Janssen Research & Development*

Clinical Protocol

A Randomized, Two-Period, Double-Blind Placebo-Controlled and Open-Label, Multicenter Extension Study to Determine the Long-Term Safety and Tolerability of JNJ-54861911 in Subjects in the Early Alzheimer's Disease Spectrum

Protocol 54861911ALZ2004; Phase 2
Amendment 6

JNJ-54861911

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Amendments below are listed beginning with the most recent amendment.

Amendment 6 (6 Sep 2017)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment:
To provide information on how unblinding and analysis at the end of the double-blind treatment phase of the trial will be carried out;
To indicated that a number of sites will be given the opportunity to use eMeds smart technologies to manage clinical trials supplies and drug compliance activities.

Applicable Section(s)	Description of Change(s)
Synopsis	Included text indicating that a number of sites will be given the opportunity to use the eMeds smart technologies to manage clinical trials supplies and drug compliance activities.
Section 1.1 Background	Updated the list of completed and ongoing studies to be aligned with the status as of the cutoff date of the present amendment (6 September 2017)
Section 3.1 Overview of Study Design	Included text indicating that a number of sites will be given the opportunity to use the eMeds smart technologies to manage clinical trials supplies and drug compliance activities.
Section 3.3 Interim Analysis of Data	Created a new section in the protocol to clarify under what circumstances the Sponsor may perform an unblinded review of safety and biomarker data prior to the last subject's completion of the double-blind treatment phase. In addition it was clarified that when the parent study (eg, 54861911ALZ2002 [and potential future Phase 1b and Phase 2 studies]) is completed and its clinical database is closed, the randomization codes from the parent study will be released to the sponsor study team. The sponsor will be unblinded at that time, but the investigator and subjects will continue to be blinded to treatment during double-blind treatment phase, until the last subject has completed that phase, and the database from that phase has been reviewed, corrected as necessary, and locked. At that point, the sponsor will perform analyses of key safety, biomarker, and efficacy variables, as detailed in a prespecified statistical analysis plan.
Section 11.6 Interim Analysis	Applied editorial changes for clarity. Reiterated the newly-introduced text in Section 3.3 Interim Analysis of Data, including the statement that following the sponsor's review of additional analyses of key safety, biomarker, and efficacy variables, specific measures in place, including a locked database from the double-blind phase, will ensure that there will be no bias introduced by this measure
Section 16.2.3 Informed Consent	Included text to indicate that an appendix to the 54861911ALZ2004 Informed Consent Form will be used for subjects participating in eMeds

Amendment 5 (27 Mar 2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment:
To add new monitoring guidelines and stopping rules for liver enzymes during the first 3 months of treatment and to provide additional information on the management of elevated liver enzymes.

Applicable Section(s)	Description of Change(s)
Rationale: following a new safety report of drug-induced hepatotoxicity (based on biopsy results) in a subject in Study 54861911ALZ2003, whose treatment assignment was unblinded and the subject found to be on 25 mg JNJ-54861911, increased frequency of liver enzyme monitoring in the first 3 months of dosing has been introduced. Guidelines for discontinuation of treatment due to abnormal liver enzymes and for the evaluation and management of such cases have been introduced	
Synopsis - Time and Events Schedule and Section 1.2 Overall rationale for the Study	Hematology and serum chemistry assessments to be performed every 2 weeks for 12 weeks (from Week 52 to Week 64, inclusive) Hematology and serum chemistry assessments to be performed every 4 weeks for 12 weeks (from Week 64 to Week 76, inclusive)
Section 3.2 Study Design Rationale Safety Evaluations	Specified that as a result of the newly identified case of drug-induced hepatotoxicity, if at any time during treatment a subject has an ALT or AST result that is ≥3× ULN, the test should be repeated within 24 - 72 hours and, if confirmed, the further evaluation and management procedures described in Attachment 1 should be followed
Section 3.3.1 Individual Criteria for Stopping Study Treatment	Updated the specific individual rules for stopping study treatment as a result of elevations of liver enzymes between Weeks 52 and 64, as well as after Week 64
Section 9.1.4 Open-Label Treatment Phase	Updated text to specify the frequency that subjects in the open-label phase of the study would have their safety laboratory tests monitored. The safety monitoring would take place every 2 weeks for the first 12 weeks, every 4 weeks for the next 12 weeks, every 8 weeks for the next 24 weeks, and every 12 weeks thereafter.
Section 10.2 Discontinuation of Study Treatment	Updated text to include liver enzyme elevation between Weeks 52 and 64: clarified the different categories of ALT and AST elevations as well as total bilirubin and other symptoms. Updated text to also include liver enzyme elevations after Week 64: added the different categories of ALT and AST elevations as well as total bilirubin and other symptoms.
Section 12.3.5 Adverse Drug Reactions	Clarified that any SAE related to elevated liver enzymes should be reported as described in the study protocol. In addition, any cases of elevated liver enzymes that result in discontinuation of study treatment should be reported as an SAE, following the reporting requirements also described in the protocol
Attachment 1: Evaluation of Increased Liver Enzymes	Updated instructions were provided on the process to follow whenever per protocol assessments for a given subject indicated an elevation of ALT or AST ≥3×ULN

Amendment 4 (26 Oct 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to specify that hepatic enzyme elevations will be classified as "adverse drug reactions" (ADRs) and to clarify the reporting of those events that are considered serious. Additionally, the text is modified and updated related to dermatologic and ophthalmologic/OCT examinations. The text related to re-consenting subjects who have experienced cognitive decline is updated and clarified in sections regarding the informed consent process. An overall risk-benefit assessment is added in the protocol.

Applicable Section(s)	Description of Change(s)
Rationale: Cases of elevated liver enzymes are classified under "adverse drug reactions" with serious cases of liver enzymes elevation subject to expedited reporting per commitment to Health Authority. A new attachment is added to list the criteria for liver enzyme elevations and conditions of reporting the events related to these elevations.	
12.3.2. Serious Adverse Events	Following statement was added: Discontinuation of study treatment secondary to increased liver enzyme criteria (outlined in Section 10.2) will be reported as a serious adverse event.
12.3.5. Adverse Drug Reactions	New section added to clarify reporting events of drug-induced liver enzyme elevation.
Attachment 1	Addition of attachment "Liver Enzyme Elevation Reporting"
Rationale: Given that the events of lightening of hair, lightening of skin, or ophthalmologic abnormalities are possible safety signals for this compound, instructions on classification of these events and rules for reporting them are updated and clarified in all applicable sections of the protocol.	
Synopsis, Overview of Study Design	Following text was added (in bold): Any serious adverse event **or adverse event of special interest (AESI)** must be reported to the sponsor by study site personnel within 24 hours of their knowledge of the event as outlined in the protocol.
11.5. Safety Analyses	The following text was deleted and included under Section 12.3.4. ~~Lightening of hair, lightening of skin, and treatment-emergent ophthalmological AEs that indicate retinal pathology are AEs of special interest (AESI). Adverse events of special interest will require expedited reporting.~~
12 3.4. Adverse Events of Special Interest	A new section added to clearly list the 3 types of AESIs and the reporting of these AESIs, both to the Sponsor and to Health Authorities. It was clarified that all ophthalmologic events and events of lightening of skin or lightening of the hair (serious and non-serious) are categorized as AESIs subject to expedited reporting.
Attachment 2	A new attachment added "Adverse Events of Special Interest"

Applicable Section(s)	Description of Change(s)
Rationale: The section heading updated and text added for more clarity on criteria for discontinuation of study treatment	
3.3.1. Individual Criteria for Stopping Study Treatment	Following text was added: **Events of elevated liver enzymes or increased QTc that require subjects to discontinue will be considered as serious and will be reported to Sponsor within 24 hours of the knowledge of the event.** **Re-initiation of study treatment after discontinuation should only be done after consultation with the sponsor's medical monitor and in mutual agreement between the sponsor and the study center. For details, refer to Section 10.2, Discontinuation of Study Treatment.**
Rationale: Exclusion criterion added to exclude patients with a history (within 1 year prior to enrollment) of clinically significant hepatic impairment or renal insufficiency. Subjects with ongoing clinically significant systemic diseases will also be excluded from the study.	
4.2. Exclusion Criteria, Criterion #3	Following criterion was added: **Subject has a history of moderate or severe hepatic impairment or severe renal insufficiency unless completely resolved for more than a year. Subject has clinically significant ongoing hepatic, renal, cardiac, vascular, pulmonary, gastrointestinal, endocrine, hematologic, rheumatologic, psychiatric, or metabolic conditions (eg, requiring frequent monitoring or medication adjustments, or is otherwise unstable).**
Rationale: The visit window for dermatological exam, MRI, and the OCT exam was extended to ±28 days, with a preference to have these procedures all performed before the scheduled visit date to allow the principal investigator to review at the same time he/she is seeing the subject	
Time and Events Schedule, Footnote "w"	**Footnote was updated to include an extended window period of ±28 days for dermatological exam, MRI, and OCT examinations.**
Rationale: As other AEs are being assessed during the EOT visit, C-SSRS is included in the assessment.	
Time and Events Schedule; 9.1.5. End-of-Treatment (Follow Up Visit)	C-SSRS assessment added for EOT visit to check and monitor the suicidality events (if any)
Rationale: A risk-benefit evaluation of the study was added to inform the investigators about potential risks and benefits of JNJ-54861911.	
1.2. Overall Rationale	Addition of risk-benefit evaluation subsection
Rationale: Language related to re-consenting subjects who have experienced cognitive decline to the point of clinical dementia during the study was modified and added. The subject will be allowed to remain in the study and assent or consent for continued participation (in accordance with the local law) provided that the investigator judges that the potential benefits of treatment outweigh the known and foreseeable risks.	
Synopsis, Study Population; 3.2. Study design Rationale	The following text (in bold) was added: In case the subject progresses to a dementia state during the study, the subject may remain in the study, provided that the investigator judges that the potential benefits of treatment for this subject clearly outweigh the known and foreseeable risks and **assent or** consent **(as applicable)** for continued participation is obtained from a representative determined in accordance with the local law.

Applicable Section(s)	Description of Change(s)
4. Subject Population	In case the subject progresses to a dementia state during the study, the subject may remain in the study, provided that the investigator judges that the potential benefits of treatment for this subject clearly outweigh the known and foreseeable risks and **assent or** consent **(as applicable)** for continued participation is obtained from a representative determined in accordance with the local law
9.1.4. Open-label Treatment Phase	Text was modified as follows: In case of progression to a dementia state (CDR ≥1) during the course of the study, the subject may go through the consenting process for which a legal representative may provide a renewed assent or consent, as applicable, in accordance with local regulations.
16.1. Study-Specific Design Considerations	Text was modified as follows: In case the subject progresses to a dementia state during the study, the subject may remain in the study, provided that the investigator judges that the potential benefits of treatment for this subject clearly outweigh the known and foreseeable risks and **assent or** consent (**as applicable**) for continued participation is obtained from a representative determined in accordance with the local law.
16.2.3. Informed Consent	Following text was added: A subject who has cognitive decline during the study to the point of clinical dementia may go through the consenting process to give renewed assent or consent (provided by a legally appointed representative), as applicable, in accordance with local law or guidance
Rationale: Text describing the need for a placebo-controlled observation period of 12 months (open-label phase) to monitor treatment-emergent ARIA-edema or effusion and ARIA-hemosiderin was considered redundant and hence deleted.	
3.2. Study Design Rationale	The text was updated as follows: In addition to the (safety) MRI assessments performed **in ALZ2002 study** (if applicable), safety MRIs will be collected in this study **during both DB and OL treatment phases**, as indicated in the Time and Events Schedule, to monitor **any treatment-emergent abnormalities, including** ARIA-edema or effusion (E) and ARIA-hemosiderin (H). ~~As ARIA occurs in the absence of therapeutic interventions in some AD patients, an additional placebo-controlled observation period of 12 Months (Treatment Period 1) in the extension study is considered sufficient to monitor for treatment induced effects~~.

Applicable Section(s)	Description of Change(s)
Rationale: Text on dermatologic examination was updated to align it with other protocols for this compound and to improve clarity.	
Time and Events Schedule, footnote "p"; 9.2.6. Dermatologic Examination	The updated text (bold) is as follows: Subjects will undergo a comprehensive skin examination performed by a dermatologist at the time points listed in the Time and Events Schedule to ~~exclude~~ **detect** the presence of skin lesions or depigmentation. A digital photograph of the frontal scalp, open eyes, and eyebrows will be collected ~~to document any findings~~ **to monitor for dermatological changes. This is an essential requirement of the safety monitoring in the trial.** Whenever a skin lesion not previously documented is reported by the study subject or the investigator, in addition to a dermatological exam by the dermatologist, ~~if deemed medically/clinically relevant~~ digital images of the lesion will be acquired ~~at baseline~~ **at the time the lesion is discovered** and at follow-up visits with a frequency which is deemed appropriate by the sponsor of the study. Duration of follow-up of newly documented skin lesions or depigmentation might extend beyond the treatment period, as judged adequate by the sponsor to ensure the safety of ~~participants~~ **subjects** in this study.
Rationale: The observations from studies support the safe coadministration of JNJ-54861911 together with BRCP substrates rosuvastatin and metformin without influencing the PK of either the BCRP substrates or JNJ-54861911. Also updated text to reflect the fact that the clinical DDI study has been done and the data indicated no interaction	
8. Prestudy and Concomitant Therapy	The following text was deleted: ~~As co-administration with JNJ-54861911 25 mg once daily may result in increase in drug concentrations of drugs that are substrates of BCRP, OCT-2, MATE1 or MATE2-K, clinical judgment should be used in the use of these substrates. A list of known substrates of BCRP, OCT-2, MATE1 or MATE2-K can be found in Attachment 1.~~ ~~In vitro data indicate that JNJ-54861911 is an inhibitor of certain drug transporters (see Section 1.1, Background). A clinical DDI study is being planned to evaluate the clinical relevance of in vitro findings. Until the clinical DDI study results are available, concomitant use of procainamide, an OCT-2 substrate with a narrow therapeutic index is prohibited during the study~~.
Rationale: Text was updated to clarify that certain assessments will be performed prior to first dosing in this study only if these assessments were not adequately conducted in 54861911ALZ2002 study from which the subjects rolled over and continued in this study.	
9.1.3. Double-blind Treatment Phase	The text (in bold) was updated as follows: Following assessments **will be performed prior to first dose in the current study at time points mentioned below <u>only</u> if no adequate assessments were conducted in ALZ2002 study (the assessments listed below 6 months and 9 months prior to dosing may also be performed during the screening period in case of any logistical issues).**
9.2.7. Optical Coherence Tomography and Ophthalmologic Examination	The text was updated as follows: A baseline (Day 1 [predose or earlier]) OCT and ophthalmologic examination will be conducted only if no adequate assessments were obtained in 54861911ALZ2002 study within 9 months of first dosing in this study.

Applicable Section(s)	Description of Change(s)
Rationale: Text updated to align the information on changes in the ongoing and completed studies with the current version of the Investigator's Brochure (IB)	
1.1. Background	Section was updated with addition of description for 2 completed studies (54861911ALZ1008 and 54861911ALZ1011 studies) and 2 ongoing studies (54861911ALZ1012 and 54861911ALZ2003 studies). The QT findings for 54861911ALZ1001 and 54861911ALZ1003 studies were deleted as they provide an additional rationale for the tQT study but are not definitive in themselves. The findings from the ongoing 54861911ALZ2002 study are also updated.
Rationale: The text was obsolete. Hence deleted from protocol.	
Attachment 1	Deleted from text.
Rationale: To provide clarity to the text	
Throughout the protocol (except Time and Events Schedule)	"Treatment Period 1" was replaced with "double-blind treatment phase" and "Treatment Period 2" was replaced with "open-label phase"
Throughout the protocol	The term "extension" from "extension study" was deleted; however it is retained in the protocol title.
Throughout the protocol	The term "liver function tests" replaced by "elevated liver enzymes"
Time and Events Schedule	The term "Treatment Period 1" was deleted from the heading.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 3 (14 June 2016)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment:

The overall reason for the amendment is to add adverse events of special interest to Section 11.5 (Safety Analyses).

Applicable Section(s)	Description of Change(s)
Rationale: Lightening of hair, lightening of skin, and treatment-emergent ophthalmological AEs that indicate retinal pathology will be recorded as AEs of special interest	
11.5 Safety Analyses	Lightening of hair, lightening of skin and treatment-emergent ophthalmologic adverse events that indicate retinal pathology were added as adverse events of special interest. These events will now be recorded and have expedited reporting

Amendment 2 (8 April 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: To reduce the 10-mg treatment to 5-mg of JNJ-54861911 for Treatment Period 2, to increase the frequency of hematology and chemistry assessments in the study, and other required changes which were relevant to the study.

Applicable Section(s)	Description of Change(s)
Rationale: A new safety signal for potential liver injury has been identified and is under investigation. As the safety signal may be dose related, a strategic decision was made to decrease the low dose from 10 mg to 5 mg in order to increase the likelihood of having a dose that would ultimately not require monitoring of hepatic enzymes. The 5 mg dose still provides adequate target engagement -- modeled median $A\beta_{1-40}$ decrease in CSF, based on 28 days treatment data, of 52% (95% CI: 27-72).	
Synopsis; 3.1 Overview of Study Design; 3.2 Study Design Rationale; 5 Treatment Allocation and Blinding; 6 Dosage and Administration; Throughout the protocol	References to the 10-mg dose were removed and replaced with the updated 5-mg dose for Treatment Period 2.
Rationale: As a result of the identification of a new safety signal for potential liver injury, additional study visits were added to the study procedures for more frequent monitoring of liver function tests. Subjects entering Treatment Period 1 will already have had 6 months of monthly monitoring in the parent study; therefore, they will have monitoring every 8 weeks for the first 24 weeks of Treatment Period 1 and on 2 additional occasions for the remaining 28 weeks of Treatment Period 1 (i.e., Weeks 36 and 52). In Treatment Period 2, since subjects that had been receiving placebo will be for the first time exposed to JNJ-54861911, all subjects will be monitored monthly for 6 months, every 2 months for the next 6 months, and then every 3 months thereafter.	
Time and Events Schedule (Treatment Period 1); Time and Events Schedule (Treatment Period 2); 9 Study Evaluations	For Treatment Period 1, added new study visits at Week 8 and Week 16 for additional monitoring of liver function tests. As such, liver function tests (hematology and chemistry assessments) will be performed at Weeks 8, 16, 24, 36, and 52. For Treatment Period 2, added an increase in the frequency of liver function tests (hematology and chemistry assessments) to be performed every 4 weeks for the first 24 weeks, 8 weeks for the next 24 weeks, and every 12 weeks thereafter.
Rationale: In the Introduction section, updated the safety and tolerability results for study 54861911ALZ2002 in order to include the new safety signal for potential liver injury.	
1.1 Background	Updated the safety and tolerability results for study 54861911ALZ2002 in order to include the new safety signal for potential liver injury.
Rationale: Based on the dose reduction from 10 mg to 5 mg, Figure 5 was updated to highlight the 5 mg column, and the text was updated to match the figure.	
3.2 Study Design Rationale (Figure 5)	Adjustments were made to the text and to the figure on the expected reduction in CSF Aβ based on the dose reduction.
Rationale: Owing to the identification of a new safety signal for potential liver injury based on the results from study 54861911ALZ2002, the Individual Stopping Criteria section was updated to include elevation of liver enzymes.	
3.3.1 Individual Stopping Criteria	Updated section to include individual stopping rules for subjects with 1 (or more) changes in liver function tests.
Rationale: Deleted an erroneous exclusion criterion.	
4.2 Exclusion Criteria	Deleted exclusion criterion 2 regarding subjects having a reliable informant (relative, partner, or friend). This is an inclusion criterion that was erroneously added to the exclusion criteria section.

Applicable Section(s)	Description of Change(s)
Rationale: Updated language regarding treatment allocation and blinding for clarity.	
5 Treatment Allocation and Blinding	Language pertaining to treatment allocation and blinding was updated in order to specify that an IWRS will be utilized to assign blinded study drug kits in this study (Treatment Period 1 and Treatment Period 2). In addition, both the investigator and subject will be blinded during Treatment Period 1 of the study.
Rationale: Because previous nonclinical in vitro data indicated that JNJ-54861911 might be an inhibitor of P-gp, a conservative approach was taken by not permitting digoxin or dabigatran etexilate use during the trial. New data shows there is no clinically relevant P-gp inhibition by JNJ-54861911.	
8 Prestudy and Concomitant Therapy; Attachment 1 Non-Restricted Substrates of BCRP, OCT-2, MATE1 or MATE2-K	P-gp was removed from the list of transporters.
Rationale: Added language in the Study Evaluations section to indicate that ophthalmologic examination and OCT will be carried out only in those subjects who had these in the parent protocol 54861911ALZ2002, for clarity.	
9.1.3 Double-Blind Treatment Phase (Treatment Period 1); 9.1.4 Open-Label Treatment Phase (Treatment Period 2); 9.2.7 Optical Coherence Tomography and Ophthalmologic Examination	Added language to specify that ophthalmologic examination and OCT will be carried out only in those subjects who had these in the parent protocol 54861911ALZ2002.
Rationale: Owing to the identification of a new safety signal for potential liver injury based on the results from study 54861911ALZ2002, the Discontinuation of Study Treatment section was updated to include elevation of liver enzymes.	
10.2 Discontinuation of Study Treatment	Updated section to include that study treatment may be discontinued for subjects with 1 (or more) changes in liver function tests for clarity. Specified that liver function tests greater than 3x ULN should be repeated/confirmed within 48 to 72 hours.
Rationale: Criteria pertaining to withdrawal from the study were updated for clarity.	
10.3 Withdrawal From the Study	Updated for clarity.

Amendment 1 (2 October 2015)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union

The overall reason for the amendment: To clarify that subjects who have progressed to dementia (CDR≥1) in the parent protocol (54861911ALZ2002) will not be enrolled in Study 54861911ALZ2004, In addition, in the case where the subject progresses to a dementia state during the study, the subject may remain in the study, provided that the investigator judges that the potential benefits of treatment for this subject clearly outweigh the known and foreseeable risks and consent for continued participation is obtained from a representative determined in accordance with the local law.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify that subjects who have progressed to dementia (CDR≥1) in the parent protocol (54861911ALZ2002) will not be enrolled in Study 54861911ALZ2004, and that a subject may remain in the study if he or she progresses to a dementia state during Study 54861911ALZ2004	
Synopsis Subject Population	Subjects who have progressed to dementia (CDR≥1) or who are incapable of providing informed consent will not be enrolled in the study. If a subject progresses to dementia during the study, the subject may remain in the study provided that the investigator judges that the potential benefits of treatment for the subject clearly outweigh the known and foreseeable risk, and consent for continued participation is obtained. Treatments indicated for this condition, such as memantine or cholinesterase inhibitors are permitted after the Sponsor has been notified
Section 3.2. Study Design Rationale	Idem as above
Section 4. Subject Population	Idem as above
Section 16.1. Study-Specific Design Considerations	Idem as above
Rationale: To remove reference to the caregiver co-signing the consent for subjects in a dementia state (CDR≥1) to enroll in the study	
Section 9.1.2. Screening Phase	Deleted reference to the caregiver co-signing the consent for subjects in a dementia state (CDR≥1) to enroll in the study. Also deleted previous reference to a subject's legal representative required to sign the informed consent depending on a subject's disease state.
Section 9.1.4. Open-Label Treatment Phase (Treatment Period 2)	Deleted reference to the caregiver co-signing the consent for subjects in a dementia state (CDR≥1) to enroll in the study.
Section 16.2.3. Informed Consent	Clarified through a re-write, that "in the case of subjects that have become demented during the course of the study, a legally accepted representative, if applicable" must give written consent. Removed a previous reference to "care giver". For grammatical clarity only, removed 2 additional references to this text
Rationale: To provide clarity to the text	
Section 4.1. Inclusion Criteria	Inserted "of the parent protocol"
Section 8. Prestudy and Concomitant Therapy	Inserted "if clinically indicated, after notification of the Sponsor"
Section 16.1. Study-Specific Design Considerations	Inserted "to become apparent"

SYNOPSIS

A Randomized, Two-Period, Double-Blind Placebo-Controlled and Open-Label, Multicenter Extension Study to Determine the Long-Term Safety and Tolerability of JNJ-54861911 in Subjects in the Early Alzheimer's Disease Spectrum

JNJ-54861911 is a BACE inhibitor (BACEi) being developed by Janssen Research and Development (JRD) for the treatment of early Alzheimer's disease (AD) by reducing production of amyloid-beta (Aβ) fragments.

This Phase 2 study will include subjects in the early AD spectrum, i.e., subjects described under the parent protocol (Study 54861911ALZ2002) as asymptomatic at risk for Alzheimer's dementia[16,54,59] as well as subjects with prodromal Alzheimer's disease (pAD)[1,14,15], who have completed a Phase 1b or Phase 2 clinical trial with JNJ-54861911. This Phase 2 study is performed to investigate primarily the longer term safety and tolerability of JNJ-54861911, beyond initial clinical trials, supporting longer term treatment with JNJ-54861911. This study will continue to run until registration of JNJ-54861911 or until emerging safety issues arise as defined by the Data Review Committee (DRC) that would warrant termination of the study. Due to its potentially long treatment duration in comparison with the parent protocols, subjects enrolled in this study may be more likely to experience clinical benefit.

OBJECTIVES AND HYPOTHESIS

Primary Objective

The primary objective of this study is to evaluate the long-term safety and tolerability of JNJ-54861911 in subjects in the early AD spectrum who have completed a Phase 1b or Phase 2 clinical trial with JNJ-54861911 (e.g., Study 54861911ALZ2002), who are willing to continue their assigned treatment.

Secondary Objectives

The secondary objectives of this study in subjects in the early AD spectrum are:

- To assess the maintenance of JNJ-54861911 effects on markers of Aβ processing ($Aβ_{1-37}$, $Aβ_{1-38}$, $Aβ_{1-40}$, $Aβ_{1-42}$) in cerebrospinal fluid (CSF) and plasma.
- To assess the relationship of changes in CSF and plasma Aβ species ($Aβ_{1-37}$, $Aβ_{1-38}$, $Aβ_{1-40}$, $Aβ_{1-42}$) with safety.
- To assess changes in CSF p-tau, t-tau and/or additional alternate biomarkers of neurodegeneration following long term treatment with JNJ-54861911.
- To assess the plasma and CSF pharmacokinetics of JNJ-54861911 in a patient population using a population PK approach and explore its relationship with efficacy and safety parameters.
- To provide ongoing access to JNJ-54861911.

Exploratory Objectives

The exploratory objectives are:

- To explore if JNJ-54861911 will slow the rate of cognitive decline, the perceived cognitive function, and performance of everyday activities.
- To assess the annual conversion rate of subjects treated with JNJ-54861911 to the different stages/phases of the AD spectrum.

- To explore the potential relationship of markers of neurodegeneration (volumetric magnetic resonance imaging [MRI], CSF t-tau or p-tau) with cognitive decline and/or response to treatment with JNJ-54861911.

Hypothesis

This is a study to collect primarily long-term safety and tolerability data. There is no formal hypothesis testing planned for this long-term study which is an extension of 54861911ALZ2002 study.

OVERVIEW OF STUDY DESIGN

This is a randomized, two-period, double-blind (DB) placebo controlled and open-label (OL), multi-center, parallel-group study assessing primarily the long-term safety and tolerability of JNJ-54861911 in subjects in the early AD spectrum who have completed a Phase 1b or Phase 2 clinical study with JNJ-54861911.

This study will be an outpatient study. The Time and Events Schedule provides an overview on the visit frequency and assessments to be performed each visit.

For subjects enrolled in this study, the study will consist of a screening phase, 2 sequential treatment periods i.e., a 12-Month DB treatment phase (placebo-controlled) and an open-label (OL) phase (active), followed by an End-of-Treatment visit. Treatment in OL phase will continue until registration of JNJ-54861911; unless safety issues emerge as determined by the DRC that would warrant termination of the study.

Subjects in the early AD spectrum, enrolled in ongoing or future clinical trials with JNJ-54861911 (Phase 1b or Phase 2 studies) will be provided the opportunity to participate in this study upon completion of their treatment period under the parent protocol. Subjects participating in this study do not have to complete the End-of-Treatment visit (follow-up) visit under the parent protocol.

Enrollment in this study should be completed (Day 1 of DB treatment phase) as soon as possible, but within 6 weeks, following completion of their treatment period under the parent protocol (54861911ALZ2002 study) of currently ongoing or any future Phase 1b or Phase 2 studies with JNJ-54861911.

As a consequence no maximal number of subjects in the early AD spectrum to be enrolled is currently defined.

Subjects will sign the informed consent and be screened for eligibility during the Screening Phase. Eligibility in this study requires that subjects have recently completed their treatment period as described under the parent protocol in study 54861911ALZ2002 or any ongoing/future Phase 1b or Phase 2 JNJ-54861911 clinical studies.

Eligible subjects enrolled in this study will receive either JNJ-54861911 (10 mg or 25 mg once daily [q.d.]) or placebo (q.d.). Subjects will continue with their current treatment regimen established in the parent JNJ-54861911 study (e.g. for 54861911ALZ2002 placebo or JNJ-54861911) for a period of 52 Weeks (12 Months) (placebo-controlled DB treatment phase). Subjects who have received under the parent an active dose different from 10-mg or 25-mg JNJ-54861911 will be receiving the closest dose available in the DB treatment phase (10-mg or 25-mg JNJ-54861911; e.g. subjects receiving 50 mg in study 54861911ALZ2002 will be assigned to 25 mg JNJ-54861911).

Following the initial 52-Week (12-Month) DB treatment phase in this study, subjects receiving placebo in the DB treatment phase will be randomized with equal chance to one of two active JNJ-54861911 dose levels (i.e., 5-mg q.d. JNJ-54861911 or 25-mg q.d. JNJ-54861911) for continuous treatment in OL phase. As such all subjects will receive active (JNJ-54861911) OL treatment during the OL phase. In addition, subjects who were receiving 10 mg q.d. JNJ-54861911 will have their dose reduced to 5 mg q.d. in order

to harmonize the dosage with that of the Phase 2b/3 program, while subjects who were receiving 25 mg q.d. will continue to receive that dosage.

During the Treatment Phases (DB and OL treatment phases), primarily safety and tolerability will be monitored at regular intervals (e.g., magnetic resonance imaging [MRI], physical and neurological examination, suicidality risk assessment, vital signs, 12-lead electrocardiogram (ECG), safety labs, dermatologic and ophthalmologic examinations). Pharmacokinetics (CSF and plasma), and pharmacodynamics (PD) effects by means of biomarkers (fluid [CSF and plasma samples] and imaging [volumetric MRI]) will be explored at the time points listed in the Time and Events Schedule. In addition, effects of JNJ-54861911 on cognition (e.g., Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Mini Mental State Examination (MMSE) and California Verbal Learning Test – Second Edition [CVLT-II]) will be assessed at regular intervals. The subject's clinical status will be assessed during the study by means of the Clinical Dementia Rating Scale (CDR). Investigators will monitor and assess subjects for disease progression. Subjects in the early AD spectrum who develop dementia due to AD during enrollment in this study will be allowed to continue participation in the study, except if emerging data would show continued treatment could potentially be harmful.

A number of sites will be given the opportunity to use the eMeds smart technologies to manage clinical trials supplies and drug compliance activities. This will be done following subject informed consent.

An End-of-Treatment visit (or phone call) for a safety assessment should take place approximately 30 days after the last dose of study drug. The study is considered completed with the last End-of-Treatment safety assessment for the last subject participating in the study or upon a decision by the sponsor to terminate the study.

The Time and Events Schedule provides an overview on the visit frequency and assessments to be performed for each treatment period (DB and OL treatment phases).

Any serious adverse event or adverse event of special interest (AESI) must be reported to the sponsor by study-site personnel within 24 hours of their knowledge of the event as outlined in the protocol.

A DRC will be established to review the safety and tolerability data or any other relevant data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study.

In addition an interim review of blinded or unblinded data by an Interim Analysis Committee may be performed at any time as described in Section 11.6, Interim Analysis.

SUBJECT POPULATION

Subjects in the early AD spectrum, i.e., subjects asymptomatic at risk for Alzheimer's dementia and prodromal AD subjects at time of enrollment in 54861911ALZ2002 study, who have completed their treatment period as defined under the parent protocol in a Phase 1b or Phase 2 clinical study with JNJ-54861911 will be provided the opportunity to participate in this study. If not defined in 54861911ALZ2002 study, completion of the treatment period is defined as having completed all study related procedures of the last visit of the treatment period under the in 54861911ALZ2002 study.

Subjects who have progressed to dementia in the in 54861911ALZ2002 study (CDR ≥ 1) or who are incapable of providing informed consent will not be enrolled.

In case the subject progresses to a dementia state during the study, the subject may remain in the study, provided that the investigator judges that the potential benefits of treatment for this subject clearly outweigh the known and foreseeable risks and then the assent or consent (as applicable) for continued participation is obtained from a representative determined in accordance with the local law. In cases where a subject has progressed to dementia, treatments indicated for this condition (e.g., memantine or cholinesterase inhibitors) are permitted after notification of the sponsor.

Screening for eligible subjects should be performed as soon as possible, but within 6 weeks following completion of their treatment period in ALZ2002 study until administration of the study drug. A screening phase of up to 12 weeks may be allowed following written approval of the Sponsor.

The inclusion and exclusion criteria for enrolling subjects in this study are described in more detail in Section 4.

DOSAGE AND ADMINISTRATION

Study medication will be provided as JNJ-54861911 tablets, strengths 5-mg, 25-mg and matching placebo, blister packed. All tablets (JNJ-54861911/placebo) are physically identical.

Eligible subjects enrolled in this study will participate in 2 sequential treatment phases/periods as described above, i.e.

- **Double-blind treatment phase:** a 52-week (12 Months) placebo-controlled DB treatment phase. Eligible subjects enrolled in this study will receive either JNJ-54861911 (10-mg or 25-mg q.d.) or placebo (q.d.). Subjects will continue on their current treatment regimen assigned in 54861911ALZ2002 study (placebo, 10-mg or 25-mg q.d. JNJ-54861911). Subjects who received an active dose different from 10-mg or 25-mg JNJ-54861911 under 54861911ALZ2002 study will be receiving the closest dose available in DB treatment phase (e.g., subjects receiving 50 mg in study 54861911ALZ2002 will be assigned to 25 mg JNJ-54861911).
- **Open-label phase:** an open label treatment phase during which subjects who received placebo in DB treatment phase will be randomized with equal chance to one of two JNJ-54861911 dose levels, i.e. 5-mg q.d. JNJ-54861911; or 25-mg q.d. JNJ-54861911. Subjects receiving JNJ-54861911 in DB treatment phase will continue their treatment as open label in the OL phase.

During the entire study (DB and OL treatment phases) subjects will self-administer once daily (q.d.) study drug (JNJ-54861911/placebo) with a glass of non-carbonated water, after completion of breakfast or a light snack, during the morning hours, according to the instructions provided by the investigator. During scheduled visits, subjects will self-administer their study medication on site as described above. On Day 1 study drug administration will be administered following completion of all predose assessment and will not be limited to morning hours.

If a subject realizes before 2:00 PM that he/she forgot to take their daily dose, he/she will be instructed to take the daily dose even if late (before 2:00 PM).

If a subject realizes after 2:00 PM he/she forgot to take his/her daily dose, he/she will be instructed not to take any dose during that day, but resume dosing the following day.

Subjects who are no longer capable of ensuring treatment compliance in the judgment of the investigator (e.g., due to progression to dementia) have to be supported in study drug handling and administration (e.g., care giver or nurse practitioner). In cases where support cannot be provided subjects should be discontinued from treatment and withdrawn from the study.

SAFETY EVALUATIONS

The primary objective of this study is to assess the long-term safety and tolerability of JNJ-54861911 in subjects in the early AD spectrum. As such, regular safety assessments will be performed as listed in the Time and Events Schedule. These safety assessments include but are not limited to: vital signs, ECG, physical and neurological examination, adverse events, safety labs, suicidality risks (Columbia Suicide Severity Rating Scale [C-SSRS]), dermatologic and ophthalmologic examinations and MRI. Protocol amendment 5 was written to include more frequent monitoring of serum chemistry and hematology, guidelines for discontinuation of treatment due to abnormal liver enzymes and guidelines for evaluation and management of such cases.

Specific dermatologic and ophthalmologic examinations have been implemented in this study as potential BACE1- or BACE2-linked toxicities (e.g. melanin deposition changes and retinal abnormalities) have been described in the literature (e.g., BACE1 or BACE2 knock-out mice). With the exception of fur discoloration resulting in progressive lightening of the fur from normal dark brown to paler cream or grey, which was seen in one species only (Tg mice in the 6 month carcinogenicity study), however, these toxicities have not been observed in nonclinical chronic studies with JNJ-54861911.

In addition to the (safety) MRI assessments performed in 54861911ALZ2002 (if applicable), safety MRIs will be collected in this study during both DB and OL treatment phases, as indicated in the Time and Events Schedule, to monitor for amyloid related imaging abnormalities (ARIA)-edema or effusion (E) and ARIA-hemosiderin (H). In case of any safety related changes observed (e.g., ARIA-E or H), additional safety MRIs may be collected at a frequency as recommended by the DRC.

Any changes observed in any of the safety measures performed that are considered not clinically significant or do not have a direct clinical symptomatology as assessed by the investigator, should be closely monitored, with a potential increased safety monitoring frequency as deemed appropriate by the investigator. In addition, these findings will be presented to the DRC, who will make recommendations regarding the safety and continuation of the study as per its charter.

PHARMACOKINETIC EVALUATIONS

Venous blood samples for analysis of JNJ-54861911 will be collected at the time points indicated in the Time and Events Schedule.

CSF samples for analysis of JNJ-54861911 concentrations will be obtained at the time points indicated in the Time and Events Schedule.

COGNITION, FUNCTION AND CLINICAL STATUS

Cognitive evaluations (RBANS, MMSE and CVLT-II) and functional outcome measures (Cognitive Function Index [CFI]) will be applied in this study at different time points as indicated in the Time and Events Schedule to explore the subject's cognitive performance/progression and function over time.

In addition during course of the study the subject's clinical status will be assessed regularly by means of the Clinical Dementia Rating Scale as indicated in the Time and Events Schedule.

BIOMARKER EVALUATIONS

Fluid (CSF and plasma samples) biomarkers samples and imaging biomarker assessments (MRI) will be performed as listed in the Time and Events Schedule to assess the potential and continuous effects of JNJ-54861911 on the pathological and pathophysiological processes of AD. In addition, these biomarker assessments will be performed to assess if potential treatment effects of JNJ-54861911 are consistent with the putative effects of BACE inhibition.

During the course of the study the continuous effects of JNJ-54861911 on the pathophysiological processes of AD will be monitored by the DRC.

All subjects will undergo an MRI in this study at the time points indicated in the Time and Events Schedule for primarily safety reasons. However, potential treatment effects may be assessed with MRI as well.

STATISTICAL METHODS

Sample Size Determination

This study is not powered according to statistical calculations. The number of subjects enrolled will depend on the number of subjects from other JNJ-54861911 studies who are willing to enroll in this study.

Statistical Analysis

Descriptive statistical analyses will be performed for all subjects receiving at least one dose of study drug. Analyses may be prepared separately for DB and OL treatment phases, and may be performed separately for subgroups of subjects according to previous study participation as well as for the combined population of all subjects participating in this study, where appropriate. Summaries may also be presented by baseline CDR global score.

Data Review Committee (DRC)

A DRC will be established to review/monitor the study data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study. The committee will meet periodically to review interim study data including the biomarker data (fluid [CSF, plasma] and imaging [volumetric MRI]).

After the review, the DRC will make recommendations regarding the safety and continuation of the study. The details will be provided in a separate DRC charter.

The DRC responsibilities, authorities, and procedures will be documented in its charter.

TIME AND EVENTS SCHEDULE

Phase	Screening	Double-Blind Treatment Phase							Open-Label Treatment Phase	End-of-Treatment Visit (or phone call) or Early Withdrawal[n]
Treatment Period		Period 1							Period 2	
Time Period		*Day 1 to Week 52 (Month 12)*							*>Week 52 (>Month 12)*	
Study Visits: Day/Week/Month	*0 to 6 weeks*	*Day 1*	*Week 8*	*Week 12*	*Week 16*	*Week 24*	*Week 36*	*Week 52 (Month 12)*[n]		*30 days post last dose*
Visit Window		*0*	*+/- 12 days*	*+/- 12 days*	*+/- 12 days*	*+/- 12 days*	*+/- 12 days*	*+/- 12 days*	*+/- 12 days*	*+/- 12 days*
Study Procedures										
Screening/Administrative									See separate **Time and Events Schedule Treatment Period** 2	
Informed consent	X									
Inclusion/exclusion criteria	X									
Medical History and Demographics	X									
Prestudy therapy	X									
Preplanned surgery/procedure(s)	X									
Study Drug Administration										
Randomization								X[o]		
Dispense study drug		X		X		X	X	X[o]		
Self-Administer study drug[a]		X----------						----------X		
Drug accountability		X		X		X	X	X		
Drug return				X		X	X	X		
Safety Assessments										
Physical and Neurological examination		X[b,c]						X		
Vital signs		X[b,c]				X		X		
Body Weight		X[b,c]						X		
12-lead ECG[d]		X[c,s]				X[s]		X[s]		
Temperature		X[b,c]				X		X		
Dermatologic Examination[p,x]		X[c,e,f]				X		X		
Ophthalmologic Examination		X[c,e,f,]				X[m]		X[m]		

Phase	Screening	Double-Blind Treatment Phase							Open-Label Treatment Phase	End-of-Treatment Visit (or phone call) or Early Withdrawal[n]
Treatment Period		Period 1							Period 2	
Time Period		*Day 1 to Week 52 (Month 12)*							*>Week 52 (>Month 12)*	
Study Visits: Day/Week/Month	*0 to 6 weeks*	*Day 1*	*Week 8*	*Week 12*	*Week 16*	*Week 24*	*Week 36*	*Week 52 (Month 12)*[n]		*30 days post last dose*
Visit Window		*0*	*+/- 12 days*	*+/- 12 days*	*+/- 12 days*	*+/- 12 days*	*+/- 12 days*	*+/- 12 days*	*+/- 12 days*	*+/- 12 days*
Study Procedures										
OCT[r,x]		X[c,e,f,]				X		X		
C-SSRS (baseline)		X[c,g]								
C-SSRS (since last visit)		X[c,g]		X		X	X	X		X
Cognitive & Functional Evaluations[h]									See separate **Time and Events Schedule Treatment Period** 2	
RBANS		X[b or i]				X		X		
MMSE		X[b or i]						X		
CVLT-II				X						
CFI		X[b or i]				X		X		
Clinical Scales[h]										
CDR		X[b or i]						X		
Clinical Laboratory Assessments										
Hematology, Chemistry		X[b,c]	X		X	X	X	X		
Urinalysis		X[b,c]				X		X		
Pharmacokinetics										
Blood Sample collection		X[c,s]				X[c,s]		X[c,s]		
Fluid Biomarkers										
Blood sample collection		X[c]				X[c]		X[c]		
CSF sample collection[j]		X[c,k]						X[j]		
Imaging										
MRI[q,x]		X[c,f,i]				X		X		
Ongoing Subject Review										
Concomitant therapy	X	X		X		X	X	X	X	X
Adverse events	X	X		X		X	X	X	X	X

TIME AND EVENTS SCHEDULE (OPEN-LABEL TREATMENT PHASE)

Phase	Open-Label Treatment Phase						
Treatment Period	Treatment Period 2						
Time Period	>52 weeks						
Study Visit	**Every 2 weeks**	**Every 4 weeks**	**Every 8 weeks**	**Every 12 weeks**	**Every 24 weeks(*)**	**Every 48 weeks(*)(#)**	**Every 96 weeks(*)(#)(¥)**
Visit Window	*+/- 3 days*	*+/- 12 days*	*+/- 12 days*	*+/- 12 days*	*+/- 12 days*	*+/- 12 days*	*+/- 12 days*
Study Procedures							
Drug accountability/Treatment compliance				X			
Drug return (previous visit)				X			
Drug Dispensing				X			
Self-Administer study drug[a]	X----------						----------X
Physical and Neurological examination						X	
Body Weight						X	
12 Lead ECG				X[l,s]	X[s]		
Body Temperature					X		
Supine and standing vital signs (systolic and diastolic blood pressure and pulse)				X			
Clinical safety laboratory assessments – hematology, serum chemistry– under fasted conditions, when feasible	X[t]	X[u]	X[v]	X[w]			
Clinical safety laboratory assessments – urinalysis–under fasted conditions, when feasible					X		
Dermatological Examination[p,x]						X	
Ophthalmological Examination[m]						X	
OCT[r,x]						X	
C-SSRS (since last visit)				X			
RBANS					X		
MMSE						X	
CFI					X		
CDR						X	
Blood sample collection for plasma JNJ-54861911 concentrations					X[c,s]		
Blood sample collection for PD/biomarkers					X[c]		
CSF sample collection (~12 mL) by single lumbar puncture for PK/PD/biomarker assessment.[j]							X[j]
MRI[q,x]						X	
Adverse Event and Concomitant Medication				X			

Abbreviations = CDR: Clinical Dementia Rating Scale; CFI: Cognitive Function Index; CSF: cerebrospinal fluid; C-SSRS: Columbia Suicide Severity Rating Scale; CVLT-II: California Verbal Learning Test – Second Edition; DRC: Data Review Committee; ECG: electrocardiogram ; MRI: Magnetic Resonance Imaging; MMSE: Mini Mental State Examination; OCT: Optical Coherence Tomography; PK: pharmacokinetic(s); PD: pharmacodynamics; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status.

TIME AND EVENTS SCHEDULE (FOOTNOTES)

Footnotes

[a] Subjects will self-administer study drug (once daily) with a glass of water following breakfast or a light snack. Study drug administration will take place during the morning hours. During scheduled visits when ECG or blood samples for JNJ-54861911 concentrations in plasma are to be obtained subjects will self-administer their study medication on site as described above. On Day 1 study drug administration will not be time limited.

[b] Baseline (predose) only if no (adequate) assessment was obtained under the parent protocol at the last study visit of the treatment phase.

[c] Must be performed predose.

[d] At all time points, triplicate ECGs are required, i.e., 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

[e] Only if no adequate assessment was obtained under the parent protocol within 9 months of first dosing in this study.

[f] May be performed during screening in case of logistical issues.

[g] C-SSRS baseline: Only to be completed if no C-SSRS assessment was performed under the parent protocol; C-SSRS since last visit: to be completed if the C-SSRS assessment was performed under the parent protocol.

[h] The RBANS will be completed first followed by the CDR and MMSE if the raters for RBANS and CDR are independent. If the raters for RBANS and CDR are the same, the CDR will be performed first, followed by the RBANS and MMSE.

[i] Only if no adequate assessment was obtained under the parent protocol 6 months prior to first dosing in this study.

[j] CSF samples (12 mL/sample; baseline and on treatment samples) should be taken at approximately the same time of day (with an allowable window of 3 hours), with the on treatment samples being collected postdose. In Treatment Period 2 (>52 weeks) it is intended to collect if possible on-treatment CSF samples every 96 weeks until study completion. Subjects may opt not to have these punctures being performed. CSF samples collected will be used for biomarker and PK analysis.

[k] Only if no on-treatment CSF sample was collected under the parent protocol (54861911ALZ2002 study).

[l] Only during the first 12 week visit of the open-label treatment phase.

[m] Ophthalmologic examination will be performed only if: 1) if there was an abnormality present at the screening/baseline examination; 2) if the investigator detects new ophthalmological findings or visual symptoms; 3) if OCT reveals new findings. The ophthalmologic examination should be performed by the same ophthalmologist who completed the initial ophthalmologic examination at screening/baseline.

[n] If a subject discontinues study treatment the subject will be asked to complete the Week 52 assessments, including CSF sampling, if not yet obtained earlier. In addition, and at a minimum the subject will be asked to complete the End-of-Treatment Visit (Follow-up visit) as per Time and Events Schedule.

[o] At Week 52 subjects will be dosed according to treatment allocation assigned to in Treatment Period 1. Randomization to Treatment Period 2 and dispensation of study medication for Treatment Period 2 will only be performed following completion of all week 52 assessments.

[p] Whenever a skin lesion not previously documented is reported by the study subject or the investigator, in addition to a dermatological exam by the dermatologist, digital images of the lesion will be acquired at the time the lesion is discovered and at follow-up visits with a frequency which is deemed appropriate by the sponsor of the study. Duration of follow-up of newly documented skin lesions or depigmentation might extend beyond the treatment period, as judged adequate by the sponsor to ensure the safety of subjects in this study.

[q] Additional MRI scans may be collected based on emerging safety data with a frequency as recommended by the DRC.

[r] At sites where OCT is available.

[s] 2 to 4 hours postdose.

[t] Hematology and serum chemistry assessments to be performed every 2 weeks for 12 weeks (from Week 52 to Week 64, inclusive).

[u] Hematology and serum chemistry assessments to be performed every 4 weeks for 12 weeks (from Week 64 to Week 76, inclusive).

[v] Hematology and serum chemistry assessments to be performed every 8 weeks for 24 weeks (> Week 76 and ≤ Week 100).

[w] Hematology and serum chemistry assessments to be performed every 12 weeks after Week 100.

[x] Assessments can be done not only on the visit date but also within the visit window of +/- 28 days, with a preference to have these procedures performed prior to the scheduled visit.

** In addition to the assessments performed every 12 weeks.*

 # In addition to the assessments performed every 24 weeks.

¥ In addition to the assessments performed every 48 weeks.

ABBREVIATIONS

Aβ	amyloid β (beta)
AD	Alzheimer's disease
ALT	alanine aminotransferase
APP	amyloid precursor protein
ARIA-E	Amyloid related imaging abnormality – edema
ARIA-H	Amyloid related imaging abnormality –hemosiderin
AST	aspartate aminotransferase
AUC	area under curve
BA	Bioavailability
BACE	β-secretase
BACE1	β-secretase 1 (also known as beta-site APP cleaving enzyme 1)
BACE2	β-secretase 2 (also known as beta-site APP cleaving enzyme 2)
BACEi	BACE inhibitor
b.i.d.	Twice daily
BQL	below the limit of quantification
C-SSRS	Columbia Suicide Severity Rating Scale
CDR	Clinical Dementia Rating Scale
CDR-SB	Clinical Dementia Rating Scale – Sum of Boxes
CFI	Cognitive Function Index
CI	confidence interval
C_{max}	maximum or "peak" concentration (Cmax) of a drug observed after its administration
CNS	central nervous system
CrCl	creatinine clearance rate
CRF	case report form (paper or electronic as appropriate for this study)
CSF	cerebrospinal fluid
CVLT-II	California Verbal Learning Test – Second Edition
CYP	cytochrome P450
DIAT	Diaminothiazine
DDI	drug-drug interaction
DRC	Data Review Committee
DTP	data transfer plan
ECG	Electrocardiogram
eDC	Electronic Data Capture
FLAIR	Fluid attenuated inversion recovery
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GSH	Glutathione
HDPE	high-density polyethylene
IC_{50}	The concentration of a compound that is required for 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IWRS	Interactive Web Response System
JRD	Janssen Research and Development
LC-MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
MAD	Multiple ascending dose
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini Mental State Examination
MRI	Magnetic resonance imaging
NFT	Neurofibrillary tangles
NOAEL	No observed adverse effect level

pAD	Prodromal Alzheimer's disease
OCT	Optical Coherence Tomography
PD	Pharmacodynamic(s)
PDPH	Post-dural puncture headache
PET	Positron emission tomography
PHFs	paired helical filaments
PK	Pharmacokinetic(s)
PQC	Product Quality Complaint
POM	Proof of mechanism
q.d.	once daily
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RBC	Red blood cell
SAD	single ascending dose
sAPP	soluble amyloid precursor protein
SOP	Standard operating procedure
t_{max}	time to reach the maximum plasma/CSF concentration
WBC	white blood cells

1. INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease associated with aging. AD patients suffer from cognition deficits and memory loss as well as behavioral problems such as anxiety and agitation. With the increasing number of elderly in the population, AD is a growing medical concern. Currently available therapies for AD merely treat the symptoms of the disease and include acetylcholinesterase inhibitors to improve cognitive properties as well as anxiolytics and antipsychotics to control the behavioral problems frequently associated with AD.

The hallmark pathological features of AD patients are neurofibrillary tangles (NFT) which consist of hyperphosphorylated tau protein and amyloid plaques, whose main constituent is amyloid-beta (Aβ). $A\beta_{1-42}$ peptide is over-represented in amyloid deposits. $A\beta_{1-42}$ has a high tendency to aggregate, forming oligomers and fibrils, as well as amyloid in neuritic plaques. Aβ accumulation and amyloid deposition are believed to be early, key events in the pathogenesis of AD according to the amyloid cascade hypothesis.[29,40] The oligomers and fibrils have been demonstrated to be neurotoxic.

Agents that prevent the formation of Aβ overall or $A\beta_{1-42}$ specific have been proposed to be disease-modifying agents for the treatment of AD. Aβ is generated from the amyloid precursor protein (APP). The N-terminus of Aβ is cleaved by β-secretase1 (BACE1), and then γ-secretase cleaves the C-terminal end. In this process, BACE1 cleavage is the first and rate limiting step. In addition to $A\beta_{1-42}$, γ-secretase cleavage can result in other Aβ fragments (e.g., $A\beta_{1-40}$, $A\beta_{1-38}$, and $A\beta_{1-37}$), from which $A\beta_{1-40}$ is the predominant cleavage product. These Aβ forms can also aggregate to form oligomers and fibrils. Thus, inhibitors of BACE1 prevent the formation of $A\beta_{1-42}$ as well as $A\beta_{1-40}$, $A\beta_{1-38}$, and $A\beta_{1-37}$ and would be potential therapeutic agents in the treatment of AD. In support of this hypothesis is the observed correlation between the catalytic efficiency of BACE1 for its substrate APP and the occurrence of AD. The Swedish APP mutant (KM670/671NL), a more efficient substrate for BACE1 (10x), causes a rare familial form of AD that is inherited in the dominant Mendelian fashion. On the other end of the spectrum is an allelic variant of APP (A673T), a less efficient substrate for BACE1 (± 0.5x), which is protective against sporadic AD.[38]

JNJ-54861911 is a BACE inhibitor (BACEi) being developed by Janssen Research and Development (JRD) for the treatment of (early) AD by reducing production of Aβ fragments.

This Phase 2 study will include subjects in the early AD spectrum, i.e., subjects described as asymptomatic at risk for Alzheimer's dementia[16,54,59] as well as subjects with prodromal Alzheimer's disease (pAD)[1,14,15], who have completed a Phase 1b or Phase 2 clinical trial with JNJ-54861911. This Phase 2 study is performed to investigate primarily the longer term safety and tolerability of JNJ-54861911, beyond initial clinical trials, supporting longer term treatment with JNJ-54861911. This study will continue to run until registration of JNJ-54861911 or until emerging safety issues arise as defined by the Data Review Committee (DRC) that would warrant termination of the study. Due to its potentially long treatment duration, subjects enrolled in this study may be more likely to experience clinical benefit.

For the most comprehensive nonclinical and clinical information regarding JNJ-54861911, refer to the latest version of the Investigator's Brochure and Addenda for JNJ-54861911.[37]

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

JNJ-54861911 is a BACE inhibitor being developed for the treatment of AD. JNJ-54861911 reduces production of Aβ fragments by inhibiting BACE1 processing of APP, with the aim of reducing AP formation. JNJ-54861911 has been demonstrated to be potency potent reducer of Aβ, both in nonclinical models, as well as in initial clinical studies.[37]

Nonclinical Studies

Pharmacologic Profile

[redacted]

Safety Profile

[redacted]

[redacted]

Clinical Studies

For the most comprehensive clinical information regarding JNJ-54861911, refer to the latest version of the Investigator's Brochure for JNJ-54861911.[37]

Study 54861911ALZ2004 will be an extension study for subjects in the early AD spectrum who have completed a Phase 1b or Phase 2 clinical trial with JNJ-54861911.

Study 54861911ALZ2004 is the third study in subjects in the early (predementia) AD spectrum following the proof of mechanism (POM) study (54861911ALZ1005) and the 6-month safety study (54861911ALZ2002). The POM study 54861911ALZ1005 is being performed to confirm a drug interaction with the intended enzyme (BACE) at the intended target location (brain) at the intended dose range (placebo q.d., 10 mg q.d. and 50 mg q.d. JNJ-54861911) following 1 month of treatment in subjects with early (predementia) AD, while the 6-month safety study (54861911ALZ2002) is being performed to provide safety information in preparation for the longer term treatment studies.

Twelve clinical studies have been completed; 9 of these studies were of short duration and in healthy subjects: Studies 54861911ALZ1001 and 54861911ALZ1002 evaluated the safety, tolerability, PK, and pharmacodynamics (PD) of single and multiple ascending oral doses of JNJ-54861911 in healthy subjects; Study 54861911ALZ1003 examined the relative bioavailability of a solid formulation of JNJ-54861911 in comparison with a suspension formulation and the effect of high fat/high calorie food on the PK of a 25 mg tablet formulation in healthy subjects; Study 54861911ALZ1006 evaluated the safety, tolerability, PK, and PD of single ascending doses in healthy Japanese male subjects; Study 54861911ALZ1007 was a thorough QT study to evaluate ECG intervals in healthy subjects; Study 54861911ALZ1009 investigated the effects of strong CYP 3A4 and amide hydrolase inhibitor on the single-dose PK of JNJ-5481911 in healthy male subjects; Study 54861911ALZ1010 investigated effects of single and multiple daily doses of JNJ-54861911 once daily on the PK of midazolam, tolbutamide, and caffeine, (substrates of CYP3A4, CYP2C9, and CYP1A2, respectively) in healthy male subjects; Study 54861911ALZ1011 was a 3-period crossover study to evaluate the relative oral bioavailability and food effect of JNJ-54861911 tablet after single-dose administration in healthy elderly subjects; and Study 54861911ALZ1012 was an open-label, fixed-sequence, single-center, 2-panel study to investigate the PK interaction between JNJ-54861911 and transporter substrates rosuvastatin and metformin.

Three additional completed studies had treatment durations of 4 weeks and longer, as well as participants in the target population: Study 54861911ALZ1005 was a double-blind, placebo-controlled, randomized, 4-week, multiple-dose, proof-of-mechanism study in subjects with early Alzheimer's disease investigating the effects of JNJ-54861911 on Aβ processing in CSF and plasma; Study 54861911ALZ1008 was a double-blind, placebo-controlled, randomized, 4-week, multiple-dose, proof-of-mechanism study in Japanese subjects asymptomatic at risk for Alzheimer dementia (ARAD) investigating the effects of JNJ-54861911 on Aβ processing in cerebrospinal fluid (CSF) and plasma; Study 54861911ALZ2002 was a phase 2a randomized, double-blind, placebo-controlled, parallel-group, multi-center study investigating the safety and tolerability of JNJ-54861911 in subjects in the early (predementia) Alzheimer's disease spectrum.

As of 6 September 2017, there are 2 ongoing clinical studies: Study 54861911ALZ2003, a phase 2b/3 randomized, double-blind, placebo-controlled, parallel group, multicenter study investigating the efficacy and safety of JNJ-54861911 in subjects who are asymptomatic at (risk for developing Alzheimer's dementia, and Study 54861911ALZ2004, a randomized, 2-period, double-blind placebo-controlled and open-label, multicenter extension study to determine the long-term safety and tolerability of JNJ-54861911 in subjects in the early Alzheimer's disease spectrum.

Pharmacokinetics

Final pharmacokinetic (PK) results from a SAD study are presented in this section. Preliminary PK results from multiple-ascending dose (MAD) and relative BA studies are also presented.

In the SAD study 54861911ALZ1001, 1-mg JNJ-54861911 was administered to healthy young subjects followed by single-dose administration of JNJ-54861911 in elderly subjects with doses ranging from 1 to 150 mg. The pharmacokinetics of JNJ-54861911 was characterized by rapid absorption and multiphasic decline in all treatment groups. Plasma JNJ-54861911 concentrations increased dose proportionally between 1 mg and 150 mg, reaching C_{max} at approximately 0.75 to 2.0 hours postdose. In elderly subjects, dose-normalized mean exposure results ranged from 4.93 to 8.39 ng/mL for C_{max} and 84.9 to 104 ng.h/mL for AUC_{∞} across all doses. On average, mean half-life ($t_{1/2}$) seemed to increase slightly from the 1- to 10-mg dose and seemed to be similar thereafter (range 9.0 to 16.1 hours). The 1-mg dose pharmacokinetics in young healthy subjects was comparable to that of the elderly subjects. JNJ-54861911 levels in CSF were assayed only in elderly subjects. All concentrations were below the limit of quantification (BQL) for the 2 lowest doses (1 and 3 mg), but increased dose-proportionally from 30 to 150 mg. Maximal mean concentrations were reached between 2.0 and 3.0 hours with levels ranging from 2.94 to 22.7 ng/mL.

JNJ-54861911 in urine was analyzed only for the 2 highest doses (90 and 150 mg). The fraction excreted of unchanged JNJ-54861911 in urine as a percent of the dose was similar for both doses (0.315% and 0.381%, respectively) and represented renal clearance rates of 0.593 and 0.780 mL/min for the 90- and 150-mg doses, respectively.

For assessable doses, JNJ-54861911 plasma exposure was similar between males and females with male:female ratios for C_{max} of 0.987 and 0.820, and for AUC_{last} of 0.814 and 0.667 for the 30- and 150-mg dose groups, respectively.

In the MAD study 54861911ALZ1002, JNJ-54861911 steady-state plasma C_{max} and AUC_{τ} increased approximately dose-proportionally across the doses studied. Steady-state plasma levels were reached by Day 5. Median t_{max} was slightly delayed with multiple dosing compared to a single dose (multiple dose range: 2.00 to 4.00 hours; single dose range: 0.75 to 2.00 hours). The mean $t_{1/2}$ on Day 14 ranged from 14.4 to 18.5 hours across all doses studied. Mean accumulation ratios across all doses for steady-state C_{max} and AUC_{τ} on Day 14 ranged from 1.27 to 1.73 and 1.34 to 2.17, respectively. The mean renal clearance values between Day 1 and Day 14 were similar (0.111 vs 0.115 L/h).

Preliminary results from the ongoing 54861911ALZ1012 study showed the mean PK parameters of rosuvastatin and metformin were similar following single-dose administration with and without JNJ-548161911 25 mg at steady state. The 90% confidence interval (CI) of geometric mean ratios for Cmax and AUC were well within the 80% to 125% boundaries of no effect. Therefore, this study concluded no clinically significant drug-drug interaction between JNJ-548161911 and the substrates of transporters BCRP, MATE-1, MATE-2, and OCT-2.

In the relative BA/food-effect study 54861911ALZ1003 in older male subjects (aged 55 to 75 years), comparable BA was observed between tablet and suspension formulations after administration of an oral dose of 25 mg. In this study, food had little effect on JNJ-54861911 exposure across subjects after oral administration of tablet formulation in the presence of high fat/high calorie food. When C_{max} and AUC_{∞} in the fed state were compared to the fasted state ($Frel_{fed/fasted}$) values of 96.1% and 114% were obtained for C_{max} and AUC_{∞}, respectively. Median t_{max} was delayed by 1.5 hours in the fed state (median t_{max} 3.00 hours [0.75 - 8.00]) in comparison with the fasted state (median t_{max} 1.50 hours [0.75 - 3.50]).

Only minor metabolites were observed in human plasma from Study 54861911ALZ1002, and none of them was human specific. In Studies 54861911ALZ1001 and 54861911ALZ1002, the AUC ratio of DIAT metabolite to parent compound was below 10% and the C_{max} ratio of DIAT metabolite to parent compound ranged from 4% to 7%. Other metabolites identified in human plasma showed lower exposure.

The effect of once daily administration of 200 mg of itraconazole, a strong inhibitor of cytochrome P450 3A4 (CYP3A4) activity, on the pharmacokinetics of JNJ-54861911 was evaluated in a clinical DDI study (Study 54861911ALZ1009). Preliminary results indicate that in the presence of itraconazole 200 mg q.d., JNJ-54681911 C_{max} and AUC_{∞} increased by 13% and 82% respectively.

The clinical DDI study to evaluate the interaction potential of JNJ54861911 as perpetrator when co-administered with a drug cocktail of CYP3A4, CYP2C9, and CYP1A2 substrates (Study 54861911ALZ1010) has recently been completed. Preliminary results of this trial do not show a clinically relevant effect of JNJ54861911 on the activity of CYP3A4, CYP1A2 or CYP2C9.

Pharmacodynamics

In Study 54861911ALZ1001, a dose-dependent decrease in plasma $A\beta_{1-40}$ levels was observed (Figure 1). Onset of inhibition was fast, with strongest reduction of $A\beta_{1-40}$ levels during the first 4 hours postdose. At the 1 mg dose after 2.5 hours, 42% inhibition was achieved with no significant further $A\beta_{1-40}$ reductions. At the 3 mg dose, 57% inhibition was achieved after 4 hours; at higher doses (10, 30, 90, and 150 mg) 70% to 80% inhibition was achieved at 4 hours postdose. After 4 hours, the percent mean change from baseline values of $A\beta_{1-40}$ levels remained relatively stable up to 36 hours postdose at higher doses, while lower doses (e.g., 1 mg) showed a trend towards normalization before that time point. No notable changes from baseline were observed in subjects receiving placebo.

CSF was only collected in elderly subjects. CSF Aβ measurements showed an increase in CSF $A\beta_{1-40}$ levels over baseline especially early. Over the first 6 hours, no apparent treatment effect was observed at any dose. At doses of 1 and 3 mg, no strong treatment effects were observed at any time during the observation period. At higher doses, after 6 hours a dose-dependent reduction of CSF $A\beta_{1-40}$ levels was observed, which continued in the 150-mg group until the end of the observation period at 36 hours, while lower active doses trended towards normalization earlier (Figure 2).

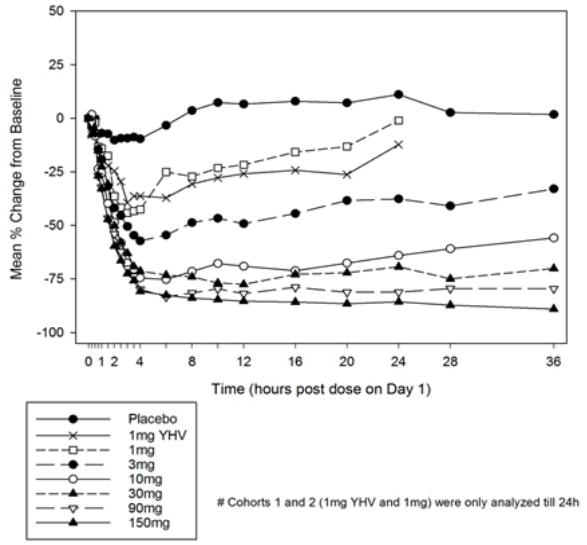


Figure 1: Plasma $A\beta_{1-40}$ Mean Percent Change From Baseline Following Single Dose Administration of JNJ-54861911

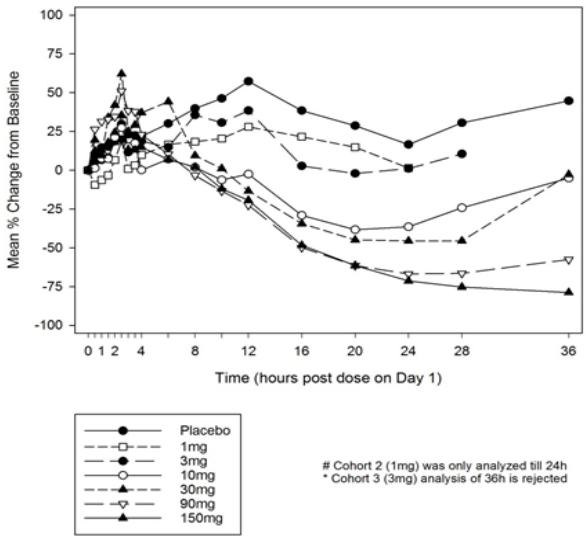


Figure 2: CSF $A\beta_{1-40}$ Mean Percent Change From Baseline following Single Dose Administration of JNJ-54861911

In Study 54861911ALZ1002, marked dose-dependent reductions in plasma $A\beta_{1-40}$ levels were observed in subjects receiving a q.d. oral suspension of JNJ-54861911 at doses of 5, 30, 50, and 90 mg, as well as 25-mg tablet (Figure 3). These reductions were relatively stable during the 36-hour postdose observation period. In parallel, a dose-dependent decrease in the CSF $A\beta_{1-40}$ levels was observed compared with the Day 1 predose baseline (Figure 4). Similar to the observed $A\beta_{1-40}$ reductions in plasma, all reductions were stable during the 36-hour postdose observational period. Towards the end of the observation period there was a trend towards normalization, which was more pronounced at the lowest dose of 5 mg. This trend was only seen 24-hour postdose, at which time in a therapeutic situation the next dose would have been given. $A\beta_{1-40}$ reductions were dose dependent: 50% at 5 mg/day, between 85% and 90% at 30 mg/day, around 90% at 50 mg/day, and between 90% and 95% at 90 mg/day. Reductions in subjects dosed with the 25-mg tablet were similar to the 30-mg oral suspension.

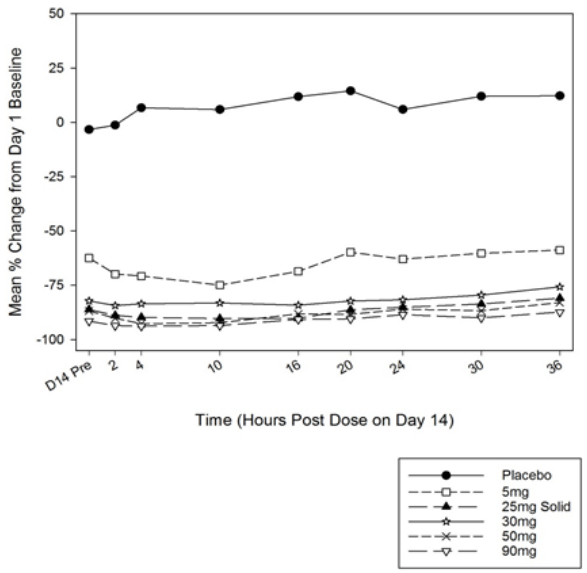


Figure 3: Plasma $A\beta_{1-40}$ Mean Percent Change on Day 14 in Relation to Baseline Day 1 Following Multiple Dose Administration of JNJ-54861911.

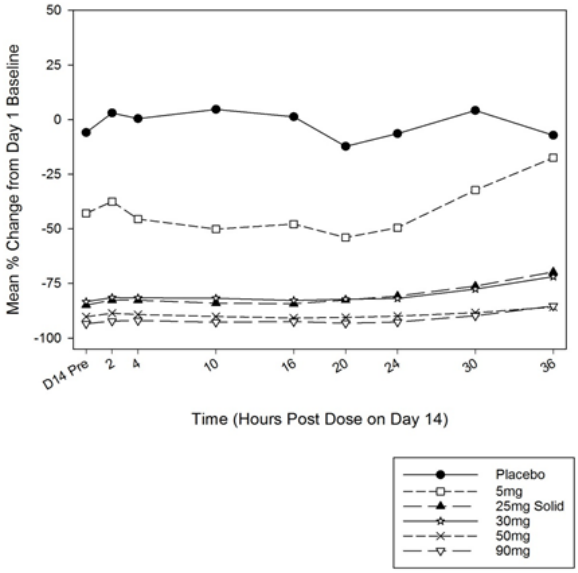


Figure 4: CSF $A\beta_{1-40}$ Mean Percent Change on Day 14 in Relation to Baseline Day 1 Following Multiple Dose Administration of JNJ-54861911

Pharmacokinetic/Pharmacodynamic Modeling

Single Dose Modeling: The main goal of this analysis was to develop a population PK/pharmacodynamic (PD) (PopPK/PD) model to characterize the kinetics of JNJ-54861911 in plasma and CSF, and to quantify the impact of JNJ-54861911 exposure on reduction of $A\beta_{1-40}$ levels in plasma and CSF following single doses. The CSF concentration of JNJ-54861911 that inhibits the CSF synthesis rate of $A\beta_{1-40}$ by 50% was estimated as 0.77 ng/mL, which corresponds to a plasma concentration of approximately 24.44 ng/mL.

Multiple Dose Modeling: The main objective of this analysis was to develop an exploratory PopPK/PD model to describe the relationship between JNJ-54861911 PK and the PD effect on $A\beta_{1-40}$, both in the CSF and in plasma, following multiple oral q.d. doses of JNJ-54861911. The PK and PD data included in this analysis were from Cohorts 1 to 4 of Study 54861911ALZ1002 (dose levels of 30, 90, 5, and 50 mg q.d. of JNJ-54861911, oral suspension). The average plasma and CSF steady-state exposures as well as average CSF $A\beta_{1-40}$ reductions following q.d. dosing of JNJ-54861911 were assessed. Results showed that the estimated daily dose providing 50% average CSF $A\beta_{1-40}$ reduction at steady-state is approximately 6 mg, while a dose of 50 mg q.d. achieves approximately 90% CSF $A\beta_{1-40}$ reduction. For higher doses the dose-response curve levels off rapidly, and hence, the model-predicted response improves only marginally in the dose range of 50 to 150 mg.

QTcF Modeling: A model-based exploratory analysis of exposure and Fridericia-corrected QT (QTcF) data from Cohort 6 of Study 54861911ALZ1002 did not show a statistically significant relationship between JNJ-54861911 mean exposure and the associated mean QTcF change from Day 0 (i.e., a predose, full-baseline profile over 24 hours).

Safety and Tolerability

In Study 54861911ALZ1001, 43 (76.8%) of 56 subjects experienced at least one adverse event (33 [78.6%] of 42 subjects who received a single oral dose of JNJ-54861911 and 10 [71.4%] of 14 subjects who received placebo). In Study 54861911ALZ1002, 40 (76.9%) of 52 subjects who received JNJ-54861911 and 12 (66.7%) of 18 subjects who received placebo experienced at least one adverse event. In Study 54861911ALZ1003, no notable differences in the incidence of adverse events were observed specific to the type of formulation or dosing under fed or fasted conditions.

The most common adverse events across these three clinical studies in subjects receiving JNJ-54861911 were headache and back pain. Both events are typically associated with the lumbar puncture procedure. In subjects receiving placebo (Studies 54861911ALZ1001 and 54861911ALZ1002), the most common adverse events were headache, abdominal pain, and contact dermatitis. There were no severe or serious adverse events observed in subjects receiving JNJ-54861911 across the 3 studies, and no adverse events led to discontinuation of study drug. Most adverse events were considered by the investigator as not related or doubtfully related to the study drug. There were no clinically significant treatment- or dose-related effects observed in clinical laboratory evaluations, neurologic and physical examination, and or vital signs.

A 6-month Phase 2a safety study with JNJ-54861911 (54861911ALZ2002) in subjects who have early AD (predementia) was initiated in December 2014, and this study was followed by the present study (54861911ALZ2004). Both studies provide information on the safety of JNJ-54861911 in the target population. In study 54861911ALZ2002 the blood values of hepatic enzymes in some patients were increased, indicating potential for liver injury. Importantly, there were no symptoms clearly related to these elevations, and upon discontinuation of the drug, the liver enzyme values have decreased toward normal, and there were no lasting effects. The further investigation of this signal is continuing; to date (17 March 2017), more than 200 subjects have received JNJ-54861911 or placebo in studies longer than 1 month of treatment. Eleven subjects (9 on active drug, 1 on placebo, 1 blinded) have experienced an elevation in liver enzymes >3×upper limit of normal (ULN) in these studies. None of these subjects had symptoms related to these elevations in liver enzymes. One of these subjects, participating in Study 54861911ALZ2003 (a Phase 2b/3 study investigating the efficacy and safety of JNJ-54861911 in subjects who are asymptomatic at risk for developing Alzheimer's dementia), was the subject of a new safety report of drug-induced hepatotoxicity (based on biopsy results). The treatment assignment was unblinded and the subject was found to be on 25 mg JNJ-54861911. As this subject's increase in ALT and AST were observed in Month 1, increased frequency of monitoring in the first 3 months of dosing has been introduced.

Based upon this case, the protocol is being modified to include more frequent monitoring of serum chemistry and hematology (indicated in the Time and Events Schedule and Section 9.1.4), guidelines for discontinuation of treatment due to abnormal liver enzymes (Section 3.4.1 and Section 10.2), and guidelines for evaluation and management of such cases (Attachment 1).

1.2. Overall Rationale for the Study

This Phase 2 study in subjects in the early AD spectrum is performed to investigate primarily the long term safety and tolerability of JNJ-54861911, beyond initial clinical trials. Subjects in the early AD spectrum who have completed a Phase 1b or Phase 2 clinical study with JNJ-54861911 will be provided the opportunity to participate in this study. The study will provide safety and tolerability data supporting long term treatment with JNJ-54861911, which will be placebo-controlled initially for the first 12 months, but will then continue with active dose arms only thereafter. This study will continue to run until registration of JNJ-54861911 or until emerging safety issues arise as defined by the DRC that would warrant termination of the study. Due to its potentially long treatment duration, subjects enrolled in this study may be more likely to experience clinical benefit.

Risk-Benefit Evaluation of Study 54861911ALZ2004

To date (29 July 2016), 9 clinical studies have been completed. Overall, JNJ-54861911 has been safe and well tolerated in the completed clinical studies at various dose ranges (1-10 mg, 25-50 mg, and 90-150 mg) in healthy young male and healthy elderly male and female subjects and at dosages of 5 to 50 mg in subjects in the early AD spectrum.

Subjects in the early (predementia) AD spectrum, aged 50 to 85 years inclusive, who will receive no direct therapeutic benefits from study participation, will be enrolled in this study. This is an extension of the parent study, 54861911ALZ2002 which was the second study with JNJ-54861911 in this population, following an earlier proof-of-mechanism study (54861911ALZ1005).

The early (predementia) AD spectrum defined in this study includes subjects who are asymptomatic but at risk for AD (aged 65 to 85 years inclusive) as well as subjects with pAD (aged 50 to 85 years inclusive). Subjects who are classified as asymptomatic at risk for AD are cognitively and functionally normal as defined by the Clinical Dementia Rating Scale (CDR; CDR of 0), but have a biomarker pattern consistent with AD. Subjects with pAD have some limited cognitive impairment (CDR = 0.5), are still functionally normal and have a biomarker pattern consistent with AD, but as yet are not demented (predementia stage).

Potential subjects have been fully informed of the risks and requirements of the study. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

As a result of the newly identified case of drug-induced hepatotoxicity, the protocol has been modified to include more frequent monitoring of serum chemistry and hematology (see Time and Events Schedule and Section 9.1.4), guidelines for discontinuation of treatment due to abnormal liver enzymes (Sections 3.4.1 and 10.2), and guidelines for evaluation and management of such cases (Attachment 1).

Based on the preclinical data, 3 potential risks of JNJ-54861911 in humans have been identified: QT interval prolongation, epileptic seizures, and hypopigmentation or discoloration of fur.

A thorough QT trial, has been performed in 64 healthy subjects using a 4-way, 7-day cross-over design evaluating a JNJ-54861911 dose of 50 mg/day as well as supratherapeutic dose of 150 mg/day, and including moxifloxacin 400 mg to confirm assay sensitivity. The 150-mg dose showed a prolongation of QTc interval, i.e., the maximum mean difference and 90% confidence intervals (CI) between JNJ-54861911 150 mg and placebo was 15.5 msec (12.92, 18.06) at Day 7, 1 hour and 30 min. The 50-mg dose showed a maximum mean difference from placebo of 6.6 msec (90% CI: 4.02, 9.12) at Day 7, 1 hour. In both groups the observed changes were pronounced 1-4 hours after dosing. Results of the PK/PD modelling data from the 54861911ALZ1007 study showed that at a JNJ-54861911 once daily dose of 25 mg, the median changes in the QTcF, as well as the 90% population interval, are expected to be well below 5 msec.

Preclinical data also suggest a potential risk of epileptic seizures, based on a 1-month dog toxicology study, in which short-lasting convulsions and tremors were reported within 2 hours after dosing 100mg/kg/day. The NOAEL in that study was 10mg/kg/day. The highest dose in this clinical study will be 25 mg/day. Plasma drug concentrations in human subjects dosed 25 mg/day were shown in a previous experiment to be approximately 8 times lower than the concentration that cause no convulsions in the dog (e.g. 10 mg/kg/day). In the 9-month study dog no CNS effects up to the highest dose, i.e. 60 mg/kg/day were observed, with exposures of C_{max} 3.55 µg/mL (♂) and 5.35 µg/mL (♀). Compared to the plasma drug concentrations expected in human subjects dosed 25 mg/day these are approximately 16.9 to 25.5 fold lower than the concentration in the 9-month study that did not cause any CNS side effects.

Fur discoloration (progressive lightening from normal dark brown to paler cream or grey) was observed from Day 85 onwards in animals dosed at 100 mg/kg/day or higher in a 6-month mouse carcinogenicity study that was conducted at doses ranging from 30 to 600 mg/kg/day. This discoloration appeared partly reversible after a 3-month recovery period. Histopathological examination did not reveal any changes in skin or pigmented parts of the eye, neither were ophthalmologic changes seen. This finding is in line with BACE2-linked toxicity (e.g. melanin deposition changes and retinal abnormalities), that have been described in the literature (e.g. BACE1- or BACE2 knock-out mice). In this study, cases of hypopigmentation or lightening of the hair should result in dermatological consultation with digital photography of the lesions; if these are deemed adverse events, they should be reported to the sponsor in an expedited manner.

Strong CYP3A4 inhibitors may have a modest effect on plasma concentrations of JNJ-54861911. Based upon 2 studies (54861911ALZ1009 and 54861911ALZ1010), it is recommended that drugs that are moderate to strong inhibitors of CYP3A4 should be taken with care, under the assumption that a moderate increase of JNJ-54861911 could be seen. Additional to the potential compound-related risks, there are study procedure related risks. Most of these are standard clinical assessments with limited risk associated for the subject (e.g. blood draw, ECG, MRI and PET).

To reduce the maximum possible theoretical risks associated with lumbar punctures including cerebral herniation (due to pre-existing intracranial hypertension) and spinal epidural hematoma with compression of the cauda equina, additional eligibility criteria and other preventive action

are put in place. Medical conditions contraindicating a lumbar puncture will be excluded. To reduce the risk of post-dural puncture headache (PDPH) caused by persistent CSF leakage, subjects are preferably placed on bed, rest in a supine position during sampling. To avoid the introduction of an infection into the CSF (which is a rare complication), lumbar puncture is performed under sterile conditions. Prior to the puncture, all subjects will be examined thoroughly for (possible) topical infections or local dermatological condition at the puncture site, of which their presence will lead to exclusion of the subject. All CSF collections will be performed under aseptic conditions. Irritation of nerve roots, possibly caused upon insertion of the needle is usually benign and self-limiting. The CSF puncture sites (L3-L4 or L4-L5) will prevent spinal cord trauma. Only experienced and qualified physicians are allowed to perform the applicable procedures. Coagulation tests at screening and an eye exam with fundoscopy are performed at screening to exclude intracranial hypertension.

The total blood volume to be collected will not exceed 450 mL annually, which is considered to be safe and acceptable in comparison to a Red Cross blood donation.

A placebo arm is necessary to allow for an accurate assessment of the safety and tolerability of the study drug; the use of placebo over the 6 month treatment period in the parent study, 54861911ALZ2002, and in the first 12 months of this study, extends this assessment into the longer term. Since there is, at this moment, no treatment available for subjects at risk for AD or subjects in the earliest AD spectrum, the use of placebo is warranted. Throughout the course of the study, the Sponsor will have the option based on recommendations by the Data Review Committee, or based upon newly emerging safety, biomarker or efficacy data from ongoing or completed JNJ-54861911 studies, to revise the dose levels in this study.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

The primary objective of this study is to evaluate the long-term safety and tolerability of JNJ-54861911 in subjects in the early AD spectrum that have completed a Phase 1b or Phase 2 clinical trial with JNJ-54861911 (e.g. Study 54861911ALZ2002), who are willing to continue their assigned treatment.

Secondary Objectives

The secondary objectives of this study in subjects in the early AD spectrum are:

- To assess the maintenance of JNJ-54861911 effects on markers of Aβ processing ($A\beta_{1-37,}$ $A\beta_{1-38,}$ $A\beta_{1-40,}$ $A\beta_{1-42}$) in CSF and plasma.
- To assess the relationship of changes in CSF and plasma Aβ species ($A\beta_{1-37,}$ $A\beta_{1-38,}$ $A\beta_{1-40,}$ $A\beta_{1-42}$) with safety.
- To assess changes in CSF p-tau, t-tau and/or additional alternate biomarkers of neurodegeneration following long term treatment with JNJ-54861911.

- To assess the plasma and CSF pharmacokinetics of JNJ-54861911 in a patient population using a population PK approach and explore its relationship with efficacy and safety parameters.
- To provide ongoing access to JNJ-54861911.

Exploratory Objectives

The exploratory objectives are:

- To explore if JNJ-54861911 will slow the rate of cognitive decline, the perceived cognitive function, and performance of everyday activities.
- To assess the annual conversion rate of subjects treated with JNJ-54861911 to the different stages/phases of the AD spectrum.
- To explore the potential relationship of markers of neurodegeneration (volumetric magnetic resonance imaging [MRI], CSF t-tau or p-tau, with cognitive decline and/or response to treatment with JNJ-54861911.

2.2. Hypothesis

This is a study to collect primarily long-term safety and tolerability data. There is no formal hypothesis testing planned for this long-term study which is an extension of 54861911ALZ2002 study.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, two-period, double-blind (DB) placebo controlled and open-label (OL), multi-center, parallel-group study assessing primarily the long-term safety and tolerability of JNJ-54861911 in subjects in the early AD spectrum that have completed a Phase 1b or Phase 2 clinical study with JNJ-54861911.

This study will be an outpatient study. The Time and Events Schedule provides an overview on the visit frequency and assessments to be performed each visit.

For subjects enrolled in this study, the study will consist of a screening phase and 2 sequential treatment phases, i.e., a 12-month double-blind (DB) treatment phase (placebo-controlled) and an open-label (OL) phase (active), followed by an End-of-Treatment visit. Treatment in OL phase will continue until registration of JNJ-54861911; unless safety issues emerge as determined by the DRC that would warrant termination of the study.

Subjects in the early AD spectrum, enrolled in ongoing or future clinical trials with JNJ-54861911 (Phase 1b or Phase 2 studies) will be provided the opportunity to participate in this study upon completion of their treatment period under the parent protocol. Subjects participating in this extension study do not have to complete the end-of-treatment visit (follow-up) visit under the parent protocol.

Subjects who provide consent to enroll in this protocol and who meet the inclusion criteria, may start at Day 1 of the DB treatment phase in lieu of the end of treatment visit in 54861911ALZ2002 study. For subjects that have completed the end of treatment visit in the 54861911ALZ2002 study enrollment in this study should be completed (Day 1 of DB treatment phase) as soon as possible, but within 6 weeks, following completion of their treatment period under the parent protocol (54861911ALZ202 study) of currently ongoing or any future Phase 1b or Phase 2 studies with JNJ-54861911. A screening phase of up to 12 weeks may be allowed following written approval of the Sponsor.

As a consequence no maximal number of subjects in the early AD spectrum to be enrolled is currently defined.

Subjects will sign the informed consent and be screened for eligibility during the Screening Phase. Eligibility in this study requires that subjects have recently completed their treatment period as described in study 54861911ALZ2002 or any future Phase 1b or Phase 2 JNJ-54861911 clinical studies.

Eligible subjects enrolled in this study will receive either JNJ-54861911 (10 mg or 25 mg q.d.) or placebo (q.d.). Subjects will continue with their current treatment regimen established in the parent JNJ-54861911 study (e.g. for 54861911ALZ2002 placebo or JNJ-54861911) for a period of 52 Weeks (12 Months) (placebo-controlled DB treatment phase). Subjects who have received an active dose different from 10-mg or 25-mg JNJ-54861911 in 54861911ALZ2002 study will be receiving the closest dose available in DB treatment phase (10-mg or 25-mg JNJ-54861911; e.g., subjects receiving 50 mg in study 54861911ALZ2002 will be assigned to 25 mg JNJ-54861911).

Following the initial 52-Week (12-Month) treatment phase (DB treatment phase) in this study, subjects receiving placebo in the DB treatment phase will be randomized with equal chance to one of 2 active JNJ-54861911 dose levels (i.e., 5-mg q.d JNJ-54861911 or 25-mg q.d. JNJ-54861911) for continuous treatment in OL phase. As such during OL phase, all subjects will receive active (JNJ-54861911) treatment (open-label). In addition, subjects who were receiving 10 mg q.d. JNJ-54861911 will have their dose reduced to 5 mg q.d. in order to harmonize the dosage with that of the Phase 2b/3 program, while subjects who were receiving 25 mg q.d. will continue to receive that dosage.

During the Treatment Phases (DB and OL treatment phases), primarily safety and tolerability will be monitored at regular intervals (e.g., MRI, physical and neurological examination, suicidality risk assessment, vital signs, 12-lead ECG, safety labs, dermatologic and ophthalmologic examinations). Pharmacokinetics (CSF and plasma), and PD effects by means of biomarkers (fluid [CSF and plasma samples] and imaging (volumetric MRI]) will be explored at the time points listed in the Time and Events Schedule. In addition, effects of JNJ-54861911 on cognition (e.g., Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Mini Mental State Examination (MMSE) and California Verbal Learning Test – Second Edition [CVLT-II]) will be assessed at regular intervals. The subject's clinical status will be assessed during the study by means of the Clinical Dementia Rating Scale (CDR). Investigators will

monitor and assess subjects for disease progression. Subjects in the early AD spectrum who develop dementia due to AD during enrollment in this extension study will be allowed to continue participation in the study, except if emerging data would show continued treatment could potentially be harmful. An End-of-Treatment visit (or phone call) for a safety assessment should take place approximately 30 days after the last dose of study drug. The study is considered completed with the last End-of-Treatment safety assessment for the last subject participating in the study or upon a decision by the sponsor to terminate the study.

A number of sites will be given the opportunity to use the eMeds smart technologies to manage clinical trials supplies and drug compliance activities. This will be done following subject informed consent.

The Time and Events Schedule provides an overview on the visit frequency and assessments to be performed for each treatment period (DB and OL treatment phases).

Any serious adverse event or adverse event of special interest (AESI) must be reported to the sponsor by study-site personnel within 24 hours of their knowledge of the event as outlined in the protocol.

A DRC will be established to review the safety and tolerability data or any other relevant data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study.

In addition an interim review of blinded or unblinded data by an Interim Analysis Committee may be performed at any time as described in Section 11.6, Interim Analysis.

3.2. Study Design Rationale

Blinding, Control, Study Phase/Periods, Treatment Groups and Treatment Duration

Subjects enrolled in this study will participate in 2 sequential treatment phases/periods:

- **DB treatment phase:** a 52-Week (12-Month) placebo-controlled double-blind treatment phase. Eligible subjects enrolled will receive either JNJ-54861911 (10-mg or 25-mg q.d.) or placebo (q.d.). Subjects will continue on their current treatment regimen assigned under the 54861911ALZ2002 study (placebo, 10-mg or 25-mg q.d. JNJ-54861911). Subjects who received an active dose different from 10-mg or 25-mg JNJ-54861911 in 54861911ALZ2002 study will be receiving the closest dose available in the DB treatment phase (i.e. subjects receiving 50 mg in study 54861911ALZ2002 will be assigned to 25 mg JNJ-54861911).
- **OL treatment phase:** an open-label treatment phase during which subjects who received placebo in DB treatment phase will be randomized with equal chance to one of two JNJ-54861911 dose levels (5-mg q.d. or 25-mg q.d. JNJ-54861911). Subjects who were receiving 10 mg q.d. JNJ-54861911 will have their dose reduced to 5 mg q.d., while subjects who were receiving 25 mg q.d. will continue to receive that dosage.

A treatment duration of 52 weeks in the DB treatment phase combined with the duration of treatment under the parent protocols is deemed sufficient to assess any emergent safety aspects (treatment induced effects) of JNJ-54861911 in relation to placebo treatment as outlined below

('Safety Evaluations'). A placebo control of 52 weeks in this study is considered to be acceptable as efficacy of JNJ-54861911 has not yet been demonstrated, no treatment is available yet and subjects can continue on normal standard care (symptomatic treatment) as outlined in Section 8. Prestudy and Concomitant Therapy.

A placebo control will be used in the DB treatment phase (Day 1 to Week 52 [Month 12]; placebo-controlled) to explore the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment during the first year of treatment in this study. It is yet unclear in which time frame potential adverse event patterns may arise. It may be difficult to separate them from actual aging or AD-related patterns (e.g., cognitive decline, MRI microhemorrhages, amyloid related imaging abnormalities-edema or effusion [ARIA-E]). To control for these factors a placebo group is warranted over a limited time.

Upon completion of the DB treatment phase, subjects receiving placebo will be randomized in to active treatment in the OL treatment phase. Randomization will be used to minimize bias in the assignment of previously treated placebo subjects to treatment groups and to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) are evenly balanced across treatment groups. Blinded treatment in the DB treatment phase will be used to reduce potential bias during data collection and evaluation of clinical endpoints as well as adverse events.

For subjects enrolled in this study, each subject will continue study treatment (in the OL treatment phase):

- until registration of JNJ-54861911
- until emerging safety issues arise as determined by the DRC that would warrant termination of the study
- until subject withdraws consent or other reasons for withdrawal as defined in Section 10.3.

Population

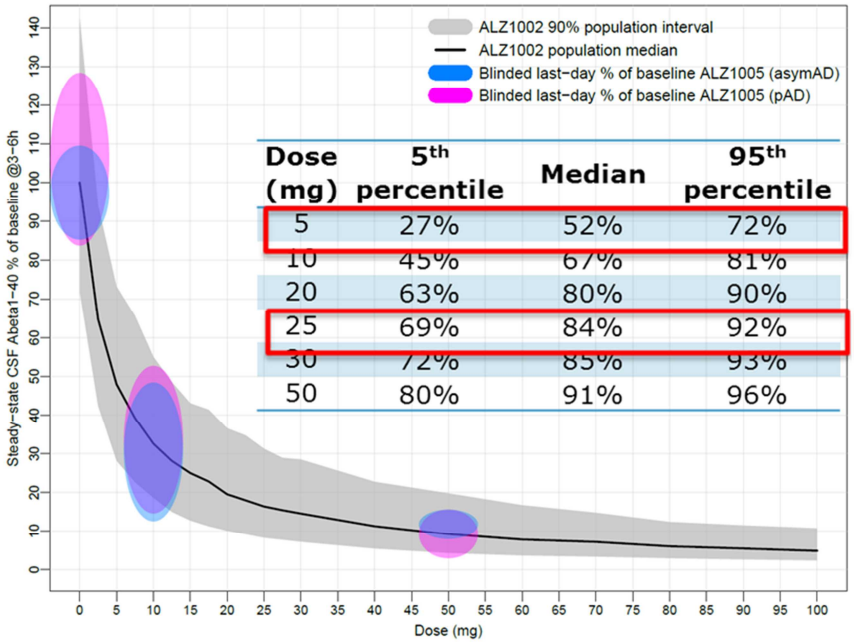
The population included in this study will be subjects in the early AD spectrum, enrolled in ongoing or future clinical trials with JNJ-54861911 (Phase 1b or Phase 2 studies) who completed their treatment period as defined under the parent protocol (54861911ALZ2002 study). If not defined in 54861911ALZ2002 study, completion of the treatment period is defined as having completed all study related procedures of the last visit of the treatment period in 54861911ALZ2002 study.

The early AD spectrum defined at time of enrollment in 54861911ALZ2002 study includes 1) subjects who are classified as asymptomatic at risk for Alzheimer's dementia who are cognitively and functionally normal (CDR = 0), but have a biomarker pattern consistent with early stage AD (preclinical stage); and 2) subjects with pAD who have some limited cognitive impairment (CDR = 0.5), are still functionally normal, and have a biomarker pattern consistent with early stage (predementia) AD, but have as yet no dementia (predementia stage). Subjects that have progressed to dementia in 54861911ALZ2002 study (CDR ≥1) or who are incapable of

providing informed consent will not be enrolled. In case the subject progresses to a dementia state during the study, the subject may remain in the study, provided that the investigator judges that the potential benefits of treatment for this subject clearly outweigh the known and foreseeable risks and assent or consent (as applicable) for continued participation is obtained from a representative determined in accordance with the local law. In cases where a subject has progressed to dementia, treatments indicated for this condition (e.g., memantine or cholinesterase inhibitors) are permitted after notification of the sponsor.

Rationale for Dose Selection

The optimal level of therapeutic Aβ reduction is not known and cannot be assumed from preclinical models or early phase clinical studies, as the proposed effect on the disease pathology is expected to require chronic treatment. Results from Phase 1 studies with JNJ-54861911 have confirmed observations in transgenic animal models in showing that this compound results in profound reductions in brain Aβ levels. As described in Section 1.1, data from completed SAD and MAD studies in healthy older subjects and from the preliminary analyses of the proof of mechanism study in a population with early AD spectrum showed dose-dependent reductions in $A\beta_{1-40}$ in plasma and CSF following oral JNJ-54861911 administration. As shown in Figure 5 below, preliminary data from the proof of mechanism study showed that the median reduction in CSF $A\beta_{1-40}$ with a 25 mg/day dose (84%) was only minimally increased (i.e., by ~ 6% to 91%) with a doubling of the dose to 50 mg/day. At a dose of 10 mg/day, the median reduction in CSF $A\beta_{1-40}$ is about 67%, and at the lower dose of 5 mg/day, the median reduction is about 52%.



Dose (mg)	5th percentile	Median	95th percentile
5	27%	52%	72%
10	45%	67%	81%
20	63%	80%	90%
25	69%	84%	92%
30	72%	85%	93%
50	80%	91%	96%

Figure 5: Modelling of CSF $A\beta_{1-40}$ Reduction in Subjects in the Early Alzheimer's Disease Spectrum (preliminary data from study 54861911ALZ1005; Abbreviations CSF, cerebrospinal fluid)

As noted in Section 1.1, PK/PD modeling based on a thorough QT trial, 54861911ALZ1007, showed that at a JNJ-54861911 dose of 25 mg q.d., the median changes in the QTcF, as well as the 90% population interval, are expected to be well below 5 msec.

During the course of the study, the Sponsor will, however, have the option based on recommendations by the DRC or based upon newly emerging safety, biomarker or efficacy data from ongoing or completed JNJ-54861911 studies, to revise the dose levels for OL treatment phase to:

- Maintain the 2 selected active dose levels (equal randomization of the placebo treated subjects)
- Adjust the dose level for one or both of the selected active doses
- Drop one active dose level (subjects allocated in OL treatment phase to the dose level dropped will be reassigned in OL treatment phase to the remaining active dose level)
- Assign all placebo subjects to a single active dose level

In the current study, subjects will be asked to take JNJ-54861911 with breakfast preferably or after a light snack, but no significant impact of food on drug exposure is expected. Considering that the target population in this study is an elderly age group, rationale to conduct this study under fed condition is mainly from the perspective of convenience to the study subjects.

Safety Evaluations

The primary objective of this study is to assess the long-term safety and tolerability of JNJ-54861911 in subjects in the Early AD spectrum. As such, regular safety assessments will be performed as listed in the Time and Events Schedule. These safety assessments include but are not limited to: vital signs, ECG, physical and neurological examination, adverse events, safety labs, suicidality risks (Columbia Suicide Severity Rating Scale [C-SSRS]), dermatologic and ophthalmologic examinations, and MRI. A more detailed description on the safety assessments applied is provided in Section 9.2, Safety Evaluations. The DRC may decide to reduce, drop or even increase frequency over time of specific safety assessments if (newly obtained) data collected in this study or from ongoing or future studies would support this decision.

Specific dermatologic and ophthalmologic examinations, as described in Section 9.2, Safety Evaluations have been implemented in this study as potential BACE1- or BACE2-linked toxicities (e.g. melanin deposition changes and retinal abnormalities) have been described in the literature (e.g. BACE1 or BACE2 knock-out mice). With the exception of fur discoloration resulting in progressive lightening of the fur from normal dark brown to paler cream or grey, which was seen in one species only (Tg mice in the 6 month carcinogenicity study), however, these toxicities have not been observed in nonclinical chronic studies with JNJ-54861911. Note that cases of lightening of skin, lightening of hair or ophthalmological adverse events are considered adverse events of special interest (AESI) and are subject to reporting timelines as described in Section 12.3.4.

As a result of the newly identified case of drug-induced hepatotoxicity, if at any time during treatment a subject has an ALT or AST result that is ≥3× ULN, the test should be repeated within 24 - 72 hours and, if confirmed, the further evaluation and management procedures described in Attachment 1 should be followed.

In addition to the (safety) MRI assessments performed under the 54861911ALZ2002 study (if applicable), safety MRIs will be collected in this study during both DB and OL treatment periods, as indicated in the Time and Events Schedule, to monitor any treatment-emergent abnormalities including ARIA-edema or effusion (E) and ARIA-hemosiderin (H). Additional annual MRIs will be collected in OL period. If any safety related changes are observed (e.g. ARIA-E), additional safety MRIs may be collected at a frequency recommended by the DRC.

In case of any changes observed in any of the safety measures performed that are considered not clinically significant or do not have a direct clinical symptomatology as assessed by the investigator, they should be closely monitored, with a potential increased safety monitoring frequency as deemed appropriate by the investigator. In addition, these findings will be presented to the DRC, who will make recommendations regarding the safety and continuation of the study as per its charter.

Biomarker Collection

Fluid (CSF and plasma) and imaging (MRI) biomarker assessments will be performed to assess the potential and continuous effects of JNJ-54861911 on the pathological and pathophysiological processes of AD. In addition, these biomarker assessments are performed to assess if potential treatment effects of JNJ-54861911 are consistent with the putative effects of BACE inhibition.

During the course of the study the continuous effects of JNJ-54861911 on the pathophysiological processes of AD will be monitored by the DRC.

Reduction in CSF Aβ over time will confirm the continuous activity of JNJ-54861911 based on its mechanism of action. It will allow the confirmation that a continuous reduction in CSF Aβ is feasible over the entire treatment duration that may lead to a potential therapeutic effect. The primary CSF biomarker read out to confirm engagement of JNJ-54861911 at the intended target site is CSF $A\beta_{1-40}$.

In addition to the hallmark pathological feature of brain amyloidosis, AD is also characterized by the downstream neuropathological feature of NFTs consisting mainly of hyperphosphorylated tau proteins, with properties that enable fibril formation. The work of Braak[5] and others have shown the progressive increase of brain tau in disease using postmortem immunohistochemical methods. In addition, neurofibrillary (tau) tangles are linked to the duration and severity of AD.[33] Tau PET imaging is an exploratory *in vivo* method to measure brain tau burden and can track accumulation. Early results with [^{18}F]-T807 PET suggest that the signal intensity and spread is linked to the severity of the cognitive impairment[9], which parallels earlier pathology based observations by Braak, Hyman and others. Further, as the neurons die, the tau fragments are released into the extracellular space and appear to be elevated in AD patient's CSF.[3,4] CSF t-tau

and p-tau are suggested to reflect different aspects of brain damage; t-tau reflects acute/chronic neuronal damage, while p-tau reflects tau phosphorylation and tangle formation.[30,49] Hyperphosphorylated epitopes of tau (high p-tau) in the CSF are rather specific to AD and, high p-tau is well correlated with high t-tau in subjects with AD.[35] It can therefore be concluded that tau protein in CSF (t-tau and p-tau) is an indicator of neuronal degeneration, but an increase in p-tau is more specific in AD and less prevalent in other neurodegenerative diseases.

Tau proteins are normally associated with tubulin polymers to stabilize the microtubule system essential for normal neuronal function.[43] However, tau is abnormally phosphorylated in AD and is the main component in paired helical filaments (PHFs), which then associate laterally to form NFTs in the cytoplasm of many neurons.[10,11,12,23,24] These tangles initially form intra-neuronally and as the neurons die, the tau tangles are released into the extracellular space and appear to be elevated in AD patient's CSF.[26] Together with low $A\beta_{1-42}$, high p-tau in CSF can help differentiate between AD patients and healthy elderly and is the best predictive marker for progression of mild cognitive impairment (MCI) subjects into AD.[4,6,18,19,20,27,28,44] The increase in hyperphosphorylated tau in CSF is relatively specific to AD and therefore separates AD from other neurodegenerative disorders.[25] As change in CSF p-tau levels is a marker for neurodegeneration, they are believed to be predictive of changes in cognition over time.

Volumetric MRI has been used extensively to measure atrophy rates in treatment trials of AD as the relationship between atrophic changes and neuron loss is well established and correlates well with clinical measures.[36,45,52,54,55,58,63,64,65] All subjects will receive MRIs at the time point indicated in the Time and Events Schedule to assess safety (monitor for ARIA-E and ARIA-H). The sequences included are described in a separate MRI imaging manual, but will also include a volumetric sequence besides the sequences for safety assessments. The global and regional brain volumes obtained from the volumetric MRI sequence will be reported.

Cognition and Functional Outcome Measures

Cognitive evaluations (RBANS, MMSE and CVLT-II) and functional outcome measures (Cognitive Function Index [CFI]) will be applied in this study at different time points as indicated in the Time and Events Schedule to explore the subject's cognitive performance/progression and function over time. A description of these tests is provided in Section 9.4, Cognition, Function and Clinical Status. The selected tests are included to test for signs of cognitive and functional decline. The cognitive measures used in this study are aligned to the measures applied in our Phase 1b (e.g., 54861911ALZ1005) and Phase 2 (e.g., 54861911ALZ2002) studies.

The progression of cognitive deficits is the most prominent early marker of AD, but different cognitive domains have been demonstrated to progress at a different speed.[57] The RBANS was selected as a cognitive measure to assess cognitive decline as it is a widely used measure to differentiate healthy normal subjects from those with early disease and AD patients, is predictive of functional status, correlates with the CDR[31], biomarkers[22,62] and cognition[17] in this early population.

The MMSE is a brief, validated 30-point questionnaire that is widely used to screen for cognitive impairment.[21] The lower the score the more pronounced the impairment. The MMSE will be used in this study to cross compare with other JNJ-54861911 trials.

The CVLT-II is a face-to-face comprehensive neuropsychological measure of verbal memory in individuals 16 to 89 years old, designed to quantify components of verbal learning, retention and retrieval.[13] This test will be administered only to subjects who had completed it in the parent protocol.

The CFI is an instrument to track early changes in abilities to perform high-level activities of daily living and the subjects' perception of their own ability to perform cognitively demanding functional tasks.

The RBANS, MMSE, CVLT-II and CFI are described in more detail in Section 9.4.

Clinical Scales

The CDR is a global clinical scale with established diagnostic and severity-ranking utility widely used in clinical trials yielding global and Sum of Boxes (SB) scores. The CDR global score is used in AD trials as a global measure of disease progression. The CDR is well-established in MCI and AD studies.

The CDR is described in more detail in Section 9.4.2.

3.3. Interim Analysis of Data

No prespecified interim analysis of unblinded data during the DB treatment phase is planned by the clinical team. However, depending on the recruitment, or in support of regulatory filings for upcoming studies, or for any other reason the Sponsor deems necessary, an unblinded review of safety and biomarker data prior to the last subject's completion of the DB treatment phase might be conducted by an internal Interim Analysis Committee. If any such review is conducted it will be documented in an Interim Analysis Committee charter prior to the unblinding. The constitution of the Interim analysis committee will be documented in the Interim Analysis Committee charter and may include Sponsor study team members.

As noted in Section 5, when the parent study (eg, 54861911ALZ2002 and potential future Phase 1b and 2 studies) is completed and its clinical database is closed, the randomization codes from the parent study will be released to the sponsor study team. Thus, the sponsor will be unblinded at that time, but the investigator and subjects will continue to be blinded to treatment during the DB treatment phase, until the last subject has completed that phase, and the database from that phase has been reviewed, corrected as necessary, and locked. At that point, the sponsor will perform analyses of key safety, biomarker, and efficacy variables, as detailed in a prespecified statistical analysis plan.

Following the sponsor's review of these analyses, information on an individual subject's treatment allocation during the DB phase will be made available upon request by the investigator. As subjects that remain in the study will all be receiving open label JNJ-54861911

at that time, and as no change or alteration of the locked database from the DB phase will be possible, there should be no bias introduced by this measure.

3.4. Stopping Criteria

3.4.1. Individual Criteria for Stopping Study Treatment

In this Phase 2 study the following specific individual rules for stopping study treatment will apply (see Section 10.2 for details):

- A subject has a mean QTcF interval of >500 msec if confirmed upon repeat ECG, and/or mean QTcF increase versus baseline of >60 msec if confirmed upon repeat ECG, after consultation with the sponsor's medical monitor (all based on triplicate recordings).
- The investigator believes that for safety reasons (e.g., adverse event) it is in the best interest of the subject.
- Between Weeks 52 and 64, treatment must be discontinued if any of the following occurs:
  - ALT or AST >5× ULN
  - ALT or AST >3× ULN and total bilirubin >2× ULN or international normalized ratio (INR) >1.5
  - ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia >5%
- After Week 64, treatment must be discontinued if any of the following occurs:
  - ALT or AST >8× ULN
  - ALT or AST >5× ULN for more than 2 weeks
  - ALT or AST >3× ULN and total bilirubin >2× ULN or INR >1.5
  - ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia >5%
- A subject who meets any of the withdrawal criteria described in Section 10.3.

Events of elevated liver enzymes or increased QTc that require subjects to discontinue will be considered as serious and will be reported to Sponsor within 24 hours of the knowledge of the event.

3.4.2. Protocol Stopping Criteria

A DRC will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study (see Section 11.7, Data Review Committee). The committee will meet periodically to review interim data. After the review, the DRC will make recommendations regarding the safety and continuation of the study. The details will be provided in a separate DRC charter.

4. SUBJECT POPULATION

Subjects in the early AD spectrum, i.e., subjects asymptomatic at risk for Alzheimer's dementia and prodromal AD subjects at time of enrollment under the parent protocol, who have completed a Phase 1b or Phase 2 clinical study with JNJ-54861911 will be provided the opportunity to participate in this study. Subjects that have progressed to dementia in the parent protocol (CDR ≥1) or who are incapable of providing informed consent will not be enrolled.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling a subject in the study. In case the subject progresses to a dementia state during the study, the subject may remain in the study, provided that the investigator judges that the potential benefits of treatment for this subject clearly outweigh the known and foreseeable risks and assent or consent (as applicable) for continued participation is obtained from a representative determined in accordance with the local law. In cases where a subject has progressed to dementia, treatments indicated for this condition (e.g., memantine or cholinesterase inhibitors) are permitted after notification of the sponsor.

For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study.

1. Criterion modified per amendment.

1.1 Subjects in the early AD spectrum at time of enrollment meeting all pertinent inclusion and exclusion criteria of the parent protocol, must have very recently completed their treatment in a Phase 1b or Phase 2 JNJ-54861911 clinical study (e.g., 54861911ALZ2002) under the parent protocol. Enrollment in this study should be completed (Day 1 of DB treatment phase) as soon as possible, but within 6 weeks, following completion of their treatment period under the parent protocol. If not defined under the parent protocol, completion of the treatment period is defined as having completed all study related procedures of the last visit of the treatment period under the parent protocol. A screening phase of up to 12 weeks may be allowed following written approval of the Sponsor.

2. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

3. Criterion modified per amendment.

3.1 Each subject must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study.

4. Subjects must have a reliable informant (relative, partner, or friend). The informant must be willing to participate as a source of information and has at least weekly contact with the subject (contact can be in-person, via telephone or other audio/visual communication). The informant must have sufficient contact such that the investigator feels he/she can provide meaningful information about the subject's daily function. If possible, an alternate informant meeting these criteria who can replace the primary informant should be identified prior to randomization.

4.2. Exclusion Criteria

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

1. Any condition or situation which, in the opinion of the investigator, may put the subject at significant risk, may confound the study results, or may interfere significantly with subject's participation in the study.

2. The use of concomitant medications known to prolong the QT/QTc interval.

3. Subject has a history of moderate or severe hepatic impairment or severe renal insufficiency unless completely resolved for more than a year. Subject has clinically significant ongoing hepatic, renal, cardiac, vascular, pulmonary, gastrointestinal, endocrine, hematologic, rheumatologic, psychiatric, or metabolic conditions (eg, requiring frequent monitoring or medication adjustments, or is otherwise unstable).

NOTE: Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Avoid donating blood for at least 90 days after completion (i.e., final dose administration) of the study.

2. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy is advised to use a barrier method of birth control e.g., either 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.

3. All men must also agree not to donate sperm during the study and for 3 months after receiving the last dose of study drug.

4. For any prohibitions or restrictions related to concomitant medication see also Section 8. Prestudy and Concomitant Therapy.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Subjects enrolled in this study will participate in 2 sequential treatment periods i.e.

- DB treatment phase: a 52-Week (12-Month) placebo-controlled, double-blind, treatment period; and
- OL treatment phase: a (partially) randomized open-label treatment period (until registration)

During the DB treatment phase, subjects will receive either JNJ-54861911 (10-mg or 25-mg q.d.) based on their current treatment/dosing regimen assigned under the parent protocol (54861911ALZ2002 or any future studies) as described in Section 6, Dosage and Administration.

In the OL phase, subjects who received placebo in the DB treatment period will be automatically randomized to active treatment (JNJ-54861911 5-mg or 25-mg q.d.) as described in Section 6, Dosage and Administration. Subjects who were receiving 10 mg q.d. JNJ-54861911 in DB treatment phase will have their dose reduced to 5 mg q.d., while subjects who were receiving 25 mg q.d. will continue to receive that dosage.

Procedures for Randomization

Subjects who received placebo during the DB treatment phase will be randomly assigned with equal chance to one of two treatment groups in the OL phase based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced using permuted blocks across the 2 treatment groups.

For both DB and OL treatment phases, an interactive web response system (IWRS) will be utilized to assign the blinded study drug kits in this study. For DB treatment phase study drug kits will be assigned based on their treatment allocation in 54861911ALZ2002 study; for non-placebo subjects in OL phase, subjects who were receiving 10 mg q.d. JNJ-54861911 in DB treatment phase will have their dose reduced to 5 mg q.d., while subjects who were receiving 25 mg q.d. will continue to receive that dosage.

The blister packs and kit assignment will be managed by the IWRS for both the blinded and unblinded phase of the study.

Since the investigator will be blinded to treatment assignment in the DB treatment phase, the IWRS will automatically determine the appropriate medication kits to assign. Subjects who were receiving 10 mg q.d. JNJ-54861911 in the DB treatment phase will have their dose reduced to 5 mg q.d. in the OL phase, while subjects who were receiving 25 mg q.d. will continue to receive

that dosage. Subjects receiving placebo in the DB treatment phase will be randomized with equal chance to either 5 mg q.d or to 25 mg q.d. Neither the randomization number nor the fact that a subject was randomized for OL phase will be known to the investigator, thus allowing the blind to be maintained while DB treatment phase is still ongoing.

The total number of subjects on placebo to be randomized to active treatment in this study will be determined by the number of subjects enrolling who previously were allocated to placebo in 54861911ALZ2002 study.

Central randomization will be implemented in conducting OL phase of this study for subjects previously receiving placebo. Central randomization minimizes the imbalance in the distribution of the number of subjects across treatment. Based on the algorithm, the IWRS will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject.

Central randomization will be used to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are evenly balanced across treatment groups.

During the DB treatment phase (placebo-controlled), both the investigator and the subject will be blinded to reduce subjective influences on safety and tolerability data.

Blinding

The investigator will not be provided with randomization codes for the parent protocol (54861911ALZ2002 study) or the randomization numbers for this study until all subjects of the parent protocol have completed DB treatment phase and subsequent database lock or freeze has occurred. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

Under normal circumstances, the blind should not be broken by the investigator until all subjects from the 54861911ALZ2002 study enrolled in this study have completed DB treatment phase of the study and the DB treatment phase database for those subjects is finalized.

Otherwise, the blind should be broken by the investigator only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may, in an emergency, determine the identity of the treatment by contacting the IWRS. It is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. 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 IWRS, in the appropriate section of the case report form (CRF), and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

Subjects who have had their treatment assignment unblinded are not required to return for scheduled evaluations except for the End-of-Treatment visit (Follow-up visit).

When the parent study (e.g. 54861911ALZ2002 and potential future Phase 1b and 2 studies) is completed and its clinical database is closed, the randomization codes from the parent study will be released to the sponsor study team. Thus the sponsor will be unblinded at that time, but the investigator and subjects will continue to be blinded to treatment during the DB treatment phase.

6. DOSAGE AND ADMINISTRATION

Study medication will be provided as JNJ-54861911 tablets, strengths 5-mg, 25-mg and matching placebo. Study medication will be blister packed. All tablets (JNJ-54861911/placebo) are physically identical.

A study-site investigational product manual including instructions for dispensing, storage (on site and at home) and intake of the study medication will be supplied to the study-site.

Study-site personnel will instruct subjects on how to store study drug for at-home use as indicated for this protocol.

Eligible subjects enrolled in this study will participate in 2 sequential treatment periods:

- **Double-blind treatment phase:** a 52-week (12 Months) placebo-controlled, double-blind treatment phase. Eligible subjects enrolled will receive either JNJ-54861911 (10-mg or 25-mg q.d.) or placebo (q.d.). Subjects will continue on their current treatment regimen assigned under the parent protocol (placebo, 10-mg or 25-mg q.d. JNJ-54861911). Subjects who received an active dose different from 10-mg or 25-mg JNJ-54861911 under the parent protocol will be receiving the closest dose available in the DB treatment phase (i.e. subjects receiving 50 mg in study 54861911ALZ2002 will be assigned to 25 mg JNJ-54861911).
- **Open-label phase:** an open-label treatment phase during which subjects who received placebo in the DB treatment phase will be randomized to one of two JNJ-54861911 dose levels:
  - 5-mg q.d. JNJ-54861911; or
  - 25-mg q.d. JNJ-54861911

Randomization (for placebo subjects) to OL phase and dispensing of study medication for OL phase will only be performed following completion of all Week 52 assessments.

During the DB treatment phase, study drug kits will be assigned based on their treatment allocation under the parent protocol; for nonplacebo subjects in the OL phase, subjects who were receiving 10 mg q.d. JNJ-54861911 in the DB treatment phase will have their dose reduced to 5 mg q.d., while subjects who were receiving 25 mg q.d. will continue to receive that dosage.

During the course of the study, the Sponsor will have the option based on recommendations by the DRC or based upon newly emerging safety, biomarker or efficacy data from ongoing or completed JNJ-54861911 studies, to revise the dose levels for OL phase to:

- Maintain the 2 selected active dose levels (equal randomization of the placebo treated subjects)
- Adjust the dose level for one or both of the selected active doses
- Drop one active dose level (subjects allocated in the OL phase to the dose level dropped will be reassigned in the OL phase to the remaining active dose level)
- Assign all placebo subjects to a single active dose level

During the treatment phases of this study dispensing and redispensing of their study medication will take place at the visits indicated in the Time and Events Schedule. On Days of re-dispensing subjects will hand in their medication package dispensed previously and drug accountability will be performed.

Following last dosing, subjects will hand in their study medication received previously and final drug accountability will be performed.

During the study (DB and OL treatment phases) subjects will self-administer q.d. study drug (JNJ-54861911/placebo) with a glass of non-carbonated water, after completion of breakfast or a light snack, during the morning hours, according to the instructions provided by the investigator. During scheduled visits subjects will self-administer their study medication on site. On Day 1, study drug administration will be administered following completion of all predose assessment and will not be limited to morning hours.

If a subject realizes before 2:00 PM that he/she forgot to take their daily dose, he/she will be instructed to take the daily dose even if late (before 2:00 PM).

If a subject realizes after 2:00 PM he/she forgot to take his/her daily dose, he/she will be instructed not to take any dose during that day, but resume dosing the following day.

7. TREATMENT COMPLIANCE

The investigator or designated study-site personnel will maintain a log of all study drug dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study.

Study drug will be self-administered by subjects. As such the number of study drug dispensed will be recorded and compared with the number returned.

At study visits, study drug will be self-administered on site, which will be witnessed by designated study-site personnel at the study sites.

Subjects will receive instructions on compliance with study drug administration upon study medication (blisters) dispensed. During the course of the study, the investigator or designated study-site personnel will be responsible for providing additional instruction to re-educate any subject who is not compliant with taking the study drug.

Subjects who are no longer capable of ensuring treatment compliance in the judgment of the investigator (e.g. due to progression to dementia) have to be supported in study drug handling and administration (e.g. care giver or nurse practitioner). In case support cannot be provided subjects should be discontinued from treatment and withdrawn from the study.

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy therapies administered up to 30 days before screening must be recorded at screening.

Concomitant therapies must be recorded throughout the study beginning with signing of the initial informed consent until the End-of-Treatment visit (Follow-up visit). Concomitant therapies should also be recorded beyond this time only in conjunction with new or worsening adverse events until resolution of the event.

Progression of symptoms associated with AD should be recorded in the eCRF and any symptomatic treatment therefore will be documented until the End-of-Treatment visit (Follow up visit).

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; nonpharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study drug must be recorded in the CRF. Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a subject into the study.

Treatment with cognitive enhancers (e.g., cholinesterase inhibitors) or drugs intended for the treatment of cognitive deficits prior to enrollment in the extension study is allowed.

New therapies or therapy adaptations that are expected to have an impact on cognitive performance (e.g., cholinesterase inhibitors or memantine), will be permitted if clinically indicated, after notification of the Sponsor. Before a subject starts, stops or changes a dose of a therapy expected to have an impact on cognition, the Sponsor's medical monitor must be contacted in part to determine if specific clinical measures (e.g., cognitive measures) should be performed prior to the modification of concomitant medication regimen.

Use of benzodiazepines for treatment on an as-needed basis for insomnia or daily dosing as anxiolytics is permitted. If they are being given chronically, use of sedatives or hypnotics should be avoided for 24 hours before administration of cognitive tests. If sedating medication is given for MRI at any visit or for any short-term use, then all cognitive assessments must be administered at least 4 half-lives hours after administration of the sedative.

Stable use of pain medications will be permitted. Short-term use of narcotics is allowable if not administered within 4 half-lives hours prior to cognitive assessments.

Other concomitant medications that affect central nervous system (CNS) function may be given if efforts are made to keep the dose unchanged throughout the study. Doses of these compounds

should remain constant from 6 weeks prior to first dosing (Day 1 of the DB treatment phase). To avoid effects on cognitive measures, the following apply:

- Subjects should not stop receiving any medications that affect CNS function during the study
- Subjects should not add any medications that affect CNS function to the treatment regimen, unless medically necessary.
- Subject should not change doses of medication that affect CNS function

In cases of unforeseen starting, stopping or changing of stable doses of a therapy that affect CNS function occurs during the study, the Sponsor's medical monitor must be contacted to determine if the subject should continue in the study or not, and whether or not specific clinical measures (e.g., cognitive measures) should be performed.

In relation to CSF sampling, unless otherwise specified in this section, local site instructions related to concomitant therapy will be followed.

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

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the visits as well as the frequency and timing of assessments applicable to this study. A visit window of +/-12 calendar days will be allowed for all visits, unless otherwise indicated in the Time and Events Schedule. All visits are in principle single day visits however they may be performed over multiple days within the allowed visit window in cases of logistical issues or a subject's preference.

All subjects within the early (predementia) AD spectrum enrolled in this study being subjects asymptomatic at risk for AD and subjects with pAD, will follow the same procedures as listed in this section unless otherwise specifically indicated.

Information regarding handling, shipment, and labeling of biological samples (including safety labs) will be provided in a separate lab manual.

For CSF sampling, local site standard operating procedures (SOPs) may be applied for performing the actual lumbar puncture (not the collection), provided they are at least as restrictive as the criteria defined in this protocol or lab manual.

Separate imaging manuals and charters will be provided, describing the MRI imaging procedures, data acquisition and handling.

Any changes to the lab manual and imaging manuals/charters will not result in a protocol amendment.

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 attending physician.

The time points for individual measures may be changed (with or without affecting the overall frequency of these investigations) prior to and during the study based on newly obtained data (e.g., interim analysis, DRC) to allow for optimal fit to the actual safety or PK/PD profile of the study drug. This modification may result in a change in the overall frequency of the individual measures (e.g., safety measures, blood and CSF samplings) provided the maximal total blood and/or CSF volume collected per subject defined will not be exceeded. Such modifications, where performed only to allow optimal fit to the actual safety, PK/PD profile of the study drug, will not be considered to be an amendment to the protocol.

Cognitive testing should always be performed before medical procedures that could be stressful for the subjects (for example blood draws, CSF collection, etc.). If sedating medication is given for MRI at any visit or for any short-term use then all cognitive assessments must be administered/completed either before or at least 4 half-lives after administration of the sedative. Additionally, all neuropsychological testing and CSF collections should be performed at approximately the same time on each day these are performed. All neuropsychological tests should be administered by the same rater to reduce potential variability. In between different cognitive tests, adequate breaks should be taken to ensure optimal performance. Details on the different cognitive tests and functional outcome measures, alternative versions and forms to be used, sequence of performance, rater training and staff qualification required, will be described in a separate manual. Any changes to this manual will not result in a protocol amendment.

Venous blood will be collected for all blood-based analysis. When assessments occur at the same time point, the blood samples for PK and Biomarker analysis must always be collected as close to the scheduled time as possible, followed by the CSF sample for PK and Biomarker analysis. Other measurements may be done earlier than specified time points if needed. Actual dates and times of assessments will be recorded in the source documentation and CRF or lab requisition form.

Blood may be drawn by using a cannula or by venipuncture.

The exact times for each blood draw or assessment will be recorded in the CRF or lab requisition form. The order of multiple assessments within one protocol time point should also be the same throughout the study.

Vital signs will be recorded from the opposite arm from which the blood samples are being taken.

Blood pressures and ECGs should be recorded approximately 5 to 10 minutes before PK blood samples are taken.

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

The volume of blood collected per subject will be detailed in a separate lab manual.

For each subject, the maximum amount of blood drawn from each subject in this study will not exceed 450 mL per calendar year. For CSF no more than 24 mL annually (2 CSF collections) will be collected.

9.1.2. Screening Phase

Before any study specific procedures are conducted and following an explanation of the purpose and risks of the study, subjects will sign an informed consent form (ICF).

Subjects who provide consent to enroll in this protocol and who meet the inclusion criteria, may start at Day 1 of the DB treatment phase in lieu of the end of treatment visit in 54861911ALZ2002 study. For subjects who have completed the end of treatment visit in the 54861911ALZ2002 study, enrollment in this study should be completed (Day 1 of the DB treatment phase) as soon as possible, but within 6 weeks, following completion of their treatment period under the parent protocol of currently ongoing or any future Phase 1b or Phase 2 studies with JNJ-54861911. A screening phase of up to 12 weeks may be allowed following written approval of the Sponsor.

After giving initial written informed consent, subjects will be screened to assess their eligibility for the study according to the inclusion and exclusion criteria defined for this study.

Recording of adverse events/concomitant medication will start following consent and will continue until completion of the study.

During screening following assessments/procedures will be performed:

- Review of inclusion and exclusion criteria
- Complete/Review Medical History and Demographics
- Complete/Review Prestudy Therapy
- Review preplanned surgery/procedures
- Record adverse events and concomitant medication

Eligible subjects will be provided the opportunity to participate in the DB treatment phase and OL phase of the study described further below.

Subjects participating in this study may progress to a dementia state (CDR ≥ 1) during course of the study. In such cases the informed consent may require a signature of the subject's legal representative as per local regulations.

9.1.3. Double-Blind Treatment Phase

Day 1

Subjects who successfully complete the screening examination will visit the clinical site on Day 1 of the DB treatment phase during the morning hours.

Prior to dosing following (baseline) assessments will be performed:

- C-SSRS (since last visit [or baseline if no C-SSRS was collected under the parent protocol])
- Blood sample collection for plasma JNJ-54861911 concentrations
- Blood sample collection for pharmacodynamics/biomarkers
- (Optional) CSF sample collection (~12 mL) by single lumbar puncture for PK/PD/biomarker assessment (baseline) after eligibility has been confirmed, provided no on-treatment sample was collected under the parent protocol
- 12-lead ECG recording
- Adverse event and concomitant medication will be reviewed

Following assessments will be performed prior to first dose in the current study at time points mentioned below only if no adequate assessments were conducted in ALZ2002 study (the assessments listed below 6 months and 9 months prior to dosing may also be performed during the screening period in case of any logistical issues):

1. At the last study visit of the treatment period:
    - Physical examination
    - Neurological examination
    - Body weight
    - Body temperature
    - Supine and standing vital signs (systolic and diastolic blood pressure and pulse)
    - Clinical safety laboratory assessments under fasted conditions, when feasible (including hematology, serum chemistry, and urinalysis)

2. 6 months prior to first dosing in this study (the assessments listed below may also be performed during the screening period in case of any logistical issues):
    - MRI

3. 9 months prior to first dosing in this study (the assessments listed below may also be performed during the screening period in case of any logistical issues).
    - Dermatological Examination

- Ophthalmological Examination (only in subjects completing the ALZ2002 parent study)
- Optical Coherence Tomography (OCT; at sites where OCT is available, in subjects completing the 54861911ALZ2002 parent study)

Eligible subjects will be assigned on Day 1 predose to the same treatment regimen in this study as received under 54861911ALZ2002 study as described in Section 6, Dosage and Administration.

Study medication will be dispensed (incl. drug accountability) and administered as outlined in Section 6, Dosage and Administration. Subjects will self-administer their study medication q.d. as instructed.

On Day 1 dosing will not be time limited and will be performed following completion of the baseline (predose) assessments.

Following dosing on Day 1 following assessments will be performed:

- 12-lead ECG recording at 2 to 4 hours postdose
- Blood sample collection for plasma JNJ-54861911 concentrations at 2 to 4 hours postdose
- MMSE*
- CFI*
- CDR*
- RBANS*

** This assessment scheduled on Day 1 may be performed either predose or postdose provided they have not been collected under the parent protocol 1) at the last study visit of the treatment phase or 2) 6 months prior to first dosing in this extension study.*

During DB treatment phase, following Day 1, subjects will return to the investigational site at regular time points as indicated in the Time and Events Schedule and further described below.

Week 8

Subjects will visit the site at Week 8 during the morning hours. Study medication will be self-administered on site as outlined in Section 6, Dosage and Administration.

Clinical safety laboratory assessments (hematology and serum chemistry) will be performed under fasted conditions, when feasible, as specified in the Time and Events Schedule. Assessments can be performed pre or post dose unless otherwise indicated.

Week 12

Subjects will visit the site at Week 12 during the morning hours. Study medication will be self-administered on site as outlined in Section 6, Dosage and Administration.

The following assessments will be performed at Week 12 as specified in the Time and Events Schedule. Assessments can be performed pre or post dose unless otherwise indicated.

- Drug accountability/Treatment compliance will be assessed. Study medication received on Day 1 will be handed in and new medication will be dispensed.
- C-SSRS (since Day 1)
- CVLT-II, in subjects who had this assessment in the parent study
- Adverse events and concomitant medication will be reviewed

Week 16

Subjects will visit the site at Week 16 during the morning hours. Study medication will be self-administered on site as outlined in Section 6, Dosage and Administration.

Clinical safety laboratory assessments (hematology and serum chemistry) will be performed under fasted conditions, when feasible, as specified in the Time and Events Schedule. Assessments can be performed pre or post dose unless otherwise indicated.

Week 24

Subjects will visit the site at Week 24 during the morning hours. Study medication will be self-administered on site as outlined in Section 6, Dosage and Administration.

The following assessments will be performed at Week 24 as specified in the Time and Events Schedule. Assessments can be performed pre or postdose unless otherwise indicated.

- Drug accountability/Treatment compliance will be assessed. Study medication received at Week 12 will be handed in and new medication will be dispensed.
- 12-lead ECG recording (2 to 4 hours postdose)
- Body temperature
- Supine and standing vital signs (systolic and diastolic blood pressure and pulse)
- Clinical safety laboratory assessments under fasted conditions, when feasible (including hematology, serum chemistry and urinalysis)
- Dermatological examination
- Ophthalmological examination(*) (only in subjects completing the ALZ2002 parent study)
- OCT (at sites where OCT is available, and only in subjects completing the ALZ2002 parent study)
- C-SSRS (since last visit)
- RBANS
- CFI
- Blood sample collection for plasma JNJ-54861911 concentrations (predose and 2 to 4 hours postdose)

- Blood sample collection for pharmacodynamics/biomarkers (predose)
- MRI
- Adverse events and concomitant medication will be reviewed

(*) *An ophthalmological examination will only be performed if: 1) if there was an abnormality present at the screening/baseline examination; 2) if the investigator detects new ophthalmological findings or visual symptoms; 3) if OCT reveals new findings. The ophthalmologic examination should be performed by the same ophthalmologist who completed the initial ophthalmologic examination at screening/baseline.*

Week 36

Subjects will visit the site at Week 36 during the morning hours. Study medication will be self-administered on site as outlined in Section 6, Dosage and Administration.

The following assessments will be performed at Week 36 as specified in the Time and Events Schedule. Assessments can be performed pre or post dose unless otherwise indicated.

- Drug accountability/Treatment compliance will be assessed. Study medication received at Week 24 will be handed in and new medication will be dispensed.
- C-SSRS (since last visit)
- Clinical safety laboratory assessments under fasted conditions, when feasible (hematology and serum chemistry)
- Adverse events and concomitant medication will be reviewed

Week 52 (last visit [DB treatment phase])

Subjects will visit the site at Week 52 during the morning hours. Study medication will be self-administered on site as outlined in Section 6, Dosage and Administration. At Week 52 subjects will be dosed according to the treatment allocation assigned to in the DB treatment phase.

Randomization to OL treatment phase and dispensing of study medication for OL phase will only be performed following completion of all Week 52 assessments.

The following assessments will be performed at Week 52 as specified in the Time and Events Schedule. Assessments can be performed pre or postdose unless otherwise indicated.

- Physical and Neurological examination
- Body Weight
- 12-lead ECG recording (2 to 4 hours postdose)
- Body temperature
- Supine and standing vital signs (systolic and diastolic blood pressure and pulse)

- Clinical safety laboratory assessments under fasted conditions, when feasible (including hematology, serum chemistry and urinalysis)
- Dermatological examination
- (For subjects who completed the parent study, ALZ2002) Ophthalmological examination(*)
- (For subjects who completed the parent study, ALZ2002) OCT (at sites where OCT is available)
- C-SSRS (since last visit)
- RBANS
- MMSE
- CFI
- CDR
- Blood sample collection for plasma JNJ-54861911 concentrations (predose and 2 to 4 hours postdose)
- Blood sample collection for pharmacodynamics/biomarkers (predose)
- (Optional) CSF sample collection (~12 mL) by single lumbar puncture for PK/PD/biomarker assessment. Baseline and Week 52 [Month 12] CSF samples should be taken at approximately the same time of day (with an allowable window of 3 hours), with the Week 52 (Month 12) sample being collected postdose.
- MRI
- Adverse events and concomitant medication will be reviewed
- Drug accountability/Treatment compliance will be assessed. Study medication received at Week 36 will be handed in and new medication (for OL phase) will be dispensed.
- Randomization (OL phase): only following completion of all Week 52 assessments.

(*) *An ophthalmological examination will only be performed if: 1) if there was an abnormality present at the screening/baseline examination; 2) if the investigator detects new ophthalmological findings or visual symptoms; 3) if OCT reveals new findings. The ophthalmologic examination should be performed by the same ophthalmologist who completed the initial ophthalmologic examination at screening/baseline.*

Note: If a subject discontinues study treatment before completion of DB treatment phase or is withdrawn during DB treatment phase, he or she will be asked to complete the Month 12 (Week 52 assessments).

9.1.4. Open-Label Treatment Phase

Following completion of DB treatment phase (Week 52 assessments) subjects will continue in OL phase. In OL phase, subjects who received placebo in the DB treatment phase will be randomized to open-label active treatment (JNJ-54861911; Week 52 of DB treatment phase) as described above and in Section 6, Dosage and Administration. Subjects receiving JNJ-54861911 in the DB treatment phase will continue their assigned treatment as open-label in OL phase.

Study medication will be self-administered on site as outlined in Section 6, Dosage and Administration.

During OL treatment phase, the subjects will visit the investigational site at regular time points (morning hours) as indicated in the Time and Events Schedule.

In case of progression to a dementia state (CDR ≥ 1) during course of the study, the subject may go through the consenting process for which a legally appointed representative may provide a renewed assent or consent, as applicable, in accordance with local regulations.

Subjects entering the OL treatment phase will remain blinded with respect to prior treatment assignment (placebo vs active drug) in the 54861911ALZ2002 study and in the DB treatment phase of this study. During the OL treatment phase, all subjects will have monitoring of safety laboratory tests every 2 weeks for the first 12 weeks, every 4 weeks for the next 12 weeks, every 8 weeks for the next 24 weeks, and every 12 weeks thereafter. The assessments to be performed and the frequency of assessments during the OL treatment phase are described in the following Table.

Assessment/Frequency	Every 2 weeks	Every 4 weeks	Every 8 weeks	Every 12 weeks	Every 24 weeks (*)	Every 48 weeks (*)(#)	Every 96 weeks (*)(#)(¥)
Drug accountability/Treatment compliance				X			
Drug return (previous visit)				X			
Drug Dispensing				X			
Physical and Neurological examination						X	
Body Weight						X	
12 Lead ECG				$X^{\alpha,£}$	$X^{£}$		
Body Temperature					X		
Supine and standing vital signs (systolic and diastolic blood pressure and pulse)				X			
Clinical safety laboratory assessments – hematology, serum chemistry – under fasted conditions, when feasible	X^{β}	X^{γ}	X^{δ}	X^{ε}			
Clinical safety laboratory assessments – urinalysis – under fasted conditions, when feasible					X		
Dermatological Examination						X	
Ophthalmological Examination[§]						X	
OCT (at sites where OCT is available)						X	
C-SSRS (since last visit)				X			
RBANS					X		
MMSE						X	
CFI					X		
CDR						X	
Blood sample collection for plasma JNJ-54861911 concentrations (predose)					$X^{\exists,£}$		
Blood sample collection for PD/biomarkers (predose)					$X^{\exists}$		
CSF sample collection (~12 mL) by single lumbar puncture for PK/PD/biomarker assessment.							X
MRI						X	
Adverse Event and Concomitant Medication				X			

(*) In addition to the assessments performed every 12 weeks. (#) In addition to the assessments performed every 24 weeks. (¥) In addition to the assessments performed every 48 weeks. (§) An ophthalmological examination will only be performed in subjects who had completed the parent study, ALZ2002, if: 1) if there was an abnormality present at the screening/baseline examination; 2) if the investigator detects new ophthalmological findings or visual symptoms; 3) if OCT reveals new findings. The ophthalmologic examination should be performed by the same ophthalmologist who completed the initial ophthalmologic examination at screening/baseline; (∃) predose; (£) 2 to 4 hours postdose; (α) only during the first 12 week visit of the OL treatment phase. (β) assessments performed every 2 weeks for 12 weeks (> Week 52 and ≤ Week 64). (γ) assessments performed every 4 weeks for 12 weeks (> Week 64 and ≤ Week 76). (δ) assessments performed every 8 weeks for 24 weeks (> Week 76 and ≤ Week 100). (ε) assessments performed every 12 weeks after Week 100.

In the OL treatment phase (>52 weeks) it is intended to collect if possible on-treatment CSF samples every 96 weeks until study completion. Subjects may opt not to have these punctures being performed.

For subjects enrolled in this study, subjects will continue study treatment (in the OL phase):

- until registration of JNJ-54861911
- until emerging safety issues arise as determined by the DRC that would warrant termination of the study
- until subject withdraws consent or other reasons for withdrawal as defined in Section 10.3.

Upon decision to stop study participation for any of the reasons described above subject will be asked to return to the investigational site to hand in their study medication. Drug accountability will be performed. No new medication will be dispensed.

In addition subjects will be asked to complete the End-Of-Treatment Visit as described in Section 9.1.5, End-of-Treatment Visit (Follow Up Visit).

9.1.5. End-of-Treatment Visit (Follow Up Visit)

An End-of-Treatment visit (or phone call) for a safety assessment should take place approximately 30 days after the last dose of study drug. This will consist of at least a review of Adverse Events and concomitant medication and C-SSRS assessment (since the last visit). The study is considered completed with the last End-of-Treatment safety assessment for the last subject participating in the study or upon a decision by the sponsor to terminate the study.

Investigators may recontact the subject to obtain long-term follow-up information to determine the subject's safety or survival status (refer to Section 16.2.3, Informed Consent).

9.2. Safety Evaluations

During the treatment phases regular safety assessments will be performed as listed in the Time and Events Schedule. These safety assessments include but are not limited to: vital signs, ECG, physical and neurological examination, adverse events, safety labs, suicidality risks (C-SSRS), dermatologic and ophthalmologic examinations, and MRI.

The DRC may decide to reduce, eliminate or even increase frequency over time of specific safety assessments in case (newly obtained) data collected in this extension study or from ongoing or future studies would support this decision.

Details regarding the DRC are provided in Section 11.7.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF.

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

9.2.1. Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

9.2.2. Colombia Suicide Severity Rating Scale (C-SSRS)

Consistent with regulatory guidance, any occurrence of suicide-related thoughts and behaviors will be assessed. An interview to assess the risk of suicidal ideation and behavior will be conducted at the time points listed in the Time and Events Schedule.

The C-SSRS is a measure of the spectrum of suicidal ideation and behavior that was developed in the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment[48]. The C-SSRS is a clinical interview providing a summary of both ideation and behavior that can be administered during any evaluation or risk assessment to identify the occurrence and intensity of suicidal thoughts and suicidal behaviors. It can also be used during treatment to monitor for clinical worsening.

If a suicide-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 will be provided.

9.2.3. Vital Signs

Vital signs (body temperature, pulse/heart rate, blood pressure) will be collected at the time points indicated in the Time and Events Schedule.

9.2.4. Electrocardiogram

Twelve-lead ECGs will be collected at the time points listed in the Time and Events Schedule.

At all-time points, triplicate ECGs are required, i.e., 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes 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 mark abnormalities. A description of the overall assessment (i.e., normal or abnormal plus reason) will be made and a copy of the trace 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.

9.2.5. Physical and Neurological Examination

The study investigator or other authorized and appropriately qualified designee will perform the physical and neurological examinations, including vibration sense (by use of a tuning fork).

Newly presenting ophthalmological findings or visual symptoms will be assessed by the investigator, and if deemed medically relevant, the subject will be referred to the ophthalmologist for evaluation.

Body weight will be measured as per the Time and Events Schedule.

The neurological examination will assess at minimum cranial nerves, motor system, sensory function and coordination.

9.2.6. Dermatologic Examination

Subjects will undergo a comprehensive skin examination performed by a dermatologist at the time points listed in the Time and Events Schedule to detect the presence of skin lesions or depigmentation. A digital photograph of the frontal scalp, open eyes, and eyebrows will be collected to monitor for dermatological changes. This is an essential requirement of the safety monitoring in the trial.

Whenever a skin lesion not previously documented is reported by the study subject or the investigator, in addition to a dermatological exam by the dermatologist, digital images of the lesion will be acquired at the time the lesion is discovered and at follow-up visits with a frequency which is deemed appropriate by the sponsor of the study. Duration of follow-up of newly documented skin lesions or depigmentation might extend beyond the treatment period, as judged adequate by the sponsor to ensure the safety of subjects in this study.

Comparison to the dermatological examinations performed in 54861911ALZ2002 study will be made if applicable.

9.2.7. Optical Coherence Tomography and Ophthalmologic Examination

Both the ophthalmologic examination and OCT will be carried out only in those subjects who had these in 54861911ALZ2002 study.

The ophthalmologic examination will include funduscopic and slit lamp examination, and testing of acuity and intraocular pressure, and will be performed at the time points listed in Time and Events Schedule.

OCT will be performed in all subjects at sites where OCT is available at the time points indicated in the Time and Events Schedule.

A baseline (Day 1 [predose or earlier]) OCT and ophthalmologic examination will be conducted only if no adequate assessments were obtained in 54861911ALZ2002 study within 9 months of first dosing in this study. Otherwise the assessment performed in 54861911ALZ2002 study will serve as baseline. Baseline assessments in this study may be performed during screening for logistical reasons.

During the treatment phase, an ophthalmologic examination, as described above, will only be performed at the time points indicated in the Time and Events Schedule if: 1) if there was an

abnormality present at the initial examination at screening/baseline; 2) if the investigator detects new ophthalmological findings or visual symptoms during a physical examination; 3) if OCT reveals new findings.

At the times of follow-up general physical examinations indicated in the Time and Events Schedule, newly presenting ophthalmological findings or visual symptoms will be assessed by the same qualified person who completed the screening visit. If deemed medically relevant, the subject will be referred to the ophthalmologist for further evaluation.

The on-treatment ophthalmologic examinations should be performed by the same ophthalmologist who completed the initial ophthalmologic examination at screening/baseline in the extension study or under the parent protocol.

9.2.8. Magnetic Resonance Imaging

All subjects will receive an MRI in this study at the time points indicated in the Time and Events scheduled for primarily safety reasons.

An additional baseline MRI may be collected (during screening or Day 1) in case subjects are enrolled from future JNJ-54861911 studies who did not obtain an adequate MRI under the parent protocol 6 months prior to first dosing in this study. For subjects who participated in study 54861911ALZ2002 no baseline MRI scan is to be collected as an MRI was collected at Month 6 under the parent protocol.

Collection of MRI data is primarily for safety reasons. MRI scans will be collected during DB treatment phase (up to and including Week 52 [Month 12]) and OL treatment phase (annual). Additional MRI scans may be collected based on emerging safety data (e.g., ARIA-E or H) with a frequency as recommended by the DRC.

Imaging sequences for all pre-specified protocol MRI studies will consist of an identical set of pulse sequences, including FLAIR and T2* sequences, as described in the MRI imaging manual.

Global and regional brain volumes and regional cortical thickness will be derived from the volumetric MRI sequence and will include both cross sectional absolute measurements and longitudinal volume change. The regional volumes and regional cortical thicknesses that will be chosen for this study will include those anatomical areas that are most affected in AD.

All MRI data collected (screening and on treatment) will be sent to a core imaging lab for quality control purposes and for data management, image processing, data analysis, and archiving.

MRI image evaluation will be performed by a core imaging lab.

9.2.9. Clinical Laboratory Tests

Blood samples (under fasted conditions whenever feasible) for serum chemistry and hematology and a random urine sample for urinalysis will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring

during the study in the adverse event section of the CRF. The laboratory reports must be filed with the source documents. The following tests will be performed at a central laboratory appointed by the Sponsor:

- Hematology Panel

-hemoglobin
-hematocrit
- red blood cell (RBC) count
- white blood cell (WBC) count with differential
-platelet count

- Serum Chemistry Panel

-sodium
-potassium
-chloride
-bicarbonate
-blood urea nitrogen (BUN)
-creatinine
-glucose
-aspartate aminotransferase (AST)
-alanine aminotransferase (ALT)
-gamma-glutamyltransferase (GGT)
-total and direct bilirubin
-magnesium
-alkaline phosphatase
-creatine phosphokinase (CPK)
-lactic acid dehydrogenase (LDH)
-uric acid
-calcium
- phosphate
-albumin
-total protein
-cholesterol
-triglycerides
-high density lipid protein
-low density lipid protein

- Urinalysis

Dipstick
-specific gravity
-pH
-glucose
-protein
-blood
-ketones
-bilirubin
-urobilinogen
-nitrite
-leukocyte esterase

Flow Cytometry
-RBC
-WBC
-epithelial cells

Sediment
-crystals
-casts
-bacteria

If there is discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically.

The use of local laboratories is allowed in cases where initiation of treatment or safety follow-up is time-critical and the central laboratory results are not expected to be available before the need to begin dosing or if actions need to be taken for safety reasons.

9.3. Biomarkers

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis described will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early, completion of biomarker assessments is based on justification and intended utility of the data

9.3.1. Fluid Biomarkers

9.3.1.1. CSF Biomarkers

During the DB treatment phase, all eligible subjects enrolled may have two optional CSF samples (12 mL per sample) collected by single lumbar punctures, one at baseline (only if no on-treatment CSF sample was collected under the parent protocol e.g., Month 6 CSF collection in study 54861911ALZ2002; otherwise the on-treatment CSF sample collected in 54861911ALZ2002 study may serve as baseline sample in this study) and one on-treatment (Week 52).

In the OL treatment phase (>52 weeks) it is intended to collect if possible on-treatment CSF samples every 96 weeks until study completion. Subjects may opt not to have these punctures being performed.

CSF samples should be taken at approximately the same time of day (with an allowable window of 3 hours), with the on-treatment samples being collected postdose.

During the course of the study the continuous (therapeutic) effects of JNJ-54861911 on the pathophysiological processes of AD may be reviewed by the DRC (CSF Aβ and CSF tau peptides or an alternate biomarker of neurodegeneration).

CSF p-tau (and possibly additional downstream markers of neurodegeneration) will be the primary CSF biomarker results used to assess and predict a potential therapeutic effect of JNJ-54861911.

CSF $A\beta_{1-40}$, is the primary CSF biomarker result used to confirm target engagement by JNJ-54861911. Aβ fragments of different length are produced by cleavage of the APP by BACE and the γ-secretase complex in the brain and excreted into CSF. While cleavage by BACE and γ-secretase leads to Aβ fragments, cleavage by α-secretase prevents Aβ fragment formation. BACE cleavage initiates the Aβ production at the N-terminal end of the Aβ fragment, which then is further processed at the C-terminal end by the γ-secretase complex. As Aβ turnover rates are rapid, inhibition of BACE results in a reduction of all Aβ fragments in CSF.

In addition to CSF p-tau and CSF $A\beta_{1-40}$, other amyloid, AD and compound-related biomarkers in CSF and plasma may be assessed such as, but not limited to, additional Aβ fragments ($A\beta_{1-37}$, $A\beta_{1-38}$, and $A\beta_{1-42}$), soluble amyloid precursor proteins (sAPP), t-tau, and additional downstream biomarkers of neuroinflammation, neurodegeneration, and neuronal injury such as VILIP-1, YKL-40 and others. Where appropriate consent is obtained, samples will also be stored for future research after the clinical study is completed (where local regulations permit).

9.3.1.2. Plasma Biomarkers

Aβ fragments can be measured in plasma, similar to in CSF, but are more difficult to measure due to interference with other plasma proteins. Current assays have not been validated to the same extent for plasma as for CSF.

Venous blood samples will be collected for the analysis of $A\beta_{1-37,1-38,1-40,1-42}$ at the time points indicated in the Time and Events Schedule.

9.3.2. Imaging Biomarkers

9.3.2.1. Magnetic Resonance Imaging

All subjects will receive an MRI in the extension study at the time points indicated in the Time and Events Schedule for primarily safety reasons. However, potential treatment effects may be assessed with MRI as well.

See Section 9.2.8, MRI for a description on the MRI assessment.

9.4. Cognition, Function and Clinical Status

Cognitive evaluations (RBANS, MMSE, and CVLT-II) and functional measures (Cognitive Function Index [CFI]) will be applied in this study at different time points as indicated in the Time and Events Schedule to explore the subject's cognitive performance/progression and function over time.

In addition during course of the study the subject's clinical status will be assessed regularly by means of the CDR as indicated in the Time and Events Schedule.

During the course of the study on occasions when multiple cognitive assessments and clinical scares are to be performed the same visit day, the RBANS will be completed first followed by the CDR and MMSE if the raters for RBANS and CDR are independent. If the raters for RBANS and CDR are the same, the CDR will be performed first, followed by the RBANS and MMSE. For a given subject, the same sequence will be followed throughout the study.

Details on the different cognitive tests, versions and forms to be used as well as their sequence of performance will be described in a separate manual.

The RBANS and CVLT-II must be conducted by an experienced, trained, and qualified neuropsychologist.

The CDR and MMSE may be conducted by a study physician, clinical psychologist, research assistant or clinical study nurse specialist who has been trained and qualified in the study processes.

9.4.1. Cognitive Evaluations

9.4.1.1. Repeatable Battery for the Assessment of Neuropsychological Status

The RBANS is a 20 to 25 minute battery developed for cognitive assessment, detection, and characterization of dementia in the elderly as well as neuropsychological screening for younger patients[50]. The time to administer is dependent on disease severity, but shorter if the participant is more impaired. The RBANS includes 12 subtests that measure the following 5 indices:(1) Attention Index consists of Digit Span and Coding; (2) the Language Index consists of Picture Naming and Semantic Fluency subtests; (3) the Visuospatial/Construction Index is made up of Figure Copy and Line Orientation subtests; (4) the Immediate Memory Index is comprised of List Learning and Story Memory subtests, and (5) the Delayed Memory Index consists of List Recall, List Recognition, Story Recall and Figure Recall subtests. Research has demonstrated that the RBANS is predictive of functional capacity (i.e., driving) in MCI patients[2], correlated with the CDR in MCI and AD[31] and AD biomarkers[22,62] and cognition[17]. The RBANS is administered face-to-face and available in over 30 languages and has been used in multinational clinical trials including AD trials.[39,42,51]

9.4.1.2. Mini Mental State Examination

The MMSE is a brief, validated 30-point questionnaire that is used to screen for cognitive impairment.[21] The MMSE rates subjects on orientation (total score, 10), registration (total score, 3), attention, calculation (total score, 5), recall (total score, 3), and language (total score, 9). The maximum score is 30. The lower the score the more pronounced the impairment.

9.4.1.3. California Verbal Learning Test – Second Edition

The CVLT-II is a face-to-face comprehensive neuropsychological measure of verbal memory in individuals 16 to 89 years old. It is designed to quantify components of verbal learning, retention and retrieval.[13] The CVLT-II differs from the original CVLT in that new word stimuli are used, new and larger normative database was collected, addition of a forced choice recognition procedure at the end, as well as computerized scoring. Sixteen (16) words are read out to the participants five times with the instruction to memorize as many words as possible each time. Each of the words belongs to one of four categories: thus, there are four fruits, four herbs and spices, etc. The participants are asked to recite the words they could recollect immediately following each presentation (immediate recall or IR) and after an interval of at least 20 minutes (delayed recall or DR), which is then followed by a 32 item recognition subtest.

9.4.2. Clinical Scales and Functional Measures

9.4.2.1. Clinical Dementia Rating Scale – Sum of Boxes

The CDR is a global clinical scale with established diagnostic and severity-ranking utility widely used in clinical trials yielding global and Sum of Boxes (SB) scores (CDR-SB). The CDR global

score is used in AD trials as a global measure of disease progression. The CDR is rated based on subject and informant reports. It does not directly rely on psychometric tests thereby avoiding learning effects. The CDR has also been adapted for routine clinical use in tertiary clinics and chronic care facilities. The CDR assesses three domains of cognition (memory, orientation, judgment/problem solving) and three domains of function (community affairs, home/hobbies, personal care) using semi-structured interviews of both the study subject and a companion/informant carried out by a trained rater and scored using a standard methodology. Each domain is rated on a 5-point scale of functioning as follows: (0) no impairment; (0.5) questionable impairment; (1) mild impairment; (2) moderate impairment; and (3) severe impairment (personal care is scored on a 4-point scale without a 0.5 rating available). An algorithm is used for integrating the information obtained into an overall score, i.e., "CDR Global" score ranging from 0 to 3 with 0 having no dementia and 3 having severe dementia.

The scores for the six domains (ranging from 0 to 3) tested can be summed to obtain the CDR Sum of Boxes or CDR-SB score, with scores ranging from 0 to 18.

The CDR-SB scores can be used to stage patients.[47]

The CDR comprehensively assesses both cognitive and functional disability in AD patients and is expected to be particularly useful for studies in early stages of AD.[7]

During the study the CDR will be audiotaped (including informant information) and reviewed centrally. The subject's and informant's approval or disapproval for such recording will be documented in the source documents.

9.4.2.2. Cognitive Function Index (CFI)

The CFI is a modified version of the Mail-in Cognitive Function Screening Instrument[60], a subject- and study partner-reported outcome measure developed by the Alzheimer's Disease Cooperative Study (ADCS). This assessment includes 15 questions that assess the subject's perceived ability to perform high level functional tasks in daily-life and their sense of overall cognitive functional ability. Study subjects and their study partners independently rate the subject's abilities.

9.5. Pharmacokinetics

9.5.1. Evaluations

Venous blood samples for analysis of JNJ-54861911 in plasma will be collected at the time-points indicated in the Time and Events Schedule.

Blood samples will be used to evaluate the plasma pharmacokinetics of JNJ-54861911. Samples collected for analyses of JNJ-54861911 plasma concentration may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period or for the evaluation of relevant biomarkers.

The CSF samples (12 mL each) collected for biomarker research as outlined in Section 9.3.1.1 CSF Biomarkers, will be used, in addition to analysis of relevant biomarkers concentrations, for the analysis of JNJ-54861911 concentrations.

9.5.2. Analytical Procedures

Pharmacokinetics

Plasma will be analyzed to determine concentrations of JNJ-54861911 using a validated, specific, and sensitive LC-MS/MS method by or under the supervision of the sponsor. JNJ-54861911 concentrations will be analyzed in CSF (only post-dose samples) with a qualified LC-MS/MS assay.

If required, some plasma and CSF samples may be analyzed to document the presence of circulating metabolites using a qualified research method.

9.5.3. Pharmacokinetic Parameters

Population PK analysis of plasma and CSF concentration-time data of JNJ-54861911 will be performed using nonlinear mixed-effects modeling. Data may be combined with those of a selection of Phase 1 studies to support a relevant structural model. Based on the individual plasma and CSF concentration-time data, if sufficient data are available, the following PK parameters of JNJ-54861911 may be estimated at steady state in subjects receiving a dose of JNJ-54861911 using population PK modeling:

C_{max} maximum plasma/CSF concentration

$AUC\tau$ area under the plasma/CSF concentration-time curve from 0 to τ hours post dosing (time τ is the dosing interval)

CSF-related parameters will only be estimated if allowed by the model, due to the limited number of samples collected for each subject. Additional analyses may be conducted according to a population PK analysis plan and results will be presented in a separate report.

The parameters of interest for the statistical analysis will be the log-transformed estimated dose normalized AUC and C_{max}. All ratios will be calculated as differences of least square means of the appropriate model on the log-scale, and will be presented after back-transformation to the original sale with the corresponding 90% confidence intervals (CIs).

Based on the individual plasma concentration-time data, using the actual dose taken and the actual sampling times, PK parameters and exposure information of JNJ-54861911 will be derived using population PK modelling. Baseline covariates (e.g., body weight, age, sex, CrCL, race) may be included in the model, if relevant.

9.6. Sample Collection and Handling

PK and PD (biomarker) sampling/assessment times and sampling volumes can be adapted without protocol amendment provided that the maximal volume collected per subject specified per protocol will not be exceeded.

Refer to the Time and Events Schedule for the timing and frequency of all sample collections.

The exact dates and times of blood and CSF sampling must be recorded in the CRF or lab requisition form.

Baseline and on-treatment CSF samples should be taken at approximately the same time of day (with an allowable window of 3 hours), with the on-treatment samples sample being collected postdose.

For CSF sampling, local site SOPs may be applied for performing the actual lumbar puncture (not the collection), provided they are at least as restrictive as the criteria defined per protocol.

Instructions for the collection, handling, storage, and shipment of samples will be provided in a separate lab manual. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the lab manual.

All the assays and instruments used in this study will be performed by trained operators at the Sponsor or designated laboratories in Europe or the US on coded samples.

Venous blood samples and CSF samples may be stored and used for future analysis of JNJ-54861911 metabolites and exploratory proteomics and metabolomics or other markers related to AD or neuropsychiatric disorders. Additionally markers of blood brain barrier integrity or subtle procedure related inflammatory changes may be examined.

Samples may be provided to external partners for exploratory (CSF) biomarker research related to AD upon completion of the study.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

Subjects are considered to have completed the study if they discontinued treatment with JNJ-54861911 (provided by the sponsor) for any reason (i.e., disease progression, unacceptable toxicity, sponsor terminates the study, or alternative access to JNJ-54861911 becomes available and feasible (i.e., commercial source of JNJ-54861911) and had a follow-up safety assessment approximately 30 days after the last dose of JNJ-54861911. Subjects who die while receiving treatment also are considered to have completed the study.

10.2. Discontinuation of Study Treatment

If a subject's study treatment must be discontinued before the end of the treatment regimen, this will not result in automatic withdrawal of the subject from the study.

The following specific individual rules for stopping study treatment will apply:

- Mean QTcF interval of > 500 msec if confirmed upon repeat ECG, and/or mean QTcF increase versus baseline of > 60 msec if confirmed upon repeat ECG (all triplicate recordings).
- The investigator believes that for safety reasons (e.g., adverse event) it is in the best interest of the subject.
- Liver enzyme elevation between Weeks 52 and 64, including any of the following:
  - ALT or AST >5× ULN
  - ALT or AST >3× ULN and total bilirubin >2× ULN or INR >1.5
  - ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia >5%
- Liver enzyme elevation after Week 64, including any of the following:
  - ALT or AST >8× ULN
  - ALT or AST >5× ULN for more than 2 weeks
  - ALT or AST >3× ULN and total bilirubin >2× ULN or INR >1.5
  - ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia >5%

Re-initiation of study treatment should only be done after consultation with the sponsor medical monitor and in mutual agreement between the sponsor and the study center. If a subject permanently discontinues study treatment before the end of the treatment phase, the subject will be asked to complete the Week 52 assessments, including CSF sampling, if not yet obtained earlier. At a minimum, the subject will be asked to complete the End-of-Treatment Visit (Follow-up visit) as per the Time and Events Schedule.

10.3. Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent or assent
- Death
- Noncompliance

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject.

Subjects who are withdrawn will not be replaced.

Any subject who withdraws after receiving the study drug will be asked, if not yet obtained, to have the Week 52 assessment performed. At least the subjects should have a follow-up evaluation as described in Section 9.1.5

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). 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.

11. STATISTICAL METHODS

Subjects enrolled in this study will be self-selected as they will be provided the option to participate in this study upon completion of treatment in a Phase 1b or Phase 2 study with JNJ-54861911.

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. Descriptive statistical analyses will be performed for all subjects receiving at least one dose of study drug in this study. Analyses may be performed separately for both DB and OL treatment phases. After all subjects have completed the DB treatment phase, a database lock for the DB treatment phase will take place upon which unblinded statistical analyses may be generated, and a study report for DB treatment phase may be prepared. Analyses may be performed separately for subgroups of subjects according to previous study participation as well as for the combined population of all subjects participating in this study, where appropriate. Summaries may also be presented by baseline CDR global score.

11.1. Subject Information

For all subjects who receive at least one dose of study drug descriptive statistics will be provided.

11.2. Sample Size Determination

The study is not powered according to statistical calculations. The number of subjects enrolled will depend on the number of subjects from other JNJ-54861911 studies who are willing to enroll in this extension study.

11.3. Pharmacokinetic Analyses and Pharmacokinetic/Pharmacodynamic Analysis

Population PK modeling of plasma and, if possible, CSF concentrations of JNJ-54861911 will be undertaken. In view of the sparse sampling foreseen for this study, data may be combined with a selection of Phase 1, Phase 1b, and Phase 2 data (e.g., from studies 54861911ALZ1001, 54861911ALZ1002, 54861911ALZ1005, and/or 54861911ALZ2002) in order to support a relevant structural model.

PopPK/PD analysis of biomarkers and/or cognitive markers may also be performed, and a suitable dose- and/or exposure-response model may be developed. If necessary or relevant for the analysis, Phase 1 and Phase 2 data may be integrated to inform the model structure or key parameter values.

A snapshot date for PK samples to be analyzed may be defined, if required, and documented in a data transfer plan (DTP) according to the applicable standard operating procedures and work instructions. Samples collected before this date will be analyzed for JNJ-54861911 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.

Details of the analyses will be described in a PopPK/PD analysis plan and results will be provided in a separate report.

11.4. Pharmacodynamic Analyses

11.4.1. Biomarker Analyses

11.4.1.1. Fluid Biomarkers

Percent changes from baseline in CSF Aβ species ($A\beta_{1-37}$, $A\beta_{1-38}$, $A\beta_{1-40}$, $A\beta_{1-42}$) and sAPP total, as well as fragments (sAPPα, sAPPβ) will be summarized at each scheduled time point using descriptive statistics and presented graphically by treatment period and treatment group.

Similar analyses will be performed for plasma $A\beta_{1-40}$ and sAPP total, as well as fragments (sAPPα, sAPPβ).

Exploratory analyses may be performed for CSF p-tau, t-tau and additional downstream biomarkers of neuroinflammation, neurodegeneration, and neuronal injury. Results of these analyses may be presented in a separate report.

11.4.1.2. Imaging Biomarkers

Changes from baseline in brain volumes and cortical thickness (regional and global) as measured by volumetric MRI will be summarized using descriptive statistics.

11.4.2. Cognition, Function and Clinical Status

Cognitive evaluations (RBANS, MMSE, and CVLT-II) and functional measures (Cognitive Function Index [CFI]) will be applied in this study at different time points as indicated in the Time and Events Schedule to explore the subject's cognitive performance/progression and function over time.

In addition during course of the study the subject's clinical status will be assessed regularly by means of the Clinical Dementia Rating Scale as indicated in the Time and Events Schedule.

Measurements will be summarized at each scheduled time point using descriptive statistics.

11.5. Safety Analyses

All subjects receiving at least one dose of study drug will be included in the safety analysis. Descriptive statistics will be computed.

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the treatment phase (i.e., treatment-emergent adverse events, and adverse events that have worsened since baseline) will be included in the analysis. For each adverse event, the percentage of subjects who experience at least one occurrence of the given event will be summarized by treatment group. Adverse events will also be tabulated by severity and by relationship to study drug and will be presented by treatment group. Serious adverse events will be summarized separately.

Summaries will be provided for all subjects receiving at least one dose of study drug in this study, and will include adverse events from this study as well as any preceding studies (e.g., study JNJ-54861911ALZ1005, JNJ-54861911ALZ2002 or any future Phase 1b or Phase 2 JNJ-54861911 clinical studies) as applicable for subjects who previously participated in that study, where appropriate.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who withdraw due to an adverse event, or who experience a severe or a serious adverse event. Subjects with AESIs may be counted or listed.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point, and for changes from baseline.

The number and percentage of subjects experiencing a laboratory result below or above normal reference ranges will be provided for each laboratory analyte by treatment group.

A listing of subjects with any laboratory result outside the reference ranges will be provided.

Electrocardiogram (ECG)

Heart rate and ECG intervals (RR, PR, QRS, and QT) as well as corrected QT intervals according to Bazett's formula (QTcB) and Fridericia's formula (QTcF) from the 12-lead ECG will be summarized at baseline and at each scheduled time point and for changes from baseline using descriptive statistics.

The number and percentage of subjects with at least 1 occurrence of a treatment-emergent potentially clinically important QTc measurement (QTc value >450, >480, or >500 ms) or with a change from baseline in QTc >30 ms will be summarized by treatment group.

Data listings of subjects with any potentially clinically important values (QTc value >450, >480, or >500 ms) or with a change from baseline in QTc >30 ms will be provided.

Vital Signs

Descriptive statistics of pulse, blood pressure (systolic and diastolic) (supine and standing), temperature and body weight values and changes from baseline will be summarized at each scheduled time point.

Physical and Neurological Examination

The number and percentage of subjects with a change from normal at baseline to abnormal at any postbaseline exam will be tabulated by treatment group.

Subjects with abnormal findings will be presented in a data listing.

Dermatologic and Ophthalmologic Examination

Results of the dermatologic and ophthalmologic examinations (incl. OCT) will be presented by treatment group. Subjects with abnormal findings will be presented in a data listing.

Columbia Suicide Severity Rating Scale (C-SSRS)

Results from the C-SSRS will be tabulated by treatment group for all subjects receiving at least one dose of study drug in this study.

Safety MRI

The number and percentages of subjects with presence of ARIA-E, ARIA-H, and other MRI abnormalities found in the safety MRI assessments will be tabulated by treatment group.

11.6. Interim Analysis

No prespecified interim analysis of unblinded data during the DB treatment phase is planned by the clinical team. However, depending on the recruitment, or in support of regulatory filings for upcoming studies, or for any other reason the Sponsor deems necessary, an unblinded review of safety and biomarker data prior to the last subject's completion of the DB treatment phase might be conducted by an internal Interim Analysis Committee. If any such review is conducted it will be documented in an Interim Analysis Committee charter prior to the unblinding. The

constitution of the Interim analysis committee will be documented in the Interim Analysis Committee charter and may include Sponsor study team members.

As noted in Section 5, when the parent study (e.g. 54861911ALZ2002 and potential future Phase 1b and 2 studies) is completed and its clinical database is closed, the randomization codes from the parent study will be released to the sponsor study team. Thus, the sponsor will be unblinded at that time, but the investigator and subjects will continue to be blinded to treatment during the DB treatment phase, until the last subject has completed that phase, and the database from that phase has been reviewed, corrected as necessary, and locked. At that point, the sponsor will perform analyses of key safety, biomarker, and efficacy variables, as detailed in a prespecified statistical analysis plan.

Following the sponsor's review of these analyses, information on an individual subject's treatment allocation during the DB phase will be made available upon request by the investigator. As subjects that remain in the study will all be receiving open label JNJ-54861911 at that time, and as no change or alteration of the locked database from the DB phase will be possible, there will be no bias introduced by this measure.

11.7. Data Review Committee

A DRC will be established to monitor the study data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study. The committee will meet periodically to review interim study data including the safety data as well as biomarker data (fluid [CSF, plasma] and imaging [vMRI]).

The CSF and Imaging biomarker data (e.g., CSF Aβ and CSF tau peptides or another marker of neurodegeneration; vMRI) will be reviewed periodically by the DRC to assess the continuous potential therapeutic effect of JNJ-54861911 over time on the pathophysiologic processes underlying AD in subjects asymptomatic at risk for developing Alzheimer's dementia.

After the review, the DRC will make recommendations regarding the safety and continuation of the study. The details will be provided in a separate DRC charter.

The DRC will consist of at least one medical expert in AD and at least one statistician. The DRC statistician will not be part of the Sponsor study team and as such will not otherwise be involved in the study conduct or the final statistical analysis of this study. The DRC responsibilities, authorities, and procedures will be documented in its charter.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established SOPs (SOPs) 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.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event 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 non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])[34]

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 adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event 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 subject 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 were 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 should 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 subject 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 adverse event occurs for which there is evidence suggesting a causal relationship between the study drug and the event (e.g., 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 (e.g., all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For JNJ-54861911, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure (Reference Safety Information included the IB).[37]

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (e.g., confirmed by dechallenge). An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by dechallenge and rechallenge).

12.1.3. 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 should use clinical judgment in assessing the severity of events not directly experienced by the subject (e.g., laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Inadvertent or accidental exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, e.g., name confusion)
- A subject experiences elevations in liver enzymes as specified in Attachment 1.

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

12.3. Procedures

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety). Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All other events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event

management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all serious adverse events that are unlisted (unexpected) and associated with the use of the study drug. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee (IEC) that approved the protocol unless otherwise required and documented by the IEC.

For all studies with an outpatient phase, including open-label studies, the subject 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 subject 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 staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding all serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in 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 drug or to factors unrelated to study conduct

- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Discontinuation of study treatment secondary to increased liver enzyme criteria (outlined in Section 10.2) will be reported as a serious adverse event.

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). 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 serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- For convenience the investigator may choose to hospitalize the subject for (part of) the duration of the treatment period.

The cause of death of a subject in a study, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

12.3.3. Pregnancy

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

12.3.4. Adverse Events of Special Interest

All initial reports of lightening of skin or hair, or treatment-emergent ophthalmologic AEs must be reported to the Sponsor by the investigational staff within 24 hours of their knowledge of the event even if these events do not meet the definition of an SAE. Additional information on the reporting of AESIs is found in Attachment 2.

12.3.5. Adverse Drug Reactions

Elevated liver enzymes have been identified as an ADR. Any SAE related to elevated liver enzymes should be reported as described in Section 12.3.2. In addition, any cases of elevated liver enzymes that result in discontinuation of study treatment should be reported as an SAE, following reporting requirements outlined in Section 12.3.2.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e., any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel as soon as possible after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

The JNJ-54861911 solid dosage formulation will be supplied as 5- and 25-mg film-coated tablets. These are round, white to off-white tablets, containing 5- or 25-mg of JNJ-54861911, compendial-grade of D-mannitol, low-substituted hydroxypropyl cellulose, triethyl citrate, hydroxypropyl cellulose, magnesium stearate, and Opadry 03A48081.

The JNJ-54861911 placebo tablets will be supplied as film-coated tablets, matching visually to the active tablets. These are round, white to off-white tablets, containing compendia grade of D-mannitol, microcrystalline cellulose, magnesium stearate triethyl citrate, and Opadry 03A48081. JNJ-54861911/placebo will be manufactured and provided under the responsibility of the sponsor.

14.2. Packaging

The study drug will be blister packed. For both DB and OL treatment phases, blinded study drug kits will be assigned based on their treatment allocation under the parent protocol. However for OL treatment phase investigator and subject can be unblinded to treatment despite the use of blinded treatment kits (for logistical reasons). All JNJ-54861911/placebo solid formulation study drug will be dispensed in child-resistant packaging.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

All study medication will be stored in a secure area with restricted access.

The JNJ-54861911 and placebo solid dosage formulation must be stored at controlled room temperatures ranging from 15°C to 30°C, as indicated on the product specific labeling.

Additional guidance and detailed instructions for the clinical site dosing procedures and storage conditions are described in the Dose Preparation Instructions/ Pharmacy manual or equivalent document.

Refer to the Dose Preparation Instructions/Pharmacy Manual for additional guidance on study drug dispensing, dosing process, and handling.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects must be instructed to return all original containers, whether empty or containing study drug.

Study drug 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 drug, and study drug returned by the subject, 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 drug, or used returned study drug for destruction, will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes, and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug 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 drug will be supplied only

to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with, but not limited to, the following supplies:

- Investigator Brochure for JNJ-54861911
- Pharmacy manual/study site investigational product manual
- Laboratory manual
- Imaging Manual
- Cognition Manual
- IWRS Manual
- eDC Manual
- Sample ICF
- Subject diaries

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Subjects in the early AD spectrum who have completed a Phase 1b or Phase 2 clinical study with JNJ-54861911 will be provided the opportunity to participate in this study, focused on providing primarily safety and tolerability data supporting long-term treatment with JNJ-54861911 in subsequent studies (Phase 3) as well as ongoing access to JNJ-54861911. The study treatment duration in this study of subjects in the early (predementia) AD spectrum is supported by the available toxicology and clinical data (see Investigator's Brochure).[37]

The early (predementia) AD spectrum defined in this study includes subjects who are asymptomatic but at risk for Alzheimer's dementia as well as subjects with pAD who recently completed a Phase 1b or Phase 2 JNJ-54861911 study.

Examples of JNJ-54861911 studies in the same target population are an earlier POM study (54861911ALZ1005) and a 6-month safety study (54861911ALZ2002).

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects 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 subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

Subjects that have progressed to dementia (CDR ≥1) in the parent study 54861911ALZ2002, or who are incapable of providing informed consent will not be enrolled. In case the subject progresses to a dementia state during the study, the subject may remain in the study, provided that the investigator judges that the potential benefits of treatment for this subject clearly outweigh the known and foreseeable risks and assent or consent (as applicable) for continued participation is obtained from a representative determined in accordance with the local law. In cases where a subject has progressed to dementia, treatments indicated for this condition (e.g., memantine or cholinesterase inhibitors) are permitted after notification of the sponsor.

A DRC has been established to monitor the study data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study.

Specific dermatologic and ophthalmologic examinations, as described in Section 9.2, Safety Evaluations, have been implemented in this study as potential BACE1- or BACE2-linked toxicities (e.g. melanin deposition changes and retinal abnormalities) have been described in the literature (e.g. BACE1 or BACE2 knock-out mice). With the exception of fur discoloration resulting in progressive lightening of the fur from normal dark brown to paler cream or grey, which was seen in one species only (Tg mice in the 6 month carcinogenicity study), these toxicities have not been observed in preclinical studies with JNJ-54861911.

Subjects participating in this study may have direct benefit as a consequence of the longer treatment duration, however to date efficacy of this compound has not been proven. Effects on slowing down the rate of cognitive decline are only expected to become apparent after a treatment duration of approximately 3 years based on evidence from previous longitudinal studies in this field (Alzheimer's Disease Neuroimaging Initiative [ADNI] and the Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing [AIBL]).

A placebo arm is warranted and necessary to allow for an accurate assessment of the safety and tolerability of the study drug. The placebo arm will be limited in time to the first 12 months of this study. Combined with the duration of treatment under the parent protocols (e.g., 6 months) an additional 12-month placebo-controlled period in this study is deemed sufficient to assess any emergent safety aspects (treatment induced effects) of JNJ-54861911 in relation to placebo treatment. In addition at this moment there is no treatment available for subjects at risk for Alzheimer's dementia or subjects in the earliest AD spectrum so the use of placebo in an individual subject is not harmful, nor does it prevent them from the use of an indicated active treatment. Treatment with placebo dosing is not equivalent to non-treatment. All medication treatment will occur within the context of carefully supervised and supportive care.

The optimal level of therapeutic Aβ reduction is not known and cannot be assumed from preclinical models or early phase clinical studies, as the proposed effect on the disease pathology is expected to require chronic treatment. Results from Phase 1 studies with JNJ-54861911 have confirmed observations in transgenic animal models in showing that this compound results in profound reductions in brain Aβ levels. As described in Section 1.1, data from completed SAD and MAD studies in healthy older subjects and from the preliminary analyses of the proof of mechanism study in a population with early AD spectrum showed dose-dependent reductions in

$A\beta_{1-40}$ in plasma and CSF following oral JNJ-54861911 administration. As shown in Figure 5 below, preliminary data from the proof of mechanism study showed that the median reduction in CSF $A\beta_{1-40}$ with a 25 mg/day dose (84%) was only minimally increased by ~ 7% (i.e., to 91%) with a doubling of the dose to 50 mg/day. At a lower dose of 10 mg/day, the majority of subjects in this study showed more than a 50% reduction in CSF $A\beta_{1-40}$. However, during the course of the study as indicated in Section 3.2. Study Design Rationale, the Sponsor will have the option based on recommendations by the DRC or based upon newly emerging safety, biomarker or efficacy data from ongoing or completed JNJ-54861911 studies, to revise the dose levels for the OL treatment phase.

A thorough QT trial, 54861911ALZ1007, has been performed in 64 healthy subjects (final report not yet available) using a 4-way, 7-day cross-over design evaluating a JNJ-54861911 dose of 50 mg/day as well as supratherapeutic dose of 150 mg/day, and including moxifloxacin 400 mg to confirm assay sensitivity as described in Section 1.1, Background. PK/PD modeling was performed to assess the relationship between JNJ-54861911 plasma concentrations and effect on QTcF prolongation, using data from the 54861911ALZ1007 study. Results of this modeling activity showed that at a JNJ-54861911 once daily (q.d.) dose of 25 mg, the median changes in the QTcF, as well as the 90% population interval, are expected to be well below 5 msec.

The normal choroid plexus produces CSF at a continuous rate of 20 mL/hour resulting in a daily CSF production of 500 mL on average. The total CSF volume at any given time is about 150 mL, so in normal conditions there is a complete wash-out of the CSF volume approximately 4 times per day.[45] At each CSF sampling point a sample of 12 mL will be collected, which is considered to be acceptable, in reference to the daily CSF production rate. Equal and even higher volumes of CSF up to 108 mL (over 36 hours) have been collected in previous studies (54861911ALZ1001 and 54861911ALZ1002) and were well tolerated by subjects in the same age range as that of subjects who will be included in the current study.

Possible theoretical risks associated with lumbar punctures include: procedural pain during insertion of needle, spinal headache (also called post-dural puncture headache [PDPH]), epidural infection, spinal cord trauma / nerve root trauma, spinal / epidural hematoma and cerebral herniation. To reduce these possible risks maximally, additional eligibility criteria and other preventive action were put in place under the parent protocols.

PDPH is the most common and most important complication inherent to the dural puncture. PDPH is caused by persistent CSF leakage. To reduce the risk of CSF leakage subjects are preferably placed on bed, rest in a supine position during sampling.

The possible introduction of an infection into the CSF (e.g. resulting in meningitis) is a rare complication. To avoid this, the lumbar puncture is performed under strict sterile conditions. Local SOPs will be followed for the performance of the lumbar puncture. All CSF collections will be performed under aseptic conditions.

The normal puncture sites will be respected in this study (L3-L4 or L4-L5).

Only experienced and qualified physicians are allowed to perform the applicable procedures.

The total blood volume to be collected will not exceed 450 mL annually, which is considered to be acceptable in comparison to a Red Cross blood donation.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

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

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

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/institutional review board (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 subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects 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 subjects
- 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 subjects, data or study conduct), the ICF, applicable recruiting materials, and subject 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 subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects 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 subjects, 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. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

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)].

16.2.3. Informed Consent

Each subject (or, in the case of subjects that have become demented during the course of the study, a legally acceptable representative, if applicable) must give written consent 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 is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the

subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy. An appendix to the 54861911ALZ2004 ICF will be used for subjects participating in eMeds.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects 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 subject will receive for the treatment of his or her disease. Finally, they will be told that the investigator will maintain a subject 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 subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject, is authorizing such access, including permission to obtain information about his or her survival status, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

The subject (or legally acceptable representative if applicable), 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 should be appropriately recorded by means of either the subject's (or his or her legally acceptable representative's) personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

If the subject (or legally acceptable representative if applicable) is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject (or legally acceptable representative, if applicable) is obtained.

A subject who has cognitive decline during the study to the point of clinical dementia may go through the consenting process to give renewed assent or consent (provided by a legally appointed representative), as applicable, in accordance with local law or guidance.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study 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 subjects confidential.

The informed consent obtained from the subject (or his or her legally acceptable representative, if applicable) includes 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. This consent also addresses the transfer of the data to other entities and to other countries.

The subject 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. 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.

Exploratory biomarker and PK research is not conducted under standards appropriate for the return of data to subjects. 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 subjects 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.

16.2.5. 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-54861911, to understand AD, to understand differential drug responders, and to develop tests/assays related to JNJ-54861911 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. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3, Withdrawal From the Study (Withdrawal From the Use of Samples in Future Research).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. 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 non-acceptance, except when necessary to eliminate immediate hazards to the subjects, 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 IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information page(s) provided separately). Except in emergency situations, this contact should 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 CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

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

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug 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, subject 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 (e.g., Form FDA 1572), if applicable
- Documentation of investigator qualifications (e.g., 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 subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (e.g., 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 (e.g., accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

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

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the CRF: subject 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 adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

Subject- and investigator-completed scales and assessments designated by the sponsor (such as but not limited to RBANS and CDR) may be recorded directly into an electronic device and in such instances will be considered source data.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator

before the study and will be described in the monitoring guidelines (or other equivalent document).

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

17.5. Case Report Form Completion

CRFs are provided for each subject in electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the CRF.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in CRFs prepared by the sponsor. Data must be entered into CRFs in English. Study site personnel must complete the CRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (e.g., pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible. The investigator must verify that all data entries in the CRFs are accurate and correct.

All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or study-site personnel must adjust the CRF (if applicable) and complete the query.

If corrections to a CRF are needed after the initial entry into the CRF, this can be done in 3 different ways:

- 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).
- Study site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can generate a query for resolution by the study-site personnel.

17.6. 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, direct transmission of clinical laboratory and ECG 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 CRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review CRFs 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.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each subject, 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.

17.8. 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 will compare the data entered into the CRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF 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 documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents 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 documentation 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.

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed with the last study assessment for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close a 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 termination.

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 subjects by the investigator
- Discontinuation of further study drug development

17.10. 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 and comparison with the CRFs. Subject 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 should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding JNJ-54861911 or the sponsor's operations (e.g., 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 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-54861911, 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 CRF data from all study sites that participated in the study, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. 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. 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 subject 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 International Committee of Medical Journal Editors 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 12 months of the availability of the final data (tables, listings, graphs), 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 Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

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Attachment 1: Evaluation of Increased Liver Enzymes

The following process should be followed whenever per protocol assessments for a given subject indicate an elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3× upper limit of normal (ULN):

1. Initial Investigation

Within 24 to 72 hours of receipt of abnormal laboratory results, the investigator and study site are to perform the following:

a. Repeat blood sampling:
   - Chemistry (include amylase if subject has abdominal pain or vomiting)
   - Complete hematology with eosinophil count
   - International normalized ratio (INR)
   - Hepatitis serology:
     - Hepatitis A: anti HAV IgG, anti HAV IgM
     - Hepatitis B : HBsAg, anti-HBc, anti-HBs
     - Hepatitis C: anti-HCV
     - Hepatitis E: anti-HEV IgG and IgM
     - Epstein Barr virus (EBV): anti-VCA IgG and IgM, anti-EBNA IgG
     - CMV: anti-CMV IgG and IgM.)
   - Anti-nuclear antibody (ANA)
   - One 5 mL sample of plasma for exploratory studies to evaluate the potential cause or risk factors for drug-related liver injury.

b. Collect detailed history of present illness and additional medical history, to include:
   - Recent abdominal pain, pruritis, rash
   - Prior abnormal liver tests, liver disease, exposure to hepatotoxins, diabetes, obesity, marked hypertriglyceridemia, gallstone disease or family history of gallstone or liver disease
   - Record alcohol use, other medications including acetaminophen, nonsteroidal anti-inflammatory drugs and over-the-counter herbal, vitamin, special diets, or nutritional supplements; any recent change in prescription drugs with start and stop dates; exposure to environmental chemical agents, or recreational drug use.

c. Perform a full physical exam, with specific comments on:
   - Palpable liver, size, tenderness
   - Palpable spleen, size, tenderness
   - Jaundice
   - Stigmata of chronic liver disease: spider angiomata, gynecomastia, palmar erythema, testicular atrophy

d. Schedule mandatory hepatic/pancreatic ultrasound

2. Follow-up Blood Sampling and Ongoing Contact with Medical Monitor

After the initial investigation, regardless of results, serum chemistry is to be performed (using the central lab retest kit) per the schedule below (Table 1) and close contact with the medical monitor with a minimal contact frequency (as outlined in the table) is also expected.

Table 1: Minimum Schedule for Follow-Up Blood Sampling and Contact with Medical Monitor

	AST or ALT Levels From Most Recent Laboratory Values			
	≥5×ULN	≥3, <5×ULN	>1, <3×ULN	WNL
Blood sampling frequency	2× per week	1× per week	Once every 2 weeks until sponsor approves reduction to 1× per month	1× per month until 3 consecutive months within normal limits, then Resume the standard, per protocol schedule
Frequency of site contact with medical monitor	1× per week	1 x per week	1× per month	Once, just prior to resumption of the standard, per protocol schedule
Abbreviations: ALT=alanine aminotransferase, AST=aspartate aminotransferase; ULN=upper limit of normal; WNL=within normal limits				

3. Hepatology/Gastroenterology Consult

Mandatory, urgent hepatology/gastroenterology consult must be conducted if any of the following occurs:

- AST or ALT ≥8× ULN
- AST or ALT ≥3× ULN with symptoms
- AST or ALT ≥3× ULN and total bilirubin ≥2 mg/dL
- AST or ALT ≥5× ULN persists for >1 week
- AST or ALT ≥3× ULN persists for >2 weeks

4. Discontinuation of Study Treatment:

Between Weeks 52 and 64, treatment must be discontinued if any of the following occurs:

- ALT or AST >5× ULN
- ALT or AST >3× ULN and total bilirubin >2× ULN or INR >1.5
- ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia >5%

After Week 64, treatment must be discontinued if any of the following occurs:

- ALT or AST >8× ULN

- ALT or AST > 5× ULN for more than 2 weeks
- ALT or AST >3× ULN and total bilirubin >2× ULN or INR >1.5
- ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia >5%

5. SAE Reporting

Subjects who meet the criteria for discontinuation of study treatment should have the event reported as an SAE and should follow the SAE reporting process as outlined in Section 12.3.2 of the protocol.

6. Continuation or Resumption of Study Treatment:

Study treatment may continue in asymptomatic subjects who do not meet the discontinuation rules, however, the investigator/site must adhere to the blood sampling and contact with Medical Monitor schedule in Table 1.

For subjects resuming treatment after an interruption of less than 7 days, the blood sampling schedule in Table 1 should be followed. In case treatment is resumed after interruption of more than 7 days, resumption of treatment must be discussed with and approved by the sponsor medical monitor. In these cases, follow-up blood sampling should occur weekly for the first month and thereafter Table 1 should be followed. Dosages should be at the same level as before the interruption.

Attachment 2: Adverse Events of Special Interest

The following events are considered to be events of special interest:

- Lightening of skin
- Lightening of hair
- Ophthalmologic adverse events

Cases of lightening of skin or lightening of hair should result in dermatological consultation with digital photography of the lesions; if these are deemed adverse events, they are to be categorized as AESIs, and should be reported to the sponsor within 24 hours of the knowledge of the event. Site to record these events on the adverse events eCRF page checked as AESI, with expedited reporting.

Treatment-emergent ophthalmological adverse events should be categorized as AESIs. Site to record this adverse event on the adverse event eCRF page checked as "AESI", with expedited reporting. An examination by the ophthalmologist who performed the initial examination at screening should be requested when new ophthalmological findings or visual symptoms emerge, or if OCT reveals new findings.

INVESTIGATOR AGREEMENT

JNJ-54861911

Clinical Protocol 54861911ALZ2004 Amendment 6

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 drug, 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): Gerald P. Novak, M.D.

Institution: Janssen Research & Development, L.L.C.

Signature: [redacted] Date: 6 Sept 2017

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.