doody 2014; Egan 2019; Henley 2019; Honig 2018; Roche 2019; Salloway 2014). These negative trials have informed future trials in the following ways: (1) clinical diagnosis alone is inadequate and results in heterogeneous study populations, (2) it is important to ensure the study population contains the pathology targeted by the intervention but, while necessary, this is not sufficient since (3) it is possible that, depending on the MOA of the intervention, the pathology may be too advanced for the intervention to have appreciable effects. These important learnings lead to the conclusion that future studies should consider the MOA of an intervention and include biomarker-defined populations that contain the pathology targeted at the correct pathophysiologic and clinical stage, as far as currently operationally feasible.

Recent discoveries enabled by ATN biomarkers show that pathological changes in AD begin 10 to 20 years before the onset of MCI (Bateman 2012; Villemagne 2013). During this "preclinical stage" (Sperling 2011), progression of AD pathophysiology can be tracked with CSF and imaging biomarkers that correlate temporally and anatomically with cognitive decline. Aβ is considered the earliest detectable pathological change in AD. Patients with biomarker (CSF or PET imaging) evidence of pathologic Aβ levels are considered to have an AD pathologic change and to be on the AD continuum (Jack 2018). The clinical spectrum of AD severity can be described as a continuum that spans from preclinical AD (Aβ positive, cognitively unimpaired) to prodromal AD/MCI due to AD (Aβ positive, MCI), and mild, moderate, and severe dementia (Aβ positive, cognitive and functional impairment).

Cognitively unimpaired individuals with elevated brain beta amyloid plaque perform worse than those without beta amyloid accumulation (Mormino 2017). However, in symptomatic AD stages, cognitive decline is less associated with brain amyloid burden but correlated more strongly with

pathologic tau in the form of intracellular NFT (aggregated tau) on autopsy or measured with tau PET (Nelson 2012; Pontecorvo 2017).

Braak and Braak first proposed neuropathologic staging of AD (Braak stages I-VI) using NFT distribution in autopsy specimens and similar patterns have been observed in living patients using tau PET (Braak 1991; Schwarz 2016). In general, the more widespread the NFTs, the more severe the clinical stage of AD.

Nonclinical models have shown that extracellular phosphorylated tau seeds (p-tau, aggregated tau) can induce abnormal tau accumulation (NFTs) or "tauopathy" in neurons (Mohamed 2013). A leading hypothesis is that tauopathy may propagate throughout the brain in a prion-like fashion from one brain region to another. This propagation process is hypothesized to involve externalization of tau seeds that can be taken up by nearby neurons and induce further tauopathy. This propagation of tauopathy could be interfered with using tau immunotherapy and this is currently considered a promising approach with several clinical programs underway.

JNJ-63733657 is being developed by Janssen Research & Development for the treatment of AD, namely the prevention or slowing of clinical (cognitive and functional) decline. JNJ-63733657 is a humanized IgG1/κ monoclonal anti-tau antibody. JNJ-63733657 binds with high affinity to PHF-tau, consisting of p-tau, and binds very weakly to non-p-tau. Specifically, JNJ-63733657 binds to p-tau at the phosphorylation site "p217+tau". This is in contrast to the N-terminal anti-tau monoclonal antibodies that have recently failed in Phase 2 (AC Immune 2020; Florian 2023; Fleisher 2022). It is possible that binding to the N-terminus disadvantages these antibodies since this region is commonly cleaved by proteases, leaving less tau available for the antibodies to bind. JNJ-63733657 has demonstrated reduction of tau seeding in both an in vitro cellular depletion study and an in vivo preclinical animal model following peripheral injection.

This Phase 2 study for JNJ-63733657 will assess the possible slowing of clinical (cognitive and functional) decline seen in prodromal AD and mild AD dementia (Early AD). In addition, effects of JNJ-63733657 on the accumulation of tau, as measured by tau PET, will also be explored. Additional efficacy, safety, biomarker, PK, immunogenicity, and health outcomes data will be obtained in the LTE Treatment Period.

For the most comprehensive nonclinical and clinical information regarding JNJ-63733657, refer to the latest version of the IB for JNJ-63733657.

Throughout the protocol:

- The term "study intervention" refers to JNJ-63733657 and placebo in the Double-blind Treatment Period, and refers to JNJ-63733657 in the LTE Treatment Period, as defined in Section 6.1, Study Interventions Administered.
- The term "JNJ-63733657" refers to the International Nonproprietary Name "posdinemab."
- The term "sponsor" refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.
- The term "participant" refers to the common term "subject."

- The term "Early AD" refers to the study population of prodromal AD and mild AD dementia (CDR-GS=0.5).
- The term "iADRS" refers to the integrated AD Rating Scale for Mild Cognitive Impairment (iADRS-MCI) in this study.

2.1. Study Rationale

Based on learnings from past AD disease-modifying trials, this study was designed to match the MOA of the intervention to the population most likely to respond. The study will evaluate whether JNJ-63733657 can slow clinical (cognitive and functional) decline in participants with Early AD with evidence of elevated brain tau (T+) and assess its safety and tolerability. To explore whether the study intervention can slow propagation of pathologic tau seeds, biomarkers such as tau PET will be used to measure tau propagation. Additionally, the study will explore the effect of slowing tau propagation on downstream neurodegeneration by measuring biomarkers such as NfL in blood, CSF, and brain volumes (using volumetric MRI). Additional efficacy, safety, biomarker, PK, immunogenicity, and health outcomes data will be obtained in the LTE Treatment Period.

These data may inform whether JNJ-63733657 has an effect in Early AD, and further help to identify the population most responsive to treatment based on baseline biomarker signature (eg, tau burden) in the disease spectrum.

The study population will be identified by tau PET to ensure presence of the target pathology (eg, pathologic tau).

In order to most efficiently identify this population and avoid unnecessary radiation exposure, a plasma biomarker (within a prespecified eligibility range) will be used to screen for individuals within the desired clinical stages for evidence suggestive of elevated brain tau (T+ status). The presence of pathologic tau will be confirmed for all included participants using tau PET as detailed in a separate Imaging Manual/Charter. Participants with inadequate (ie, too little) or widespread (ie, too much) tau, as defined in the Imaging Manual/Charter, will be excluded. Recent studies (Fleisher 2018; Therriault 2023) have demonstrated strong association of positive tau PET with elevated amyloid levels on amyloid PET. Therefore, amyloid status will not be confirmed in screening but will be measured in all randomized participants by a plasma assay.

Overall, selecting participants using tau PET will ensure a similar pathophysiologic stage in the clinically defined Early AD participants, increase the likelihood of clinical and biomarker progression, decrease heterogeneity and increase the probability of benefit based upon MOA (ie, excluding participants with widespread tau who may not benefit from prevention of tau propagation).

2.2. Background

Nonclinical Studies

Pharmacokinetics in Animals

JNJ-63733657 demonstrated linear PK with C_{max} and AUC_{∞} increasing in an approximately dose-proportional manner in cynomolgus monkey, marmosets, and Sprague Dawley rats following IV administration. In Göttingen minipigs, JNJ-63733657 exposures increased less than

dose-proportionally. Anti-drug antibodies were detected in the repeat-dose GLP studies. CSF/serum concentration ratios ranged from 0.055% to 0.177% in cynomolgus monkeys, from 0.07% to 0.14% in rats, and from 0.20% to 0.25% in minipigs, consistent with CSF distribution profiles of humanized IgG monoclonal antibodies.

Safety Pharmacology

No JNJ-63733657-related effects were noted on cardiovascular, respiratory, or CNS parameters evaluated during the 6-week GLP repeat-dose toxicity study with a 6-week recovery period conducted in Göttingen minipigs, nor in the 4-week non-GLP repeat-dose tolerability study in cynomolgus monkeys.

Toxicology

The toxicologic profile of JNJ-63733657 was characterized in repeat-dose IV studies in Sprague Dawley rats, Göttingen minipigs, and cynomolgus monkeys of up to 26, 6, and 4 weeks duration, respectively, and also included assessments of safety pharmacology endpoints and local tolerance. In vitro studies evaluated human tissue cross-reactivity, human serum compatibility, and hemolytic potential. JNJ-63733657 binds to a phosphorylated variant (p217+) of the tau protein which is present in rats and minipigs and not cynomolgus monkeys; thus, pivotal GLP repeat-dose toxicology studies were conducted in rats and minipigs only. There were no adverse effects of IV administration of JNJ-63733657 in rats, minipigs, or cynomolgus monkeys. Therefore, the no observed adverse effect level in the repeated dose studies was the highest dose tested: 200 mg/kg/week in minipigs and cynomolgus monkeys (no histopathology), and 300 mg/kg/week in rats. There were no JNJ-63733657-related effects on male and female fertility in rats along with absence of effects on maternal or fetal development when tested up to 300 mg/kg/week in rats or rabbits. There was no membrane specific binding of JNJ-63733657 to human tissues; JNJ-63733657 was compatible with human serum and exhibited no hemolytic potential. JNJ-63733657 was well tolerated in a subcutaneous local tolerance study when tested in male Göttingen minipigs at single doses of 207 and 700 mg and in an intermittent 7-day subcutaneous local tolerance study in female Göttingen minipigs at 5.9 mL (~1,033 mg) per injection site using auto-injectors (IB Posdinemab 2025).

Clinical Studies

Three Phase 1 clinical trials have been completed (defined as a study for which a final Clinical Study Report is available) in humans: 63733657EDI1001, 63733657EDI1002, and 63733657ALZ1001. Refer to the IB for more details of these studies.

Study 63733657EDI1001 was a 2-part randomized, placebo-controlled, double-blind, SAD/MAD study to investigate the safety and tolerability, PK, and PD of JNJ-63733657 in healthy participants and in participants with prodromal or mild AD. Part 1 refers to the SAD part of the study and Part 2 refers to the MAD part of the study. Both parts have been completed. Participants in the SAD cohorts were healthy participants aged 55 to 75 years, dosed with JNJ-63733657 at a dosage of 1, 3, 10, 30, or 60 mg/kg, or placebo. Participants in the MAD cohorts were healthy participants or participants with prodromal or mild AD aged 55 to 80 years, dosed with JNJ-63733657 at a dosage of 5, 15, 30, or 50 mg/kg, or placebo.

In Part 1 (SAD study), a total of 30 healthy participants received JNJ-63733657 and 10 healthy participants received placebo. In Part 2 (MAD study), a total of 16 healthy participants and 13 participants with prodromal or mild AD have received either JNJ-63733657 or placebo.

Study 63733657EDI1002 was a randomized, placebo-controlled, double-blind, SAD study to investigate the safety, tolerability, PK, and PD of JNJ-63733657 in healthy Japanese participants aged 55 to 75 years. Participants were dosed with JNJ-63733657 at a dosage of 3, 15, or 60 mg/kg (N=18) or placebo (N=6).

Study 63733657ALZ1001 was an open-label, single-dose study in healthy Chinese participants to evaluate the PK, safety, tolerability, and immunogenicity of a single dose of JNJ-63733657. In Study 63733657ALZ1001, a total of 10 healthy Chinese participants aged 56-69 years received a single dose of JNJ-63733657.

Study 63733657EDI1003 completed database lock on 11 June 2025 for safety and 20 June 2025 for PK. This study is a 3-part, randomized, open-label, single-center, single-dose study to assess the safety, tolerability, bioavailability, and PK of JNJ-63733657 administered as a subcutaneous infusion using a syringe pump and as an IV infusion in healthy adult participants. This study also compared the PK, safety, and tolerability of the 500 mg/vial, 50 mg/mL and 1000 mg/vial, 175 mg/mL products in healthy adult participants.

Pharmacokinetics

In the SAD part of study 63733657EDI1001, a linear PK was observed in serum following single IV dose administration of JNJ-63733657 from 1-60 mg/kg. The C_{max} and AUC were approximately dose-proportional in the tested dose range. The mean serum $t_{1/2}$ ranged between 18.1 days and 26.4 days for all cohorts and the CSF/serum ratio ranged between 0.191% and 0.450% for all cohorts. In the MAD part of study 63733657EDI1001, a linear PK was observed in serum from 5-50 mg/kg for both AD participants and healthy participants. The mean serum $t_{1/2}$ ranged between 18.3 days and 27.1 days after the third IV dose, which is similar to Part 1. The mean serum ratio of C_{max} of the third and first dose ranged between 1.15 and 1.26 and was comparable for all cohorts. The mean serum ratio of AUC_{τ} of the third and first dose ranged between 1.39 and 1.59 and was comparable for all cohorts. CSF/serum ratio ranged between 0.164% and 0.401% for all cohorts across all sampling points and was comparable for all cohorts.

In a separate Japanese Phase 1 SAD study (63733657EDI1002), serum concentrations after single IV administration of 3, 15, and 60 mg/kg JNJ-63733657 were comparable between healthy Japanese and non-Japanese participants.

In Study 63733657ALZ1001, after administration of a single 60 mg/kg IV dose of JNJ-63733657 in healthy Chinese volunteers at 60 mg/kg, serum concentrations were comparable between healthy Chinese and non-Chinese participants in the single-dose studies 63733657EDI1001 and 63733657EDI1002.

Refer to the IB for more details on the completed Phase 1 studies described above and the PK results from the 63733657EDI1003 study that completed database lock on 20 June 2025.

Pharmacodynamics

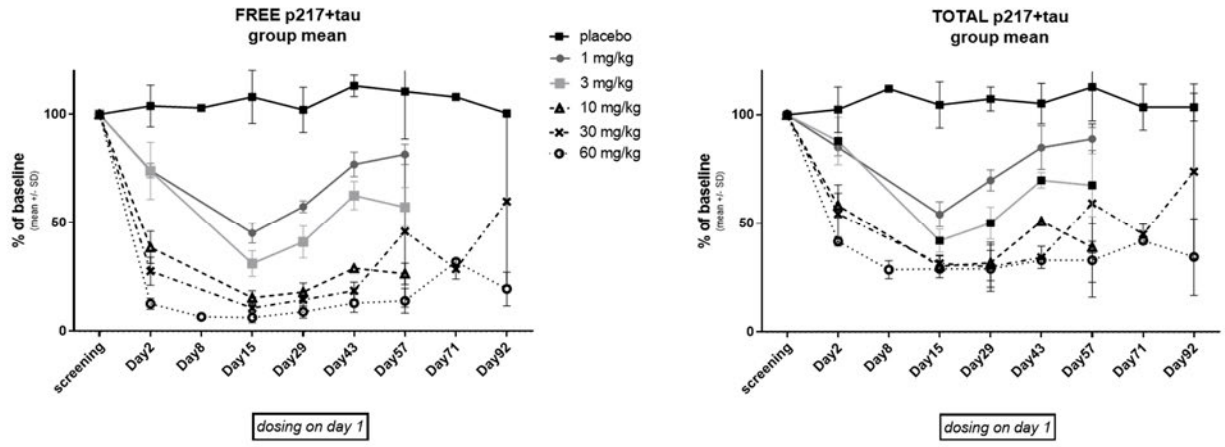
The core epitope of tau recognized by JNJ-63733657 contains phosphorylation at amino acid 217, with potentially other phosphorylation sites nearby. This target is termed "p217+tau". Pharmacodynamic effects in the SAD/MAD study were assessed by quantifying changes in CSF p217+tau, free (that not complexed with JNJ-63733657) and total. The PD response of antibody binding to p217+tau in CSF is used as an indicator of the true target engagement of the tau seed (aggregated PHF-tau) in the interstitial fluid, which cannot be directly measured in humans.

SAD Part 1 of Study 63733657EDI1001

CSF free p217+tau levels from the SAD cohort in healthy participants showed that all 30 participants receiving JNJ-63733657 exhibited reductions in free p217+tau, while all 10 participants receiving placebo exhibited stable free p217+tau levels, illustrating epitope engagement (Figure 3, left panel). The maximum reduction was seen at Day 8 to 15, then began to rebound but did not return to baseline by Day 57. The percent of baseline total p217+tau in each dose group at Day 15 was: placebo = 105%, 1 mg/kg = 54%, 3 mg/kg = 42%, 10 mg/kg = 30%, 30 mg/kg = 32%, and 60 mg/kg = 29% (see Figure 3). While the baseline p217+tau concentration was variable amongst participants (0.4-4.5 pg/mL), all participants in a given cohort exhibited a similar percent reduction in p217+tau. The reduction in total p217+ tau suggests clearance.

In summary, JNJ-63733657 reduced levels of free and total p217+tau in a dose-dependent manner, while not significantly impacting the levels of other tau species (data not shown). These data suggest JNJ-63733657 specifically affects levels of tau containing the p217+tau epitope and demonstrates epitope engagement in the CSF.

Figure 3: Dose-dependent Reductions (Mean ±SD) in CSF Free and Total p217+tau Following a Single IV Dose of JNJ-63733657 (Placebo or 1-60 mg/kg) in Healthy Participants



MAD Part 2 of Study 63733657EDI1001

Following multiple dose administration in AD participants (15 mg/kg and 30 mg/kg) and healthy participants (5 mg/kg and 50 mg/kg), JNJ-63733657 dose-dependently decreased free and total p217+tau in CSF; the mean levels were reduced over at least 85 days (28 days after the last dose). There were dose-dependent reductions in free and total p217+tau at all postdose timepoints

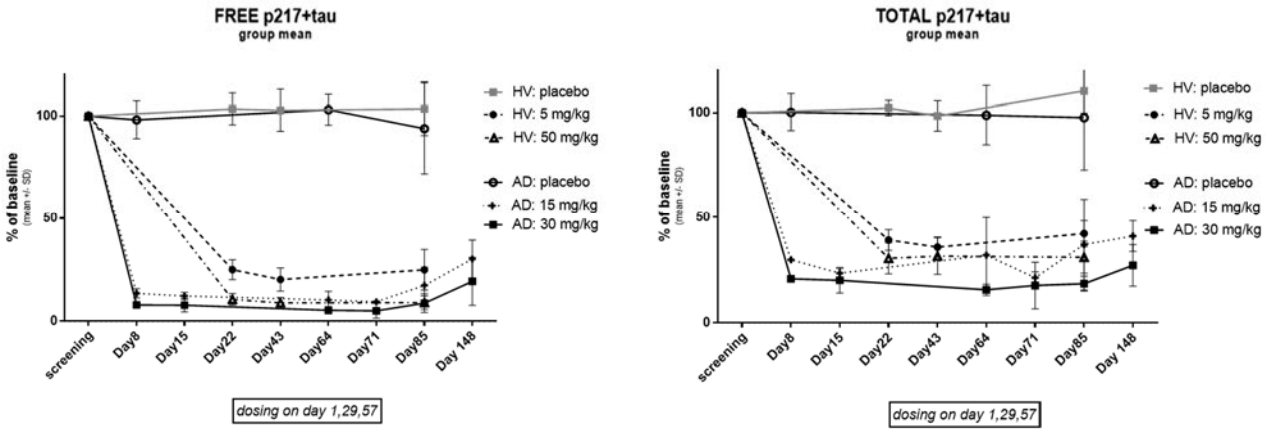
evaluated (Day 8 up to Day 85 or Day 148; Figure 4) whereas the placebo-treated participants had stable levels of p217+tau.

The percent reduction (% of baseline) was relatively consistent within each cohort, and dose-dependent and sustained decreases in free and total CSF p217+tau were observed. With monthly dosing, no rebound in CSF p217+tau level was observed over at least 85 days (28 days after the last dose), suggesting sustained maximal impact of JNJ-63733657. The percent of baseline total CSF p217+tau in each dose group at Day 71 or Day 85 was: HV placebo = 110%, HV 5 mg/kg = 42%, HV 50 mg/kg = 31%, AD placebo = 98%, AD 15 mg/kg = 29%, AD 30 mg/kg = 18% (Figure 4). The reduction in total p217+ tau suggests clearance.

Despite higher baseline levels of p217+tau in AD participants, the percent reduction of p217+tau by JNJ-63733657 was comparable to that seen in healthy participants (Figure 4).

No JNJ-63733657-induced change was seen in plasma neurofilament light protein.

Figure 4: Dose-dependent Reductions (Mean ±SD) in CSF Free and Total p217+tau Following Multiple IV Doses of JNJ-63733657 in Healthy Participants (5 mg/kg and 50 mg/kg) and AD Participants (15 mg/kg and 30 mg/kg)



Study 63733657EDI1002

Pharmacodynamic effects of JNJ-63733657 in healthy Japanese participants were explored by quantifying changes in CSF p217+tau (total and free), total Tau, and pTau181 using the same assays that were utilized in Study 63733657EDI1001.

Dose-dependent reductions of free and total p217+ tau in CSF were observed. At Day 15, the total p217+tau was reduced to 50%, 36%, and 35% of the baseline value for JNJ-637336573 3 mg/kg, 15 mg/kg, and 60 mg/kg group, respectively. These effects were comparable to non-Japanese (Study 63733657EDI1001) participants.

Refer to the IB for more details on the completed Phase 1 studies described above, and the PD results from the 63733657EDI1003 study that completed database lock on 20 June 2025.

Immunogenicity

In Study 63733657EDI1001, 11 out of 53 participants (8 in Part 1 and 3 in Part 2) were positive for treatment-emergent anti-drug antibodies, of which 2 had a highest peak titer of 1:360.

In Study 63733657EDI1002, 1 out of 18 participants treated with JNJ-63733657 (3 mg/kg dose group) was positive for treatment-emergent anti-drug antibodies, with a peak titer of 1:23.

In Study 63733657ALZ1001, among the 10 participants who received JNJ-63733657, 4 participants (40.0%) were considered positive for anti-drug antibodies to JNJ-63733657 post-dose. Three participants had a peak titer of 1:22.5 and 1 participant had a peak titer of 1:360. The participant who had the peak titer of 1:360 also showed faster clearance of the drug, similar as what was observed in EDI1001 with the same titer. Other participants with marginal anti-drug antibodies showed similar PK.

Refer to the IB for more details on the completed Phase 1 studies described above, and the immunogenicity results from the 63733657EDI1003 study that completed database lock on 20 June 2025.

Safety Studies

Study 63733657EDI1001

Part 1

There were no deaths reported in Part 1. Two SAEs ("stress related hypertension" and "suspected post spinal headache") were reported for 1 participant receiving placebo.

TEAEs reported by >10% of the 30 participants receiving JNJ-63733657 included post lumbar puncture syndrome (33.3% and 20.0% for JNJ-63733657 and placebo, respectively), headache (30.0% and 30.0%, respectively), hypercholesterolemia (20.0% and 0%, respectively), and nausea (13.3% and 20.0%, respectively).

No clinically significant laboratory (including cholesterol), MRI, or ECG abnormalities were observed in participants treated with JNJ-63733657.

Part 2

There were no deaths or premature discontinuation of participants from the MAD part of study due to AEs. There was 1 SAE of renal neoplasm in 1 participant with AD (15 mg/kg JNJ-63733657). This SAE was considered not related to the study intervention.

TEAEs reported by >10% of participants receiving JNJ-63733657 included headache (JNJ-63733657, 30.4%; placebo, 33.3%), back pain (JNJ-63733657, 21.7%; placebo, 0%), and post lumbar puncture syndrome (JNJ-63733657, 13.0%; placebo, 0%).

Study 63733657EDI1002

There were no deaths, SAEs, or AEs leading to premature termination of study participation in Study 63733657EDI1002.

TEAEs occurred in 4 participants (66.7%) who received placebo and 11 participants (61.1%) who received JNJ-63733657 (4, 3, and 4 participants in the 3, 15, and 60 mg/kg groups, respectively). TEAEs reported by more than 1 participant in any JNJ-63733657 treatment group included nasopharyngitis, gingivitis, and increased CRP. In the placebo group, no AEs occurred in more than 1 participant.

There were no clinically significant abnormalities in vital signs, laboratory tests (including CRP), or ECGs.

Study 63733657ALZ1001

There were no deaths, SAEs or discontinuations due to AEs in Study 63733657ALZ1001. No SAEs were reported. TEAEs occurred in 8 participants (80.0%). Two TEAEs were reported by more than 1 participant: arthralgia and back pain were reported by 2 participants each. No important safety issues were identified. There were no clinically important changes in laboratory values.

Refer to the most recent version of the IB for detailed safety findings on the Phase 1 studies.

Ongoing Studies

In Study 63733657EDI1003 (database lock complete, Clinical Study Report pending), no significant safety findings were reported (IB Posdinemab Edition 8 Addendum 1 2025). The safety and tolerability of the 1000 mg/vial, 175 mg/mL product was acceptable and similar to the safety and tolerability of the 500 mg/vial, 50 mg/mL product.

In the current fully-recruited ongoing Study 63733657ALZ2002 (N=523), one SAE of drug induced liver injury (DILI) that met Hy's Law criteria and 2 SAEs of suspected DILI were reported as of 28 November 2024 (IB Posdinemab 2025). In all 3 cases, the investigators considered the SAEs to be possibly related to blinded study intervention (JNJ-63733657 1000 mg or 3000 mg, or placebo); upon sponsor review of the SAEs, it was determined they met SUSAR criteria. Consequently, increased hepatic safety monitoring procedures have been added to the study protocol. Refer to the IB for more details of these blinded cases.

No other significant safety findings were reported in ongoing Study 63733657ALZ2002 up to the time of this amendment.

2.3. Benefit-Risk Assessment

More detailed information about the known and expected benefits and risks of JNJ-63733657 may be found in the IB.

2.3.1. Risks for Study Participation

JNJ-63733657 is an investigational drug. As reported in Section 2.2, safety data are available from nonclinical studies, as well as from Part 1 (SAD) and Part 2 (MAD) of Phase 1 Study 63733657EDI1001 and also the SAD study conducted in Japan (63733657EDI1002), and in China (63733657ALZ1001). No deaths or discontinuations due to an AE were reported in any participant treated with JNJ-63733657 in the completed Phase 1 studies.

When these clinical trials were completed, no important identified or potential risks attributable to JNJ-63733657 had been determined, and no safety signals had been identified in data from nonclinical studies or published scientific literature.

Ongoing studies: Based on a blinded review of data from this ongoing study (63733657ALZ2002), in December 2023 the sponsor designated DILI as an important potential risk for JNJ-63733657 (IB Posdinemab 2025). The sponsor has observed 17 participants (3.2% of all treated) with ALT

and/or AST elevations ≥3xULN as of 28 November 2024. It is unknown whether these participants with hepatic enzyme elevations are receiving JNJ-63733657 or placebo. The sponsor is providing regular updates to the unblinded IDMC and receives their recommendations on study conduct. All participants have predose ALT and AST values reviewed within 14 days of dosing and no participants with treatment-emergent ALT>1.5xULN or AST≥3xULN are permitted to be dosed. Appendix 7 provides additional hepatic safety monitoring assessments, including liver chemistry stopping criteria and the requirements for follow-up assessments.

All participants will be closely monitored by means of AEs, vital signs, ECGs, physical and neurological examinations, MRI, and clinical laboratory safety tests.

Other hypothetical risks may relate to infusion-related reactions and procedural complaints.

Possible risks associated with lumbar puncture include: procedural pain during insertion of needle, spinal fluid may leak slowly after the lumbar puncture, spinal headache (also called post-dural puncture headache), epidural infection, spinal cord trauma/nerve root trauma, spinal/epidural hematoma, and cerebral herniation. To minimize these possible risks, additional eligibility criteria and other preventive actions are in place. Potential participants with medical conditions contraindicating a lumbar puncture will not be considered for this procedure.

MK-6240 is investigational but it carries no known risks beyond that of other PET tracers (small amount of radiation exposure, risks associated with an IV administration such as bruising and bleeding).

2.3.2. Benefits for Study Participation

No clinical benefit of treatment with JNJ-63733657 has been demonstrated to date, but the MOA indicates a potential for a clinically meaningful effect for participants treated in this study. This includes the potential to slow the underlying pathophysiology of AD and thereby slow its clinical course.

2.3.3. Benefit-Risk Assessment for Study Participation

Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with JNJ-63733657 are justified by the anticipated benefits that may be afforded to symptomatic participants with biomarker-defined AD.

Potential participants will be fully informed of the risks and requirements of the study. Only participants who are able to understand the risks, benefits, and potential AEs, and provide consent voluntarily at the time of screening will be enrolled.

Participants will be informed of their eligibility status based on plasma p217+tau and tau PET during screening. This will involve a discussion of potential risks of worsening of cognitive deficits or other symptoms of AD. Only participants willing and capable of participating in this disclosure process are eligible for participation.

Participants who progress to more advanced clinical stages of AD during the study should be assessed for understanding of potential risks/benefits of participation by the investigator and may continue in the study at the discretion of the investigator.

In addition to potential compound related risks, there may be study procedure related risks (eg, venipuncture, lumbar puncture, ECG, MRI, PET). Overall, these are standard clinical assessments with limited associated risks. MK-6240 is investigational but it carries no known risks beyond that of other PET tracers (small amount of radiation exposure, risks associated with an IV administration such as bruising and bleeding).

3. OBJECTIVES AND ENDPOINTS

3.1. Double-blind Treatment Period

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.
Secondary	
• KEY: 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.
• KEY: To evaluate changes in functional status between participants treated with JNJ-63733657 versus placebo as measured by the ADCS-ADL-MCI.	• Change from baseline on the ADCS-ADL-MCI total score at Week 104.
• 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.
• 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 postbaseline.	• 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 postbaseline through Week 104.
• 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.

Objectives	Endpoints
• 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 SoA (Section 1.3).
• To evaluate the immunogenicity (presence of anti-drug antibodies in serum) of JNJ-63733657 following chronic treatment.	• Anti-drug antibodies in serum at time points per the SoA (Section 1.3).
• 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, C-SSRS, and brain MRI.	• 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 BP and pulse, temperature, and weight. – Brain MRI. – Assessment of suicidality with C-SSRS.
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 p-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.

Objectives	Endpoints
• To explore the potential relationship of biomarkers of tau and neurodegeneration (eg, CSF p-tau, total 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 (eg, CSF p-tau, total tau, NfL, neurogranin, tau PET, volumetric MRI) and change from baseline in clinical decline (eg, 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.

3.2. Long-Term Extension Treatment Period

Exploratory Objectives	Endpoints
• To evaluate the effect of Early Start JNJ-63733657 versus Delayed Start JNJ-63733657 on clinical decline as measured by the iADRS, a composite of cognition and function.	• Change from the double-blind baseline on the iADRS total score at Year 1 of the LTE and to the end of the LTE.
• To evaluate the effect of Early Start JNJ-63733657 versus Delayed Start JNJ-63733657 on cognitive decline as measured by the ADAS-Cog13.	• Change from the double-blind baseline on the ADAS-Cog13 total score at Year 1 of the LTE and to the end of the LTE.
• To evaluate changes in functional status between participants treated with Early Start JNJ-63733657 or Delayed Start JNJ-63733657 as measured by the ADCS-ADL-MCI.	• Change from the double-blind baseline on the ADCS-ADL-MCI total score at Year 1 of the LTE and to the end of the LTE.
• To evaluate the effect of Early Start JNJ-63733657 compared with Delayed Start JNJ-63733657 on cognitive decline, as measured by the RBANS Total Scale Index Score.	• Change from the double-blind baseline on the RBANS Total Scale Index Score at Week 64 of the LTE and to the end of the LTE.
• To evaluate the effect of Early Start JNJ-63733657 compared with Delayed Start JNJ-63733657 as measured by the 5 RBANS indices and 12 subtests comprising the RBANS.	• Change from the double-blind baseline in each of the 5 individual RBANS indices and each of the 12 subtests comprising the RBANS at Week 64 of the LTE and to the end of the LTE.
• To evaluate the effect of Early Start JNJ-63733657 on clinical progression compared with Delayed Start JNJ-63733657 as measured by the CDR-SB.	• Change from the double-blind baseline on the CDR-SB at Year 1 of the LTE and to the end of the LTE.
• To evaluate changes in neuropsychiatric/behavioral status between participants treated with Early Start JNJ-63733657 compared with Delayed Start JNJ-63733657 as measured by the NPI.	• Change from the double-blind baseline in NPI at Year 1 of the LTE and to the end of the LTE.
• To evaluate the effect of Early Start JNJ-63733657 compared with Delayed Start JNJ-63733657 on proportion of participants progressing from CDR-GS	• 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 the double-blind baseline to Year 1 of the LTE and to the end of the LTE.

Exploratory Objectives	Endpoints
0 to 0.5 or higher, 0.5 to 1 or higher, or 1 to 2 or higher, from baseline during the LTE.	
• To evaluate changes in functional status between participants treated with Early Start JNJ-63733657 versus Delayed Start JNJ-63733657 as measured by the Amsterdam IADL.	• Change from the double-blind baseline on the Amsterdam IADL at Week 64 of the LTE and to the end of the LTE.
• To evaluate changes in quality of life between participants treated with Early Start JNJ-63733657 versus Delayed Start JNJ-63733657 as measured by the QOL-AD.	• Change from the double-blind baseline on the QOL-AD at Year 1 of the LTE and to the end of the LTE.
• To evaluate the relationship between dose and PK of JNJ-63733657 on clinical efficacy, safety, and biomarker assessments.	• Modeling of JNJ-63733657 dose and concentrations with efficacy, safety, and biomarkers through Year 1 of the LTE and through the end of the LTE.
• To evaluate the effect of Early Start JNJ-63733657 on the accumulation and/or propagation of tau pathology compared with Delayed Start JNJ-63733657, as measured by tau PET.	• Change from the double-blind baseline in brain tau burden, as measured by tau PET at Year 1 of the LTE and to the end of the LTE.
• To evaluate the effect of Early Start JNJ-63733657 on levels of total, free, and bound p217+tau fragments in CSF compared with Delayed Start JNJ-63733657.	• Change from the double-blind baseline in CSF concentrations of total, free, and bound p217+tau fragments at Year 1 of the LTE and to the end of the LTE.
• To evaluate the effect of Early Start JNJ-63733657 on changes in brain volume as measured by volumetric MRI compared with Delayed Start JNJ-63733657.	• Change from double-blind baseline at Year 1 of the LTE, and to the end of the LTE, in hippocampal, whole brain, and ventricular volume using MRI.
• To explore the effects of Early Start JNJ-63733657 on markers of Aβ pathophysiology and downstream markers of neuronal injury, neurodegeneration, and inflammation in CSF and/or plasma/serum compared with Delayed Start JNJ-63733657.	• Change from double-blind baseline at Year 1 of the LTE, and to the end of the LTE, in markers of Aβ pathophysiology, neuronal injury, neurodegeneration or inflammation as measured in CSF and/or plasma/serum.
• To investigate the long-term 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, C-SSRS, and brain MRI.	• Nature, frequency, severity, and timing of AEs, discontinuations due to AEs, and SAEs during the LTE • Evaluation of other safety parameters in the LTE, 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 BP and pulse, temperature, and weight. – Brain MRI. – Assessment of suicidality with C-SSRS.
• To investigate the long-term safety and tolerability of 500 mg/vial, 50 mg/mL and 1000 mg/vial, 175 mg/mL JNJ-63733657 in participants with Early AD,	• Nature, frequency, severity, and timing of AEs, discontinuations due to AEs, and SAEs separately

Exploratory Objectives	Endpoints
during the LTE, as assessed by AEs, SAEs, early discontinuations due to AEs, ECGs, laboratory evaluations, physical and neurological examinations, vital signs, C-SSRS, and brain MRI.	for the 500 mg/vial, 50 mg/mL and 1000 mg/vial, 175 mg/mL dose periods of the LTE • Evaluation of other safety parameters separately for the 500 mg/vial, 50 mg/mL and 1000 mg/vial, 175 mg/mL dose periods of the LTE, 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 BP and pulse, temperature, and weight. – Brain MRI. – Assessment of suicidality with C-SSRS.
• To evaluate differences in resource utilization (caregiver time, hospitalizations, changes in housing, etc) between participants treated with Early Start JNJ-63733657 versus Delayed Start JNJ-63733657 as measured by RUD-Lite.	• Change from the double-blind baseline in resource utilization (eg, caregiver time, hospitalizations, changes in housing) on RUD-Lite at Year 1 of the LTE and to the end of the LTE.

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESIS

JNJ-63733657 binds to p-tau, and it is hypothesized that it will decrease tau spread and thereby slow clinical decline as measured by the iADRS, a composite of cognition and function, as compared with participants receiving placebo.

4. STUDY DESIGN

4.1. Overall Design

This is a global, multicenter, double-blind, placebo-controlled, randomized, parallel-group study, with an active treatment, dose-blinded LTE Treatment Period, assessing the ability of JNJ-63733657 to slow clinical (cognitive and functional) decline 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, PK, immunogenicity, and health outcomes data will be obtained in the LTE Treatment Period.

Early AD is defined by having an abnormal cognitive performance (CDR-GS=0.5 with memory box score ≥0.5 in the absence of any other evidence of brain disease explaining the cognitive deficit) (Jack 2018), with only mild impairment in daily activities, as well as a biomarker pattern indicative of amyloid and tau pathology:

- Elevated tau (T+) within a prespecified 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 status and will not receive results.

For all enrolled participants, the study will consist of:

- a 90-day (13 weeks) screening period (may be extended up to 120 days with prior approval from the 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 of 13 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 of the Double-blind Treatment Period 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 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 (as specified in the SoA [Section 1.3]). A study partner can be a relative or friend indicated by the participant, who is at least 18 years old, or a legal adult, who may or may not live with the participant, who has at least 10 hours of contact with the participant each week, and who is available for face-to-face contact with the study site staff at each visit requiring study partner attendance. For visits not requiring study partner attendance, if someone other than the study partner (ie, a different legal adult) accompanies the participant to the visit, the study partner must be available for telephone contact by the study site. As participants in this study have MCI or mild dementia (ie, CDR-GS=0.5), and should be capable of providing informed consent at the time of study entry, the primary role of the study partner will be as informant. As judged by the investigator, study partners should have adequate literacy to participate and be judged to have high likelihood of completing the study with the participant. Prior to study assessments, study partners will receive oral and written information about the study and will sign a Study Partner ICF.

After giving initial written informed consent, participants will be screened over a period of up to 90 days to assess their eligibility for the study according to the inclusion and exclusion criteria. To allow for treatment of transient conditions, laboratory retesting, scheduling of MRI and tau PET, and/or operational delays, the Screening Period of 90 days may be extended up to 120 days with prior approval from the 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.

Participants who progress to more advanced clinical stages of AD during the study should be assessed for understanding of potential risks/benefits of participation by the investigator and may continue in the study at the discretion of the investigator.

In the Double-blind Treatment Period, eligible participants will be assigned randomly (central randomization) to 1 of 3 treatment groups: 1 of 2 dosages of JNJ-63733657 (1000 or 3000 mg) or placebo at a ratio of 1:1:1. Following randomization using the RTSM system (eg, IWRS), participants will enter a Double-blind Treatment Period of variable duration (maximum of 4.5 years).

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.

The assigned LTE dose (1000 mg or 3000 mg) for a participant will be unblinded to the Sponsor after the Double-blind Treatment Period is completed but will initially remain blinded to the clinical sites and participants. At each participant’s LTE Visit 18 (LTE Week 68), or later if

required (eg, pending IRB/Ethics Committee approvals), the RTSM system (eg, IWRS) will begin assigning the new JNJ-63733657 drug product (1000 mg/vial, 175 mg/mL). At this time, the participant's assigned JNJ-63733657 dose in the LTE Treatment Period will be unblinded and the 1000 mg/vial, 175 mg/mL product will continue to be used for the remainder of the LTE Treatment Period.

After the Double-blind Treatment Period is completed, the Sponsor will be unblinded to the double-blind treatment assignment. To minimize any impact on the planned LTE analyses, clinical sites and participants will continue to remain blinded to double-blind treatment assignment for all participants.

The study intervention (JNJ-63733657 or placebo) will be administered IV every 4 weeks; infusions will take place at a constant rate over approximately 60 minutes, followed by an IV flush, as described in the IPPI. The infusion duration may be increased if issues of tolerability are encountered. Infusions are to be monitored by the principal investigator/designated study staff in a designated hospital/clinic setting. The dose levels of JNJ-63733657 selected for this study are in the dose range expected to reduce CSF p217+tau from baseline by approximately 93% at a dose of 1000 mg and approximately 98% at a dose of 3000 mg, based on analyses of the SAD/MAD study (63733657EDI1001) (see Section 4.3).

Study procedures will be performed as per the SoA (Section 1.3).

A mandatory pharmacogenomic (DNA) blood sample will be collected from all participants at the start of the Double-blind Treatment Period. If necessary, the DNA sample may be collected at a later time point without constituting a protocol deviation. DNA samples may also be further analyzed for additional genetic factors that may influence PK, PD, immunogenicity, safety, and/or tolerability of JNJ-63733657, or that may relate to AD pathways or other neurodegenerative diseases, if it is hypothesized that this may help with the interpretation of the clinical data. Determination of APOE status may be through plasma or DNA analysis.

Missing data in clinical trials can lead to problems that undermine the scientific credibility of causal conclusions. The most common reason for missing data is participants who discontinue the assigned treatment because of AEs, lack of efficacy, or inconvenience. In order to reduce missing data in this study, if a participant discontinues double-blind study intervention for reasons other than withdrawal of consent (or behavioral dissent) for participation in the study prior to completion of the Double-blind Treatment Period, the participant should complete the remaining scheduled visits/study procedures (without study intervention administration) per the SoA (Section 1.3) through Week 104 of the Double-blind Treatment Period. Refer to Section 8.1.2 for additional guidance regarding these participants. For discontinuations:

- If full participation in study procedures is considered too burdensome, then the focus should be on collecting primary and secondary clinical outcome measures (ADAS-Cog13, CDR-SB, RBANS, ADCS-ADL-MCI), tau PET, PK, and clinical laboratory safety tests (particularly in those with abnormal results at the time of discontinuation of study intervention), and reducing other assessments.
- If a participant remains in the Double-blind Treatment Period without study intervention administration, then PK and monthly clinical laboratory safety tests would need to continue

throughout 90 days after the last dose of study intervention or longer if clinically indicated (eg, to follow up an SAE until resolution).

- If a participant discontinues the double-blind study intervention (for reasons other than withdrawal of consent [or behavioral dissent]) prior to the completion of the Double-blind Treatment Period and declines to further participate in the Double-blind Treatment Period assessments without study intervention administration, then the participant will have an ET/End of DB visit performed as soon as possible after the last dose of study intervention. The participant will then return to the site for safety follow-up visits approximately 30, 60, and 90 days after the last dose of study intervention.

A target of approximately 480 participants with Early AD will be enrolled in this study with approximately 160 participants planned per treatment group in the Double-blind Treatment Period. The sample size determination is detailed in Section 9.5.

A diagram of the overall study design and a diagram of the transition from Double-blind to LTE Treatment Periods are provided in Figure 1 and Figure 2 in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

Blinding, Control, Study Periods, Intervention Groups

In the double-blind, placebo-controlled Treatment Period, the participant, study partner, investigator, study site personnel, and sponsor will be blinded to treatment allocation.

A placebo control will be used in the Double-blind Treatment Period to establish the frequency and magnitude of changes in clinical efficacy, safety, and biomarker endpoints that may occur in the absence of active intervention.

Despite the availability of AD treatments that target amyloid plaque, there is still a need for additional therapies targeting other pathophysiologies to have the greatest benefit for patients. Current standard of care AD medications (AChEIs and/or memantine) are permitted in this study in accordance with eligibility criteria and the guidance described in Section 6.8. Therefore, participants are able to receive standard of care AD treatment (AChEIs and/or memantine) plus placebo. AD treatment(s) that target the underlying pathophysiology of AD (eg, anti-amyloid therapies) are not permitted during screening or to be administered concomitantly with study intervention at any time during the Double-blind Treatment Period or in the LTE Treatment Period.

Randomization will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups.

The randomization in the Double-blind Treatment Period will be stratified to balance intervention groups across region (North America, Europe, Australia, and Japan) and baseline tau burden on tau PET (low versus high as described in the Imaging Charter) with an allocation ratio of 1:1:1 to JNJ-63733657 (1000 or 3000 mg) or matching placebo.

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 outlined in Section 4.1 Overall Design above. Details on the blinding of the LTE dose assignment and the double-blind treatment assignment during the LTE Treatment Period are also provided in Section 4.1 Overall Design.

Study Population

The target population for the study will consist of participants aged 55 to 80 years, inclusive at the time of initial consent, with sporadic Early AD, with biomarker evidence of pathological p-tau protein within a prespecified range for eligibility (evaluated first by plasma prescreen and confirmed by pathologic tau on tau PET) (T+). Since this definition of T+ using tau PET is strongly associated with elevated cerebral amyloidosis (Fleisher 2018; Therriault 2023), these participants are highly likely to have both elevated brain amyloid and tau (A+T+). Participants with Early AD have AD with MCI or mild dementia (ie, CDR-GS=0.5), and so represent an important stage for potential intervention aimed at slowing the pathophysiological process. The study population is considered AD with MCI or dementia in the National Institute on Aging-Alzheimer's Association ATN research framework (Jack 2018) as shown in Table 1.

Table 1: Biomarker Profiles (ATN) and Cognitive Stage Categories

Biomarker Profile	Cognitive Stage		
	Cognitively Unimpaired	**Mild Cognitive Impairment**	**Dementia**
A- T- N-	Normal AD biomarkers, cognitively unimpaired	Normal AD biomarkers, with MCI	Normal AD biomarkers, with dementia
A+ T- N-	Preclinical AD pathologic change	AD pathologic change, with MCI	AD pathologic change, with dementia
A+ T+ N-	Preclinical AD	AD with MCI (prodromal AD)	AD with dementia
A+ T+ N+			
A+ T- N+	AD concomitant suspected non-AD pathologic change, cognitively unimpaired	AD and concomitant suspected non-AD pathologic change, with MCI	AD and concomitant suspected non-AD pathologic change, with dementia
A- T+ N-	Non-AD pathologic change, cognitively unimpaired	Non-AD pathologic change, with MCI	Non-AD pathologic change, with dementia
A- T- N+			
A- T+ N+			

The population included in this study includes participants with clinical stage 3 and 4 under the updated 2018 FDA draft guidance entitled "Early Alzheimer's Disease: Developing Drugs for Treatment."[a] This biomarker-defined study population was chosen to ensure presence of the target pathology (pathologic tau).

In order to avoid radiation exposure and simplify screening, a plasma biomarker (within a pre-specified eligibility range) will be used to screen for individuals within the desired clinical stage for the presence of p-tau (T+). The presence of pathologic tau will be confirmed for all included participants using tau PET as described in a separate Imaging Charter. This will ensure a

[a] Originally issued in 2013 as "Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease."

similar pathophysiologic stage within the clinical stage of sporadic Early AD, increase likelihood of clinical and biomarker progression (Fleisher 2018), decrease heterogeneity and increase the probability of benefit based upon MOA (ie, excluding participants with widespread tau who may not benefit from prevention of tau propagation). A plasma biomarker assessing elevated brain tau (eg, p217+tau) has shown early promise but has not been validated for use in large scale, global clinical trials as sole biomarker entry criteria. Therefore, in this study, the plasma biomarker of elevated brain tau (within a prespecified range) will be used only as a prescreen to determine participants who are T+ for the purpose of continuing in screening with tau PET. Participants who meet pathologic tau criteria on tau PET are likely to be A+ on amyloid PET (Fleisher 2018, Maass 2019). Therefore, amyloid PET will not be used in this study to avoid unnecessary radiation exposure and participant/site burden. Lumbar puncture will be optional in this study. Therefore, CSF will not be used as a prescreen.

Because pattern and rapidity of tau propagation may be different between sporadic and familial ADAD (Gordon 2019), participants with known ADAD will be excluded.

Study Duration

Study participants are followed in the Double-blind Treatment Period for a maximum duration of up to 4.5 years, with longest follow-up for those participants enrolled earliest.

Limited longitudinal ADAS-Cog13 data available in the study population (Early AD defined by tau PET tracer inclusion/exclusion cutoffs) create uncertainty in placebo progression rates but adequate progression will be required to see treatment separation. 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 (Oxtoby 2018).

The last participant randomized in the study will have the opportunity to receive up to 104 weeks of double-blind treatment. The Double-blind Treatment Period will continue until all participants have had the opportunity to complete the Week 104 visit.

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 of the Double-blind Treatment Period will be discontinued from the Double-blind Treatment Period to either enter the LTE Treatment Period (if eligible) or proceed to the safety follow-up visits (for participants not entering the LTE Treatment Period).

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.

DNA and Biomarker Collection

It is recognized that genetic variation can be an important contributory factor to interindividual differences in intervention distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to an intervention. The goal of the pharmacogenomic component is to collect DNA to allow the identification of genetic factors that may influence the PK, PD, efficacy safety, or tolerability of JNJ-63733657 and to identify genetic factors associated with AD. Further details are presented in Section 8.8.

DNA samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

Cerebrospinal Fluid Sampling

Participants will have the option of contributing CSF samples (approximately 12 mL/sample), collected by single lumbar puncture at regular time points during the study. CSF samples will be used for: (1) assessment of JNJ-63733657 concentrations as a measure of blood-CSF penetration and (2) assessing PD effects (biomarker response) of JNJ-63733657 by measuring total and free p217+tau fragments, which allows the determination of p217+tau bound to JNJ-63733657. In addition, samples may be used for exploratory biomarker research, including understanding relationships between the various biomarkers and clinical outcomes and identification of novel biomarkers that could identify responders to JNJ-63733657.

Single lumbar punctures will be separated by approximately 52 weeks. No more than approximately 48 mL of CSF in total will be collected over a period of up to approximately 4.5 years in the Double-blind Treatment Period of this study and no more than approximately 60 mL of CSF will be collected in the LTE Treatment Period of this study. As such, the total sampling volume proposed in this study is considered to be acceptable given the daily CSF production rate of approximately 500 mL/day.

CSF samples will be obtained in the Double-blind Treatment Period and the LTE Treatment Period per the SoA (Section 1.3).

Pharmacodynamics/Biomarkers

The planned PD assays will be used to explore the MOA and pharmacologic activity of JNJ-63733657. The goal of the biomarker analyses is to explore the PD effects of JNJ-63733657, which may aid in the evaluation of the exposure-clinical response relationship. In future trials, it may help to explain interindividual variability in clinical outcomes upon treatment or to identify population subgroups that respond differently to a drug.

Biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

PD effects will be explored by quantifying changes in CSF p217+tau (total, free, and bound to JNJ-63733657 as the difference between total and free p217+tau) associated with administration of JNJ-63733657 and will serve as an indicator of target engagement (ie, binding to the tau seed). In addition, changes in blood p217+tau may be explored.

PD response of antibody binding to p217+tau (monomeric tau) in the CSF is a surrogate for the true target engagement of the tau seed (aggregated PHF-tau) in the interstitial fluid in the brain, which cannot be directly measured. Neither the relationship between the amount of extracellular seed and the amount CSF p217+tau fragments nor the p217 epitope density is known.

Exposure to JNJ-63733657 or disease may alter the proteolytic pattern of tau being released to the CSF. To better understand how JNJ-63733657 affects tau biology, tau fragment profiles in CSF may be explored.

Cognitive and Functional Outcome Measures

Clinical endpoints in this study include composite measures of cognition and function measuring overall clinical progression (iADRS and CDR-SB), cognitive tests (RBANS and ADAS-Cog13), and functional outcome measures (ADCS-ADL-MCI and Amsterdam IADL), which will be administered at the time points indicated in the SoA (Section 1.3). The selected tests are included to evaluate the cognitive and functional decline among participants and to determine which of these assessments are most sensitive to disease progression in the study population.

Cognitive decline is the earliest measurable clinical manifestation of AD; however, different cognitive domains have been shown to progress at different rates (Storandt 2009), with episodic memory, executive function, and orientation showing change early in the course of the disease (Grober 1988, van Harten 2013).

The iADRS, the primary outcome measure in this study, is a combination of ADAS-Cog13 and ADCS-ADL-MCI and is therefore a cognitive/functional composite. In various versions, it has been demonstrated to detect change with good signal/noise ratios and effect sizes that generally fall between individual components when evaluated in MCI, mild, and moderate AD dementia populations (Liu-Seifert 2017, Wessels 2015).

The ADAS-Cog13 is a measure of cognitive performance that has been widely used historically in clinical trials of MCI and dementia stages of AD but may be less sensitive to change in earlier preclinical AD populations (Cano 2010, Raghavan 2013).

The ADCS-ADL-MCI is an instrument used to track early changes in function such as the ability to perform high-level ADL. The scale is administered to the study partner (informant) by a site rater.

The RBANS has been less widely used but includes measures of multiple cognitive domains and has been shown to differentiate healthy normal individuals from those with MCI or AD dementia, to be predictive of functional status (Badenes 2008), and to correlate with the CDR (Ho 2015), biomarkers (Grober 1988, Wilson 2009), and other measures of cognition (Duff 2013).

The CDR-SB is a global scale with 'face' validity, in that it assesses the influence of cognitive loss on the ability to conduct everyday activities (Morris 1997). The CDR-GS, calculated from the CDR using a scoring algorithm, is well established for staging AD and has been used extensively in trials of MCI and AD dementia (Rikkert 2011). Change in progression of CDR-SB as well as proportion of participants progressing in CDR-GS from one stage to another will be analyzed.

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 inclusion of the various functional assessments will inform the most sensitive, clinically relevant measure that is most useful for future clinical development of JNJ-63733657 in this Early AD, biomarker-defined population.

Psychobehavioral Symptoms

The NPI is a measure of neuropsychiatric symptomatology based on study partner interview that is included to assess new onset or worsening of neuropsychiatric symptoms. It measures frequency, severity and caregiver distress. It is included as a measure of efficacy (ie, delayed onset of neuropsychiatric symptoms) and safety.

Safety Evaluations

Safety evaluations for this study will include monitoring of AEs, physical and neurological examinations, clinical laboratory tests (hematology, clinical chemistry, and urinalysis), ECGs, vital sign measurements (including temperature, supine and standing systolic and diastolic BP, and supine and standing pulse), C-SSRS, and brain MRI (see below), as specified in the SoA (Section 1.3).

Magnetic Resonance Imaging

A brain MRI will be obtained at screening from all participants to identify any pre-existing pathology and to rule out any signs of elevated intracranial pressure prior to lumbar puncture. The screening eligibility brain MRI will be performed to document that there is no other clinically relevant disease that could impair the participant's cognitive status independent of the AD-related pathology. Brain volume will also be assessed. MRIs will be repeated as indicated in the SoA (Section 1.3) to evaluate for any inflammatory process, although not anticipated. Additionally, an MRI will be obtained as clinically indicated if any change in neurologic function is noted during the study.

The MRI sequences included are described in a separate MRI Manual/Charter. All MRI data will be assessed locally by a qualified reader for safety and sent to a core imaging laboratory for central reading, quality control, data analysis, data management, and archiving if needed.

Health Outcomes Assessments

The RUD-Lite is included 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 QOL-AD is a questionnaire aimed at measuring quality of life and will be completed by both the participant and the study partner.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks (which may include discomforts related to study intervention administration or procedures to obtain laboratory samples and neuroimaging, side effects related to intervention, etc.) and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily at study entry will be enrolled. Refer to Section 10.3.3 (Informed Consent Process).

Despite the availability of AD treatments that target amyloid plaque, there is still a need for additional therapies targeting other pathophysiologies to have the greatest benefit for patients. Current standard of care AD medications (AChEIs and/or memantine) are permitted in this study in accordance with eligibility criteria and the guidance described in Section 6.8. Therefore, participants are able to receive standard of care AD treatment plus placebo and the use of a placebo control in this study is ethically justified. AD treatment(s) that target the underlying pathophysiology of AD (eg, anti-amyloid therapies) are not permitted at any time during screening and not permitted to be used concomitantly with study intervention at any time in the Double-blind Treatment Period or in the LTE Treatment Period.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the American Red Cross.

Participants undergoing PET scanning will be exposed to radiation. The radiation exposure will not exceed limits set by local regulations, and as such, will be in the range that is acceptable for diagnostic procedures.

4.2.1.1. Ethical Considerations for Participants Unable to Consent During the Study

As stated above, only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily at study entry will be enrolled. Participants who progress to more advanced clinical stages of AD during the study (ie, after enrollment) should be assessed in a manner consistent with clinical practice for understanding of potential risks/benefits of participation by the investigator and may continue in the study if deemed by the investigator to have capacity to make the decision to remain in the study.

If it is necessary to reconsent participants due to relevant new study information and the participant can no longer provide informed consent due to cognitive decline during the study, a legally

designated representative, which may or may not be the study partner, must confirm with their signature on the ICF that they provide permission for the participant to continue in the study. Written permission by this legally designated representative may be obtained through various sources as determined by regulations as well as study and patient preferences. Refer to Section 10.3.3 (Informed Consent Process).

For participants who can no longer provide informed consent, behavioral assent (Black 2010) may be acceptable if agreed upon by the legally designated representative or study partner and the principal investigator, and if permissible per local regulations. This includes situations where a legally designated representative is not available, if permissible per local regulations. Behavioral assent is defined as behavior that shows willingness to participate, including but not limited to compliance with study procedures, willingness to attend study visits, and other cooperative behavior. Conversely, participants who show sustained behavioral dissent should be considered for withdrawal from the study in consultation between the study partner and the principal investigator. Examples of behavioral dissent include but are not limited to resistance (becoming upset, agitated, refusing) to attend site visits, completing study scales, completing safety testing, etc. Participants who assent to a study and later show evidence of sustained behavioral dissent should not be maintained in the study against their will. The medical monitor is available for consultation, if needed, but the decision to withdraw or maintain the participant from/in the study will be made by the investigator in close collaboration with the study partner (and legally designated representative if not the study partner) as noted above.

4.3. Justification for Dose

The dosages of JNJ-63733657 for this study are 1000 and 3000 mg. The dose selection is based on drug exposures in serum and CSF, effect of the intervention on p217+tau species in CSF in the study participants with AD or healthy participants, and safety and tolerability of the drug (Section 2.2).

The dosages of JNJ-63733657 selected for use in the LTE Treatment Period will be the same doses used in the Double-blind Treatment Period, 1000 mg and 3000 mg. This allows participants to continue receiving the same dose that they received in the Double-blind Treatment Period. Those receiving placebo in the Double-blind Treatment Period will be rerandomized to 1 of these 2 doses. The LTE is currently designed to evaluate both 1000 mg and 3000 mg in a dose-blinded manner because it is anticipated that at the time when the first participant enters the LTE Treatment Period, the Double-blind Treatment Period will still be ongoing for the rest of the participants, and data will not yet be available to inform on dose selection.

In the combined Phase 1 SAD/MAD study (63733657EDI1001), JNJ-63733657 exhibited approximately dose-proportional PK in both serum and CSF, within the tested dose range, in both SAD (1 to 60 mg/kg, single IV dose) and MAD (5 to 50 mg/kg, 3 monthly IV doses) parts of the study. The $t_{1/2}$ of JNJ-63733657 ranged between 18.1 to 27.1 days in serum and the elimination of the drug from CSF mirrored that of the serum. The PK profile was consistent between AD participants and healthy participants, including Japanese participants.

Since the target engagement of the tau seed (aggregated PHF-tau) in the interstitial fluid cannot be directly assessed in the brain, the binding of JNJ-63733657 to p217+tau in the CSF is considered

an indirect indicator of target engagement response. In the SAD part of the Phase 1 study, dose-dependent reductions of p217+tau were observed in healthy participants (see Section 2.2). In the MAD part of the study, despite the higher baseline levels of p217+tau in participants with AD, the magnitude of p217+tau reduction, expressed as percentage change from baseline, by JNJ-63733657 was comparable to that seen in healthy participants.

The extent of target engagement needed for efficacy is unknown, but the assumption is that a sustained p217+tau reduction in CSF is required for efficacy. To facilitate the prediction of CSF p217+tau reduction by JNJ-63733657, a PK/PD model was established. In this model, fixed dosing of JNJ-63733657 resulted in overall similar exposure compared with body weight-based dosing for equivalent doses. Based on the simulations, JNJ-63733657 at a dose of 1000 mg will reduce free p217+tau from baseline in CSF by approximately 93% in participants with AD. At a dose of 3000 mg, JNJ-63733657 will reduce free CSF p217+tau from baseline by approximately 98% in participants with AD, which approaches the maximum reduction of p217+tau.

JNJ-63733657 has been generally safe and well tolerated up to 60 mg/kg following single doses, and up to 50 mg/kg following multiple doses. No safety and tolerability issues have been observed in completed studies to date. JNJ-63733657 at dosages of 1000 and 3000 mg (corresponding to 12.5 and 37.5 mg/kg, respectively, for an 80-kg individual) is expected to be well tolerated.

4.4. End of Study Definition

End of Study Definition

The end of study is when the last randomized participant has either withdrawn consent or has completed their last study visit.

The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

End of Double-blind Treatment Period Definition

The Double-blind Treatment Period will be of variable duration, continuing until all participants have had the opportunity to receive double-blind treatment for 104 weeks. The maximum treatment duration 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 of the Double-blind Treatment Period 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 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 availability of the LTE Treatment Period at the clinical site, then the participant will remain in the Double-blind Treatment Period receiving double-blind study intervention until after the LTE Treatment Period becomes available.

After the LTE Treatment Period becomes available at the site, the participant 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 (if not entering the LTE Treatment Period).

The end of the Double-blind Treatment Period is when all participants complete the Week 104 visit or an ET visit (if discontinuing the Double-blind Treatment Period prior to Week 104 visit).

End of Long-Term Extension Treatment Period Definition

The end of the LTE Treatment Period is when the last participant in the LTE completes the End of LTE Treatment Period visit.

5. STUDY POPULATION

Screening for eligible participants will be performed within 90 days before the first administration of the study intervention (may be extended up to 120 days with prior approval from the 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). Participants that exceed 120 days may be required to repeat select study procedures. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures is allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

The investigator will be asked to record the clinical diagnosis of prodromal AD (AD with MCI) or mild AD dementia based upon significance of cognitive impairment upon daily function.

For a discussion of the statistical considerations of participant selection, refer to Section 9.5, Sample Size Determination.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

Age

1. Criterion modified per Amendment 1:

    1.1. 55 to 80 years of age, inclusive, at the time of initial consent.

Type of Participant and Disease Characteristics

2. Criterion modified per Amendment 1:

    2.1. Early AD: Gradual and progressive subjective decline in the participant's cognition over at least the past 6 months, as reported by the participant and

informant (study partner) and CDR-GS of 0.5 and memory box score ≥0.5 at screening.

3. Evidence of pathologically elevated tau (T+) as defined first in plasma as directed in a separate Laboratory Charter/Manual. Only plasma T+ participants will undergo a tau PET scan at screening to confirm T+ status.

4. Evidence of pathologic tau on a screening tau PET scan reviewed centrally by a qualified reader, as prespecified in a separate Imaging Charter.

5. Able to read and write and with a minimum 5 years of formal education as reported by participant and study partner at screening.

6. Willing to participate in this study (signed written informed consent) and to comply with the study protocol.

7. Have a designated study partner who has adequate literacy to participate and be judged to have high likelihood of completing the study with the participant.

Weight

Not applicable.

Sex and Contraceptive/Barrier Requirements

8. Criterion modified per Amendment 2:

   8.1. Female participants must be (as defined in Appendix 5, Contraceptive and Barrier Guidance) not of childbearing potential; that is, they must be either:

   a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in female participants not using hormonal contraception or HRT, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

   b. permanently sterile (for the purpose of this study)

   - Permanent sterilization methods include hysterectomy, or bilateral salpingectomy, or bilateral oophorectomy.

   - Has congenital abnormalities resulting in sterility.

9. Male participants who are sexually active with a woman of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal

foam/gel/film/cream/suppository or partner with occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository) during the study and up to 16 weeks after the last dose of study intervention. In addition, their female partner should also use a highly effective method of birth control (eg, hormonal contraception) for at least the same duration. A male study participant whose female partner is pregnant should use a condom during the study and up to 16 weeks after the last dose of study intervention.

10. Male participants must agree not to donate sperm for the purpose of reproduction during the study and up to 16 weeks after receiving the last dose of study intervention.

Informed Consent

Refer to Inclusion Criterion 6.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

Medical Conditions

1. Criterion modified per Amendment 1:

    1.1. Participants with CDR-GS ≥2 at predose baseline CDR administration.

2. Participants who fulfill diagnostic criteria for MCI or dementia/mild or major neurocognitive disorder suspected to be due to any etiology other than AD (eg, MCI/dementia due to frontotemporal lobar degeneration, diffuse Lewy body disease, Parkinson's disease, cerebrovascular disease, normal pressure hydrocephalus, head injury, drug or alcohol abuse/dependence, anoxic brain injury, etc).

3. Criterion modified per Amendment 1:

    3.1. GDS-30 score >12.

4. Criterion modified per Amendment 1:

    4.1. HIS >4.

5. Known carriers of a PSEN1, PSEN2, or Amyloid Precursor Protein mutation associated with ADAD or any other neurodegenerative disease.

6. Participants with extensive, widespread tau pathology, as measured by tau PET (as described in the Imaging Charter).

7. Criterion modified per Amendment 1:

   7.1. Criterion modified per Amendment 2:

   7.2. Has received acetylcholinesterase inhibitors or memantine, and/or other permitted AD medication at a stable dose for less than 2 months at the start of screening. (Note: If a participant has recently stopped acetylcholinesterase inhibitors, and/or memantine, he or she must have discontinued treatment at least 2 months before the start of screening). Concomitant use of AD therapies that target the underlying pathophysiology of AD (eg, anti-amyloid or anti-tau therapies) are not permitted.

8. Criterion modified per Amendment 1:

   8.1. Criterion modified per Amendment 2:

   8.2. Has received medications that affect the CNS, except treatments for AD (as detailed in Exclusion Criterion 7), for less than 2 months; that is, doses of chronic medications that effect the CNS should be stable for at least 2 months before the start of screening. If a participant has recently stopped a chronic medication that effects the CNS, he or she must have discontinued treatment at least 2 months before the start of screening. Chronic use of benzodiazepines is not permitted.

9. Presence of any neurological, psychiatric, or medical conditions associated with a long-term risk of significant cognitive impairment or dementia including, but not limited to, pre-manifest Huntington's disease, multiple sclerosis, Parkinson's disease, Down's syndrome, active alcohol/drug abuse or major psychiatric disorders including, but not limited to, schizophrenia, schizoaffective disorder, or bipolar affective disorder or current episode of major depressive disorder.

10. Criterion modified per Amendment 1:

    10.1. Criterion modified per Amendment 2:

    10.2. Presence of thyroid disease or dysfunction, unless in the opinion of the investigator it does not require treatment or a change to existing medication.

11. History of epilepsy, fits, or unexplained blackouts other than vasovagal syncope within 10 years before screening.

12. Known allergies, hypersensitivity, or intolerance to JNJ-63733657 or its excipients (IB: JNJ-63733657).

13. Criterion modified per Amendment 1:

    13.1. History of substance use disorder according to most current version of the Diagnostic and Statistical Manual of Mental Disorders criteria within the past 5 years before screening or positive test result(s) for other drugs of abuse (including barbiturates, opiates, cocaine, amphetamines, and benzodiazepines) at screening (except if related to current treatment).

14. Criterion modified per Amendment 2:

    14.1. Any current medical conditions that, in the opinion of the investigator or sponsor's medical monitor, are clinically significant and might make the participant's participation in an investigational study unsafe, eg, uncontrolled or unstable disease of any major organ system; history within the last 6 months of any acute illness of a major organ system requiring emergency care or hospitalization, including revascularization procedures; severe renal or hepatic failure; unstable or poorly controlled diabetes mellitus, hypertension, or heart failure; malignant neoplasms within the last 3 years (except for basal or squamous cell carcinoma in situ of the skin, or cervix in female participants, or localized prostate cancer in male participants that, in the opinion of the investigator, is considered cured with minimal risk of recurrence); any clinically relevant abnormalities in blood parameters included in local site routine assessments; severe loss of vision, hearing or communicative ability.

15. Any conditions or planned prolonged periods of absence (eg, vacation) preventing cooperation or completion of the required assessments in the study, as judged by the investigator.

16. Criterion modified per Amendment 1:

    16.1. Criterion modified per Amendment 2:

    16.2. Clinically significant abnormal physical examination, neurological examination, or vital signs at screening or baseline (Day 1 predose); or laboratory findings at screening.

17. Has ALT≥2×ULN, AST≥3×ULN, and/or total bilirubin ≥2×ULN at screening. Participants with diagnosed Gilbert's Syndrome are permitted.

18. History of a positive test for HIV antibody, or tests positive for HIV at screening.

19. Criterion modified per Amendment 2:

19.1. QTcB >450 msec (males) or >470 msec (females), as evaluated by the central ECG vendor at screening. ECGs will be performed in triplicate and participants will be excluded if more than 1 of the 3 QTcB measurements are >450 msec (males) or >470 msec (females). Note: ECG measurements may be repeated once; for any potentially clinically significant findings, the site will manage the participant as per standard clinical practice.

20. Any contraindications for MRI.

21. Criterion modified per Amendment 1:

21.1. Criterion modified per Amendment 2:

21.2. Any evidence of intracranial pathology which, in the opinion of the investigator or the central imaging reader and/or the sponsor (as outlined in the MRI Charter), may affect cognition including, but not limited to, brain tumors (benign or malignant), aneurysm or arteriovenous malformations, territorial stroke (excluding smaller watershed strokes), recent hemorrhage (parenchymal or subdural), or obstructive hydrocephalus. Participants with an MRI scan demonstrating markers of small vessel disease (eg, white matter changes or lacunar infarcts) or microbleeds judged to be clinically insignificant, are allowed.

22. Signs of increased intracranial pressure (eg, based on clinical or MRI examination).

23. As determined by the principal investigator, participant is participating in another clinical trial or other medical research that is not scientifically or medically compatible with this study at screening or for the duration of their participation in the current study.

Prior/Concomitant Therapy

24. Participant has received an investigational drug (including passive immunization) or used an investigational medical device for AD within 3 months or 5 half-lives, whichever is longest, before the baseline visit (Day 1), or has previously completed or withdrawn from this study or other JNJ-63733657 studies.

25. Criterion modified per Amendment 2:

25.1. Participant has previously received an active vaccine for AD (eg, tau, amyloid).

Prior/Concurrent Clinical Study Experience

Refer to exclusion criteria 23 and 24.

Diagnostic Assessments

Not applicable.

Other Exclusions

26. Diminished decision-making capacity that renders the individual not capable of consenting or completing study assessments in the opinion of the principal investigator.

27. History of any suicidal behavior (attempt, interrupted, aborted, or preparatory) in the past 6 months prior to screening.

28. Past or planned exposure to ionizing radiation that in combination with the planned administration with study tau PET ligand would result in a cumulative exposure that exceeds local recommended exposure limits.

29. Is an employee of the investigator or study site with direct involvement in the proposed study or other studies under the direction of that investigator or study site, or is a family member of an employee or the investigator.

30. Currently resides in a residential nursing facility. Participants who must be admitted for rehabilitation to a nursing facility during the study may continue in the study if they are able to complete study procedures.

31. Does not have good venous access, precluding frequent blood draws and IV infusions every 4 weeks.

32. Criterion modified per Amendment 1:

    32.1. Any other factors in the opinion of the investigator and/or sponsor that could contraindicate participation in the study or suggest inappropriate clinical stage of AD (eg, discordance of CDR-GS and RBANS DMI).

33. Planning to take, or currently taking, an approved treatment that targets the underlying pathophysiology of AD (eg anti-amyloid therapies). If a participant has discontinued an approved treatment that targets the underlying pathophysiology of AD (eg, anti-amyloid therapies), there must be at least 3 months or 5 half-lives, whichever is longest, between the last dose of the treatment and Day 1 of the Double-blind Treatment Period.

34. Vitamin B12 or folate levels below the central laboratory lower limit of normal, unless in the opinion of the investigator it does not require treatment.

Note: Principal investigators must ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that the participant no longer meets all eligibility criteria, then the participant must be excluded from participation in the study. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Appendix 3.

Concordance of Screening Step I CDR-GS and RBANS Delayed Memory Index Score

Concordance of the CDR-GS assessment (Screening Step I) with the RBANS DMI score (from Screening Step I) will be verified during screening. A RBANS DMI ≤85 consistent with 1 SD below the age-normalized mean, indicating presence of cognitive symptoms, will be considered concordant with a CDR-GS of 0.5. If the RBANS DMI score and the CDR-GS are concordant for a participant, that participant's CDR score and assignment to the Early AD population will be considered confirmed. The investigator will be asked to record the clinical diagnosis of prodromal AD (AD with MCI) or mild AD dementia based upon significance of cognitive impairment upon daily function.

If discrepancies are noted between CDR-GS and DMI, consensus between the principal investigator and sponsor's medical monitor will be necessary to include the participant. The principal investigator will be asked to provide evidence to the sponsor's medical monitor to support the determination of the Early AD stage of disease despite one of the criteria (either an RBANS or CDR) not being met. This will be followed by the medical monitor review of that evidence and discussion with the principal investigator to resolve the discrepancy. The goal of attaining consensus is to obtain agreement that the participant is in the Early AD clinical stage, regardless of discordant scores, and then to document that agreement for each individual case in the source record form. Actual RBANS scores and CDR ratings would not be changed in either case (unless the principal investigator agreed that he/she did not have good evidence and had in fact rated the CDR "in error"), in which case, in consultation with the medical monitor, the CDR-GS may be changed and the reasons for the change documented in the case record.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the study to be eligible for participation:

1. Refer to Section 6.8, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.
2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).
3. Participants will abstain from recreational drugs for 24 hours prior to each visit.

4. It is recommended participants minimize/refrain from alcohol use in the several days leading up to blood collection for clinical laboratory safety tests and 24 hours prior to each visit.
5. It is recommended participants avoid or minimize taking concomitant medications that could be associated with transient increases in hepatic/liver chemistry laboratory tests (eg, acetaminophen).
6. Avoid donating blood products during the study and for at least 90 days after completion (ie, final follow-up visit) of the study.

5.4. Screen Failures

Limited retesting of abnormal screening laboratory or ECG values will be allowed once, especially if the abnormality is the result of an acute medical condition that is not exclusionary, faulty equipment, or error in obtaining samples; retesting for such abnormalities can occur after the medical condition or other situation has resolved or is appropriately treated/addressed. Additional retesting is not permitted without medical monitor approval.

In some cases, participants who screen fail for reasons that are subsequently addressed may be considered for rescreening after approval by the sponsor's medical monitor. Scenarios to be considered include: previous screening was not completed within protocol time windows, delay in obtaining past medical history, mild or asymptomatic medical conditions that required further evaluation to demonstrate stability, and medications that had not been stable for a sufficient period.

Participants approved for rescreening must sign a new ICF and undergo appropriate screening evaluation according to the SoA (Section 1.3.1), confirmed by the sponsor's medical monitor. This may include interim medical history, safety assessments, clinical laboratory assessments, and ECG. If tests of fluid biomarkers (plasma/CSF) or imaging were completed and valid, they may not need to be repeated if confirmed by the sponsor's medical monitor. Screening cognitive and other endpoint evaluations should follow the SoA (Section 1.3.1); if screening cognitive evaluations were completed previously, the medical monitor or designee should be consulted for guidance on whether and when to repeat.

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants must be assigned new participant numbers.

Criteria for Temporarily Delaying Enrollment, Randomization, Administration of Study Intervention

There are no criteria for temporarily delaying enrollment or randomization.

Refer to Appendix 7 for hepatic safety monitoring assessments, including criteria for interrupting/stopping administration of study intervention based on abnormalities in hepatic chemistry tests.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Interventions Administered

Designation	**Product**	
Investigational Medicinal Product	JNJ-63733657 (1000 mg, 3000 mg), placebo	
Auxiliary Medicinal Product	Nonauthorized	MK-6240
	Justification for Nonauthorized Use	A suitable tau radiotracer EU-authorized was not identified. MK-6240 was selected because: • It is more widely accessible than other unapproved tau radiotracers; and • It provides better performance (greater dynamic range, less off-target binding in the basal ganglia) than first-generation unapproved tau radiotracers.

All other study-specified medications are considered concomitant medications (see Section 6.8).

JNJ-63733657 (500 mg/vial, 50 mg/mL) and Matching Placebo

JNJ-63733657 drug product (500 mg/vial, 50 mg/mL) and matching placebo are supplied as a final vialed product that must be stored refrigerated at 2°C to 8°C and be protected from light as described on the label.

The drug product and placebo should be prepared as per the label and/or IPPI. Drug product and placebo for IV administration must be administered with in-line filtration. Refer to the JNJ-63733657 IB for the study intervention target formulation and detailed list of excipients; the formulation for the placebo will be similar, but without JNJ-63733657. JNJ-63733657 (500 mg/vial, 50 mg/mL) and matching placebo appear as clear to slightly yellow solutions.

JNJ-63733657 (500 mg/vial, 50 mg/mL) will be manufactured and provided under the responsibility of the sponsor. The investigational supplies (JNJ-63733657 and placebo) will be uniquely packaged to assure that they are appropriately managed throughout the supply chain process. JNJ-63733657 and placebo will be packaged in individual participant kits. Each kit will consist of 2 vials of JNJ-63733657 or placebo packaged inside a protective outer carton. Each carton will be uniquely labeled with a medication identification number. Labels will contain information to meet the applicable regulatory requirements. Refer to the Pharmacy Manual/Study Site IPPI for additional guidance on study intervention preparation, handling, and storage.

JNJ-63733657 (1000 mg/vial, 175 mg/mL)

JNJ-63733657 drug product (1000 mg/vial, 175 mg/mL) is supplied as a final vialed product that must be stored refrigerated at 2°C to 8°C and be protected from light as described on the label.

The drug product should be prepared as per the label and/or IPPI. Drug product for IV administration must be administered with in-line filtration. Refer to the JNJ-63733657 IB for the study intervention target formulation and detailed list of excipients. JNJ-63733657 (1000 mg/vial, 175 mg/mL) appears as a clear to yellow solution.

JNJ-63733657 (1000 mg/vial, 175 mg/mL) will be manufactured and provided under the responsibility of the sponsor. It will be uniquely packaged to assure that it is appropriately managed throughout the supply chain process. JNJ-63733657 will be packaged in individual participant kits. Each kit will consist of 1 vial of JNJ-63733657 packaged inside a protective outer carton. Each carton will be uniquely labeled with a medication identification number. Labels will contain information to meet the applicable regulatory requirements. Refer to the Pharmacy Manual/Study Site IPPI for additional guidance on study intervention preparation, handling, and storage.

All Administered Study Interventions

Refer to Section 6.3 for information regarding randomization/assignment of study intervention.

Predose ALT and AST results must be reviewed prior to each study intervention administration. Dosing is not permitted for any participant with treatment-emergent predose ALT>1.5xULN or AST≥3xULN (tested within 14 days prior to dosing). Retesting once is allowed if ALT>1.5xULN but <3xULN. The study intervention will be administered under the supervision of the investigator or his/her designee in a designated hospital/clinic setting.

A physician must be immediately available at the site at all times during the administration of study intervention. A single dose of JNJ-63733657 or placebo will be administered by IV infusion at a constant rate to each participant in the arm via a separate line using an administration set with a filter, as described in the IPPI. Consult the medical monitor if there are any questions or concerns regarding administration of the study intervention in the arm. The infusion duration will be approximately 60 minutes, followed by an IV flush, and may be increased if tolerability issues are encountered. Study intervention administration must be captured in the source documents and the eCRF. Refer to the Pharmacy Manual/Study Site IPPI for the procedure and additional guidance on study intervention administration.

Infusion-Related Reactions

Participants will be monitored for infusion-related reactions on study intervention dosing days. For any infusion-related reactions of any grade/severity at the time of the infusion, manage the participant's symptoms as appropriate. Best supportive care should be administered, as applicable. Management of infusion-related reactions may require reduction in the rate of infusion or interruption/stopping the infusion. The time of stopping/interrupting the infusion, infusion rate, total volume infused, symptoms related to infusion-related reactions, and further steps need to be recorded in the patient chart and/or eCRF.

Infusion-related reactions are AESIs (see Section 10.4.1, Adverse Events Definitions and Classifications) and should be recorded in the eCRF as per eCRF completion guidelines.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

The JNJ-63733657 drug product is supplied at pH 6.0 and filled aseptically in glass vials, closed with a 20-mm stopper.

The JNJ-63733657 drug product must be stored protected from light and refrigerated at 2°C to 8°C until use. Drug product will be diluted with normal saline (0.9% sodium chloride) prior to IV administration.

The study intervention will be prepared by the pharmacist or other appropriately licensed and authorized health professional according to the treatment assignment.

Refer to the Pharmacy Manual/Study Site IPPI for additional guidance on study intervention preparation, handling, and storage.

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study.

The study intervention administered to the participant must be documented on the intervention accountability form. All study intervention will be stored and disposed of according to the sponsor's instructions. Study site personnel must not combine contents of the study intervention containers.

Study intervention must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention will be documented on the intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

Potentially hazardous materials containing hazardous liquids should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes.

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study interventions are provided in the Site Investigational Product Binder.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

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 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 outlined in Section 4.1 Overall Design above. Details on the blinding of the LTE dose assignment and the double-blind treatment assignment during the LTE Treatment Period are also provided in Section 4.1 Overall Design.

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.

Data that may potentially unblind the intervention assignment (ie, study intervention serum concentrations 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.

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 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. In an emergency the investigator may determine the identity of the treatment by contacting the RTSM system (see IWRS Manual). Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented by the RTSM system (eg, IWRS) and in the source document. The documentation received from the RTSM system (eg, IWRS) indicating the code break must be retained with the participant's source documents in a secure manner.

Participants who have had their intervention assignment unblinded should continue to return for scheduled evaluations.

All participants that enter the LTE Treatment Period of variable duration will receive 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 outlined in "Intervention Allocation" above. Details on the blinding of the LTE dose assignment and the double-blind treatment assignment during the LTE Treatment Period are also provided in Section 4.1 Overall Design.

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 (eg, 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. The Sponsor Committee of the IDMC -- an unblinded pharmacometrician and/or a subset of internal experts who are not directly involved in study conduct, data review, analysis or interpretation -- could be given access to potentially unblinding data, including PK, immunogenicity, and other relevant data to allow for updating safety monitoring algorithms or for evaluating possible etiologies of AESIs, if necessary. This will be documented in the IDMC or other respective committee charter and/or operational plan, if applicable (Section 10.3.6). To maintain the blind for the Double-blind Treatment Period, interim analyses during the LTE Treatment Period will only occur after the Double-blind Treatment Period has completed and the double-blind treatment assignment has been unblinded to the sponsor.

6.4. Study Intervention Compliance

Single doses of JNJ-63733657 or matching placebo will be administered as IV infusions by qualified study site personnel and the details of each administration will be recorded in the eCRF (including date, start and stop times of the IV infusion, and volume infused).

Study site personnel will maintain a log of all study intervention administered. Study intervention supplies for each participant will be inventoried and accounted for.

If a participant has missed/held 3 consecutive doses of study intervention during the LTE Treatment Period, the medical monitor should be contacted to discuss the current status of the participant.

6.5. Dose Modification

Dose/dosage adjustment by the investigator is not permitted in the double-blind and LTE Treatment Periods; however, the study intervention infusion rate can be reduced, or the infusion stopped, if required for tolerability reasons, as per clinical judgment of the investigator. This must be overseen by medically-qualified study site personnel (principal or subinvestigator unless an immediate safety risk appears to be present). Additional details on study intervention administration are provided in Section 6.1.

6.6. Continued Access to Study Intervention After End of the Double-blind Treatment Period

Following completion of the Double-blind Treatment Period, participants may have an option to participate in the LTE Treatment Period.

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 of the Double-blind Treatment Period 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 the LTE Treatment Period). Refer to Section 8.1.4 for details regarding the LTE Treatment Period.

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.

6.7. Treatment of Overdose

Formal information regarding overdosage and abuse potential of JNJ-63733657 is not available to date and overdosage is not foreseen due to the controlled administration of the drug substance (JNJ-63733657). General supportive measures for any AE should be taken as appropriate.

6.8. Concomitant Therapy

Prestudy therapies taken at a stable dose up to 2 months before the start of screening must be recorded.

Concomitant therapies must be recorded throughout the study beginning with start of screening until the end-of-study visit (follow-up visit). All therapies (prescription or over-the-counter medications, including vaccines [including any authorized for emergency use or fully approved, eg, COVID-19 vaccination]), vitamins, herbal supplements; nonpharmacologic therapies such as electrical stimulation, acupuncture, or other specific categories of interest) different from the study intervention must be recorded in the eCRF. Recorded information will include a description of the name and type of therapy, duration/dates of use, dosing regimen, route of administration, and indication. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a participant into the study.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Concomitant Alzheimer's Disease Therapies Potentially Enhancing Cognition

Standard of care treatments for AD are allowed during the study including AChEIs (donepezil, rivastigmine, galantamine) and/or memantine, provided they have been taken at a stable dosage for at least 2 months before the start of screening. Dosing of these medications should remain stable throughout the study, since starting, stopping, or changing doses could interfere with clinical outcome measures. If a participant has recently stopped one of these medications, they should have been off the medication for at least 2 months prior to screening for this study. Participants are not required to be taking an AChEI, memantine, and/or other permitted AD at study entry. Similarly, vitamins, nutraceuticals, and cognitive training as treatment for cognitive decline associated with AD are allowed but should be stable for at least 2 months prior to the start of screening.

If a participant must start, stop, or change dose of an AD therapy, the medical monitor should be contacted prior to the change to determine if, and when, clinical outcome measures should be administered.

After 1 year in the LTE, sites are not required to contact the medical monitor regarding changing an AD therapy, but should consider the timing of the change in relation to cognitive assessments. It is recommended that starting, stopping, or changing doses of these medications is performed as soon after the latest cognitive assessment as feasible to allow sufficient time prior to the next cognitive assessments.

Treatments that target the underlying pathophysiology of AD (eg, anti-amyloid therapies), are not permitted at any time during screening and not permitted to be concomitantly administered with study intervention at any time during the Double-blind Treatment Period or during the LTE Treatment Period. Participants who take such a treatment in screening will be screen failed and any randomized participant who takes such a treatment during a prohibited time will be discontinued from study intervention.

Concomitant Therapies Adversely Affecting Cognition

Benzodiazepines: The continuous (daily) use of benzodiazepines is not permitted during the study; however, occasional intake of short-acting benzodiazepines is allowed. If a participant requires intermittent treatment with benzodiazepines, the interval from last dose of the benzodiazepine and the subsequent cognitive assessment must be a minimum of 4 half-lives for that compound or 24 hours, whichever is longer. If a benzodiazepine or other sedating medication is given for a study procedure (eg, MRI, PET scan, lumbar puncture) at any visit or for any short-term use, then all cognitive assessments must be administered and completed either before, or at least 24 hours, or 4 half-lives, after administration of the sedative, whichever is longer.

Non-benzodiazepine benzodiazepine receptor agonists: Chronic use of these medications are not permitted. If used as needed or for short-term use during the study, the interval from last dose of the medication and subsequent cognitive assessment must be a minimum of 4 half-lives for that compound or 24 hours, whichever is longer.

Anticholinergic medications: Strongly anticholinergic medications should be used with caution in the elderly due to adverse effects on cognition and potential to cause delirium. If medically required, the interval from last dose of the anticholinergic medication and the subsequent cognitive assessment must be a minimum of 4 half-lives for that compound or 24 hours, whichever is longer.

Opioid and related medications: Other medications that affect CNS function and are used as needed or for short-term use during the study (ie, opioid containing medications used for cough, pain, etc.) are permitted but the interval from last dose of the medication and subsequent cognitive assessment must be a minimum of 4 half-lives for that compound or 24 hours, whichever is longer.

Other CNS acting medications (ie, not mentioned above): Other concomitant medications that affect CNS function (ie, antipsychotics, sedatives, antidepressants, etc.) may be given if the dose is intended to remain unchanged throughout the study. Doses of these compounds should remain constant beginning from 2 months prior to the start of screening. To avoid or control effects on clinical outcomes, the following apply:

- A participant receiving a stable dose of a medication(s) that affects CNS function for at least 2 months prior to the start of screening should minimize any changes (eg, stopping the dose or changing the dose amount, schedule, or timing) of this medication during the study.
- If a participant has recently stopped one of these medications prior to the start of screening, he/she should have been off the medication for at least 2 months prior to screening for this study.
- A participant should avoid and/or minimize, if clinically appropriate, adding any medication(s) that affect CNS function during the study period.

Any chronically prescribed and medically required CNS acting medication (except use of chronic benzodiazepines or non-benzodiazepine benzodiazepine receptor agonists, which are excluded) should be taken by the participant at the same time of day throughout the study so that any effect on cognitive assessments is systematic throughout the study.

In the case of any unforeseen start, stop, or change to stable doses of a therapy that affects CNS function during the study, consider contacting the medical monitor to determine whether it is in the best interest of the participant (relative to the study) to continue participation and whether the timing of subsequent clinical outcome measures should be modified. It is recommended that there be a minimum of 6 weeks, preferably 8 weeks, between starting/changing a medication/therapy that affects CNS function and subsequent study visits with cognitive testing.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Permanent Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- The participant withdraws consent to receive study intervention.
- The participant shows behavioral dissent, indicating unwillingness to receive study intervention.
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention.
- The participant becomes pregnant. Refer to Appendix 5, Contraceptive and Barrier Guidance.
- The participant will start or has started a treatment that targets the underlying pathophysiology of AD, eg, anti-amyloid therapies.
- The participant meets permanent discontinuation criteria outlined in Appendix 7 and will not be rechallenged.
- The participant has suspected or confirmed DILI, as determined by the sponsor or designee [ie, expert consultant(s)].

If a participant discontinues study intervention for any reason other than withdrawal of consent (or behavioral dissent) before the end of the study, then the post-intervention assessments should be obtained and scheduled assessments off study intervention should be continued. If full participation in study procedures is considered too burdensome, then the focus should be on collecting primary and secondary clinical outcome measures (ADAS-Cog13, CDR-SB, RBANS, ADCS-ADL-MCI), tau PET, PK, and clinical laboratory safety tests (particularly in those with abnormal results at the time of discontinuation of study intervention), and reducing other assessments.

Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant.

The sponsor has a responsibility to collect detailed data on the reasons for post-randomization study intervention discontinuation. These reasons will be captured as part of the post-intervention assessments and reported in the eCRF.

7.1. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up.
- Withdrawal of consent.
- Behavioral dissent, indicating unwillingness to participate in study (as defined in Section 4.2.1.1).
- Death.

- Noncompliance.

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document.

Withdrawal of Consent

If the reason for withdrawal from the study is withdrawal of consent (or behavioral dissent), then no additional assessments are allowed. A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. The principal investigator should evaluate the participant and consult with study partner to understand if the participant has lost the ability to consent and if failure to comply with study participation could be behavioral dissent. If at any time during study participation the principal investigator feels the participant's AD has worsened to the point where there is a concern about the participant's ability to knowingly and/or voluntarily participate in the study, the principal investigator should consult with the study partner, legally designated representative (if applicable) and evaluate the participant for behavioral assent or dissent. The medical monitor is available for consultation, if needed, but the decision to withdraw or maintain the participant from/in the study will be made by the investigator in close collaboration with the study partner (and legally designated representative if not the study partner). Refer to Section 4.2.1 regarding ethical considerations.

Although participants who withdraw consent (or show behavioral dissent) should not have additional study assessments performed, the investigator should ensure any participant with ongoing AEs or abnormalities are followed up by their treating physician or per local regulations.

7.1.1. Withdrawal From the Use of Research Samples

A participant who withdraws from the study will have the following options regarding the optional research samples:

The collected samples will be retained and used in accordance with the participant's original separate informed consent for optional research samples.

The participant may withdraw consent for optional research samples, in which case the samples will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

Withdrawal From the Optional Research Samples While Remaining in the Main Study

The participant may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research samples will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Section 10.3.5 [Long-Term Retention of Samples for Additional Future Research] in Appendix 3). In such a case,

samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research samples.

7.2. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to randomization attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

The study site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.

Before a participant is deemed lost to follow-up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods). Locator agencies may also be used as local regulations permit. These contact attempts should be documented in the participant's medical records.

Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Overview

The SoA (Section 1.3) summarizes the frequency and timing of efficacy, PK, immunogenicity, PD, biomarker, pharmacogenomic, health outcome scales, and safety measurements applicable to this study.

Further information regarding total number, type, handling, shipment, and labeling of all biological samples will be provided in a separate Laboratory Manual. Biological samples for safety laboratory assessments will be collected, handled and labeled as per local site SOPs.

For CSF sampling, local site SOPs may be applied for performing the actual lumbar puncture (not the collection of samples), provided they are at least as restrictive as the criteria defined in this protocol or Laboratory Manual.

Any changes to the Laboratory Manual will not result in a protocol amendment.

A separate Imaging Manual will be provided describing the MRI and PET imaging procedures, data acquisition, and handling.

Unless otherwise noted in the SoA (Section 1.3), it is recommended that all clinical scales involving the participant be conducted/completed before any tests, procedures, or other consultations to prevent adversely influencing participant performance. It is recommended that they be administered at the same time, preferably in the morning, at each visit. Lack of adherence to the SoA can introduce variability into the clinical scale data. Clinical scales are to be administered while the participant/study partner are at the study site (not remotely). Guidance regarding modifications to study procedures due to a natural disaster/major disruption/pandemic are described in Appendix 6.

All study procedures are to be performed on the same day, with the exception of study procedures that have a permitted window relative to the day of the clinic visit (eg, predose laboratory safety [hematology, chemistry, CRP, INR], imaging [PET, MRI], LP for CSF, and study intervention administration, as applicable per SoA).

Predose ALT and AST results must be reviewed prior to each study intervention administration. Dosing is not permitted for any participant with treatment-emergent predose ALT>1.5xULN or AST≥3xULN (tested within 14 days prior to dosing). Retesting once is allowed if ALT>1.5xULN but <3xULN.

If a participant cannot receive study intervention at a particular visit (eg, predose ALT>1.5xULN or AST≥3xULN), the participant should complete all study procedures scheduled for this visit, except for study intervention administration. Refer to the SoA (Section 1.3) for information about performing select visits (eg, visits with no clinical scales) remotely if study intervention will not be administered at a visit.

If the predose ALT and AST values are not available on the day of the participant's clinic visit (eg, due to laboratory delay or blood sample for the central laboratory was collected at the visit), dosing may occur on a separate day from the other study procedures. In such cases:

- If the predose ALT≤1.5xULN and AST<3xULN, the participant should return to the clinical site for administration of study intervention within the permitted clinic visit window per the SoA.
- Upon return to clinic for administration of study intervention, the following study procedures should be performed on the same day as administration of study intervention: vital signs (predose) and recording of AE and concomitant therapies.

In the event of abnormal safety findings during the conduct of the study, additional measurements may be made immediately and subsequently at a frequency considered appropriate by the investigator or, if applicable, treating physician. Refer to Appendix 7 for hepatic safety monitoring assessments, including stopping criteria and guidance regarding abnormal liver chemistry tests.

Venous blood will be collected for all blood-based analyses. When assessments occur at the same time point, the blood sample for PK and biomarker (PD) analysis must always be collected as close to the scheduled time as possible, followed by the CSF sample for PK and biomarker (PD) analysis. Actual dates and times of assessments will be recorded in the source documentation and eCRF.

If multiple assessments are scheduled for the same time point, it is recommended that procedures be performed in the following sequence: ECG(s), vital signs, blood draw.

Serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

Health outcome scale data will be collected. Refer to Section 8.3 for details.

The total blood volume to be collected from each participant will be approximately (per Table 2 and Table 3):

- 22.0 mL for the Screening Period;
- 689.2 mL for the Double-blind Treatment Period (over 232 weeks, or 153 mL per year);
- 205.7 mL for LTE Treatment Period Year 1;
- 128.9 mL for LTE Treatment Period Year 2;
- 128.9 mL for LTE Treatment Period Year 3;
- 105.4 mL per year from LTE Treatment Period Year 4 and onwards; and
- 27.4 mL for the follow-up visits.

Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.

Table 2: Approximate Volume of Blood to Be Collected From Each Participant (Screening, Double-blind Treatment, and Follow-up Periods)

Type of Sample	Volume per Sample (mL)	Number of Samples per Participant	Approximate Total Volume of Blood (mL)[a]
Screening Period			
Hematology	2.0 mL	1	2.0 mL
Serum chemistry	2.5 mL	1	2.5 mL
Serology (HIV)	2.5 mL	1	2.5 mL
Vitamin B12 and folic acid	4.0 mL	1	4.0 mL
TSH	5.0 mL	1	5.0 mL
Biomarker Status	6.0 mL	1	6.0 mL
Approximate Total for Screening Period			22.0 mL
Double-blind Treatment Period			
Hematology	2.0 mL	59	118.0 mL
Chemistry	2.5 mL	59	147.5 mL
Other laboratory tests (CRP, INR, etc)	1.8 mL	59	106.2 mL
PK/Immunogenicity	8.5 mL	15	127.5 mL
Pharmacogenomics (DNA)	10.0 mL	1	10.0 mL
PD/Biomarkers	15.0 mL	12	180.0 mL
Approximate Total for Double-blind Treatment Period[b]			689.2 mL
Follow-up Period			
Hematology - Follow-up Visits	2.0 mL	3	6.0 mL
Chemistry - Follow-up Visits	2.5 mL	3	7.5 mL
Other laboratory tests (CRP, INR, etc)	1.8 mL	3	5.4 mL
Immunogenicity - Follow-up Visit	8.5 mL	1	8.5 mL
Approximate Total for Follow-up Visits[b]			27.4 mL

a. Calculated as number of samples multiplied by amount of blood per sample.
b. Repeat or unscheduled samples may be taken for safety reasons (eg, per Appendix 7) or technical issues with the samples but are not included in the total.

Note: An indwelling IV cannula may be used for blood sample collection.

Table 3: Approximate Volume of Blood to Be Collected From Each Participant (LTE Treatment Period)

Type of Sample	Volume per Sample (mL)	Number of Samples per Participant	Approximate Total Volume of Blood (mL)[a]
Long-Term Extension Treatment Period (Year 1)			
Hematology	2.0 mL	14	28 mL
Chemistry (includes fractionated bilirubin and CRP)	2.5 mL	14	35 mL
INR	1.8 mL	14	25.2 mL
PK/Immunogenicity	8.5 mL	5	42.5 mL
PD/Biomarkers	15 mL	5	75 mL
Approximate Total for LTE Treatment Period (Year 1)[b]			205.7 mL
Long-Term Extension Treatment Period (Year 2)			
Hematology	2.0 mL	13	26 mL
Chemistry (includes fractionated bilirubin and CRP)	2.5 mL	13	32.5 mL
INR	1.8 mL	13	23.4 mL
PK/Immunogenicity	8.5 mL	2	17 mL
PD/Biomarkers	15 mL	2	30 mL
Approximate Total for LTE Treatment Period (Year 2)[b]			128.9 mL
Long-Term Extension Treatment Period (Year 3)			
Hematology	2.0 mL	13	26 mL
Chemistry (includes fractionated bilirubin and CRP)	2.5 mL	13	32.5 mL
INR	1.8 mL	13	23.4 mL
PK/Immunogenicity	8.5 mL	2	17 mL
PD/Biomarkers	15 mL	2	30 mL
Approximate Total for LTE Treatment Period (Year 3)[b]			128.9 mL
Long-Term Extension Treatment Period (approximate total volume per year from Year 4 onwards)			
Hematology	2.0 mL	13	26 mL
Chemistry (includes fractionated bilirubin and CRP)	2.5 mL	13	32.5 mL
INR	1.8 mL	13	23.4 mL
PK/Immunogenicity	8.5 mL	1	8.5 mL
PD/Biomarkers	15 mL	1	15 mL
Approximate Total per year from Year 4 onwards [b]			105.4 mL

a. Calculated as number of samples multiplied by amount of blood per sample.
b. Repeat or unscheduled samples may be taken for safety reasons (eg, per Appendix 7) or technical issues with the samples but are not included in the total.
Note: An indwelling IV cannula may be used for blood sample collection.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with 0.9% sodium chloride, United States Pharmacopeia (or

equivalent) and charged with a volume equal to the dead space volume of the lock. If a mandarin (obturator) is used, blood loss due to discard is not expected.

Refer to the SoA (Section 1.3) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the Laboratory Manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Laboratory Manual.

Study-Specific Materials

The investigator will be provided with the following supplies:

- IB
- Pharmacy Manual/Study Site IPPI
- Tau PET Imaging Manual
- MRI Manual
- Laboratory Manual and associated materials (eg, kits)
- Clinical scales/kits, eCOA device, and associated materials (eg, manuals)
  a. Cognition/function
     - CDR
  b. Cognition:
     - RBANS
     - ADAS-Cog13
  c. Function:
     - ADCS-ADL-MCI
     - Amsterdam IADL
  d. Neuropsychiatric
     - NPI
  e. HIS
  f. Health Outcome Scales:
     - RUD-Lite
     - QOL-AD
  g. Safety:
     - C-SSRS
  h. GDS-30
- IWRS Manual (for RTMS system)

- ECG equipment and associated materials (eg, manual)
- CRF Completion Guidelines
- Sample ICFs (participant and study partner versions)

8.1.1. Screening Period

After giving initial written informed consent, participants will be screened over a period of up to 90 days to assess their eligibility for the study according to the inclusion and exclusion criteria. To allow for treatment of transient conditions, laboratory retesting, scheduling of MRI, tau PET, and optional lumbar puncture, and/or operational delays, the Screening Period of 90 days may be extended to 120 days with prior approval from the 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.

The complete list of assessments performed during the Screening Period is presented in the SoA (Section 1.3). Refer to Section 8.1 for additional guidance.

Flexibility for conducting some study procedures at the same visits is provided in the SoA (Section 1.3).

Sites will not be provided plasma p217+ tau and tau PET results. However, sites will be notified of the reason for screen failure (eg, not meeting plasma tau eligibility or not meeting lower or upper tau PET threshold criteria).

8.1.2. Double-blind Treatment Period

Participants participating in the Double-blind Treatment Period will visit the site every 4 weeks (±7 days).

Participants who successfully complete the screening assessments will return to the site on Day 1, at which time a series of predose baseline measurements will be performed (as listed in the SoA, Section 1.3.2). Following confirmatory review of a participant's eligibility for further participation based on the inclusion and exclusion criteria (see Section 5), eligible participants will be randomly assigned on Day 1 (baseline) to 1 of 2 dose levels of JNJ-63733657 (1000 or 3000 mg) or matching placebo in a 1:1:1 ratio. As described in Section 6.3, randomization will be stratified by region (North America, Europe, Australia, and Japan) and baseline tau burden on tau PET (low versus high, as described in the Imaging Charter).

Study intervention for the Double-blind Treatment Period will be dispensed and administered as listed in the SoA (Sections 1.3.2 and 1.3.3) and Section 6.

Following dosing on Day 1 (baseline), and during the entire Double-blind Treatment Period, treatment effects will be evaluated by means of cognitive assessments, functional outcome measures, fluid and imaging biomarkers, PK, health outcome scales, and safety and tolerability at the time points listed in the SoA (Sections 1.3.2 and 1.3.3).

The treatment effect of JNJ-63733657 on slowing cognitive decline will be assessed in all participants using ADAS-Cog13 and RBANS. Clinical (cognitive/functional) status will be assessed in all participants using the CDR-SB. Functional status will be evaluated in all

participants using the ADCS-ADL-MCI and Amsterdam IADL. Neuropsychiatric symptoms and quality of life will be assessed using the NPI and QOL-AD, respectively. The potential effects of JNJ-63733657 on the pathophysiologic processes underlying AD will be assessed with fluid biomarkers (CSF in a subset of participants and/or plasma/serum in all participants) and imaging biomarkers (MRI and tau PET). Blood and CSF samples for determination of JNJ-63733657 concentrations will be collected. Medical resource utilization will be explored with the RUD-Lite assessment.

Safety (ECG, vital signs, laboratory evaluations, MRI, physical and neurological examinations, and C-SSRS), and tolerability (AEs) will be assessed at regular intervals during the Double-blind Treatment Period, as listed in the SoA (Sections 1.3.2 and 1.3.3). Most of these safety assessments will be performed predose at the specified visit. Refer to Appendix 7 for hepatic safety monitoring assessments, including stopping criteria and guidance regarding abnormal liver chemistry tests.

In order to reduce missing data in this study, if a participant discontinues double-blind study intervention for reasons other than withdrawal of consent (or behavioral dissent) for participation in the study prior to completion of the Double-blind Treatment Period, the participant should complete the remaining scheduled visits/study procedures (without study intervention administration) per the SoA through Week 104 of the Double-blind Treatment Period. For discontinuations:

- If full participation in study procedures is considered too burdensome, then the focus should be on collecting primary and secondary clinical outcome measures (ADAS-Cog13, CDR-SB, RBANS, ADCS-ADL-MCI), tau PET, PK, and clinical laboratory safety tests (particularly in those with abnormal results at the time of discontinuation of study intervention), and reducing other assessments.
- If a participant remains in the Double-blind Treatment Period without study intervention administration, then PK and monthly clinical laboratory safety tests would need to continue throughout 90 days after the last dose of study intervention or longer if clinically indicated (eg, to follow up an SAE until resolution).
- If a participant discontinues the double-blind study intervention for reasons other than withdrawal of consent (or behavioral dissent) prior to the completion of the Double-blind Treatment Period and declines to further participate in the Double-blind Treatment Period assessments without study intervention administration, then the participant will have an ET/End of DB visit performed as soon as possible after the last dose of study intervention. The participant will then return to the site for safety follow-up visits approximately 30, 60, and 90 days after the last dose of study intervention.

Study intervention assigned to a participant who discontinued study intervention may not be assigned to another participant.

8.1.3. Transition From Double-blind Treatment Period to the Long-Term Extension Treatment Period

Eligibility Criteria for Entering the LTE Treatment Period:

- Participants are eligible for the LTE Treatment Period if they:
  - Have completed at least the Week 104 visit in the Double-blind Treatment Period, and
  - Are receiving double-blind study intervention (including participants with temporary interruption of study intervention, eg, due to ALT>1.5xULN or AST≥3xULN).
- Participants are **not** eligible for the LTE Treatment Period if they have:
  - Discontinued from the Double-blind Treatment Period prior to completing the Week 104 visit, or
  - Permanently discontinued double-blind study intervention in the Double-blind Treatment Period, even if they remain in the Double-blind Treatment Period to perform other assessments without study intervention administration.

For Participants Who Have Already Completed the Week 104 Visit After the LTE Treatment Period Becomes Available at the Clinical Site:

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 of the Double-blind Treatment Period 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 the LTE Treatment Period).

After the LTE Treatment Period becomes available at the clinical site, an ET/End of DB visit will be performed; this is the last visit of the Double-blind Treatment Period for the participant.

- For participants not entering the LTE Treatment Period: After the ET/End of DB visit, participants will proceed to the safety Follow-up Period.
- For participants entering the LTE Treatment Period: After completing the ET/End of DB visit, participants will proceed to the LTE Treatment Period. Participants can enter the LTE Treatment Period on the same day as the ET/End of DB visit, after completing the ET/End of DB visit, and receive the first dose in the LTE Treatment Period. If the first visit of the LTE Treatment Period (LTE 1) is performed on the same day or shortly after the ET/End of DB visit, some LTE 1 visit assessments may not need to be repeated; see relevant footnotes in the SoA (Section 1.3).

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, to be eligible for the LTE Treatment Period (including participants with temporary interruption of study intervention, eg, due to ALT>1.5xULN or AST≥3xULN).

For Participants Who Have Not Completed The Week 104 Visit After the LTE Treatment Period Becomes Available at the Clinical Site:

To be eligible for the LTE Treatment Period, the participant must complete the Week 104 visit, including study intervention administration (except if study intervention is temporarily interrupted), of the Double-blind Treatment Period before discontinuing the Double-blind Treatment Period and entering the LTE Treatment Period.

After the Week 104 visit, the participant will return to the clinic for their next scheduled visit, at which time an ET/End of DB visit will be performed; this is the last visit of the Double-blind Treatment Period for the participant.

- For participants not entering the LTE Treatment Period: After the ET/End of DB visit, participants will proceed to the safety Follow-up Period.
- For participants entering the LTE Treatment Period: After the ET/End of DB visit, participants will proceed to the LTE Treatment Period. Participants can enter the LTE Treatment Period on the same day as the ET/End of DB visit, after completing the ET/End of DB visit, and receive the first dose in the LTE Treatment Period. If the ET/End of DB visit and first visit of the LTE Treatment Period are not on the same day, then refer to the SoA (Section 1.3) for assessments to be performed on the first visit of the LTE Treatment Period (Week 0, LTE 1), which will depend on the interval between the ET/End of DB visit and LTE 1.

8.1.4. Long-Term Extension Treatment Period

Study intervention for the LTE Treatment Period will be assigned and administered as described in the SoA (Section 1.3) and Section 6.

Efficacy, safety, biomarker, PK, immunogenicity, and health outcomes data will be obtained in the LTE Treatment Period.

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.

If a participant discontinues the LTE Treatment Period (for reasons other than withdrawal of consent [or behavioral dissent]), the participant will have an End of LTE Treatment Period visit performed as soon as possible after the last dose of study intervention. The participant will then return to the site for safety follow-up visits performed approximately 30, 60, and 90 days after the last dose of study intervention, unless the participant is receiving a dose of the commercially available product within 30 days of the last dose of study intervention.

8.1.5. Post-treatment Period (Follow-up)

For Participants Not Entering the LTE:

Approximately 30, 60, and 90 days after the last dose of study intervention in the Double-blind Treatment Period, participants not entering the LTE will return to the site for follow-up visits. The procedures to be completed during the follow-up visits are listed in the SoA (Section 1.3.8).

If the participant remains in the Double-blind Treatment Period (without study intervention) for at least 90 days after the last dose of study intervention, a safety follow-up visit is not required after completing the Double-blind Treatment Period.

If the participant remains in the Double-blind Treatment Period (without study intervention) for a period of time but discontinues this period prior to having reached 30, 60, and 90 days after the last dose of study intervention, the participant will complete the ET/End of DB visit in the Double-blind Treatment Period, then proceed to complete the applicable safety follow-up visits (at approximately 30, 60, 90 days) after the last dose of study intervention.

For Participants in the LTE:

Approximately 30, 60, and 90 days after the last dose of study intervention in the LTE Treatment Period, participants will return to the site for follow-up visits.

If a participant discontinues the LTE Treatment Period and will receive a dose of the commercially available product within 30 days, follow-up visits are not required.

The procedures to be completed during the follow-up visits are listed in the SoA (Section 1.3.8).

Detailed reasons for discontinuation of study intervention and discontinuation from the LTE Treatment Period will be collected.

8.2. Efficacy Assessments

Cognitive and functional testing for each participant should be performed first at each visit, at approximately the same time on each day that testing occurs, and by the same raters (with data gathered from the same study partner) throughout the study to reduce potential variability. The following sections briefly describe the cognitive and functional testing that will be assessed in the study.

8.2.1. Integrated Alzheimer's Disease Rating Scale (iADRS)

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

The iADRS is a composite measure of cognition and function. It was originally developed as a combination of the ADAS-Cog 14-item cognition subscale and the instrumental ADL items from the ADCS-ADL scale. It is calculated as a linear combination of total scores of the 2 individual components (Wessels 2015). In this study, the iADRS will be a combination of ADAS-Cog13 (score 0 to 85, higher scores indicate worse cognitive performance) and ADCS-ADL-MCI (score 0 to 53, lower scores indicate worse daily function). Score calculations for the iADRS are described in (Wessels 2015), and for the version used in this study range from 0 to 138 with lower scores indicating worse performance. The iADRS score will be the primary outcome measure of this study.

8.2.2. Alzheimer's Disease Assessment Scale - Cognitive, 13-Item Version (ADAS-Cog13)

The ADAS-Cog is a rater-administered instrument that was designed to assess the severity of dysfunction in cognition characteristic of persons with AD (Mohs 1997, Rosen 1984). 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 (Kolibas 2000).

The modified ADAS-Cog 13-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. The administration of the ADAS-Cog13 should be audio recorded for quality review purposes according to locally applicable laws and regulations.

8.2.3. 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 (Galasko 1997, Pedrosa 2010). Total score ranges from 0 to 53 with higher scores indicating less impairment. An exploratory analysis on the full 24 items (23 are scored and item 24 is useful for interpreting the scale results) will also be performed with total score ranging from 0 to 69.

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

The RBANS will be administered to all participants enrolled into the study. The administration of the RBANS should be recorded (audio) for quality review purposes according to locally applicable laws and regulations. The RBANS should be performed at least twice on different occasions during the Screening Period (Screening Visits 1 and 5); see Section 1.3. The RBANS performed at Screening Visit 5 will serve as the baseline administration of the 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 (Randolph 1998). 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. Research has demonstrated that the RBANS is predictive of functional capacity (ie, driving) in MCI patients (Badenes 2008), correlated with the CDR in MCI and AD (Hobson 2010) and AD biomarkers including anti-receptor for advanced glycation endproducts (RAGE), anti-Aβ IgGs, and fluorodeoxyglucose-PET neuronal network patterns (Förster 2010, Wilson 2009) and cognition (Duff 2005). The RBANS is administered face-to-face, is available in over 30 languages, and has been used in multinational clinical trials including AD trials (Karantzoulis 2013, Kotani 2006, Randolph 1994).

A secondary outcome measure will be change in progression on the RBANS Total Scale Index Score (including variable follow-up in the Double-blind Treatment Period of earlier enrolled participants, as described in Section 4.1).

8.2.5. Clinical Dementia Rating (CDR)

The CDR (Morris 1997) 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, United States, and including categorical scoring of 0, 0.5, 1, 2, and 3), as well as CDR-SB (the continuous sum of 6 domains, up to a total score of 18, with higher scores representing worse disease state). The administration of the CDR should be audio recorded for quality review purposes according to locally applicable laws and regulation.

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

The Amsterdam IADL (Sikkes 2012, Sikkes 2013) is an outcome measure in a checklist format designed to detect early ADL changes associated with preclinical stage dementia. The test has high internal consistency and retest reliability with construct validity established by comparing estimated trait levels with clinical and demographic measures.

8.2.7. Neuropsychiatric Inventory (NPI)

The NPI is a measure of psychobehavioral disturbances (Cummings 1997), 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).

8.3. Health Outcome Scales

The RUD questionnaire is the most widely used instrument for resource use data collection in dementia, enabling comparison of costs of care across countries/territories with differing healthcare provisions (Wimo 1998, Wimo 2013). RUD was originally developed in 1998; as the full RUD tool is extensive, a shorter version, RUD-Lite, was developed to assess informal care time, ie, how many hours per day on average the primary informal caregiver provides services to the person with dementia (Wimo 2003). 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.

The QOL-AD is a 13-item questionnaire, administered in interview format to individuals with dementia (Logsdon 1999). 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.

8.4. Home Health Care and Tele-Health Visits

Home health care visits may be implemented by or with approval from the sponsor and per the clinical judgment of the investigator, where feasible and permissible by local policy.

Protocol-specified laboratory assessments (Section 1.3) for safety may be collected during home health care visits.

Study procedures should be performed at the study site (not remotely) unless otherwise specified in the protocol. Guidance regarding modifications to study procedures due to a natural disaster/major disruption/pandemic are described in Appendix 6.

8.5. Safety Assessments

Adverse events will be reported and followed by the investigator as specified in Section 8.6 and Appendix 4.

Any clinically relevant changes occurring during the study must be recorded on the AE section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the SoA (Section 1.3).

8.5.1. Physical and Neurological Examinations

The study investigator, or other authorized and appropriately qualified designee, will perform complete physical and neurological examinations at the time points listed in the SoA (Section 1.3).

Any clinically relevant changes occurring during the study must be recorded on the AE section of the eCRF. Any clinically significant abnormalities persisting at the end of the study or early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

Body weight in kg (to the nearest 0.1 kg) will be measured at the visits indicated in the SoA (Section 1.3) and the same scale will be used for all measurements.

Height is measured at Screening and ET/End of DB (if applicable) only. Height will be measured to the nearest centimeter.

8.5.2. Vital Signs

Temperature (tympanic), pulse rate, and BP will be assessed at the time points indicated in the SoA (Section 1.3). Blood pressure and pulse measurements will be assessed after 5 minutes in the supine position, and then between 1 to 3 minutes after standing, with a completely automated device. Manual techniques will be used only if an automated device is not available. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones). Orthostatic BP and pulse will be assessed by subtracting standing BP and pulse from the supine measurements.

8.5.3. Electrocardiograms

The ECGs will be performed in triplicate at the time points indicated in the SoA (Section 1.3). During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same visit as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, approximately 1 minute apart. The full set of triplicates should be completed in less than 4 minutes.

During the study, the clinical investigator will review the ECG for immediate management and to assess any abnormalities. A description of the overall assessment (ie, normal or abnormal plus reason) will be available on the tracing and a copy of the tracing will be placed with the source data. All ECGs will additionally be transmitted to be read and interpreted by a central reader appointed by the sponsor. Interpretations from the central reader will be used for eligibility and data analysis.

8.5.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry, hematology, CRP, INR, and urine samples for urinalysis will be collected as noted in the SoA and Appendix 2. The samples will be collected in fasting condition, when feasible. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study, or those that meet AE reporting criteria in Appendix 7, in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

Predose ALT and AST results must be reviewed prior to each study intervention administration. Dosing is not permitted for any participant with treatment-emergent predose ALT>1.5xULN or AST≥3xULN (tested within 14 days prior to dosing). Refer to Appendix 7 for hepatic safety monitoring assessments, including requirements for the management and follow-up of abnormal hepatic chemistry test results. Additional laboratory samples may be collected for safety evaluations as required (refer to Section 8.6.3 and Appendix 7).

8.5.5. Suicidal Ideation and Behavior Risk Monitoring

JNJ-63733657 is considered to be a CNS-active study intervention. Some CNS-active study interventions have been associated with increased risk of suicidal ideation or behavior. Although this study intervention or other similar treatments in this class have not been shown to be associated with an increased risk of suicidal thinking or behavior when given to healthy participants or participants with AD, the sponsor considers it important to monitor for such events during this clinical study.

Participants being treated with JNJ-63733657 should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should be given to discontinuing JNJ-63733657 in participants who experience signs of suicidal ideation or behavior.

Families and caregivers of participants being treated with JNJ-63733657 should be instructed to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study investigator.

Baseline assessment of suicidal ideation and behavior and intervention-emergent suicidal ideation and behavior will be assessed during the study using C-SSRS.

The C-SSRS is a measure of the spectrum of suicidal ideation and behaviors and was developed in the National Institute Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment. The C-SSRS consists of a clinical interview that can be administered during any evaluation or risk assessment to identify the occurrence and intensity of suicidal thoughts and/or behaviors. It can also be used during treatment to monitor for clinical worsening. For this study, the C-SSRS is administered in screening, at baseline, and at the time points indicated in the SoA (Section 1.3).

If a suicidal-related thought or behavior is identified at any time during the study, a thorough evaluation will be performed by a study physician and appropriate medical care provided.

8.5.6. Magnetic Resonance Imaging

All participants will receive non-contrast MRI at screening to assess eligibility. In addition, MRI will be conducted in all participants during the Double-blind Treatment Period at the time points indicated on the SoA (Section 1.3) to assess safety and potential treatment effects. Visits which include MRI allow flexibility regarding when these assessments can be performed for a visit.

If MRI is done on the same day as cognitive or other assessments (except lumbar puncture), the MRI should be performed last prior to administration of study intervention. If not performed on the same day, the MRI should be performed within 7 days prior to the visit (ie, -7 day visit window). At visits that include both MRI and lumbar puncture, the MRI should be performed prior to lumbar puncture to minimize any impact of the lumbar puncture procedure on the MRI data.

All MRI data will be assessed locally by a qualified reader (radiologist or principal investigator) for safety and sent to a core imaging laboratory for central reading, quality control, data analysis, data management, and archiving if needed.

During the double-blind and LTE Treatment Periods, for visits that include an MRI assessment, administration of study intervention may occur prior to receiving the centrally read MRI results.

MRI should be performed in compliance with the MRI Charter/Manual. The standard MRI protocol will include anatomic 3D-T1 for segmentation of brain structures (including hippocampal and whole-brain volume), as well as Fluid-Attenuated Inversion Recovery, T2* imaging to determine vascular comorbidity and microbleeds, and diffusion imaging. Analysis and review will follow a central process.

Although not reported with tau therapies in development to date, but reported in people with AD, safety monitoring for vasogenic edema, cerebral microhemorrhages, and cerebral superficial siderosis by MRI is planned to be performed at the time points indicated in the SoA (Section 1.3).

8.5.7. Assessments Performed at Screening Only

8.5.7.1. 30-Item Geriatric Depression Scale (GDS-30)

The GDS-30 is a 30-item self-report assessment used to identify depressive symptomatology in the elderly (Debruyne 2009, Yesavage 1982). The GDS-30 questions are answered "yes" or "no". One point is assigned to each answer and the cumulative score is rated on a scoring grid. The grid sets a range of 0 to 9 as "normal", 10 to 19 as "mildly depressed", and 20 to 30 as "severely

depressed". A diagnosis of clinical depression should not be based on GDS-30 results alone. The test has well-established reliability and validity with 92% sensitivity and 89% specificity when evaluated against diagnostic criteria. Although a shorter version (15 items) has been validated, the longer version is more likely to have a normal distribution -- hence is better adapted for use as a dimensional scale -- without reliance on theoretical clinical cutoff points. The larger range of items also permits a finer analysis by symptom cluster and not just overall score.

8.5.7.2. Hachinski Ischemic Scale (HIS)

The HIS is a clinical questionnaire collecting information relevant for the differentiation between the most common dementia types, AD dementia and vascular dementia. The HIS calculates the likelihood dementia is due to vascular causes (Rosen 1984). Because it systematically identifies risk factors for vascular cognitive impairment, it is a relevant screening instrument for earlier stages of AD and will be performed at screening. A cutoff score ≤4 for AD dementia and ≥7 for vascular dementia has a sensitivity of 89% and a specificity of 89% (Moroney 1997).

8.6. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, serious AEs, and PQCs, from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

Further details on AEs, SAEs, and PQCs can be found in Appendix 4.

Processes and timelines for AE reporting will be defined further in the Safety Reporting Manual.

TEAEs of special interest will be examined separately, grouped in the following categories including, but not limited to: hepatobiliary disorders/liver enzyme abnormality related AEs and infusion-related reactions.

Refer to Appendix 7 for details on hepatic safety monitoring assessments.

8.6.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All AEs and special reporting situations, whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety, or until the participant has been deemed to be a screen failure.

Refer to Section 6.1 regarding reporting and documenting of infusion-related reactions.

Refer to Appendix 7 regarding hepatic AE definitions and reporting requirements.

Serious Adverse Events

SAE definitions are presented in Section 10.4 (Appendix 4).

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study site personnel immediately.

SAEs, including those spontaneously reported to the investigator within 90 days after the last dose of study intervention, (during the safety Follow-up Period) must be reported using the SAE form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

A **possible Hy's Law case** is defined by the occurrence of ALT or AST ≥3xULN, ALP<2xULN together with TBili>2xULN (or at least doubling of direct bilirubin in known Gilbert's syndrome) or INR>1.5 (if measured). Any possible Hy's Law case is considered an important medical event and must be reported to the sponsor in an expedited manner, even before all other possible causes of hepatic injury have been excluded (Appendix 7).

Information regarding SAEs will be transmitted to the sponsor using an SAE reporting form and safety report form of the eCRF, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor immediately but no later than within 24 hours. The initial and follow-up reports of a SAE should be transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

8.6.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Solicited Adverse Events

Solicited AEs are predefined local and systemic events for which the participant is specifically questioned (see Section 8, Study Assessments and Procedures).

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which the participant is not specifically questioned.

8.6.3. Follow-up of Adverse Events and Serious Adverse Events

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE, or PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Adverse events, and the special reporting situation of pregnancy, will be followed by the investigator as specified in Appendix 4.

8.6.4. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all SUSARs. The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

8.6.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the SAE form.

If a participant becomes pregnant during the study, a determination regarding study intervention discontinuation must be made by the investigator in consultation with the sponsor. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.7. Pharmacokinetics

8.7.1. Evaluations

Venous blood samples of approximately 8.5 mL will be collected for measurement of serum concentrations of JNJ-63733657 at the time points indicated in the SoA (Section 1.3) and as indicated in Appendix 7. Samples will be collected predose, with the exception of the sample collected at Week 16 (Visit 10), which will be collected within 10 minutes of the completion of infusion from the contralateral arm.

Venous blood samples will be collected, and each serum sample will be divided into 3 aliquots (1 each for PK, anti-JNJ-63733657 antibodies, and a back-up). Samples collected for analyses of JNJ-63733657 serum concentration and immunogenicity may additionally be used to further evaluate safety or efficacy. Genetic analyses will not be performed on these serum samples.

CSF samples will be collected for measurement of CSF concentrations of JNJ-63733657 at the time points indicated in the SoA (Section 1.3) for those participants opting for lumbar puncture.

Participant confidentiality will be maintained. Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual and IDMC charter.

8.7.2. Analytical Procedures

Pharmacokinetics

Serum and CSF samples will be analyzed to determine concentrations of JNJ-63733657 using validated, specific, and sensitive methods by or under the supervision of the sponsor.

PK samples may be stored for future analysis of protein binding and the metabolite profile.

8.7.3. Pharmacokinetic Parameters and Evaluations

Parameters

Serum and CSF concentrations at each time point of measurement will be evaluated by descriptive statistics, including arithmetic mean, geometric mean, standard deviation, coefficient of variation, geometric coefficient of variation, minimum, maximum, and median.

Pharmacokinetic/Pharmacodynamic Evaluations

An exploratory objective of this study will be to evaluate the relationship between dose and PK of JNJ-63733657 on biomarker assessments and clinical efficacy.

8.8. Genetics

A mandatory pharmacogenomic blood sample (DNA) will be collected on Day 1 (baseline); however, if necessary, it may be collected at a later time point during the study. DNA samples may be analyzed if it is hypothesized that this may help clarify clinical data.

Genetic variation can be an important contributory factor to interindividual differences in drug distribution and response and can also serve as a marker for disease susceptibility and prognosis. Genetic factors may help to explain interindividual variability in clinical outcomes and may help identify population subgroups that respond differently to a drug. The goal of the pharmacogenomic component is collect DNA to allow for the possible evaluation of other genetic factors that may influence the PK, PD, immunogenicity, safety, or tolerability of JNJ-63733657 and pathways related to AD/tauopathy.

APOE is involved in several key Aβ-mediated processes associated with AD, including the distribution, clearance and/or metabolism of Aβ, altered lipid-binding properties leading to an augmentation of Aβ-mediated toxicity (eg, disruption of lysosomal storage), and formation of aggregates that may promote Aβ nucleation and plaque formation. The APOE ε4 allele is considered the most significant genetic risk factor for AD and is associated with a decreased age of onset of the disease (Verghese 2011). Increasing APOE ε4 allele dosage (0, 1, 2 alleles) has been shown to be associated with greater brain amyloid burden and greater rate of brain amyloid accumulation (Gomperts 2008), and has been suggested to influence cognitive decline (Verghese 2011). APOE ε4 may also accelerate propagation of tau pathology and neuron death in part by neuron-specific, glia-independent mechanisms (Wadhwani 2019). Determination of APOE status may be through plasma or DNA analysis.

8.9. Biomarkers

8.9.1. Tau PET

PET imaging for pathological tau will be performed at the time points indicated in the SoA (Section 1.3). A single tau imaging radiotracer (MK-6240) will be used in all tau PET scans conducted during the Screening Period, Double-blind Treatment Period, and the LTE Treatment Period of the study. MK-6240 is not an authorized medicinal product in the European Union.

Tracer retention in different brain regions (described in a separate Imaging Charter) will be determined.

Details of the tau PET imaging procedures, including information on the tracer and its administration, image acquisition, image pre- and post-processing, and image analysis will be provided in a separate Imaging Manual/Charter. MK-6240 is investigational but carries no known risks beyond that of other PET tracers (small amount of radiation exposure, risks associated with an IV administration such as bruising and bleeding).

All PET scans will be sent to a core imaging laboratory for central review for quality control purposes and for data management, data analysis, and archiving, as defined in the Imaging Manual/Charter.

8.9.2. MRI Brain Volumetric Analysis

MRI will be used to assess hippocampal, whole brain, and ventricular volume, which track brain atrophy during the course of AD. In addition, progression of or new onset of vascular burden (white matter lesions [WML], infarcts, lacunes, microbleeds, superficial siderosis) will also be assessed.

MRI was chosen because, compared to computerized tomography, it provides no radiation exposure and can determine vascular pathology while allowing for quantification of grey matter structures such as the hippocampus and other AD signature regions. MRI is also much better suited to a longitudinal setting, with early-stage subtle changes over time detected in AD sensitive regions, which can predict future cognitive decline and onset of dementia.

Changes from baseline in volumetric assessments (including hippocampal [right and left], whole brain, and ventricular volume) of MRI brain will be performed. An appropriate correction for intercranial volume will be applied.

See also Section 8.5.6.

8.9.3. Biomarker Concentrations in Cerebrospinal Fluid and/or Plasma/Serum

Changes from baseline in concentrations of biomarkers in CSF and/or plasma/serum will be measured.

8.9.3.1. Tau Proteins

Concentrations of CSF and/or plasma total tau, p181tau, and p217+tau will be measured in this study. Tau proteins are normally associated with tubulin polymers to stabilize the microtubule system essential for normal neuronal function (Lee 2006). However, tau is hyperphosphorylated in AD and is the main component in PHFs, which then associate to form NFTs in the cytoplasm of many neurons (Crowther 1989, 1992, 1994; Goedert 1989, 1993; Hampel 2010). An elevation in levels of tau is indicative of axonal injury and neurodegeneration downstream of the initiating pathology. The increase in hyperphosphorylated tau in CSF is relatively specific to AD and therefore distinguishes AD from other neurodegenerative disorders (Hampel 2004).

The core epitope of tau recognized by JNJ-63733657 contains phosphorylation at amino acid 217, with potentially other phosphorylation sites nearby. This target is termed "p217+tau". Pharmacodynamic effects in the SAD/MAD study were assessed by quantifying changes in CSF p217+tau, free and total (p217+tau complexed/bound with JNJ-63733657 plus free). The PD response of antibody binding to p217+tau (monomeric tau) in CSF is used as an indicator of the true target engagement of the tau seed (aggregated PHF-tau) in the interstitial fluid, which cannot be directly measured in humans.

Multiple sampling time points for CSF collection will permit an assessment over time of the occurrence of changes in CSF p217+tau levels or additional downstream markers of neurodegeneration (see Section 8.9.3.3) and their respective time courses. The sample collected at screening will be considered the baseline sample.

CSF collection at the assessment time points should be performed at approximately the same time of day to reduce potential variability due to the diurnal fluctuation in CSF proteins. In addition, collection and storage should utilize tubes of specific material supplied for these purposes to ensure accuracy of the measurements due to the adherence of proteins to the tubes.

8.9.3.2. Aβ Fragments

The effects of JNJ-63733657 on markers of Aβ pathophysiology (eg, $A\beta_{42}$, $A\beta_{40}$, and $A\beta_{42/40}$ [Schindler 2019]) in the CSF will be assessed at the time points indicated on the SoA (Section 1.3).

Aβ fragments may also be measured in plasma, similar to CSF, although concentrations are typically lower and more difficult to quantify due to interference with other plasma proteins.

8.9.3.3. Other Biomarkers

Other CSF and/or plasma/serum biomarkers to be assessed may include, but are not limited to, downstream markers of neuronal injury and neurodegeneration and inflammation. In addition, other biomarkers associated with AD may be explored.

8.10. Pharmacodynamics

Biomarkers are discussed in Section 8.9.

8.11. Immunogenicity Assessments

Anti-drug antibodies, including neutralizing antibodies, will be evaluated in serum samples collected from all participants according to the SoA (Section 1.3) and Appendix 7. The detection and characterization of anti-JNJ-63733657 antibodies will be performed using a validated assay method by, or under the supervision of, the sponsor. All samples collected for detection of anti-JNJ-63733657 antibodies will also be evaluated for JNJ-63733657 serum concentration to enable interpretation of the antibody data. Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study.

Serum samples will be screened for antibodies binding to JNJ-63733657 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to JNJ-63733657 and/or further characterize the immunogenicity of JNJ-63733657.

The impact of anti-drug antibodies on safety, efficacy, PK, and PD will be evaluated and may be reviewed during the study period by the IDMC as needed for safety purposes.

8.12. Medical Resource Utilization

Medical resource utilization will be explored with the RUD-Lite assessment.

8.13. Participant Medical Information Prior, During, and After the Study (Real-world Data) - Applicable to United States Only

For US participants who have provided consent for participation in this substudy, medical data (electronic health records, claims, and laboratory data from other care settings) from 5 years prior to study enrollment until 5 years after study completion may be accessed utilizing tokenization and matching procedures (ie, the generation of anonymous identifiers or "tokens" [hashed and encrypted combinations of identifying elements] to allow linking of participant data from different sources without compromising the participant's confidentiality). These data may be used for exploratory analyses to enhance understanding of the disease diagnosis, management, and outcomes and to examine possible correlations of disease parameters between data collected in the clinical trial and real-world data. The analyses involving accessed real-world medical data will be described in detail in a dedicated analysis plan.

To allow the linking of participant records from different sources, ie, data collected as part of the study as specified in the SoA (Section 1.3) and longitudinal real-world data (from 5 years prior to enrollment in the study until 5 years after study completion) such as electronic health records, claims, and laboratory data from other care settings, without compromising the participant's confidentiality, tokenization and matching procedures will be utilized. The tokenization process starts with each data provider generating a token behind the firewall via a proprietary software. Personal information such as names and dates of birth from study participants are removed from real-world data sources and replaced with encrypted, one-way, hashed identifiers, and then further encrypted using asymmetric keys in compliance with Health Insurance Portability and Accountability Act (HIPAA 1996). This encrypted anonymized information is sent for matching to the anonymized participant master index. While it is not possible to reverse the hash, source-specific tokens can be decrypted and re-encrypted so that records can be linked across sources. The result of the process is a unique anonymized identifier for each participant, which can be used to link participant records across sources.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the SAP. The SAP for the primary analysis of the Double-blind Treatment Period (Primary Double-blind Analysis) will be developed and finalized prior to database lock. The SAP for the LTE Treatment Period will be developed and finalized prior to database lock of the LTE.

The Primary Double-blind Analysis will be performed when the last participant completes the Week 104 visit of the Double-blind Treatment Period (including participants who discontinue treatment but continue in the Double-blind Treatment Period and provide off-treatment data) or withdraws prior to the Week 104 visit of the Double-blind Treatment Period. The End of Double-blind Analysis will be performed when all participants have completed at least the Week 104 visit of the Double-blind Treatment Period, or are discontinued from the Double-blind Treatment Period and are not continuing into the LTE Treatment Period and have completed the Follow-up Period (90 days after last dose of study intervention).

9.1. Statistical Hypotheses

Primary Hypothesis: Participants treated with JNJ-63733657 will show slower clinical decline on iADRS as compared with participants receiving placebo.

9.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

- The Screened Analysis Set is defined as all participants who sign the ICF.
- The Randomized Analysis Set is defined as all participants who are randomized to an intervention group for the Double-blind Treatment Period.
- Efficacy analyses for the Double-blind Treatment Period will be performed on the FAS, which is defined as all randomized participants who have received at least 1 dose of double-blind study intervention.
- Safety analyses for the Double-blind Treatment Period will be performed on the Safety Analysis Set, which is defined as all randomized participants who receive at least 1 dose of double-blind study intervention. This is the same as the double-blind FAS.
- Efficacy analyses for the LTE Treatment Period will be performed on the LTE FAS, which is defined as all participants who have received at least 1 dose of study intervention in the LTE Treatment Period and have completed at least one assessment of cognitive, functional, or clinical scales in the LTE Treatment Period.
- Safety analyses for the LTE Treatment Period will be performed on the LTE Safety Analysis Set, defined as all participants who have received at least 1 dose of study intervention in the LTE Treatment Period.

Other analysis sets may be defined in the respective SAPs.

9.3. Statistical Analyses

Efficacy analyses for the Double-blind Treatment Period 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), for the primary efficacy endpoint and for the 2 key secondary efficacy endpoints 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 9.3.1.4.

Efficacy analyses for the LTE Treatment Period will be performed on the LTE FAS as described in Section 9.3.1.7.

9.3.1. Efficacy Analyses

9.3.1.1. Primary 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.
- **Treatment:** JNJ-63733657 (1000 mg, 3000 mg) versus placebo. Current standard of care AD medications (AChEIs and/or memantine) are permitted if dosing is stable before screening and throughout the study as described in Section 6.8.
- **ICEs and Corresponding Strategy:**

ICE	Strategy
Treatment discontinuation, with or without switch to alternative disease-modifying AD therapy.	Hypothetical strategy, as if participants adhere to the study intervention and do not switch to an alternative disease-modifying AD therapy.
Adding, changing, or stopping concomitant symptomatic non-disease-modifying AD medications.	Treatment policy strategy, targeting the effect of the study intervention 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.

Analysis Under the Primary Estimand

Observations after the occurrence of the ICE of treatment discontinuation will not be included in the primary analysis, consistent with the hypothetical treatment strategy for handling this ICE. Because study intervention must be discontinued prior to the addition of any disease-modifying AD therapy, observations after the occurrence of this ICE will not be included in the primary analysis. Data after ICEs will need to be collected however to support ICEs, which will be handled with a treatment policy strategy (eg, the ICE of adding, changing, or stopping concomitant symptomatic non-disease-modifying AD medications for the primary estimand and for supplementary estimands using treatment policy strategy for some ICEs). Missing data will be handled assuming missing data arise from a missing at random mechanism.

Sensitivity analyses for the primary estimand will be conducted to assess the robustness of conclusions from the primary analysis to missing data assumptions will include a tipping point analysis using multiple imputation with delta adjustment. Other sensitivity analyses will be described in the SAP.

Supplementary Estimand(s)

Supplementary estimands will be described in the SAP as needed.

9.3.1.2. Primary Endpoint

The primary efficacy endpoint is the iADRS change from baseline at Week 104. The primary analysis population includes all randomized participants who receive at least 1 dose of study intervention. The primary analysis will be based on a MMRM. The dependent variable will be the change from baseline in the iADRS total score. The model will include age, baseline tau burden on tau PET (as a continuous variable), and iADRS baseline score 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 standard of care medication (AChEIs and/or memantine) 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 treatment effects 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 calculated for the treatment differences versus placebo at each time point.

9.3.1.3. Key Secondary Endpoints

The key secondary efficacy endpoints of cognition and function, respectively, are the change from baseline in the ADAS-Cog13 score and the change from baseline in the ADCS-ADL-MCI total score, which are the 2 scales used to compose the primary efficacy endpoint of iADRS.

The estimands for the key secondary endpoints are defined by the following components:

- **Population:** Early AD participants with pathological brain tau [T+] who have met the inclusion/exclusion criteria.
- **Endpoints and Population Level Summary:**

Key Secondary Endpoint	Population Level Summary
Change from baseline on the ADAS-Cog13 total score at Week 104.	The difference in means between each dose and placebo at Week 104.
Change from baseline on the ADCS-ADL-MCI total score at Week 104.	The difference in means between each dose and placebo at Week 104.

- **Treatment:** JNJ-63733657 (1000 mg, 3000 mg) versus placebo.

- **ICEs and Corresponding Strategy:** ICEs will be addressed using the same strategies as for the primary efficacy analysis.

For key secondary endpoints, the analysis population includes all randomized participants who receive at least 1 dose of study intervention. The analysis method for each of the 2 key secondary efficacy endpoints will be MMRM, similar to the primary endpoint. Details will be presented in the SAP.

9.3.1.4. Multiple Comparison Adjustment

Statistical adjustment will be made to account for multiplicity due to multiple dose comparisons for the primary endpoint and the key secondary endpoints (Sections 9.3.1.2 and 9.3.1.3). 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 across the 2 JNJ-63733657 dose-placebo comparisons, a Hochberg sequential gatekeeping test procedure (Dmitrienko 2008) will be applied between families of hypotheses corresponding to the endpoints, and between the 2 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. Further details of this approach will be provided in the SAP. The following is a high-level summary of the approach:

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 prespecified level of significance.

In the first stage, 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, both dose groups will be compared with placebo on the first key secondary efficacy endpoint (change in ADAS-Cog13 total score) using the Hochberg procedure with a 2-sided $\alpha=0.05$. For the final stage, 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 $\alpha=0.05$.

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 will also be ruled not statistically significant. If only 1 dose group or neither dose group is superior to placebo on the first key secondary efficacy endpoint, the procedure will stop and the comparison of each JNJ-63733657 dose group to placebo for the second key secondary endpoint will also be ruled not statistically significant.

The details of the final multiple comparison procedure will be specified in the SAP.

9.3.1.5. Other Secondary Endpoints

Each of the other secondary continuous cognitive and functional endpoints will be analyzed using similar models to those used for the primary endpoint. The proportion of participants progressing

from CDR-GS 0 to 0.5 of higher, 0.5 to 1 or higher, or 1 to 2 or higher, from baseline to postbaseline, will be summarized and 95% confidence intervals for the difference in proportions between each JNJ-63733657 dose and placebo will be provided.

9.3.1.6. Exploratory Endpoints

Details of exploratory analyses will be provided in the SAP.

9.3.1.7. Long-Term Extension

Dose groups for the LTE Treatment Period will be defined according to the double-blind randomized treatment group and the LTE Treatment Period treatment assignment. Participants randomized to placebo in the Double-blind Treatment Period who have been assigned to JNJ-63733657 1000 mg or JNJ-63733657 3000 mg in the LTE Treatment Period will be defined as "Delayed Start JNJ-63733657 1000 mg" and "Delayed Start JNJ-63733657 3000 mg," respectively. Participants randomized to JNJ-63733657 1000 mg or JNJ-63733657 3000 mg in the Double-blind Treatment Period who enter the LTE will continue the same treatment assignment and will be defined as "Early Start JNJ-63733657 1000 mg" and "Early Start JNJ-63733657 3000 mg," respectively.

Efficacy analyses for the LTE Treatment Period will be performed on the LTE FAS using descriptive statistics. Summaries of efficacy data for the LTE FAS will include the LTE Treatment Period, and, as appropriate, the combined Double-blind Treatment Period and the LTE Treatment Period, to summarize changes over time. Additional analyses may be performed for the FAS including the Double-blind Treatment Period and any data available in the LTE Treatment Period.

For each of the cognitive, functional, and clinical scales, changes during the LTE Treatment Period (LTE Weeks 12, 36, and 64 for RBANS and Amsterdam IADL; LTE Weeks 24 and 52 for all other scales) compared to the double-blind baseline will be estimated with point estimates and 95% confidence intervals from an MMRM model, comparing the Early Start JNJ 1000 mg group with the Delayed Start 1000 mg group, and the Early Start JNJ 3000 mg group with the Delayed Start 3000 mg group. Further details will be provided in the LTE SAP.

Changes from double-blind and LTE baselines at each time point through the end of the LTE Treatment Period will be summarized as well.

The proportion of participants progressing from CDR-GS 0 to 0.5 of higher, 0.5 to 1 or higher, or 1 to 2 or higher, from the double-blind baseline through the first 1 year of the LTE Treatment Period, will be summarized using survival analysis methods and 95% confidence intervals for the difference in proportions between the Early Start JNJ-63733657 1000 mg group and the Delayed Start JNJ-63733657 1000 mg group and between the Early Start JNJ-63733657 3000 mg group and the Delayed Start JNJ-63733657 3000 mg group. 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 the double-blind baseline at each timepoint through the end of the LTE Treatment Period will be summarized as well. Analyses will take into consideration the varying amount of exposure to study intervention in the double-blind period prior to entering the LTE. Further details will be provided in the LTE SAP.

9.3.2. Safety Analyses

All safety analyses for the Double-blind Treatment Period will be performed on the Safety Analysis Set. Safety analyses for the LTE Treatment Period will be performed on the LTE Safety Analysis Set. Baseline will be defined as the most recent observation on or before the initial administration of study intervention in the respective period (double-blind or LTE). Summaries of safety data during the LTE will be presented for the entire LTE period, and separately for the 500 mg/vial, 50 mg/mL and 1000 mg/vial, 175 mg/mL dose periods of the LTE, where the 1000 mg/vial, 175 mg/mL dose period start is defined as the first day of study drug administration of 1000 mg/vial, 175 mg/mL product. Further details will be provided in the respective SAPs.

Adverse Events

For participants not participating in the LTE Treatment Period, any AE occurring at or after the initial administration of study intervention through the day of last dose in the Double-blind Treatment Period plus 90 days (during the safety Follow-up Period) is considered to be treatment-emergent in the Double-blind Treatment Period. For participants participating in the LTE Treatment Period, any AE occurring at or after the initial administration of study intervention in the LTE Treatment Period through the day of last dose in the LTE Treatment Period plus 90 days is considered to be treatment-emergent in the LTE Treatment Period. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by treatment group.

Summaries, listings, datasets, or participant narratives may be provided for those participants who die, discontinue intervention due to an AE, experience a severe AE or SAE, experience a treatment-emergent AESI (eg, hepatobiliary disorders/liver enzyme abnormality related AEs, infusion-related reactions) or meet other criteria, as needed. Specific analyses will be described in the respective SAPs.

Clinical Laboratory Tests

Laboratory data including hematology, chemistry, and urinalysis will be summarized by type of laboratory test. Reference ranges and predefined thresholds (specified in the SAP) will be used in the summary of laboratory data. Mean and mean change from baseline, with 95% confidence intervals will be calculated for all laboratory analytes at each scheduled time point. Frequency tabulations will be presented in pre- versus post-intervention cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the laboratory results above or below predefined thresholds will be provided. A listing of participants with any laboratory results outside the reference ranges will be provided. A listing of participants with any results above or below predefined thresholds will also be provided.

Electrocardiograms

The ECG data will be summarized by ECG parameter. Mean and mean change from baseline, with 95% confidence intervals will be calculated at each scheduled time point. Frequency tabulations of the abnormalities will be presented.

The ECG variables that will be analyzed are heart rate, PR interval, QRS duration, QT interval, QTcB, QTcF, and QTcL (Sagie 1992). The percentage of participants with QTc interval >450 milliseconds, >480 milliseconds, or >500 milliseconds will be summarized, as will the percentage of participants with QTc interval increases from baseline >30 milliseconds or >60 milliseconds.

All clinically relevant abnormalities in ECG waveform that are changes from the baseline readings will be reported (eg, changes in T-wave morphology or the occurrence of U-waves).

Vital Signs

Vital signs including supine and standing pulse and BP (systolic and diastolic) and temperature will be summarized over time, using descriptive statistics and/or graphically. Orthostatic changes will be assessed by subtracting standing BP and pulse from the supine measurements and will be summarized. The percentage of participants with values above or below predefined thresholds will be summarized.

A listing of participants with any results above or below predefined thresholds will also be provided.

Physical and Neurological Examinations

Physical and neurological examination findings will be summarized at each scheduled time point. Frequency tabulations of the abnormalities will be presented.

Columbia Suicide Severity Rating Scale (C-SSRS)

A frequency distribution of C-SSRS scores at each scheduled time point by treatment will be provided. Shifts from the baseline visit to the most severe/maximum score during the Treatment Period will be summarized by treatment. The maximum score assigned for each participant will also be summarized into 1 of 3 categories: no suicidal ideation or behavior (0), suicidal ideation (1 to 5), suicidal behavior (6 to 10).

Brain Magnetic Resonance Imaging (MRI)

Descriptive statistics of changes from baseline will be summarized at each scheduled time point. The MRI observations including hippocampal (right and left), whole brain, and ventricular volume, and other findings will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point.

9.3.3. Other Analyses

Pharmacokinetic Analyses

If feasible, population PK analysis of serum concentration-time data of may be performed using nonlinear mixed-effects modeling, using data from the double-blind and/or the LTE Treatment Period. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline participant characteristics (demographics, laboratory variables,

genotypes, race, etc) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

A snapshot date for PK samples to be analyzed will be defined, if required. Samples collected before this date will be analyzed for in a blinded manner and included in the population PK analysis. Samples collected after the snapshot date will be analyzed at a later date, and may be included in a population PK re-analysis when they become available after database lock.

Data will be listed for all participants with available serum and CSF concentrations per intervention group, and per period (eg, double-blind or LTE). 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).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All participants and samples excluded from the analysis will be clearly documented in the study report. 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 each period (double-blind and LTE). Additional summaries will be provided to explore the relationship between concentrations of JNJ-63733657 and hepatic safety.

Biomarkers Analyses

Secondary biomarker endpoints will be summarized, including change from baseline in accumulation of brain tau burden over a minimum of 104 weeks, as measured by tau PET and change from baseline in CSF concentrations of total, free, and bound p217+tau fragments over a minimum of 104 weeks. For participants entering the LTE Treatment Period, biomarkers will be summarized over the double-blind and/or LTE Treatment Periods as appropriate. Further details will be specified in the LTE SAP.

Immunogenicity Analyses

The incidence of anti-JNJ-63733657 antibodies will be summarized for all participants who receive at least 1 dose of JNJ-63733657 and have appropriate samples for detection of antibodies to JNJ-63733657 (ie, participants with at least 1 sample obtained after their first dose of JNJ-63733657 in the respective double-blind or LTE Treatment Period). In addition, the incidence of anti-JNJ-63733657 antibodies will be summarized separately for participants with and without treatment-emergent hepatic enzyme elevations ≥3xULN.

A listing of participants who are positive for antibodies to JNJ-63733657 will be provided in the double-blind and LTE Treatment Period, respectively. The maximum titers of antibodies to JNJ-63733657 will be summarized for participants who are positive for antibodies to JNJ-63733657 in the double-blind and LTE Treatment Period, respectively.

The incidence of neutralizing antibodies to JNJ-63733657 will be measured to assess the potential relationship between anti-JNJ-63733657 antibodies and hepatic enzyme elevations. Summaries will be produced for participants who are positive for antibodies to JNJ-63733657 and have samples evaluable for neutralizing antibodies to JNJ-63733657 in the double-blind and LTE Treatment Periods, respectively.

Pharmacokinetic/Pharmacodynamic Analyses

An exploratory objective of this study will be to evaluate the relationship between dose and PK of JNJ-63733657 on biomarker assessments in the Double-blind Treatment Period, through Year 1 of the LTE Treatment Period, and through the end of the LTE Treatment Period.

Pharmacogenomic Analyses

DNA samples may be analyzed for APOE genotype and to allow for the possible evaluation of genetic factors that may influence the PK, PD, immunogenicity, safety, or tolerability of JNJ-63733657 and pathways related to AD/tauopathy. Results may be presented in a separate report.

Health Outcome Scales

Health outcome scale data will be descriptively summarized by intervention group.

9.4. Interim Analysis

Interim analyses may be performed. If conducted, these analyses will inform cognitive safety for this trial, futility for this trial, or success for the purpose of planning and potentially starting a new trial. The study will be monitored in a blinded manner to evaluate if there are any factors that may influence the results of the interim analysis, eg, regional differences. If, for example, it is noted that a particular region would contribute to the interim analysis disproportionately, the interim analysis may not be performed.

1. The first interim analysis may be conducted to assess for cognitive safety (worsening) for study intervention relative to placebo.
2. Another interim analysis to evaluate futility or success on clinical endpoints may be performed when approximately half of the randomized Early AD participants reach 104 weeks. In addition, progression of tau pathology may be assessed. Futility or success will be evaluated in the context of interim results for clinical endpoints.

For the above 2 interim analyses, an interim analysis SAP and charter will be developed detailing the planned interim analyses and how the analyses will be executed. An external, independent statistical support group will perform the interim analyses occurring during the Double-blind Treatment Period and will communicate the results to the IDMC who will make recommendations based on the rules defined in the interim analysis SAP. Unblinded PK, PD, and immunogenicity analysis may be performed by an independent pharmacometrician using data available at each interim analysis or from an IDMC safety review, as appropriate, while keeping the study team blinded. Analysis methods for this analysis, if performed, will be documented in the PK or other analysis plan as appropriate. Unblinded safety data analyses, possibly including PK and/or

immunogenicity data, may be performed by an independent pharmacometrician, an independent statistical support group, and/or other experts not part of the study team if required to assess and manage an emergent safety signal. Neither the Janssen study team members actively involved in study conduct, clinical data collection, interpretation, and analysis nor investigational site staff will have access to potentially unblinding participant-level information while the study remains blinded.

Procedures will be in place and documented in a separate charter and operational plan to ensure that the results of the interim analyses do not influence the conduct of the study, investigators, or participants.

The Primary Double-blind Analysis will be performed when the last participant completes the Week 104 visit of the Double-blind Treatment Period (including participants who discontinue treatment but continue in the Double-blind Treatment Period and provide off-treatment data) or withdraws prior to the Week 104 visit of the Double-blind Treatment Period. The End of Double-blind Analysis will be performed when all participants have completed at least the Week 104 visit of the Double-blind Treatment Period, or are discontinued from the Double-blind Treatment Period and are not continuing into the LTE Treatment Period and have completed the Follow-up Period (90 days after last dose of study intervention).

Interim analyses may be conducted by the sponsor during the LTE Treatment Period, eg, to support future study planning and/or health authority interactions. Details will be provided in the LTE interim analysis SAP.

9.5. Sample Size Determination

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 4. 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 in the Double-blind Treatment Period, provides approximately 87% power of determining successful slowing of clinical decline relative to the control arm (at Week 104 [24 months] time point), at a 2-sided Type 1 error rate of 5%. This sample size assumes an initial 7.5% annual dropout rate, an anticipated higher (13%) annual dropout rate after an approved disease-modifying therapy for AD becomes available at different times in different regions, and an accrual rate of 20 participants per month.

Table 4: 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

The study sample size may be adjusted based on midcourse study information (eg, variance estimate, dropout rate) and external data. Full details will be specified in the SAP.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

A-	without elevated brain amyloid
A+	with elevated brain amyloid
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's Disease
ADAD	autosomal dominant Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale - Cognitive
ADAS-Cog11	Alzheimer's Disease Assessment Scale - Cognitive, 11-item version
ADAS-Cog13	Alzheimer's Disease Assessment Scale - Cognitive, 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
AESI(s)	adverse event(s) of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APOE	apolipoprotein E
AST	aspartate aminotransferase
ATN	amyloid, tau, neurodegeneration
Aβ	amyloid beta; any appended subscripts refer to the length of the peptide (amino acids)
BP	blood pressure
CDR	Clinical Dementia Rating
CDR-GS	Clinical Dementia Rating - Global Score
CDR-SB	Clinical Dementia Rating - Sum of Boxes
CNS	central nervous system
CRF	case report form
CRP	C-reactive protein
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
DB	double-blind (abbreviated only in figures, tables, and when referring to "End of DB")
DILI	drug-induced liver injury
DMI	Delayed Memory Index
DNA	deoxyribonucleic acid
DRC	Data Review Committee
EC	Exclusion Criterion/Criteria (abbreviated only in Appendix 8)
ECG	electrocardiogram
eCOA	electronic clinical outcomes assessment
eDC	electronic data capture
ET	early termination
EU	European Union
FAS	full efficacy analysis set
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
FU	follow-up (abbreviated only in Appendix 8)
GCP	Good Clinical Practice
GDS-30	30-item Geriatric Depression Scale
GGT	gamma-glutamyl transferase
GLDH	glutamate dehydrogenase
GLP	Good Laboratory Practice
HAC	Hepatic Adjudication Committee
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIS	Hachinski Ischemic Scale
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
HSV	herpes simplex virus

IADL	Instrumental Activities of Daily Living
iADRS	integrated Alzheimer's Disease Rating Scale
iADRS-MCI	integrated Alzheimer's Disease Rating Scale for Mild Cognitive Impairment
IB	Investigator's Brochure
IC	Inclusion Criterion/Criteria (abbreviated only in Appendix 8)
ICE	intercurrent event
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgM	immunoglobulin M
INR	international normalized ratio
IPPI	Investigational Product Preparation Instructions
IRB	Institutional Review Board
IV	intravenous(ly)
IWRS	Interactive Web Response System
LDH	lactate dehydrogenase
LTE	Long-Term Extension
MAD	multiple ascending dose
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MOA	mechanism of action
MRI	magnetic resonance imaging
N-	without neurodegeneration
N+	with neurodegeneration
NfL	neurofilament light chain
NFT	neurofibrillary tangle
NPI	Neuropsychiatric Inventory
p217+tau	tau protein phosphorylated at amino acid 217
p181tau	tau protein phosphorylated at amino acid 181
PCC	Protocol Clarification Communication
PD	pharmacodynamic(s)
PET	positron emission tomography
PHF	paired helical filament
PK	pharmacokinetic(s)
PQC	product quality complaint
PSEN	presenilin
PT	prothrombin time
p-tau	phosphorylated tau
PTT	partial thromboplastin time
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
RAGE	receptor for advanced glycation end products
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RNA	ribonucleic acid
RTSM	Randomization and Trial Supply Management
RUD-Lite	Resource Utilization in Dementia Lite
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SoA	schedule of activities
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reactions
T-	without elevated tau

T+	with elevated tau
$t_{1/2}$	terminal half-life
TBili	total bilirubin
TEAE	treatment-emergent adverse event
TREM2	triggering receptor expressed on myeloid cells 2
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
Y/N	yes/no
YKL40	chitinase-3-like protein 1

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the SoA.

The central laboratory should be used for all protocol-required safety laboratory assessments. However, the use of a local laboratory/test is permitted, if required and local regulations permit.

The actual date of assessment and, if required, the actual time of the assessment of laboratory samples will be recorded in the source documentation and in the eCRF or laboratory requisition form.

Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td rowspan="2">Hematology</td><td>• Platelet count
• Red blood cell count
• Hemoglobin
• Hematocrit</td><td><u>Red Blood Cell (RBC) Indices:</u>
• Mean corpuscular volume (MCV)
• Mean corpuscular hemoglobin (MCH)
• % Reticulocytes</td><td><u>White Blood Cell (WBC) Count With Differential:</u>
• Neutrophils
• Lymphocytes
• Monocytes
• Eosinophils
• Basophils</td></tr>
<tr><td colspan="3">Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. An RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.</td></tr>
<tr><td>Clinical Chemistry</td><td colspan="2">• Sodium
• Potassium
• Chloride
• Bicarbonate
• Blood urea nitrogen (BUN)
• Creatinine
• Glucose (fasting)
• Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic transaminase (SGOT)
• Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase (SGPT)
• Gamma-glutamyltransferase (GGT)</td><td>• Total bilirubin (TBili)
• Fractionated bilirubin
• Alkaline phosphatase (ALP)
• Creatine phosphokinase
• Glutamate dehydrogenase (GLDH)
• Uric acid
• Calcium
• Phosphate
• Albumin
• Total protein
• Cholesterol
• Triglycerides
• Magnesium
• Vitamin B12 (screening only)
• Folic acid (screening only)</td></tr>
</table>

<table>
<tr><th>Laboratory Assessments</th><th colspan="2">Parameters</th></tr>
<tr><td rowspan="2">Routine Urinalysis</td><td><u>Dipstick</u>
• Specific gravity
• pH
• Glucose
• Protein
• Blood
• Ketones
• Bilirubin
• Urobilinogen
• Nitrite
• Leukocyte esterase</td><td><u>Sediment (if dipstick result is abnormal)</u>
• Red blood cells
• White blood cells
• Epithelial cells
• Crystals
• Casts
• Bacteria</td></tr>
<tr><td colspan="2">Dipstick and flow cytometric analysis of the urine samples will be performed in parallel, ie, in the same sample at the same time. In case of discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically. Crystals, casts, and bacteria will only be reported if they are present.</td></tr>
<tr><td>Other Screening Tests</td><td colspan="2">• Serology (HIV antibody and, for participants with elevated transaminases only, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)
• Urine drug screen (opiates [including methadone], cocaine, amphetamines, methamphetamines, barbiturates, and benzodiazepines)
• Thyroid-stimulating hormone (TSH)
• For participants undergoing lumbar puncture only - coagulation (prothrombin time [PT], partial thromboplastin time [PTT], international normalized ratio [INR])</td></tr>
<tr><td>Other Laboratory Tests (associated with scheduled timepoints and/or Appendix 7)</td><td colspan="2">• INR
• C-reactive protein (CRP)
• Ferritin
• Viral serology: Includes hepatitis A IgM antibody; HBsAg and total HBcAb (IgG and IgM antibodies) with reflex to HBV-DNA if positive; hepatitis C IgG antibody with reflex to HCV-RNA if positive; cytomegalovirus IgM antibody; Epstein-Barr virus capsid antigen IgM (or, if unavailable, heterophile antibody or monospot testing); hepatitis E IgM antibody; and HSV-1 and -2 IgG
• Serum creatine phosphokinase
• Lactate dehydrogenase (LDH)
• Serum albumin
• Fractionated ALP isoenzymes, if available
• Anti-nuclear antibody; anti-smooth muscle antibody; Type 1 anti-liver kidney microsomal antibodies; and quantitative total immunoglobulin G (IgG) or gamma globulins
• Serum acetaminophen adduct assay, if available</td></tr>
</table>

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

10.3.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and country- or territory-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Clarification Communications (PCCs)

If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a PCC may be prepared. The PCC document will be communicated to the Investigational Site, Site Monitors, Local Trial Managers, Clinical Trial Managers, and/or Contract Research Organizations, who will ensure that the PCC explanations are followed by the investigators.

The PCC document may be shared by the sites with IECs/IRBs per local regulations.

The PCC documents must NOT be used in place of protocol amendments, but the content of the PCC document must be included in any future protocol amendments.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for nonacceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

In situations where a departure from the protocol is unavoidable during the study, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact must be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendments must be submitted to the appropriate regulatory authorities in each respective country/territory, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator.
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable.
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable.
- Documentation of investigator qualifications (eg, curriculum vitae).
- Completed investigator financial disclosure form from the principal investigator, where required.
- Signed and dated Clinical Trial Agreement, which includes the financial agreement.
- Any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators.
- Documentation of subinvestigator qualifications (eg, curriculum vitae).
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable.
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

Independent Ethics Committee or Institutional Review Board (IEC/IRB)

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments.
- Sponsor-approved ICF (and any other written materials to be provided to the participants).
- IB (or equivalent information) and amendments/addenda.
- Sponsor-approved participant recruiting materials.
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable.
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB).
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants.
- Any other documents that the IEC/IRB requests to fulfill its obligation.

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct).
- Revision(s) to ICF and any other written materials to be provided to participants.
- If applicable, new or revised participant recruiting materials approved by the sponsor.
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable.
- New edition(s) of the IB and amendments/addenda.
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually).
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study intervention.
- New information that may adversely affect the safety of the participants or the conduct of the study.
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants.

- Report of deaths of participants under the investigator's care.
- Notification if a new investigator is responsible for the study at the site.
- Development Safety Update Report and Line Listings, where applicable.
- Any other requirements of the IEC/IRB.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Country/Territory Selection

This study will only be conducted in those countries/territories where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1 (Study-Specific Ethical Design Considerations).

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

10.3.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study. Refer to Required Prestudy Documentation (above) and contracts for details on financial disclosure.

10.3.3. Informed Consent Process

Written Informed Consent by the participant may be obtained through various sources as determined by regulations as well as study and/or patient preferences.

Informed Consent at Study Entry

Each participant must give consent at the time of study entry according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent must be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, if needed. The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent must be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

After informed consent for the study is appropriately obtained, the participant will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the participant.

Where local regulations require, a separate ICF may be used for the required DNA component of the study.

Informed Consent After Study Entry

If necessary, ICFs may be updated during the study and will require the participant (or legally designated representative) to sign and date.

Participants who progress to more advanced clinical stages of AD during the study should be assessed in a manner consistent with clinical practice for understanding of potential risks/benefits of participation by the investigator and may continue in the study if deemed by the investigator to have capacity to make the decision to remain in the study. See Section 4.2.1.1 (Ethical Considerations for Participants Unable to Consent During the Study).

For the purposes of this study, all references to participants who have provided consent refers to the participants who have provided consent at study entry and, during the study, have provided consent or for whom a legally designated representative has provided consent with participant assent, where required by local regulations.

10.3.4. Data Protection

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study and study partners will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes information about, and where required per applicable regulations, explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. The informed consent also provides information to address the lawful transfer of the data to other entities and to other countries/territories.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete, or make requests concerning his or her personal data in accordance with applicable data protection law. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects taking into consideration the nature of the data security breach as necessary to address other obligations such as notifying appropriate authorities in accordance with applicable data protection law.

Exploratory DNA, PD, biomarker, PK, and immunogenicity research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

10.3.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand JNJ-63733657, to understand AD, to understand differential intervention responders, and to develop tests/assays related to JNJ-63733657 and AD. The research may begin at any time during the study or the post-study storage period. Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers.

10.3.6. Committees Structure

Independent Data Monitoring Committee (IDMC)

An IDMC will be established to ensure the continuing safety of the participants enrolled in this study while the study sponsor remains blinded, and to review interim analyses of efficacy and biomarkers during the double-blind period, if performed. This committee will consist of at least

1 medical expert in the relevant therapeutic area, at least 1 statistician, and at least 1 biomarker expert; committee membership responsibilities, authorities, and procedures will be documented in the IDMC charter.

Hepatic Adjudication Committee (HAC)

The HAC, comprised of 3 hepatologists with expertise in DILI, will review all cases of potential DILI in the study in a blinded manner. The HAC will evaluate the details of each case and adjudicate to probable, possible, or unlikely DILI. The membership responsibilities and procedures for the HAC will be documented in its charter.

Data Review Committee (DRC)

A DRC may be established to evaluate potential mechanisms for hepatic abnormalities observed in study participants. Committee membership responsibilities, authorities, and procedures will be documented in its charter and an operational plan.

10.3.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding JNJ-63733657 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of JNJ-63733657 and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of pharmacogenomic or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and ICMJE guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator.

The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data, for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the interim results of clinical studies as required by law. The disclosure of the study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

10.3.8. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study site personnel before the start of the study.

The sponsor may review the eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

10.3.9. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in the CRF. All CRF entries, corrections, and alterations must be made by the investigator or authorized study site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the participant's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a participant visit and the forms must be available for review at the next scheduled monitoring visit.

All participative measurements (eg, questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study site personnel.

10.3.10. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents must be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

Clinical scales and other assessments may be recorded on paper (if applicable) or directly into an electronic device and will be considered source data.

The minimum source documentation requirements for Section 5.1 (Inclusion Criteria) and Section 5.2 (Exclusion Criteria) that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol-required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the eCRF in the protocol include the eSource system, but information collected through eSource may not be limited to that found in the eCRF.

10.3.11. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor may compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study site personnel and are accessible for verification by the sponsor study site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study site personnel. The sponsor expects that, during monitoring visits, the relevant study site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

10.3.12. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance

with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study site personnel are responsible for being present and available for consultation during routinely scheduled study site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator must immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.3.13. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8 (Essential Documents for the Conduct of a Clinical Trial), and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

10.3.14. Study and Site Start and Closure

First Act of Recruitment

The first participant screened is considered the first act of recruitment and it becomes the study start date.

Study/Site Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A

study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended intervention.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study intervention development.

10.4. Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Adverse Event Definitions and Classifications

Adverse Events (AEs)

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or noninvestigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or noninvestigational) product, whether or not related to that medicinal (investigational or noninvestigational) product. (Definition per ICH.)

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF. Refer to the "All Adverse Events" subheading under Section 8.6.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information), for time of last AE recording.

Adverse Events of Special Interest (AESIs)

Treatment-emergent AESIs will be collected in the eCRF and examined separately, grouped in the following categories including, but not limited to:

- "Hepatobiliary disorders/Liver enzyme abnormality" related AEs.
- Infusion-related reactions (excluding local infusion site reactions [eg, bruising, pain, extravasation]).

The list of AESIs (MedDRA preferred terms) will be defined in the SAP.

Serious Adverse Events (SAEs)

An SAE, based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use, is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening. (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it was more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is a suspected transmission of any infectious agent via a medicinal product.
- Is Medically Important.*

*Medical and scientific judgment must be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For JNJ-63733657, the expectedness of an AE will be determined by whether or not it is listed in the IB.

10.4.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is assessed by the investigator. The following selection must be used to assess all AEs.

- **Related:** There is a reasonable causal relationship between study intervention administration and the AE.
- **Not Related:** There is not a reasonable causal relationship between study intervention administration and the AE. The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.4.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

- **Mild**: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: Sufficient discomfort is present to cause interference with normal activity.
- **Severe**: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator must use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

10.4.4. Special Reporting Situations

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention.

- Suspected abuse/misuse of a sponsor study intervention.
- Accidental or occupational exposure to a sponsor study intervention.
- Medication error, intercepted medication error or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product; eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors).
- Exposure to a sponsor study intervention from breastfeeding.
- Reporting of participant pregnancy or participant partner's pregnancy.

Participant-specific special reporting situations must be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE must be recorded on the SAE page of the eCRF.

10.4.5. Procedures

All Adverse Events (AEs)

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient period, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Adverse Events of Special Interest (AESIs)

Treatment-emergent AESIs will be examined separately, grouped in the following categories including, but not limited to "Hepatobiliary disorders/Liver enzyme abnormality" related AEs and infusion-related reactions.

The list of AESIs (MedDRA preferred terms) will be defined in the SAP.

Serious Adverse Events (SAEs)

All SAEs that have not resolved by the end of the study, or that have not resolved upon the participant's discontinuation from the study, must be followed until any of the following occurs:

- The event resolves.
- The event stabilizes.
- The event returns to baseline, if a baseline value/status is available.
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility, routine colonoscopy, etc.)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

The cause of death of a participant in a study within 30 days of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered an SAE.

10.4.6. Product Quality Complaint Handling

Definition

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

Procedures

All initial PQCs must be reported to the sponsor by the study site personnel within 24 hours after being made aware of the event. A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.4.7. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who must be contacted regarding safety issues, PQC, or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

10.5. Appendix 5: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1 (Inclusion Criteria). Pregnancy information will be collected and reported as noted in Section 8.6.5 (Pregnancy) and in Appendix 4.

Definitions

- ***Female Participants of Childbearing Potential:*** A female participant is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).
- ***Female Participants Not of Childbearing Potential:***
  - **Premenarchal:** A premenarchal state is one in which menarche has not yet occurred.
  - **Postmenopausal:** A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in female participants not using hormonal contraception or HRT; however, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - **Permanently Sterile** (for the purpose of this study):
    - Permanent sterilization methods include hysterectomy, or bilateral salpingectomy, or bilateral oophorectomy.
    - Has congenital abnormalities resulting in sterility.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal female participant experiences menarche) or the risk of pregnancy changes (eg, a female participant becomes sexually active where pregnancy can occur), then a female participant must begin a highly effective method of contraception, as described throughout the inclusion criteria.

Contraceptive (birth control) use by male participants or female participants must be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use must be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:

USER INDEPENDENT
Highly Effective Methods That Are User Independent
Failure rate[a] of <1% per year when used consistently and correctly.

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Tubal closure (eg, bilateral tubal occlusion, bilateral tubal ligation)
- Azoospermic partner (such as vasectomized or due to medical cause). (Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the female participant of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception must be used. Spermatogenesis cycle is approximately 74 days.)

USER DEPENDENT
Highly Effective Methods That Are User Dependent
Failure rate[a] of <1% per year when used consistently and correctly.

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal, or injectable.
- Progestogen-only hormone contraception associated with inhibition of ovulation: oral or injectable.
- Sexual abstinence. (Sexual abstinence is considered a highly effective method only if defined as refraining from intercourse where pregnancy can occur during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)

NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY
Not Considered Highly Effective
Failure rate[a] of ≥1% per year.

- Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
- Male or female condom with or without spermicide.
- Cap, diaphragm, or sponge with spermicide.
- A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods).
- Periodic abstinence (calendar, symptothermal, post-ovulation methods).
- Withdrawal (coitus interruptus).
- Spermicides alone.
- Lactational amenorrhea method.

[a] Typical use failure rates may differ from those when used consistently and correctly. Use must be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

10.6. Appendix 6: Study Conduct During a Natural Disaster/Major Disruption/ Pandemic

Guidance on Study Conduct During a Natural Disaster/Major Disruption/Pandemic

It is recognized that a major disruption may have an impact on the conduct of this clinical study due to, for example, isolation or quarantine of participants and study site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being unavailable, isolated, or reassigned to critical tasks.

The sponsor is providing options for study-related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgment of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's travel to the study site is considered to be dangerous, study participation may be interrupted, and study follow-up conducted. If it becomes necessary to discontinue participation in the study, the procedures outlined in the protocol for discontinuing study intervention will be followed.

If, as a result of the major disruption scheduled visits cannot be conducted in person at the study site, they will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "Major Disruption Related" in the eCRF.

Guidance Specific to This Protocol:

- Additional guidance for study procedures that may be impacted will be provided by the sponsor at a participant, country/territory, and/or global level to determine appropriate management of the trial participant(s). This guidance does not supersede any local or government requirements or the clinical judgment of the investigator to protect the health and well-being of participants and site staff.
- Given that study data will be collected through various methods (eg, eCRF, eCOA), guidance for documenting missing data related to natural disasters/major disruptions/pandemics will be provided in the study-specific manuals and/or guidelines.
- Withdrawal from the study for reasons related to natural disasters/major disruptions/pandemics should be recorded with a designation of "Major Disruption Related." Additional guidance will be provided in the eCRF completion guidelines.
- Any AEs or SAEs considered to be related to natural disasters/major disruptions/pandemics should be recorded with a designation of "Major Disruption Related" and in accordance with any local or government requirements. Additional guidance will be provided in the eCRF completion guidelines.
- Intravenous infusion of study intervention should be administered as required in the protocol (every 4 weeks ± 7 days) to avoid impacting efficacy evaluations. This should occur at the clinic, if feasible. If not feasible due to natural disasters/major disruptions/pandemics, this could occur at home via a qualified health care professional in coordination with the sponsor. If neither option is feasible, please contact the sponsor's medical monitor or delegate for direction.
- The following study assessments/procedures could be conducted remotely by qualified health care professionals: AEs, concomitant medications.
- The following study assessments/procedures could be conducted in person via home visits by qualified health care professionals: physical examination, neurological examination, BP, pulse, weight, temperature, AEs, concomitant medications, ECGs, IV infusions, clinical laboratory tests, blood for biomarkers, PK, and C-SSRS.
- The following assessments should be conducted at the study site/imaging center, unless agreed to by the sponsor: cognitive measures (ADAS-Cog13, RBANS); clinical scales (ADCS-ADL-MCI, Amsterdam IADL, CDR, NPI, RUD-Lite, QOL-AD); imaging (MRI, PET); and lumbar punctures. To reduce missing data, some of these assessments could potentially be delayed until the participant can visit the study site/imaging center; guidance regarding delaying these assessments will be provided by the sponsor.

At sites impacted by the natural disasters/major disruptions/pandemics, clinical site GCP audits with direct impact/engagement from the clinical investigator team would not be conducted to comply with national, local, and/or organizational social distancing restrictions. Additional quality assurance activities such as remote audits or focused review of study-related documents may take place with limited impact/engagement if possible.

10.7. Appendix 7: Hepatic Safety Monitoring Assessments

"Hepatobiliary disorders/Liver enzyme abnormality" related AEs will be monitored, and additional data may be collected on dedicated pages of the eCRF.

If local requirements for hepatic safety monitoring are more stringent than those outlined in this section of the protocol, then the local requirements will take precedence.

Table 5: Hepatic Adverse Event Definitions and Reporting Requirements

Definitions	Reporting Requirements
Abnormal ALT<3xULN that is considered clinically significant	Report AE (leading to treatment interruption, if applicable) in eCRF
ALT or AST ≥3xULN and ≤5xULN **and asymptomatic**	Report AE leading to treatment interruption in eCRF
ALT or AST ≥3xULN **and** INR>1.5 (in absence of anticoagulants)	Report SAE in eCRF **and** to Global Drug Safety
Potential Hy's Law case (ALT or AST ≥3xULN **and** TBili>2xULN [or at least doubling of direct bilirubin in known Gilbert's syndrome] **without** notable increase in ALP>2xULN)	Report SAE in eCRF **and** to Global Drug Safety
ALT or AST ≥3xULN **with symptoms** (eg, general malaise, fatigue, abdominal pain, nausea, vomiting, or rash with eosinophilia)	Report SAE in eCRF **and** to Global Drug Safety
ALT or AST >5xULN (with or without TBili>2xULN)	Report SAE in eCRF **and** to Global Drug Safety

Table 6: Hepatic Follow-up Requirements

Criteria	Actions Required	Monitoring Frequency for Hepatic Chemistry Assessments
ALT or AST ≥3xULN and INR>1.5 (in absence of anticoagulants) Potential Hy's Law case [a]	• Permanently discontinue study intervention • Perform: ○ Hepatic Event Assessments - Level 1 (Section 10.7.1) within 48 hours **and** ○ Hepatic Event Assessments - Level 2 (Section 10.7.2) • Hospitalize if clinically appropriate • Report to sponsor as SAE	Twice weekly ALT, AST, ALP, TBili, fractionated bilirubin, GGT, GLDH until improvement [c]
ALT or AST		
ALT or AST >5xULN (participant is asymptomatic)	• Permanently discontinue study intervention • Perform Hepatic Event Assessments - Level 1 (Section 10.7.1) within 48 hours • Report to sponsor as SAE	At least weekly ALT, AST, ALP, TBili, fractionated bilirubin, GGT, GLDH until improvement [c]
ALT or AST ≥3xULN with symptoms [b]	• Interrupt study intervention • Perform Hepatic Event assessments - Level 1 within 48 hours (Section 10.7.1) • Hospitalize if clinically appropriate • Report to sponsor as SAE	At least weekly ALT, AST, ALP, TBili, fractionated bilirubin, GGT, GLDH until improvement [c]
ALT or AST ≥3xULN to ≤5xULN (participant is asymptomatic)	• Interrupt study intervention • Perform Hepatic Event Assessments - Level 1 (Section 10.7.1) within 72 hours • Inform sponsor	Weekly ALT, AST, ALP, TBili, fractionated bilirubin, GGT, GLDH until improvement [c]
ALT		
ALT >1.5 to <3xULN	• Interrupt study intervention if predose ALT within 14 days >1.5xULN (retesting is allowed once) • Inform sponsor	Check ALT, AST, ALP, TBili, fractionated bilirubin, GGT, GLDH once in 2 weeks (or earlier as clinically appropriate)
ALT >1 to ≤1.5xULN	• Review participant's risk factors for liver enzyme elevation	Consider checking ALT, AST, ALP, TBili, fractionated bilirubin, GGT, GLDH once in 2 weeks (or earlier as clinically appropriate)

[a] Elevated ALT or AST ≥3xULN and TBili>2xULN (or at least doubling of direct bilirubin in known Gilbert's syndrome) but without notable increase in ALP to >2xULN.
[b] General malaise, fatigue, abdominal pain, nausea, vomiting, rash with eosinophilia.
[c] Improvement is defined as consistent downward trend of ALT and/or AST elevation. Thereafter, use this table to determine the monitoring frequency for each level/stage of hepatic event.

10.7.1. Hepatic Event Assessments - Level 1

- Viral serology: Hepatitis A IgM antibody; HBsAg and total HBcAb (IgG and IgM antibodies) with reflex to HBV-DNA if positive; Hepatitis C IgG antibody with reflex to HCV-RNA if positive; cytomegalovirus IgM; Epstein-Barr virus capsid antigen IgM (or, if unavailable, heterophile antibody or monospot testing); Hepatitis E IgM; and HSV-1 and -2 IgG.
- Obtain INR, CRP, and ferritin with each hepatic chemistry assessment (per "Monitoring Frequency for Hepatic Chemistry Assessments" column in Table 6).
- Obtain blood samples at the first hepatic chemistry follow-up assessment (per "Monitoring Frequency for Hepatic Chemistry Assessments" column in Table 6) for PK and immunogenicity analysis (ie, not collected at every follow-up assessment). Additional samples may be collected, if necessary.
- Obtain serum creatine phosphokinase, LDH, and albumin.
- Obtain complete blood count with differential to assess eosinophilia.
- If ALP>2xULN: recommend obtaining abdominal imaging (eg, ultrasound) and fractionated ALP isoenzymes, if available.
- Abdominal imaging (eg, ultrasound) may also be considered for other clinical scenarios; eg, if GGT or bilirubin is elevated.
- Record the appearance or worsening of clinical symptoms of hepatic injury, or hypersensitivity, on the eCRF (when available), as per eCRF completion guidelines.
- Record use of concomitant medications (including acetaminophen, herbal remedies, supplements, recreational drugs and other over-the-counter medications).
- Record alcohol use on the eCRF (when available), as per eCRF completion guidelines.
- Obtain and appropriately store an additional serum sample for future testing.

10.7.2. Hepatic Event Assessments - Level 2 (for ALT or AST ≥3xULN and TBili>2xULN or INR>1.5)

- A specialist or hepatology consultation is recommended to guide evaluation.
- Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins.
- Serum acetaminophen adduct assay, if available, to assess potential acetaminophen contribution to hepatic injury in participants with definite or likely acetaminophen use in the preceding week.
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate hepatic disease:
  - Liver biopsy may be considered and discussed with local specialist or hepatology consult:
    - In participants with severe hepatic injury.
    - In participants when serology raises the possibility of autoimmune hepatitis.

  - In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention.
  - In participants with acute or chronic atypical presentation.
- Inform sponsor if liver biopsy is clinically indicated.
- If liver biopsy is performed, standard histopathology should be performed by a pathologist with expertise in hepatic pathology.
- In addition, it is recommended that additional liver biopsy samples are collected and shipped to the sponsor for further exploratory analyses (eg, for immunohistochemistry and lymphocyte isolation). If this is feasible, request current guidance from sponsor prior to scheduling the procedure.
- After completion of liver biopsy, complete eCRF, once available, as per eCRF completion guidelines. Provide SAE follow-up report to Global Drug Safety with procedure and results as soon as available.
- If additional samples for sponsor are collected, inform sponsor to arrange storage/shipment.

10.7.3. Additional Considerations for Hepatic Adverse Events

For any scheduled or unscheduled laboratory assessments performed locally and for any nonserious AEs, data should be entered in the eCRF within 3 working days. For SAEs, data should be entered in the eCRF within 24 hours.

An interruption (≥1 dose missed) or permanent discontinuation of the study intervention should be clearly documented and reflected in the eCRF.

Re-initiation of treatment after an interruption for a hepatic AE or SAE:

- Highest ALT and AST during the event <3xULN: re-initiation of study intervention can be considered at investigator discretion once the participant no longer meets treatment interruption criteria. Sponsor may be consulted as needed.
- Highest ALT and AST during the event ≥3xULN: re-initiation of study intervention can only be considered if **all** of the below conditions are met:
  - The participant has not met permanent treatment discontinuation criteria,
  - The participant no longer meets treatment interruption criteria, and
  - After discussion with the sponsor.

In case it is agreed to restart study intervention, it is recommended that ALT and AST are assessed weekly for the first month and then at least monthly prior to each infusion. After any re-initiation of treatment, the occurrence of new elevations ≥3xULN for the ALT or AST values will lead to permanent discontinuation of study intervention.

10.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 7 (24 January 2025)

Overall Rationale for the Amendment: To reduce burden, increase flexibility, and clarify the timing and conduct of assessments when participants transition from the Double-blind Treatment Period to the LTE Treatment Period.

The changes made to the clinical protocol 63733657ALZ2002 as part of Protocol Amendment 7 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.8, Appendix 8: Protocol Amendment History.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
1.3 SoAs.	Added exemption footnotes to the LTE SoAs (Sections 1.3.4 through 1.3.7) and Follow-up SoA (Section 1.3.8) to match similar footnotes from the DB SoAs (Sections 1.3.2 and 1.3.3). • For study participants, the footnotes now allow remote contact options for specific LTE visits when study intervention will not be administered. • For study partners, the footnotes now allow remote contact options for specific LTE and Follow-up visits in which no study partner assessments are planned and, for these visits, it indicates another legal adult can accompany the participant.	The revised footnotes make the LTE Treatment Period and the Follow-up Period consistent with the DB Treatment Period in granting exemptions that reduce burden on study participants and their partners.
1.3.3 SoA - DB Treatment Period, Continued; 1.3.4 SoA - LTE Treatment Period - Year 1.	Harmonized footnotes that specified lookback windows for determining whether assessments need to be conducted at the ET/End of DB visit and the LTE 1 visit. To reduce burden, the lookback windows are generally longer for higher-burden assessments (eg, tau PET).	The revised footnotes harmonize the LTE 1 visit with the ET/End of DB visit and reduce burden by minimizing repetition of assessments across these visits.
1.3 SoAs.	Updated the footnotes in the LTE SoAs (Sections 1.3.4 through 1.3.7) that had granted ±4 weeks for tau PET scans. These footnotes now allow longer windows only in cases with medical monitor approval (eg, for operational challenges).	This provides flexibility for tau PET scheduling if needed.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
1.1 Synopsis; 1.3 SoAs; 4 Study Design; 6.6 Continued Access to Study Intervention After End of the DB Treatment Period; 8.1.3 Transition From DB Treatment Period to the LTE Treatment Period.	Changed phrases such as "~~when~~ the LTE Treatment Period ~~is~~ available," or "~~at the time~~ the LTE Treatment Period ~~is~~ available," or "~~at the next scheduled visit~~ after the LTE Treatment Period is available" (or similar text) to state instead "after the LTE Treatment Period becomes available" (or similar text).	The former statements could have implied that the steps needed to be completed immediately. The revised statements give more flexibility.
1.3 SoAs; 8.1 Overview; 8.4 Home Health Care and Tele-Health Visits.	Added footnotes to the SoAs (Sections 1.3.2 through 1.3.8) to specify that study procedures should be performed at the study site (not remotely) unless otherwise specified in the protocol. Added similar text to Section 8.1. Added similar text to Section 8.4 (which was previously misnumbered as Section 8.3.1); renumbering of Section 8.4 caused renumbering of subsequent sections.	Clarifications and corrections.
1.3.4 SoA - LTE Treatment Period - Year 1; 8.1 Overview.	Added blood PK sampling to LTE Weeks 12 and 36 in the SoA to align with the timepoints in DB Weeks 12 and 36. Updated the number and volume of blood samples accordingly.	The blood PK samples are now matched to the PD samples, so that the exposure data can contextualize the biomarker results.
2.3.1. Risks for Study Participation.	• Recharacterized DILI observations in the "ongoing studies" section. These were previously described as a "hepatic safety signal" but are now described as "important potential risk." • Clarified timeline for characterization of risks from past (completed) studies versus this ongoing study.	Consistency with the updated IB.
1.1 Synopsis; 1.3 SoAs; 4.1 Overall Design; 8.1.2 DB Treatment Period.	Changed "~~the end~~ of the Double-blind Treatment Period" to "Week 104 of the Double-blind Treatment Period" in relevant statements about reduction of missing data.	Clarification.
1.1 Synopsis; 3.2 LTE Treatment Period; 9.3.1.7 Long-Term Extension.	Changed endpoints from "Year 1" to Week 64" for the objectives related to RBANS and Amsterdam IADL. Clarified timepoints for LTE efficacy analyses accordingly.	Correction of error. These assessments are not conducted at Week 52. The nearest RBANS and Amsterdam IADL assessments after 1 year are at Week 64.
1.3.7 SoA - LTE Treatment Period, Continued - Year 4 Through End of Study.	Clarified that RBANS assessments are not conducted every 52 weeks during this SoA. Instead, the RBANS assessments are conducted 3 months after the ADAS-Cog assessments in Years 5 and 7; this pushes the RBANS assessments into Years 6 and 8.	Correction of error.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
1.1 Synopsis; 1.3 SoAs; 4.1 Overall Design; 7 Discontinuation of Study Intervention and Participant Discontinuation/ Withdrawal; 8.1.2 DB Treatment Period.	Added PK to the list of assessments that should be pursued in relevant statements about the focus of data collection after discontinuation of a participant.	Reduction of missing data.
1.1 Synopsis; 1.3 SoAs; 2.3.1 Risks for Study Participation; 4 Study Design; 6.1 Study Interventions Administered; 6.6 Continued Access to Study Intervention After End of the DB Treatment Period 8.1 Overview; 8.1.3 Transition From DB Treatment Period to the LTE Treatment Period; 8.5.4 Clinical Safety Laboratory Assessments.	Updated statements about reviewing predose ALT results to include also reviewing AST results.	Harmonization of protocol text with Appendix 7.
10.7 Appendix 7: Hepatic Safety Monitoring Assessments.	Updated a follow-up scenario (in Table 6) that previously covered only ALT criteria to also cover AST criteria.	Completeness.
1.3.7 SoA - LTE Treatment Period, Continued - Year 4.	Deleted the unused column about "Every 12 Weeks." Deleted the subtitle row about frequency and populated the corresponding (but previously empty) subheading row as "Frequency" accordingly.	Corrections of empty and extra table fields.
8.2.3 Alzheimer's Disease Cooperative Study Activities of Daily Living for Mild Cognitive Impairment (ADCS-ADL-MCI)	Revised text that had described use of an 18-item version; this study uses a 24-item version.	Correction of error.
1.2 Schema.	Designated "Early Start" versus "Delayed Start" participants in Figure 1. Revised flow in Figure 2.	Clarity.
6.8 Concomitant Therapy.	Revised information for "other CNS acting medications" for guidance on minimizing changes during the study.	Flexibility.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
10.3.6 Committees Structure.	Changed "DRC ~~will~~ be established" to "DRC <u>may</u> be established." Deleted "~~to review a limited amount of unblinded safety data in order~~ to evaluate potential mechanisms for hepatic abnormalities."	A DRC may only review blinded data prior to database lock. A DRC may review unblinded data only after database lock and sponsor is unblinded.
10.2 Appendix 2: Clinical Laboratory Tests; 10.7 Appendix 7: Hepatic Safety Monitoring Assessments.	Deleted the phrase "~~requires study treatment interruption and/or~~," which was redundant with the retained phrase "is considered clinically significant." Harmonized the "viral serology" list in Appendix 2 with the "viral serology" list in Appendix 7.	Harmonization and clarification.
8.5.6 Magnetic Resonance Imaging.	Added "<u>diffusion imaging</u>" to the MRI assessments.	Clarification.
Footer on first page of protocol; Protocol Amendment Summary of Changes Table; 10.8 Appendix 8: Protocol Amendment History.	Changed the date for Amendment 6 from incorrect ~~19 March 2024~~ to correct <u>19 April 2024</u>.	Correction of error.
2 Introduction.	Added the following sentence: "The code 'JNJ-63733657' refers to the International Nonproprietary Name 'posdinemab'."	The name was designated after the study was initiated.
2.2 Background; 11 References.	Updated reference to Version 8 of the IB. Updated nonclinical studies to include another local tolerance study accordingly. Updated the end date for collection of recent safety findings in ongoing studies accordingly.	Contemporaneity of protocol versus relevant text in latest IB.
9.2 Analysis Sets.	Added definitions for Screened Analysis Set and Randomized Analysis Set.	Contemporaneity of protocol versus standard text in latest template.
1.1 Synopsis; 9.3.2 Safety Analyses.	Updated analysis parameters for clinical laboratory tests, ECGs, and vital signs.	
Throughout the protocol.	Implemented minor changes to phrasing, grammar, formatting, spelling, abbreviations, etc.	Minor errors were noted and minor clarifications were implemented.

Amendment 6 (19 April 2024)

Overall Rationale for the Amendment: To add a Long-Term Extension (LTE) active treatment, dose-blinded period into the study to provide participants who are receiving double-blind study intervention and have completed the Week 104 visit of the Double-blind Treatment Period with access to JNJ-63733657

treatment and to obtain additional efficacy, safety, biomarker, pharmacokinetic, immunogenicity, and health outcomes data. In addition, hepatic safety monitoring and study intervention interruption requirements have been further updated to increase the predose hepatic safety testing time window as well as the hepatic enzyme elevation criteria for treatment interruption based on evaluation of blinded hepatic safety data to date.

The changes made to the clinical protocol 63733657ALZ2002 as part of Protocol Amendment 6 are listed below, including the rationale of each change and a list of all applicable sections.

Section Number and (Abbreviated) Name	**Description of Change**	**Brief Rationale**
1.1 Synopsis; 1.3.2 & 1.3.3 SoAs - DB Treatment Period; 4.1 Overall Design	Added guidance that participants discontinuing DB study intervention should complete the remaining scheduled visits/study procedures; however, if full participation in study procedures is considered too burdensome, then the focus should be on collecting primary and secondary clinical outcome measures and reducing other assessments.	Aligned with study conduct and reduced participant burden.
1.1 Synopsis; 1.3.2, 1.3.3, 1.3.4, 1.3.5, 1.3.6, & 1.3.7 SoAs; 6.1 Study Interventions Administered; 8.1 Overview	Added that dosing is not permitted for any participant with treatment-emergent predose ALT>1.5xULN (tested within 14 days prior to dosing) and that retesting once is allowed if ALT>1.5xULN but <3xULN.	Maintained hepatic safety monitoring with updated threshold based on evaluation of blinded hepatic safety data to date.
1.1 Synopsis; 2 Introduction; 2.1 Study Rationale; 4.1 Overall Design	Indicated that additional efficacy, safety, biomarker, PK, immunogenicity, and health outcomes data will be obtained in the LTE Treatment Period.	Defined the data that will be collected during the LTE Treatment Period.
1.1 Synopsis; 1.3.2 SoA - DB Treatment Period; 4.1 Overall Design; 4.4 End of Study Definition	Clarified duration of DB Treatment Period.	Aligned with study conduct.
1.1 Synopsis; 4.1 Overall Design; 1.3.3 SoA - DB Treatment Period; 8.1.5 Post-treatment Period (Follow-up)	Removed 6-month remote FU and added timing details for FU period with visits 30, 60, and 90 days after last dose of study intervention.	The 90-day FU is the appropriate period for safety follow-up.
1.1 Synopsis; 4.1 Overall Design; 4.3 Justification for Dose	Updated CSF p217+tau reduction values based on updated model output in the IB.	Aligned with the IB.
1.2 Schema	Updated study schema containing the LTE Treatment Period. Updated Figure 2 to reflect transition from DB to LTE Treatment Period.	Aligned with study conduct.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
1.3.2 & 1.3.3 SoAs - DB Treatment Period	Added footnote for certain visits to be remote if study intervention will not be administered (eg, due to predose ALT result) and to remotely record AEs and concomitant therapies at such visits.	Allowed certain visits to be remote if a participant is not receiving study intervention, and study scales are not scheduled.
1.3.4 SoA - LTE Treatment Period - Year 1; 1.3.5 SoA - LTE Treatment Period, Continued - Year 2; 1.3.6 SoA - LTE Treatment Period, Continued - Year 3; 1.3.7 SoA - LTE Treatment Period, Continued - Year 4; 1.3.8 SoA - Follow-up Period	Added separate SoAs for LTE Treatment Period and Follow-up Period.	Aligned with study conduct.
1.3.2 & 1.3.3 SoAs - DB Treatment Period	Added footnote clarifying that participants who discontinue DB study intervention for reasons other than withdrawal of consent should still complete the remaining scheduled visits/study procedures through the end of the DB Treatment Period.	Aligned with study conduct.
1.1 Synopsis; 2.3.3 Benefit-Risk Assessment; 4.1 Overall Design; 4.2.1.1. Ethical Considerations for Participants Unable to Consent During the Study; 7.1 Participant Discontinuation/Withdrawal From the Study; 10.3.3 Informed Consent Process	Added details, including language about behavioral assent/dissent and withdrawal of consent/assent per local regulations, for participants who are unable to consent. Added new subsection for ethical considerations for participants unable to consent.	Accommodated participants who progress to more advanced clinical stages of AD during the study and are no longer able to consent.
2.2 Background; 2.3 Benefit-Risk Assessment	Updated information pertaining to clinical studies in the JNJ-63733657 program.	Provided updated information on the JNJ-63733657 program.
3 Objectives and Endpoints	Added timepoints for secondary and exploratory endpoints. Created separate objectives and endpoints tables for the DB Treatment Period and LTE Treatment Period.	Clearly defined the secondary/exploratory objectives and endpoints for the various study periods.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
4.1 Overall Design; 4.2 Scientific Rationale for Study Design; 6.3 Measures to Minimize Bias: Randomization and Blinding; 8.1.3 Transition from DB Treatment Period to the LTE Treatment Period; 8.1.4 LTE Period	Added information to the study design about LTE Treatment Period, including eligibility, timing, duration, randomization/blinding procedures, and dosages. Created new Section 8.1.3 (to detail the transition from DB Treatment Period to the LTE Treatment Period) and new Section 8.1.4 (for the LTE Treatment Period).	Defined the details of the LTE Treatment Period.
4.1 Overall Design; 8.1.2 DB Treatment Period	Added details for participants who remain in the DB Treatment Period without study intervention, and those who discontinue DB study intervention prior to the completion of the DB Treatment Period.	Provided guidance for participants who discontinue study intervention in the DB period.
4.3 Justification for Dose	Added justification for dose used in the LTE Treatment Period.	Aligned with study conduct.
4.4 End of Study Definition	Added definitions for end of LTE Treatment Period, and modified definitions for End of DB Treatment Period and end of study.	Added new end of study definitions, accounting for the addition of LTE Treatment Period.
5.3 Lifestyle Considerations	Added recommendations pertaining to alcohol and concomitant medications.	Recommended lifestyle practices that would minimize impact on hepatic laboratory results.
6.1 Study Interventions Administered; 10.4.1 AE Definitions and Classifications	Added definition of infusion-related reactions.	Clarification.
6.2 Preparation/Handling/ Storage/Accountability	Added statement on preparation of study intervention.	Clarification.
6.5 Dose Modification	Clarified that dose adjustment is not permitted in the DB and LTE Treatment Period. Clarified that reducing infusion rate or stopping infusion is allowed if there are tolerability concerns per investigator clinical judgment, and must be overseen by medical personnel.	Clarified that dose adjustments are not permitted by the investigator.
6.6 Continued Access to Study Intervention After End of the DB Treatment Period	Added information regarding how long participants can continue in the LTE Treatment Period.	Defined the duration of the LTE Treatment Period.
6.8 Concomitant Therapy	Added instructions on changing an AD therapy during the LTE Treatment Period.	Aligned with study conduct.
8.1 Overview	Added blood volume collection tables for DB and LTE Treatment Periods.	Aligned with protocol template.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
8.1 Overview	Added text stating that predose clinical laboratory safety tests can be performed within 14 days of administering study intervention.	Updated the window for predose clinical laboratory safety tests based on evaluation of blinded hepatic safety data to date.
8.1 Overview	Added text to indicate study procedures that must be performed if administration of study intervention is held or delayed.	Aligned with study conduct.
8.1 Overview	Added that all study procedures are to be performed on the same day, with the exception of study procedures that have a permitted window relative to the day of the clinic visit. Added instructions for dosing for participants with specified predose ALT values.	Aligned with study conduct.
8.1.5 Post-treatment Period (Follow-up)	Updated section with details for participants entering and not entering the LTE Treatment Period.	Aligned with study conduct.
8.3.1 Home Health Care and Tele-Health Visits	Created new section detailing the option of home health care and tele-health visits.	Provided the option of less burdensome assessments/visits for participants.
8.4.4 Clinical Safety Laboratory Assessments	Added CRP and INR safety assessments.	Included relevant assessments for evaluation of hepatic safety.
8.6.1 Evaluations	Added that CSF samples will be collected at the time points indicated in the SoA.	Clarification.
8.12 Participant Medical Information Prior, During, and After the Study (Real-world Data) - Applicable to United States Only	Created new section for accessing participant medical information via tokenization.	Allowed data to be used for exploratory analyses to enhance understanding of the disease diagnosis, management, and outcomes, and to examine possible correlations of disease parameters between data collected in the clinical trial and real-world data.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
9 Statistical Considerations; 9.4 Interim Analysis	• Added information about timing for Primary DB analysis and End of DB analysis. • Added that data collected as part of the LTE Treatment Period will be reported separately. • Added that interim analyses may be conducted during the LTE Treatment Period.	• Defined timing of statistical analyses. • Clarified analysis of the data collected for each period of the study. • Permitted interim analyses of the ongoing LTE Treatment Period.
9.2 Analysis Sets	Added definitions for efficacy and safety analysis sets for the LTE Treatment Period.	Defined the analysis sets that will be used for the LTE Treatment Period, which are distinct from the analysis sets for the DB Treatment Period.
9.3.1.7 Long-Term Extension	Created new subsection on dosing group definitions and efficacy and safety analyses for participants in the LTE Treatment Period.	To define the dose groups for the LTE and the analysis sets that will be used for statistical analysis of LTE data.
9.3.2 Safety Analyses	Added information for safety analyses performed on double-blind and LTE Treatment Periods. Added definition for treatment-emergent AEs occurring in the LTE Treatment Period.	To define the analysis sets for the DB and LTE Treatment Periods that will be used for statistical analysis of safety data. To define TEAEs in the LTE Treatment Period as distinct from those in the DB Treatment Period.
9.3.3 Other Analyses	Added details on PK, biomarker, immunogenicity, and PD analyses for participants in the LTE Treatment Period.	Clarified that analysis of PK, biomarkers, immunogenicity and PD will be specified in the separate SAPs for the DB Treatment Period and the LTE Treatment Period.
9.5 Sample Size Determination	Moved section from 9.2 to 9.5.	Aligned with protocol template.
10.2 Appendix 2: Clinical Laboratory Tests	Aligned with updates in Appendix 7; defined when central/local laboratories should be used.	Aligned with study conduct.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
10.3.6 Committees Structure	Removed information about IDMC and HAC from Sections 9.6 and 9.7, respectively; then added this information to Section 10.3.6. Added paragraph on DRC.	Aligned with protocol template. Described the role of the DRC, which will be implemented to evaluate the liver safety signal.
10.6 Appendix 6: Study Conduct During a Natural Disaster/Major Disruption/Pandemic	Edited appendix language to encompass other events that may disrupt study conduct.	Aligned with protocol template.
10.7 Appendix 7: Hepatic Safety Monitoring Assessments	• Updated AE reporting, monitoring and management guidance for hepatic events and hepatic lab abnormalities. • Added guidance for ALT >1 to ≤1.5xULN. • Added and modified diagnostic tests in Hepatic Event Assessments - Level 1. • Added guidance for liver biopsy for Hepatic Event Assessments - Level 2.	Updated hepatic safety monitoring as per evaluation of hepatic safety data to date.
10.1 Appendix 1: Abbreviations; 10.2 Appendix 2: Clinical Laboratory Tests; 10.7 Appendix 7: Hepatic Safety Monitoring Assessments	Added GLDH to Other Laboratory Tests for hepatic monitoring.	Allowed for better interpretation of hepatic data and to align with template text.
Throughout the protocol	Added "Long-Term Extension Treatment Period" to study title and all descriptions of study design.	Incorporated an LTE Treatment Period into this study to obtain additional efficacy, safety, biomarker, PK, immunogenicity, and health outcomes data.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

Amendment 5 (13 December 2023)

Overall Rationale for the Amendment: To incorporate changes to further increase hepatic safety monitoring procedures, including monthly (predose) clinical laboratory safety tests for participants receiving study intervention until the end of study, confirming ALT and AST are evaluated and within the normal range prior to study intervention administration, and requiring dosing be interrupted for any participant with ALT or AST >1xULN. Additional hepatic chemistry criteria have been added for participant management to Appendix 7 (Hepatic Safety Monitoring Assessments). These changes serve to further mitigate any potential risk of adverse events related to hepatic injury.

The changes made to the clinical protocol 63733657ALZ2002 as part of Protocol Amendment 5 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Appendix 8: Protocol Amendment History.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
1.1 Synopsis; 3 Objectives and Endpoints; 4.2 Scientific Rationale for Study Design - Safety Evaluations; 8.5 AEs, SAEs, and Other Safety Reporting; 9.4.2 Safety Analyses; 10.4.1 AE Definitions and Classifications; 10.4.5 Procedures	Added TEAEs of special interest.	Better characterized and summarized specific AEs that could be related to treatment.
1.1 Synopsis; 4.1 Overall Design; 6.1 Study Interventions Administered; 8.1.2 DB Treatment Period	Added review of ALT and AST results and requirement of ≤1xULN prior to administration of study intervention. Normal results should be confirmed within 7 days prior to dosing. A study partner is not required to accompany a participant for blood collection.	Clarified the timing of lab results review relevant to study intervention administration.
1.2 Schema; 4.1 Overall Design; 8.1.3 Post-treatment Period (Follow-up)	Added 2 safety FU visits, at 30 and 60 days after the last dose.	Allowed for monthly assessment of hematology and chemistry (including hepatic chemistry tests, CRP, and INR) during the 90-day FU period.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
1.3.2 SoA - DB Treatment Period	• Increased hematology and chemistry assessments to a monthly frequency through the end of the study. Added monthly assessments of CRP and INR through the end of the study.	• Increased hepatic safety monitoring and hepatic data interpretation.
	• Modified footnote 'f' to specify that AST and ALT results must be reviewed prior to administration of study intervention.	• Clarified the timing of lab results review relevant to study intervention administration.
	• Expanded footnote 'g' expanded to define "predose."	• Clarified and explained allowed window for timing.
	• Added note to footnote 'i' that chemistry includes fractionated bilirubin.	• Allowed for better interpretation of hepatic data.
	• Removed footnote 'p' specifying only at 96 weeks.	• Not relevant since monthly assessments are now collected.
	• Updated footnote 'q' to specify that AST and ALT results must be reviewed prior to administration of study intervention.	• Clarified the timing of lab results review relevant to study intervention administration to ensure participant safety.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
1.3.3 SoA - DB Treatment Period, Continued	• Added 2 follow-up visits to include monthly visits during the 90-day Follow-up Period. • Increased hematology and chemistry assessments to a monthly frequency. Added monthly assessments of CRP and INR. • Modified footnote 'b' to include 3 FU visits, which are not required for participants who stay in the DB period without study intervention for more than 90 days after the last dose. • Modified footnote 'c' to specify that AST and ALT results must be reviewed prior to administration of study intervention. • Removed previous footnote 'd'. • Expanded footnote 'd' to define "predose." • Added note to footnote 'f' that chemistry includes fractionated bilirubin. • Updated footnote 'o' to specify that AST and ALT results must be reviewed prior to administration of study intervention. • Removed footnote 'q' specifying Weeks 148 and 200 only.	• Aligned with monthly hepatic monitoring. • Increased hepatic safety monitoring and hepatic data interpretation. • Clarified timing of FU visits. • Clarified the timing of lab results review relevant to study intervention administration. • Not relevant to study. • Clarified and explained allowed window for timing. • Allowed for better interpretation of hepatic data. • Clarified the timing of lab results review relevant to study intervention administration to ensure participant safety. • Not relevant since monthly assessments are now collected.
2.2 Background	Updated the clinical studies subsection to reflect completion of Study 63733657ALZ1001 with inclusion of relevant results. Inclusion of relevant blinded data from Study 63733657ALZ2002 regarding hepatic cases.	Provided completeness regarding other studies and the currently ongoing study.
2.3.1 Risks for Study Participation; 8.4.4 Clinical Safety Laboratory Assessments	Specified that AST and ALT results must be conducted monthly and reviewed prior to administration of study intervention.	Increased hepatic safety monitoring and ensured participant safety.
2.3.3 Benefit-Risk Assessment for Study Participation	Addition of symptomatic to participants.	Clarification.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
4.2 Scientific Rationale for Study Design; 6.3 Measures to Minimize Bias: Randomization and Blinding; 6.5 Dose Modification	Added that participants may be rerandomized or assigned to a different treatment group if the IDMC recommends a change to a JNJ-63733657 treatment group. Added DILI to cases that are being monitored by the sponsor.	Indicated that enrolled participants could have a change in treatment if recommended by the IDMC. Clearly identified the cases being monitored.
7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal	Added "permanent" to subheading and in the text. Added criterion for permanent discontinuation for participants with suspected or confirmed DILI.	Clarification. Ensured participant safety.
8.1 Overview	Added text to describe when and how, if needed, blood collection should occur on the same day as clinical scales. Added a table for blood volume collection.	Provided guidance to the site regarding participant care. Provide transparency of blood collection volume by period.
8.5.1 Time Period and Frequency for Collecting AE and SAE Information	Added information on possible Hy's Law Cases regarding at least doubling of direct bilirubin in known Gilbert's syndrome.	Clarified Hy's Law cases.
9.7 Hepatic Adjudication Committee (HAC); 10.3.6 Committees Structure	Added a section to provide information on the Hepatic Adjudication Committee, with reference to additional details in a separate charter.	Provided information on independent adjudication of hepatic cases.
10.2 Appendix 2 - Clinical Laboratory Tests	Added guidance regarding use of central and local laboratories. Moved fractionated bilirubin to clinical chemistry tests. Added other laboratory tests (eg, ferritin) associated with required FU assessment per Appendix 7.	Clarified use of central and local laboratories. Allowed for better interpretation of hepatic data.
10.2 Appendix 2 - Clinical Laboratory Tests; 10.7 Appendix 7 - Hepatic Safety Monitoring Assessments	Removed GLDH from other laboratory tests in Appendix 2 and from template text in Appendix 10.7.	An internal hepatic committee guidance indicated that GLDH was not relevant to the disease state.
10.7 Appendix 7 - Hepatic Safety Monitoring Assessments	Updated when assessments should be conducted and associated definitions. Importantly, this included more stringent dose interruption criteria of ALT or AST >1xULN for predose tests.	Provided more stringent dose interruption criteria to ensure participant safety.
Throughout the protocol	Made minor grammatical, formatting, spelling, and abbreviation changes. Replaced "liver" with "hepatic" where appropriate.	Minor errors were noted.

Amendment 4 (12 October 2023)

Overall Rationale for the Amendment: To incorporate changes to increase hepatic safety monitoring procedures and to add liver chemistry criteria for stopping study intervention or continuing study intervention with increased monitoring to mitigate any potential risk of adverse events related to abnormalities in liver function tests. These changes were made due to a hepatic safety signal observed during blinded review of study data from this ongoing study.

The changes made to the clinical protocol 63733657ALZ2002 as part of Protocol Amendment 4 are listed below, including the rationale of each change and a list of all applicable sections.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
1.3.2 SoA - DB Treatment Period; 1.3.3 SoA - DB Treatment Period, Continued	Added more timepoints to the SoA for laboratory blood collection. These additional timepoints for laboratory safety tests (hematology, ALT, AST, GGT, ALP, TBili) will ensure that tests are performed monthly in the first 12 months of treatment and approximately every 3 months until the end of the DB Treatment Period.	Increased hepatic safety monitoring and hepatic data interpretation.
2.3.1 Risks for Study Participation; 4.2 Scientific Rationale for Study Design; 5.5 Criteria for Temporarily Delaying Enrollment, Randomization, Administration of Study Intervention; 7.1 Discontinuation of Study Intervention; 8.1 Overview; 8.1.2 DB Treatment Period; 8.4.4 Clinical Safety Laboratory Assessments; 10.2 Appendix 2: Clinical Laboratory Tests	Disclosed that a hepatic safety signal was observed in the blinded review of data from this ongoing study (63733657ALZ2002). Added Appendix 7: Hepatic Safety Monitoring Assessments, which provided liver chemistry criteria for stopping study intervention or continuing study intervention with increased monitoring.	Informed investigators/sites about a hepatic safety signal (based on blinded review of safety data from this study) and provided guidance on the management of liver chemistry abnormalities.
8.1 Overview	Updated the total blood volume drawn from maximum 496 mL to approximately 430 mL.	Corrected blood volume due to additional lab safety visits.
9.4.3 Other Analyses	Added summary statistical analyses to explore relationships between JNJ-63733657 concentrations and hepatic safety. Added analyses of incidence of anti-JNJ-63733657 antibodies with and without treatment-emergent hepatic enzyme elevations >3xULN.	To explore relationships between JNJ-63733657 concentration and hepatic safety. To assess potential relationship between anti-JNJ-63733657 antibodies and hepatic enzyme elevations.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
10.7 Appendix 7: Hepatic Safety Monitoring Assessments	Added this appendix to introduce the following: • Liver chemistry stopping criteria and follow-up assessments. • Liver chemistry increased monitoring criteria with continued study intervention.	Provided additional guidance on monitoring for and managing liver chemistry abnormalities.
10.8 Appendix 8: Protocol Amendment History	Renumbered the Protocol Amendment History as Appendix 8.	The addition of Appendix 7 (Hepatic Safety Monitoring Assessments) necessitated the renumbering of the subsequent appendix.
4.3 Justification for Dose 7.2 Participant Discontinuation/ Withdrawal From the Study 8.1 Overview 8.1.2 DB Treatment Period 8.6.1 Evaluations 8.9 Immunogenicity Assessments	Made minor text edits and clarifications for alignment.	Provided consistency within the document.
Throughout the protocol	Made minor grammatical, formatting, or spelling changes.	Minor errors were noted.

Amendment 3 (25 April 2023)

Overall Rationale for the Amendment: To incorporate changes to statistical analyses methods based on regulatory advice. In addition, to increase the sample size to mitigate any potential increase in the study discontinuation rate due to availability of disease-modifying treatments for AD.

The changes made to the clinical protocol 63733657ALZ2002 as part of Protocol Amendment 3 are listed below, including the rationale of each change and a list of all applicable sections.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
1.1 Synopsis 3 Objectives and Endpoints 4.1 Overall Design 4.4 End of Study Definition 8.2.1 iADRS 9.3 Analysis Sets 9.4.1.1 Primary Estimand 9.4.1.2 Primary Endpoint 9.4.1.3 Key Secondary Endpoints 9.5 Interim Analysis 9.6 Independent Data Monitoring Committee	The statistical analysis methods were changed as follows: • Changed from polynomial regression to MMRM for primary and key secondary endpoint analyses. • Changed model slightly due to the change from polynomial regression to MMRM indicating time as a fixed effect instead of a continuous variable. • Specified the variance-covariance structure to be used for within-participant covariance between visits (which was previously deferred to the SAP). • Removed MMRM details for the key secondary endpoints (referring to SAP). • Changed the calculation of iADRS, the primary endpoint measure, to use the intact total scores of ADAS-Cog13 and ADCS-ADL-MCI (ie, no longer excluding the dressing item). • Changed the primary estimand strategy for handling ICEs. • Specified the primary and key secondary endpoint as Week 104 (which was previously unspecified and deferred to SAP). • Changed the objective of the first interim analysis. • Changed the sample size of the second interim analysis. • Removed the third interim analysis. • Changed "populations" into "analysis sets".	Incorporated changes to statistical analyses methods based on regulatory advice.
1.1 Synopsis 4.1 Overall Design 4.2 Scientific Rationale for Study Design	Changed the duration of the DB Treatment Period from a minimum of 128 weeks to 104 weeks of DB treatment for all participants.	With the revised statistical analysis method (MMRM), 2 years of treatment provided sufficient power to assess the primary endpoint.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3.2 SoA - DB Treatment Period 4.1 Overall Design 4.2 Scientific Rationale for Study Design 6.6 Continued Access to Study Intervention After the End of the Study 8.1.2 DB Treatment Period	Clarified that when the LTE study is available at the clinical site, participants receiving DB study intervention who have completed the Week 104 visit will be discontinued from the DB Treatment Period to enter the LTE study (if eligible) or proceed to the safety FU visit, if not participating in the LTE study.	Clarification.
4.4 End of Study Definition	Clarified that the end of study visit is defined as the ET visit for participants who complete at least 104 weeks (ie, Week 104 visit) of the DB Treatment Period and who are eligible for the LTE study.	Clarification.
9.4.1.1 Primary Estimand	Updated the treatment component of the primary estimand to clarify that current standard of care AD medications (AChEIs and/or memantine) are permitted if dosing is stable before screening and throughout the study as described in Section 6.8.	Clarification.
2.2 Background	Updated information about ongoing clinical studies in line with the most recent IB update.	Aligned with new information in the IB.
2.1 Study Rationale 4.1 Overall Design 4.2 Scientific Rationale for Study Design 8.1.1 Screening Period	Clarified that the target population should have elevated tau (T+) levels within a prespecified range for eligibility, and that sites will be notified of the eligibility status but will not receive assay results.	Clarification.
1.1 Synopsis 4.1 Overall Design 7.1 Discontinuation of Study Intervention 7.2 Participant Discontinuation/ Withdrawal From the Study 4.1 Study Design	Removed study discontinuation criterion that participants starting a treatment that targets the underlying pathophysiology of AD will have to discontinue the study. In line with this, text was modified in all applicable sections of the protocol.	Participants who discontinue study intervention because they started a treatment that targets the underlying pathophysiology of AD are no longer required to also discontinue the study. If desired, they can remain in the study and complete the remaining study visits, without further study intervention dosing.
4.2 Scientific Rationale for Study Design 4.2.1 Study-Specific Ethical Design Considerations 6.8 Concomitant Therapy	Clarified that AD treatment(s) that target the underlying pathophysiology of AD (eg, anti-amyloid therapies) are not permitted **during screening or to be administered concomitantly with study intervention** at any time during ~~study participation~~ **the Double-blind Treatment Period.**	Clarification.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
1.1 Synopsis 4.1 Study Design	Clarified when participants are eligible for the optional LTE study: Following completion of the **Week 104 visit** of **the** Double-blind Treatment Period, participants may have an option to participate in a ~~separate open-label~~ **LTE** study, **when available at the clinical site**. Participants who have discontinued from the Double-blind Treatment Period **prior to completing the Week 104 visit** are not eligible for the ~~open label~~ **LTE** study. **Participants who discontinue double-blind study intervention in the Double-blind Treatment Period and agree to remain in the study (performing other assessments besides study intervention administration) are not eligible for the LTE study.**	Clarification.
1.1 Synopsis 4.1 Overall Design 9.2 Sample Size Determination	Increased the sample size from approximately 420 to 480 (ie, 160 instead of 140 per treatment group). Modified the annual dropout rate in Sections 1.1 and 9.2 as follows: This assumes a**n initial** 7.5% annual dropout rate, **an anticipated higher (13%) annual dropout rate after an approved disease-modifying therapy for AD becomes available at different times in different regions, and** an accrual rate of 20 participants per month.	Mitigated any potential increase in the study discontinuation rate due to availability of disease-modifying treatments for AD.
5.3 Lifestyle Considerations	Clarified that participants should avoid donating blood **products** during the study and for at least 90 days after completion (ie, final follow-up visit) of the study.	Clarification.
Title Page	Replaced EudraCT number with EU CTR number.	Compliance with EU CTR requirements.
1.1 Synopsis 4.1 Study Design 5 Study Population 8.1.1 Screening Period	Added "on a case-by-case basis" for the potential extension (to 120 or 180 days) of the Screening Period.	Clarification because each request will be evaluated individually, taking into consideration all relevant information.
1.1 Synopsis 4.1 Study Design 8.1.1 Screening Period	Added "operational delays" to the list of rationales to extend the Screening Period.	Clarification.
1.3.3 SoA - DB Treatment Period, Continued	Corrected footnote "e" to "d" at the follow-up visits of the hematology/chemistry and urinalysis assessments.	Correction of errors.
6.1 Study Intervention Administered	Added a table specifying the IMP and the nonauthorized Auxiliary Medicinal Product (MK-6240).	Compliance with EU CTR requirements.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
6.8 Concomitant Therapy	Added non-benzodiazepine benzodiazepine receptor agonists to the list of "Concomitant Therapies Adversely Affecting Cognition": **Non-benzodiazepine benzodiazepine receptor agonists: Chronic use of these medications are not permitted. If used as needed or for short-term use during the study, the interval from last dose of the medication and subsequent cognitive assessment must be a minimum of 4 half-lives for that compound or 24 hours, whichever is longer.**	Clarification.
1.1 Synopsis 1.3.2 SoA - DB Treatment Period 1.3.3 SoA - DB Treatment Period, Continued 4.1 Study Design 6.1 Study Interventions Administered	Clarified that study intervention will be administered over **approximately** 60 minutes instead of 60 minutes.	The flushing procedure will result in the total administration time being slightly longer than 60 minutes.
1.1 Synopsis 4.1 Study Design	Changed "in an outpatient clinical setting" to "in a designated hospital/clinic setting."	Consistency.
1.2 Schema	Revised the schematic overview of the study and the figure for the common close design.	Clarification.
2.1 Study Rationale	Added a literature reference.	A new publication became available.
4.2 Scientific Rationale for Study Design	Deleted the following text: ~~Due to the limited availability of the approved anti-amyloid therapy, it is not standard of care.~~	Standards of care were already defined in the same section.
1.3.1 SoA - Screening 8.2.4 RBANS	Corrected the following statement in Section 8.2.4: ~~To assess for and mitigate practice effects (Duff 2005),~~ **T**he RBANS will be performed at least twice on different occasions during the Screening Period (**Screening Visits 1 and 5**) ~~prior to Screening Visit 5~~ (see Section 1.3). Updated footnote 'k' in SoA - Screening accordingly, as follows: The RBANS performed at Step I ~~is to assess for and mitigate practice effects and~~ will ~~also~~ be used to assess concordance with CDR from Step I (CDR-GS of 0.5).	Correction of error.
8.4.6 Magnetic Resonance Imaging	The term "ARIA" was replaced by "vasogenic edema, cerebral microhemorrhages, and cerebral superficial siderosis."	Correction; ARIA is per definition associated with anti-amyloid treatment.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
1.1 Synopsis 8.4.6 Magnetic Resonance Imaging 8.8.2 MRI Brain Volumetric Analysis	Moved the following paragraphs from Section 8.4.6 to Section 8.8.2: MRI will be used to assess hippocampal, whole brain, and ventricular volume, which track brain atrophy during the course of AD. In addition, progression of or new onset of vascular burden (white matter lesions [WML], infarcts, lacunes, microbleeds, superficial siderosis) will also be assessed. MRI was chosen because, compared to computerized tomography, it provides no radiation exposure and can determine vascular pathology while allowing for quantification of grey matter structures such as the hippocampus and other AD signature regions. MRI is also much better suited to a longitudinal setting, with early-stage subtle changes over time detected in AD sensitive regions, which can predict future cognitive decline and onset of dementia. Added the following paragraph in Sections 1.1 and 8.8.2: Changes from baseline in volumetric assessments (including hippocampal [right and left], whole brain, and ventricular volume) of MRI brain will be performed. An appropriate correction for intercranial volume will be applied.	Provided additional information about MRI brain volumetric analysis.
Throughout the protocol	Replaced the term "open-label" with "long-term" for the extension study. Removed the references to a separate protocol for the LTE study. Replaced "Continued Access Program" with "Long-Term Extension Study" in Section 4.4.	Clarification.
4.1 Overall Design 8.1 Overview 8.6.1 Evaluations	Removed the laboratory charter.	Corrected error. The study has no laboratory charter, only a laboratory manual.
8.1 Overview	Removed the MRI Charter and Tau PET Imaging Charter from the study-specific materials provided to investigators.	Corrected errors. These imaging charters are not provided.
8.1 Overview	Moved GDS-30 to a separate category under clinical scales to be provided to the investigators.	Corrected error. The GDS-30 is not a safety assessment.
8.1 Overview	Updated the approximate maximum single-day blood volume drawn to 41 mL instead of 43 mL.	Corrected due to removal of 1 blood sample (2 mL).

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
Title Page 8.3 Health Outcome Scales 10.3.1 Regulatory and Ethical Considerations 10.3.4 Data Protection 10.6 Appendix 6	Changed "country" to "country or territory."	Aligned with template changes.
10.5 Appendix 5	Updated the contraceptive and barrier guidance.	Aligned with template changes.
10.6 Appendix 6	Updated the guidance on study conduct during the COVID-19 pandemic.	Aligned with template changes.
Throughout the protocol	Removed definitions of abbreviations within text, tables, and figures. Made minor changes in text.	Aligned with updated style guidelines and template, and corrected errors.

Amendment 2 (28 March 2022)

Overall Rationale for the Amendment: To provide more flexibility in the Screening Period to reduce the overall Screening Period duration for participants.

The changes made to the clinical protocol 63733657ALZ2002 as part of Protocol Amendment 2 are listed below, including the rationale of each change and a list of all applicable sections.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
1.1 Synopsis; 1.2 Schema; 4.1 Overall Design; 5 Study Population; 8.1.1 Screening Period	Changed the number of days that the Screening Period could be further extended from 120 days to 180 days, with medical monitor approval. Wording was updated throughout the protocol to reflect this change and limit repetition of the SoA.	Increased duration of Screening Period extension the medical monitor can approve. Removed redundancy with the SoA.
1.1. Synopsis; 1.3.2 SoA - DB Treatment Period; 1.3.3 SoA - DB Treatment Period, Continued; 4.1 Overall Design	Added ability for another legal adult at least 18 years of age to accompany participant to study visits (in place of study partner) for visits when study partner assessments are not required. Added study partner must be available for telephone contact to collect information regarding AEs and concomitant therapies. Added footnote 'c' to all weeks except 0, 24, 52, 76, 104, and 128 in SoA - DB Treatment. Added footnote 'a' to all weeks except 156, 180, 208, 232, ET, and FU in SoA - DB Treatment, Continued. Updated subsequent letters to footnotes.	Reduced study partner burden and allowed another individual (other than the study partner) to accompany the participant to study visits that do not have any study partner assessments to be completed.
1.1.Synopsis; 8.8.1 Tau PET	Identified radiotracer as MK-6240. Added text noting that MK-6240 is not a marketed product in the European Union.	To justify use of an EU unauthorized medicinal product to align with the EU CTR Regulations.
1.2 Schema	Updated Figure 1 to add footnote to Screening Period regarding extension and addition of "if applicable" to text for Follow-up Period. Updated Figure 2 to adjust projected enrollment period from 20 months (87 weeks) to 31 months (108 weeks) and then updated the example participant bars based on this.	Aligned with study conduct.
1.3.1 SoA - Screening	Renamed Step V to clarify that the entire visit is not optional; the RBANS is required and the lumbar puncture is optional.	Clarification.
1.3.1 SoA - Screening	Added footnote 'd' to Visits 3 and 4, noting that a visit to the clinical site is not required but a telephone contact will collect AE and concomitant therapy information.	To reduce participant/study partner burden, Visits 3 and 4 will not require separate visits to the clinical site. Participants will visit the imaging center and have a telephone contact.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
1.3.1 SoA - Screening	Moved prestudy therapies, preplanned surgeries, safety evaluations, clinical laboratory tests, and the C-SSRS assessment to Step I. Added footnote 'g' to some of these procedures at Step I, noting that the procedures can be performed at Step II if the clinical site prefers.	Added flexibility to when procedures are performed at Step I and Step II.
1.3.1 SoA - Screening	Removed RBANS practice assessment removed from Step III. Removed ADAS-Cog13 practice assessment from Step IV. Modified corresponding footnotes 'k' and 'l'.	To reduce participant burden, practice tests were decreased from 2 to 1 during the Screening Period (as it was determined 1 practice test was sufficient to minimize practice effects).
1.3.1 SoA - Screening	Removed previous footnote 'j' noting that the MRI should be performed after the RBANS assessment. Added footnote 'm' noting that plasma p217+tau and MRI results confirming participant eligibility are required prior to performing tau PET assessment at Step IV.	Clarification.
1.3.1 SoA - Screening	Moved collection of blood for biomarker status from Step II to Step I.	Reduced participant burden.
1.3.1 SoA - Screening	Noted that CSF sample collection was optional and footnote 'c' to Visit 5 noting that the MRI and tau PET results confirming participant eligibility are required prior to performing the lumbar puncture. Added that Visit 5 is still required for all participants.	Clarification.
1.3.1 SoA - Screening	Modified footnote 'a' to note that ADAS-Cog13 and RBANS should be separated by at least 7 days to ensure adequate time between the cognitive measures.	Clarification and allowing flexibility with study assessments/visits.
1.3.1 SoA - Screening	Modified footnote 'b' to note that clinical scale and/or cognitive measures should be conducted before other study procedures.	Clarification.
1.3.1 SoA - Screening	Modified footnote 'e' to note that the consent for the lumbar puncture is separate and can be signed at any screening visit prior to the procedure.	Clarification.
1.3.1 SoA - Screening	Modified footnote 'f' to note that the medical history includes cognitive history.	Clarification.
1.3.1 SoA - Screening	Modified footnote 'j' to note that the HIS requires data from other screening procedures (general medical history, neurologic exam) and these procedures should be performed at the same visit as the HIS. Footnote 'g' added to HIS at Step I and Step II replaces Step 1 in footnote 'g'.	Clarification.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
1.3.1 SoA - Screening	Modified footnote 'n' to reflect that the screening MRI can be performed after Step II is completed with no required minimum amount of time between Steps II and III.	Allowed flexibility with MRI procedure per request from clinical sites. Conducting MRI after other Step II screening procedures avoids MRI for participants who might be excluded by other Step II procedures.
1.3.1 SoA - Screening	Removed previous footnote 'j' and incorporated relevant parts into footnote 'n.'	Clarification.
1.3.1 SoA - Screening	Added footnote 'p' to allow collection of concomitant therapy and AEs via telephone for Steps III and IV.	Clarification.
1.3.3 SoA - DB Treatment Period, Continued; 6.6 Continued Access to Study Intervention After the End of the Study; 8.1.3 Post-treatment Period (Follow-up)	Added text to footnote 'b' regarding virtual follow-up. Moved text regarding the virtual follow-up approximately 6 months after participant's last site visit from Section 6.6 to Section 8.1.3. Replaced cross-reference to the SoA (Section 1.3) with Section 8.1.3.	Clarification.
2. Introduction	Added that Study Drug refers to JNJ-63733657 and placebo.	Clarification.
4.1. Overall Design	Removed text regarding the detailed stepwise screening process.	Eliminated redundancy with the SoA.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
5.1. Inclusion Criteria (IC 8)	Modified IC 8 as follows: Female participants must be (as defined in Appendix 5, Contraceptive and Barrier Guidance) not of childbearing potential; that is, they must be either: **a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in female participants not using hormonal contraception or HRT, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.** **b. permanently sterile (for the purpose of this study)** **- Permanent sterilization methods include hysterectomy, or bilateral salpingectomy, or bilateral oophorectomy.** **- Has congenital abnormalities resulting in sterility.** ~~a. postmenopausal (no menses for 1 year without an alternative medical cause; high FSH level [>40 IU/L or mIU/mL] in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy, however, in the absence of 1 year of amenorrhea, a single FSH measurement is insufficient); or~~ ~~b. permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy); or~~ ~~c. otherwise be incapable of pregnancy.~~	Aligned with current template language.
5.2 Exclusion Criteria (EC 7)	Modified EC 7 as follows: Has received acetylcholinesterase inhibitors **or**~~,~~ memantine, and/or other permitted AD **medication** ~~therapy~~ at a stable dose **for less than 2 months** at the start of screening ~~for less than 2 months or has less than 2 months of a stable dose on these treatments by the start of screening.~~ (Note: If a participant has recently stopped acetylcholinesterase inhibitors, and/or memantine, he or she must have discontinued treatment at least 2 months before the start of screening). Concomitant use of AD therapies that target the underlying pathophysiology of AD (eg, anti-amyloid or anti-tau therapies) are not permitted.	Clarification.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria (EC 8)	Modified EC 8 as follows: Has received medications that affect the CNS, except treatments for AD (as detailed in EC 7), for less than 2 months; that is, doses of chronic medications that effect the CNS should be stable for at least 2 months before the start of screening. **If a participant has recently stopped a chronic medication that effects the CNS, he or she must have discontinued treatment at least 2 months before the start of screening.** Chronic use of benzodiazepines is not permitted.	Clarification.
5.2 Exclusion Criteria (EC 10)	Modified EC 10 as follows: Presence of thyroid disease or dysfunction**, unless in the opinion of the investigator it does not require treatment or a change to existing medication.** ~~which is uncontrolled or untreated., defined as a thyroid-stimulating hormone (TSH) value that is outside central laboratory's normal range for TSH (ie, below the lower limit of normal or higher than the ULN); or vitamin B12 or folic acid deficiency, defined as a vitamin B12 or folate value that is below the central laboratory's lower limit of normal. Participants may be rescreened if treated and have evidence of TSH, vitamin B12, and folic acid levels within normal range for at least 3 months.~~	Defer to investigator regarding thyroid disease/dysfunction. Created new separate criterion for Vitamin B12/folate.
5.2 Exclusion Criteria (EC 14)	Modified EC 14 as follows: Any current medical conditions that, in the opinion of the investigator **or sponsor's medical monitor**, are clinically significant and might make the participant's participation in an investigational study unsafe, eg, uncontrolled or unstable disease of any major organ system; history within the last 6 months of any acute illness of a major organ system requiring emergency care or hospitalization, including revascularization procedures; severe renal or hepatic failure; unstable or poorly controlled diabetes mellitus, hypertension, or heart failure; malignant neoplasms within the last 3 years (except for basal or squamous cell carcinoma in situ of the skin, or cervix in female participants, or localized prostate cancer in male participants that, in the opinion of the investigator, is considered cured with minimal risk of recurrence); any clinically relevant abnormalities in blood parameters included in local site routine assessments; severe loss of vision, hearing or communicative ability.	Clarification.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria (EC 16)	Modified EC 16 as follows: Clinically significant abnormal physical **examination,** ~~or~~ neurological examination, **or** vital signs at screening or baseline (Day 1 predose)**;** ~~,~~ or laboratory findings at screening. ~~Participants may be rescreened if they meet inclusion criteria and do not meet any exclusion criteria after findings are treated and the participant is medically stable for at least 3 months.~~	Clarification and removal of additional information about rescreening. Rescreening requirements should not be part of assessing eligibility; addressed in separate section of protocol.
5.2 Exclusion Criteria (EC 19) 8.4.3 Electrocardiograms	Modified EC 19 as follows: (QTcB) >450 msec (males) or >470 msec (females), as evaluated by the central ECG vendor at screening ~~and by the principal investigator at Day 1, predose~~. ECGs will be performed in triplicate and participants will be excluded if more than 1 of the 3 QTcB measurements are >450 msec (males) or >470 msec (females). Note: ECG measurements may be repeated once; for any potentially clinically significant findings, the site will manage the participant as per standard clinical practice. Removed text instructing principal investigator to assess ECG for study eligibility.	Removed Day 1 predose ECG is still being performed but will not be used for eligibility. Aligned with EC 19.
5.2 Exclusion Criteria (EC 21)	Modified EC 21 as follows: Any evidence of intracranial pathology which, in the opinion of the investigator or the **central imaging reader and/or the** sponsor (as outlined in the MRI Charter), may affect cognition including, but not limited to, brain tumors (benign or malignant), aneurysm or arteriovenous malformations, territorial stroke (excluding smaller watershed strokes), recent hemorrhage (parenchymal or subdural), or obstructive hydrocephalus. Participants with an MRI scan demonstrating markers of small vessel disease (eg, white matter changes or lacunar infarcts) or microbleeds judged to be clinically insignificant, ~~or microbleeds~~ are allowed.	Clarification.
5.2 Exclusion Criteria (EC 25)	Modified EC 25 as follows: Participant has previously received an active vaccine **for AD (eg, tau, amyloid)** ~~directed to tau~~.	To include any active vaccines for AD.
5.2 Exclusion Criteria (EC 34)	Added EC 34 as follows: **Vitamin B12 or folate levels below the central laboratory lower limit of normal, unless in the opinion of the investigator it does not require treatment.**	Separated from thyroid criteria and allowed investigator to assess clinical significance of low laboratory value.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
5.4 Screen Failures	Added that additional retesting is not permitted without medical monitor approval. Added "imaging" to the statement that if imaging tests were completed and valid, they would not need to be repeated for rescreened participants if confirmed by the sponsor's medical monitor.	Clarification.
6.8 Concomitant Therapy	Updated 6 weeks to 2 months to be consistent with exclusion criteria. Clarified that vitamins, nutraceuticals, and cognitive training used as treatment for cognitive decline "associated with AD" ~~cognitive decline is associated with AD for those treatments potentially enhancing cognition that~~ should be stable for at least 2 months. Specified that participants who have recently stopped using other CNS acting medications should have been off the medication for at least 2 months prior to screening. Removed text stating that standard of care treatment for AD needs to have been taken for at least 4 months. Added text that participants are not required to be taking an AChEI, memantine, and/or other permitted AD at study entry.	Aligned with exclusion criteria. Clarification. Clarification. Clarification. Clarification.
8.1 Overview	Removed text regarding what information is being provided to sites in the Imaging Manual/Charter. Replaced text noting the exception of select screening visits, unless otherwise noted in SoA.	This information is not being provided to sites. Clarification.
8.1.1. Screening Period	Removed screening steps from Figure 5 (and associated text specifying the assessments that should be conducted at each screening visit). Added reference to SoA. Added details regarding plasma tau threshold screen failures.	Allowed flexibility in the order of assessments per request from clinical sites. Removed repetitive text to avoid inconsistencies. Clarification.
8.1.2 DB Treatment Period	Removed text regarding administration of study intervention after baseline during the DB Treatment Period and referred to SoA.	Statements that study intervention is administered "at every regular visit" (after baseline) did not account for participants who remain in the DB period without treatment.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
8.8.2.3 Other Biomarkers	Added text noting that CSF and plasma/serum biomarkers are not limited to neuronal injury and neurodegeneration and inflammation markers.	Clarification.
9.4.1.1. Primary Estimand	Removed "randomized" in regard to treatment and replaced with "assigned." Added that data after ICEs will need to be collected to support supplementary estimands. Removed information on supplementary estimands other than to state that they will be described in the SAP.	Clarification. To allow for the generation of supplementary estimands. Clarification.
9.4.1.2. Primary Endpoint	Removed some details regarding the variance-covariance structure for the primary endpoint. Indicated that an appropriate structure will be used, and the details will be outlined in the SAP.	To allow for the details of the variance-covariance structure to be explored further in the SAP.
9.4.1.3. Key Secondary Endpoints	Added details for the analysis of the key secondary endpoints.	Clarification for the analysis for key secondary endpoints to be consistent with the primary endpoint.
10.2 Appendix 2: Clinical Laboratory Tests	Removed LDH from clinical chemistry panel.	Removed from safety panel due to central laboratory issues with processing. Removal was considered to have no impact on safety.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made. Required language was incorporated to align with TransCelerate headings. Company confidential information was removed to align with the EU CTR Regulations.	Minor errors were noted. Alignment with TransCelerate and regulations.

Amendment 1 (3 September 2021)

Overall Rationale for the Amendment: The overall rationale for the Amendment is to replace the ADAS-Cog13, a cognitive measure, with the integrated Alzheimer's Disease Rating Scale (iADRS), which is a composite of cognition and function, as the primary efficacy measure of the study.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
1.1 Synopsis; 2 Introduction; 2.1 Study Rationale; 3 Objectives and Endpoints; 4.1 Overall Design; 4.2 Scientific Rationale for Study Design; 8.2.1 iADRS; 8.2.2 ADAS-Cog13; 8.2.3 ADCS-ADL-MCI; 8.2.4 RBANS; 8.2.5 CDR; 9.1 Statistical Hypotheses; 9.2 Sample Size Determination; 9.4.1 General Considerations; 9.4.2 Efficacy Analyses; 9.4.2.1 Primary Estimand; 9.4.2.2 Primary Endpoint; 9.4.2.3 Key Secondary Endpoints; 9.4.2.4 Multiple Comparison Adjustment; 9.4.2.5 Other Secondary Endpoints; 9.5 Interim Analyses	The ADAS-Cog13 was replaced with the iADRS as primary efficacy measure of the study. The wording "cognitive decline" was updated to "clinical (cognitive and functional) decline." Additionally, the ADAS-Cog13 was moved to be the first key secondary efficacy measure, followed by the ADCS-ADL-MCI. Statistical sections on primary estimand, primary endpoint, key secondary endpoints, and other secondary endpoints were added or updated accordingly, where applicable. Wording was added to account for multiplicity due to multiple dose comparisons for the primary endpoint and the key secondary endpoints. The protocol was updated throughout to reflect these changes.	To use an assessment that adequately and meaningfully measures both cognition and daily function in the early symptomatic AD patients, based on Health Authority feedback.
1.1 Synopsis; 1.3.2 SoA - DB Treatment Period; 1.3.3 SoA - DB Treatment, Continued; 4.1 Overall Design; 4.2 Scientific Rationale for Study Design; 8.1 Overview; 8.1.2 DB Treatment Period; 8.2.6 Amsterdam IADL	Removed the wording that the IADL may be performed at selected sites only. The SoA footnotes stating "at selected sites" related to IADL were removed.	The Amsterdam IADL will be performed in all regions.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
6.4 Study Intervention Compliance	Removed "and weight of IV infusion bag, including the infusion line, before and after the completion of the IV infusion" in the text. "*Single doses of JNJ-63733657 or matching placebo will be administered as IV infusions by qualified study-site personnel and the details of each administration will be recorded in the CRF (including date, start and stop times of the IV infusion,* ***and*** *volume infused, ~~and weight of IV infusion bag, including the infusion line, before and after the completion of the IV infusion)~~*."	Correction because it is not required in the study.
4.1.1 Number of Participants; 5.2 Exclusion Criteria	Moved the "Concordance of Screening Step I CDR-GS and RBANS Delayed Memory Index Score" from Section 4.1.1 to Section 5.2.	This is relevant to the study population and therefore fits better in Section 5.2.
1.1 Synopsis; 6.1 Study Interventions Administered	The following text in the body and synopsis was aligned with the SoA: A physician must be **immediately** available at the site at all times during the administration of study intervention.	For consistency within the document.
1.1 Synopsis; 4.1 Overall Design; 8.1.3 Post-treatment Period (Follow-up)	Clarified that participants who discontinue from the DB study intervention and who are unwilling to further participate in the DB Treatment Period assessments will have an ET visit, in alignment with the SoA.	Clarification and alignment with SoA.
1.1 Synopsis; 4.1 Overall Design	The following was updated from "*study partner must be at least 18 years of age*" to "*study partner must be at least 18 years of age,* ***or a legal adult.***"	Clarification.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
1.1 Synopsis; 9.4.2.2 Primary Endpoint	The following text regarding the polynomial regression model for the primary analysis was updated: *The model adjusts for the following variables: region, baseline tau burden on tau PET (**as a continuous variable** ~~low versus high~~), ~~and~~ **iADRS**~~ADAS-Cog13~~ baseline **score, sex, age, APOE ε4 carrier status (Y/N), education level (less than high school or at least some high school or greater), use of standard of care medication (AChEIs and/or memantine) at randomization (Y/N).*** *Additionally, ~~as sensitivity analysis~~, a traditional MMRM analysis will be performed. The model will include baseline **iADRS** ~~ADAS-Cog13~~ score **and baseline tau burden on tau PET** as ~~a~~ covariate**s**, and treatment, region, **sex, age, APOE ε4 carrier status, education level, use of standard of care medication (AChEIs and/or memantine) at randomization** ~~baseline tau burden on tau PET (low versus high)~~, time, and time-by-treatment interaction as fixed effects.~~,~~ **An unstructured covariance matrix will be fitted to participants to account for within-participant correlation. 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 participant random effect** ~~and a random participant effect~~.*	Alignment with change in primary endpoint and inclusion of additional variables in the model to better explain the changes in the endpoint.
9.5 Interim Analyses	The following wording was added: ***"Unblinded PK, PD, and immunogenicity analysis may be performed by an independent pharmacometrician using data available at each interim analysis, as appropriate, while keeping the study team blinded. Analysis methods for this analysis, if performed, will be documented in the appropriate SAP."***	Clarification.
8.2.1 iADRS	Wording was updated to clarify that the dressing item in the ADCS-ADL-MCI is removed for the iADRS scoring.	Dressing is a basic ADL; this study population is less likely to show change on basic ADLs.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
2.3.3 Benefit-Risk Assessment for Study Participation	It was clarified that participants will be informed of their **eligibility status based on plasma p217+tau and tauPET** ~~personal biomarker status~~ during screening. This will involve a discussion of potential risks of ~~developing or~~ worsening of cognitive deficits or other symptoms of AD.	Clarification. Correction of error.
8.1 Overview	Removed the word "additional" in the text "*~~Additional~~ serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study."*	Correction because no pregnancy testing is scheduled.
8.2.2 ADAS-Cog13; 8.2.5 CDR	Addition of reference to audio recording for ADAS-Cog13 and CDR.	For consistency with outcome measure of RBANS. (Audio recording was not mentioned in description of ADAS-Cog13 and CDR).
1.3.1 SoA - Screening; 10.2 Appendix 2: Clinical Laboratory Tests	Triiodothyronine (T3) and thyroxine (T4) were removed from the thyroid function tests.	Correction because T3 and T4 will no longer be required laboratory tests in all participants.
1.3.1 SoA - Screening; 4.1 Overall Design; 8.1.1 Screening Period	Wording was updated to clarify that the screening assessments should be performed over multiple visits***, "with at least 7 days separating each visit (ie, screening visits are not to be combined). Except where noted, study procedures for each screening visit/step are to be performed, and the results must be available and reviewed for eligibility, prior to proceeding to the next screening visit/step. The purpose of this is to reduce participant/study partner and clinical site burden of performing unnecessary screening procedures in subsequent screening visits if eligibility criteria assessed at the current visit have not been met."*** Section 4.1 and footnote "a" in Section 1.3.1 were updated accordingly.	Clarification.
1.3.1 SoA - Screening	Footnote "d" was corrected as follows: *"Includes ~~optional~~ consent for **optional** lumbar puncture procedure and collection of CSF."*	Correction.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
1.3.1 SoA - Screening	The following footnote (n) was added at the HIS assessment: ***"HIS will be started at Screening Step I but will require data from Screening Step II (eg, general medical history, neurologic exam) to complete. Participants that already have a HIS score > 4 at Screening Step I can be screen failed (ie, prior to completing the full assessment)."***	Clarification.
8.1.1 Screening Period	It was clarified that it is permitted to collect general medical history also at Step I, if preferred by the site.	To provide flexibility for the clinical site operations and/or participant.
1.3.1 SoA - Screening; 8.1.1 Screening Period	The wording that ADAS-Cog13 should be performed "no later than Day -14" during the Screening Period was removed. Footnote "i" was adapted accordingly.	Clarification.
1.3.1 SoA - Screening	In footnote "j", it was clarified that if the RBANS and MRI are not performed on the same day, MRI should be done at least 1 day before the RBANS assessment.	Clarification.
1.3.2 SoA - DB Treatment Period; 1.3.3 SoA - DB Treatment, Continued; 8.1.1 Screening Period; 8.4.6 Magnetic Resonance Imaging	The following wording was updated: *If MRI is done on the same day as cognitive or other* ***assessments (except lumbar puncture),*** *the MRI should be performed last* ***prior to administration of study intervention. If not performed on the same day, the MRI should be performed within 7 days prior to the visit (ie, -7 day visit window). At visits that include both MRI and lumbar puncture, the MRI should be performed prior to lumbar puncture to minimize any impact of the lumbar puncture procedure on the MRI data****.* ~~*In case this is not feasible, the MRI should be done at least 1 day before other visit procedures.*~~ It was also clarified that: • **All MRI data will be assessed locally by a qualified reader (radiologist or PI) for safety and sent to a core imaging laboratory for central reading, quality control, data analysis, data management, and archiving if needed.** • **During the Double-blind Treatment Period, for visits that include an MRI assessment, administration of study intervention may occur prior to receiving the centrally read MRI results.** Other applicable sections in the protocol were updated accordingly.	Clarification.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
1.3.1 SoA - Screening	In footnote "k", wording was added to clarify that ***"eligibility based on MRI should be confirmed"*** prior to performing the screening lumbar puncture or proceeding to subsequent screening step ~~and tau PET scan.~~	Clarification.
1.3.2 SoA - DB Period	The urine drug screen assessment was removed from the double-blind period.	The urine drug screen performed at screening by the central laboratory will be used for eligibility.
1.3.2 SoA - DB Period; 1.3.3 SoA - DB Treatment, Continued	The following wording was updated: *CSF sample by single lumbar puncture for participants who opt for lumbar puncture. If lumbar puncture is done on the same day as cognitive or other assessments, the lumbar puncture should be performed last* ***prior to administration of study intervention. If not performed on the same day, the lumbar puncture should be performed within 7 days prior to the visit (ie, -7 day visit window). At visits that include both MRI and lumbar puncture, the MRI should be performed prior to lumbar puncture to minimize any impact of the lumbar puncture procedure on the MRI data****.* ~~*In case this is not feasible, the lumbar puncture should be done at least 1 day before other visit procedures.*~~	Clarification.
1.3.2 SoA - DB Treatment Period; 8.4.6 Magnetic Resonance Imaging	The following wording was adapted: *Visits which include MRI* ***allow flexibility regarding when these assessments can be performed for a visit*** ~~*may be performed over multiple days within the windows defined*~~*.* Footnote "a" in the SoA of the double-blind period was adapted accordingly.	Clarification.
1.3.3 SoA - DB Treatment Period, Continued; 8.1.3 Post-treatment Period (Follow-up)	Footnote "a" in the SoA was adapted as follows: *Safety Follow-up Visit assessments to be performed 90 days (±7 days) after last dose of study intervention,* ***if not entering the open-label extension study. In addition, a safety follow-up visit is not required for select participants who discontinue study intervention but remain in the double-blind period (refer to Section 8.1.3).*** Wording in Section 8.1.3 was adapted accordingly.	Clarification.
2 Introduction	It was clarified that study intervention also refers to placebo in this study.	Clarification.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
2 Introduction 11 References	The following wording was added, including references (AC Immune 2020 and Biogen 2021): ***"This is in contrast to the N-terminal anti-tau monoclonal antibodies that have recently failed in Phase 2.[1,6] It is possible that binding to the N-terminus disadvantages these antibodies since this region is commonly cleaved by proteases, leaving less tau available for the antibodies to bind."***	Based on new information becoming available.
2.1 Study Rationale; 4.1 Overall Design	Wording was updated to clarify that *"participants with **inadequate (ie, too little) or** widespread **(ie, too much)** tau, as defined in the Imaging Manual/Charter, will be excluded."* Additionally, the following changes were made in the overall design section: *1. Scans will be reviewed centrally by a qualified reader for evidence of pathologic tau that **meets the** ~~is not widespread as~~ **prespecified eligibility criteria** outlined in a separate Imaging Charter.* *2. Sites will be notified of eligibility **status** and will not receive results.*	Clarification.
6.1 Study Interventions Administered; 8.5.1 Time Period and Frequency for Collecting AE and SAE Information	The recommended management of Infusion Reactions was added.	To accommodate for potential infusion reactions, which may occur during the study.
1.2 Schema; 4.1 Overall Design; 4.4 End of Study Definition	The end of study was more clearly defined in the text, ie, "***The end of the study is when the last participant has had up to 128 weeks of double-blind treatment and completed their last visit (ET visit if entering open-label extension study or safety follow-up visit if not entering the open-label extension study)"*** was added. A schematic overview of the common close design was added as Figure 2 in Section 1.2 and wording in Section 4.1 was adapted accordingly.	Clarification.
4.2 Scientific Rationale for Study Design	The study duration section was updated as follows: *Study participants are followed in the double-blind period for a **maximum** duration of up to 4.5 years, with longest follow-up for those participants enrolled earliest.* The following sentence was added: ***The Double-blind Treatment Period will continue until all participants have had the opportunity to receive double-blind treatment for up to 128 weeks.*** The safety evaluations section was updated to add brain MRI.	For consistency.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
4.2 Scientific Rationale for Study Design; 8.1 Overview	Wording was updated to add "approximately" before the amount of CSF to be collected.	Clarification.
5 Study Population	Wording was updated to clarify that screening for eligible participants will be performed within 90 days before **the first** administration of the study intervention.	Clarification.
4.2 Scientific Rationale for Study Design; 5.1 Inclusion Criteria (IC 1 and 2)	Inclusion Criterion 1 was modified as follows: • 55 to 80 years of age, inclusive**, at the time of initial consent** Wording was adapted in other sections of the protocol accordingly. Inclusion Criterion 2 was modified as follows: • Early AD: Gradual and progressive subjective decline in the participant's cognition over at least the past 6 months, as reported by the participant and informant (study partner) and CDR-GS of 0.5 and memory box score ≥0.5 **at screening.**	IC 1: Clarification to avoid confusion on whether age is determined at the time of initial consent or randomization. IC 2: Clarification.
1.1 Synopsis; 3 Objectives and Endpoints; 5.2 Exclusion Criteria (EC 1)	The following EC was modified: • EC 1: Participants with CDR-GS ≥**2** ~~1 during screening or~~ at predose baseline CDR administration. Protocol text related to this CDR-GS modification was adapted accordingly, where applicable.	Some variability in clinical status may occur. Therefore, EC 1 was relaxed to avoid screen failing participants with CDR-GS 1 at baseline. The categorical analysis of change in clinical stage from baseline using CDR-GS needs to include each of the 3 possibilities.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria (continued; modifications for EC 3, 7, and 8)	The following Exclusion Criteria were modified: • EC 3: GDS-30 score ~~≥11~~ **>12.** • EC 7: Has received acetylcholinesterase inhibitors, memantine, and/or other **permitted** AD therapy for less than 4 months or has less than 2 months of a stable dose on these treatments by the start of screening. (Note: If a participant has recently stopped acetylcholinesterase inhibitors, and/or memantine, he or she must have discontinued treatment at least 2 months before the start of screening). **Concomitant use of AD therapies that target the underlying pathophysiology of AD (eg, anti-amyloid or anti-tau therapies) are not permitted**. • EC 8: Has received medications that affect the CNS, except treatments for AD (as detailed in exclusion criterion ~~6~~**7**), for less than 2 months; that is, doses of chronic medications that effect the CNS should be stable for at least 2 months before the start of screening. **Chronic use of benzodiazepines is not permitted.**	EC 3: To reduce the number of screen failures due to artificially elevated GDS-30 scores related to COVID pandemic restrictions. EC 7: Updated due to regulatory approval of an anti-amyloid therapy. EC 8: Correction of reference to EC number and clarification.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria (continued; clarifications for EC 10, 13, 16, 21, and 32)	• EC 10: Presence of thyroid disease or dysfunction, **defined as a thyroid-stimulating hormone (TSH) value that is outside central laboratory's normal range for TSH (ie, below the lower limit of normal or higher than the ULN);** or vitamin B12 or folic acid deficiency**, defined as a vitamin B12 or folate value that is below the central laboratory's lower limit of normal** ~~which is uncontrolled or untreated.~~ Participants may be rescreened if treated and have evidence of TSH, vitamin B12, and folic acid levels within normal range for at least 3 months. • EC 13: History of substance use disorder according to most current version of the Diagnostic and Statistical Manual of Mental Disorders criteria within the past 5 years before screening or positive test result(s) for other drugs of abuse (including barbiturates, opiates, cocaine, amphetamines, and benzodiazepines) at screening (except if related to current treatment~~, eg, benzodiazepines~~). • EC 21: Any evidence of intracranial pathology which, in the opinion of the investigator **or the central imaging reader (as outlined in the MRI Charter)**, may affect cognition including, but not limited to, brain tumors (benign or malignant), aneurysm or ~~atrioventricular~~ **arteriovenous** malformations, territorial stroke (excluding smaller watershed strokes), recent hemorrhage (parenchymal or subdural), or obstructive hydrocephalus. Participants with an MRI scan demonstrating markers of small vessel disease (eg, white matter changes or lacunar infarcts) judged to be clinically insignificant, or microbleeds are allowed. • EC 32: Any other factors in the opinion of the investigator **and/or sponsor** that could contraindicate ~~the~~ participation ~~of the participant~~ in~~to this~~ **the** study **or suggest inappropriate clinical stage of AD (eg, discordance of CDR-GS and RBANS DMI).**	EC 10, 13, 16, 21, 32: Clarification.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
2 Introduction; 4.2 Scientific Rationale for Study Design; 4.2.1 Study-Specific Ethical Design Considerations	Clarified that although anti-amyloid treatment for AD became available, it not considered to be standard of care. Clarified that current standard of care medications (AChEIs and/or memantine) are permitted in this study if dosing is stable before screening and throughout the study so that participants may receive standard of care AD treatment in combination with placebo. The following paragraph was added in Sections 4.2 and 4.2.1: ***Despite the availability of an AD treatment that targets amyloid plaque, there is still a need for additional therapies targeting other pathophysiologies to have the greatest benefit for patients. Due to the limited availability of the approved anti-amyloid therapy, it is not standard of care. Current standard of care AD medications (AChEIs and/or memantine) are permitted in this study if dosing is stable before screening and throughout the study as described in Section 6.5. Therefore, participants are able to receive standard of care AD treatment plus placebo. AD treatment(s) that target the underlying pathophysiology of AD (eg, anti-amyloid therapies) are not permitted at any time during study participation.*** The introduction section was updated as follows: *~~Currently,~~ **tT**here are ~~no~~ **limited** disease-modifying therapies for AD, and the prevalence **of AD** is estimated to grow to 76 million worldwide by 2030 ~~without such therapies.~~* *Current~~ly~~ ~~available~~ **standard of care** therapies for AD treat the symptoms of the disease and include AChEIs and/or memantine to slow cognitive impairment, as well as treatments to control the behavioral problems frequently associated with AD, such as antidepressants or antipsychotics.*	An anti-amyloid treatment for AD was recently approved. The protocol was updated accordingly.
2.2.2 Clinical Studies; 2.2.2.1 Pharmacokinetics; 2.2.2.2 Pharmacodynamics; 2.2.2.3 Immunogenicity; 2.2.2.4.1 Study 63733657EDI1001; 2.2.2.4.2 Study 63733657EDI1002; 2.3.1 Risks for Study Participation; 4.3 Justification for Dose	The protocol was updated to mention that the MAD part of Study 63733657EDI1001 is completed. Additionally, updates were also made for the SAD part of Study 63733657EDI1001 and for Study 63733657EDI1002. The PK, PD, and safety results sections and other applicable section in the protocol have been updated accordingly. A summary of immunogenicity data has been added.	Update in line with new PK/PD/immunogenicity data with JNJ-63733657 becoming available from other studies.
1.1 Synopsis; 4.1 Overall Design;	It was clarified that most AD treatments are allowed, except for the following:	To account for potential participants who are considering taking any

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
4.2 Scientific Rationale for Study Design; 4.2.1 Study-Specific Ethical Design Considerations; 5.2 Exclusion Criteria (EC 33); 6.5 Concomitant Therapy; 7.1 Discontinuation of Study Intervention; 7.2 Participant Discontinuation/Withdrawal From the Study; 8.1.2 DB Treatment Period	***"Treatments that target the underlying pathophysiology of AD (eg, anti-amyloid therapies) are not permitted at any time during study participation. Participants who take such a treatment in screening will be screen failed and any randomized participant who takes such a treatment will be discontinued from study intervention and the Double-blind Treatment Period."*** The following Exclusion Criterion (EC 33) was added: ***"Planning to take, or currently taking, an approved treatment that targets the underlying pathophysiology of AD, eg, anti-amyloid therapies. If a participant has discontinued an approved treatment that targets the underlying pathophysiology of AD (eg, anti-amyloid therapies), there must be at least 3 months or 5 half-lives, whichever is longest, between the last dose of the treatment and Day 1 of the Double-blind Treatment Period"*** The discontinuation criteria and other applicable sections in the protocol were updated accordingly.	approved treatments that target the underlying pathophysiology of AD that may become available during the course of this study.
1.3.1 SoA - Screening; 5.2 Exclusion Criteria; 8.1 Overview; 8.1.1 Screening Period; 8.4.7.2 HIS	Text referring to the "Rosen modified Hachinski Ischemic Scale (HIS)" was replaced by the "HIS", including in Figure 5 (Section 8.1.1).	Correction because the full version of the HIS is being used in the study, not the Rosen modified version.
4.1 Overall Design	ADCS-ADL-MCI was removed from the list of the screening assessments.	Correction.
1.3.1 SoA - Screening	In footnote "j", text was added that the "***If the RBANS and MRI are not performed on the same day, MRI should be done at least 1 day before RBANS assessment.***"	Clarification.
1.3.1 SoA - Screening	A following footnote (m) was added: "***Procedure can be performed as part of Screening Step I if preferred by the clinical site"*** for the assessments of medical history, prestudy therapy, preplanned surgery/procedure(s), physical examination, neurological examination, height, weight, vital signs, and temperature.	To allow for flexibility on timing of these assessments.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
1.3.1 SoA - Screening	The following wording was adapted in alignment with Appendix 10.2: Serology (i~~ncluding~~ HIV**; if applicable, HBsAg and HCV**).	Clarification. The only serology test for everyone is HIV testing. For participants with elevated transaminases, HBsAg and HCV antibody will also be performed.
1.3.2 SoA - DB Period	Footnote "k" was adapted to correct the blood volume at the Week 16 visit to 8.5 mL.	Correction.
1.1 Synopsis; 1.3.2 SoA - DB Treatment Period; 1.3.3 SoA - DB Treatment Period, Continued; 4.1 Overall Design; 6.1 Study Interventions Administered	Addition of the text that the IP infusion will be "***followed by an IV flush.***"	To clarify that the infusion will be followed by a flush.
1.1 Synopsis; 8.2.1 iADRS; 11 References	Addition of an ADAS-Cog reference (Mohs 1997).	The most recent version of the scale is being utilized.
1.1 Synopsis; 6.1 Study Interventions Administered	Wording was updated to clarify that the medical monitor should be consulted if there are any questions or concerns regarding administration of the study intervention in the arm.	Clarification.
6.1 Study Interventions Administered	A reference to the Pharmacy Manual/Study Site IPPI for the procedure and additional guidance on study intervention administration was added.	Addition of information, for completeness.
6.4 Study Intervention Compliance	Removal of the wording that the ***"weight of IV infusion bag, including the infusion line, before and after the completion of the IV infusion"*** need to be recorded in the CRF.	This procedure is not being done in the study, rather volumes administered are tracked and recorded.
6.5 Concomitant Therapy	The concomitant therapy section was split into 2 subsections, ie, ***Concomitant AD Therapies Potentially Enhancing Cognition*** and ***Concomitant Therapies Adversely Affecting Cognition***. Additionally, several paragraphs were rearranged, including addition of subtitles.	Clarification and improvement of the flow of the text.
6.5 Concomitant Therapy (continued)	Tacrine was removed from the allowed concomitant AD treatments. It was clarified that standard of care therapies for AD are allowed during the study.	Clarification.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
6.5 Concomitant Therapy (continued)	The following text was updated:	
	Benzodiazepines: *The continuous (daily) use of benzodiazepines is not permitted during the study; however, occasional intake of short-acting benzodiazepines is allowed. If a participant requires intermittent treatment with benzodiazepines, the interval from last dose of the benzodiazepine and the subsequent cognitive assessment must be a minimum of 4 half-lives for that compound or 24 hours, whichever is longer. If a* ***benzodiazepine or other*** *sedating medication is given for a study procedure (eg, MRI, PET scan, lumbar puncture) at any visit or for any short-term use, then all cognitive assessments must be administered and completed either before, or at least 24 hours, or 4 half-lives, after administration of the sedative, whichever is longer.*	Clarification.
	Anticholinergic medications: *Strongly anticholinergic medications should be used with caution* ***in the elderly due to adverse effects on cognition and potential to cause delirium****. If* ***medically required*** ~~*used*~~*, the interval from last dose of the anticholinergic medication and the subsequent cognitive assessment must be a minimum of 4 half-lives for that compound or 24 hours, whichever is longer.*	Clarification.
	Pre-study therapies at a stable dose administered up to 6 weeks before ~~*first dose of study intervention*~~ ***the start of screening*** *must be recorded at screening.*	Clarification.
	Concomitant therapies must be recorded throughout the study beginning with start of ***screening*** ~~*the first dose of study intervention*~~ *until the end-of-study visit (follow-up visit).*	Clarification.
	Other CNS acting medications: *Other concomitant medications that affect CNS function* ***(ie, antipsychotics, sedatives, antidepressants, etc.)*** *may be given if the dose is intended to remain unchanged throughout the study.*	Clarification.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
6.5 Concomitant Therapy (continued)	*To avoid* ***or control*** *effects on clinical outcomes, the following apply,* ~~*except in cases of documented medical necessity*~~ ***and should be*** *discussed with the* ~~*sponsor or designee*~~ ***medical monitor****:* *A participant receiving a stable dose of a medication(s) that affects CNS function for at least 2 months prior to the start of screening* ~~*and*~~ *should not stop administration of this medication(s) during the study and should not change the dose* ***or the dosing schedule/timing*** *of this medication* ***during the study****.*	Clarification to decrease variability in cognitive outcome measures. To clarify that if someone requires a medication that can interfere with cognition, not only should the dose remain stable but the timing each day relative to cognitive outcomes should also be consistent over time.
6.5 Concomitant Therapy (continued)	The following paragraphs were added: ***Opioid and related medications: Other medications that affect CNS function and are used as needed or for short-term use during the study (ie, opioid containing medications used for cough, pain, etc.) are permitted but the interval from last dose of the medication and subsequent cognitive assessment must be a minimum of 4 half-lives for that compound or 24 hours, whichever is longer.*** ***Any chronically prescribed and medically required CNS acting medication (except chronic benzodiazepine use, which is excluded) should be taken by the participant at the same time of day throughout the study so that any effect on cognitive assessments is systematic throughout the study.***	To provide advice on how to manage opioid cough and pain medications. Changes made to provide clarification regarding the use of CNS-active medications
6.5 Concomitant Therapy (continued)	Wording was updated to clarify that administration of a locally approved (including emergency use-authorized) COVID-19 vaccine during the study must be recorded in the CRF.	Additions were made per recent Health Authority guidance.
7.2 Participant Discontinuation/Withdrawal From the Study	The following sentence was added: ***"If at any time during study participation the principal investigator feels the participant's AD has worsened to the point where there is a concern about the participant's ability to knowingly and/or voluntarily participate in the study, the sponsor's medical monitor should be contacted to determine whether it is in the best interest of the participant to continue participation."***	Clarification.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
8.1.3 Post-treatment Period (Follow-up)	The following 2 paragraphs were added: ***"If the participant remains in the Double-blind Treatment Period (without study intervention) for more than 90 days after the last dose of study intervention, a safety follow-up visit is not required after completing the Double-blind Treatment Period.*** ***If the participant remains in the Double-blind Treatment Period (without study intervention) for a period of time but discontinues this period prior to having reached 90 days after the last dose of study intervention, an ET visit should be performed, followed by a safety follow-up visit approximately 90 days after the last dose of study intervention."***	Clarification to address several discontinuation scenarios not previously addressed.
8.1 Overview	Clarified that, ***With the exception of select screening visits****, all clinical scales* ***involving the participant*** *should be conducted/completed before any tests, procedures, or other consultations to prevent* ***adversely*** *influencing participant* ***performance*** ~~*perceptions*~~*.*	Clarification.
8.2.4 RBANS	The protocol was revised to clarify that the RBANS should be performed at least twice on different occasions during the Screening Period prior to Screening Visit 5, and that the RBANS performed at Screening Visit 5 will serve as the baseline administration of the RBANS.	Correction since RBANS is not performed at Day 1.
8.4.3 Electrocardiograms	The following wording was clarified: *"During the study, the clinical investigator will review the ECG for study eligibility (****Day 1, predose)*** *and immediate management and to mark abnormalities."*	Clarification.
8.4.6 Magnetic Resonance Imaging	The statement that MRI can be completed in about 30 minutes was removed.	The ICFs detail expected timing of procedures.
1.1 Synopsis; 9.4.3 Safety Analyses 11 References	Added QTcL as additional ECG variable that will be analyzed. Added a literature reference related to QTcL.	Added in the protocol for consistency with the SAP.
10.2 Appendix 2: Clinical Laboratory Tests	The following wording was removed from the protocol: ~~"excluding studies of hepatic impairment or cirrhosis."~~	This is not a study of hepatic impairment or cirrhosis, so it is not applicable.

Section Number and (Abbreviated) Name	Description of Change	Brief Rationale
10.7 Appendix 7: Guidance on Study Conduct during the COVID-19 Pandemic	The protocol was updated to allow blood sampling for biomarkers via home visits during the COVID-19 pandemic. Additionally, the following statement was removed: ~~A future protocol amendment may be submitted to introduce a digital assessment that could be completed remotely or in home by the participant with assistance from the study partner or home health nurse. This would allow remote collection of cognitive data in situations similar to COVID-19 where travel to the site is restricted for safety.~~	Correction.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD MD

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	24-Jul-2025 21:30:09 (GMT)	Document Approval