

**Janssen Research & Development \*****Clinical Protocol**

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**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**

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**Protocol 54861911ALZ2003; Phase 2b/3  
AMENDMENT 6****JNJ-54861911 (atabecestat)**

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This study will be conducted under US Food and Drug Administration investigational new drug regulations (21 CFR Part 312).

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**Prepared by:** Janssen Research & Development, LLC  
**EDMS number:** EDMS-ERI-91347002, 8.0

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

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**TABLE OF CONTENTS**

<b>TABLE OF CONTENTS .....</b>	<b>2</b>
<b>LIST OF ATTACHMENTS .....</b>	<b>5</b>
<b>LIST OF IN-TEXT TABLES AND FIGURES .....</b>	<b>5</b>
<b>PROTOCOL AMENDMENTS .....</b>	<b>6</b>
<b>SYNOPSIS .....</b>	<b>31</b>
<b>TIME AND EVENTS SCHEDULE – SCREENING PHASE .....</b>	<b>41</b>
<b>TIME AND EVENTS SCHEDULE – DOUBLE-BLIND TREATMENT AND FOLLOW-UP PHASES .....</b>	<b>45</b>
<b>ABBREVIATIONS .....</b>	<b>51</b>
<b>DEFINITIONS OF TERMS .....</b>	<b>53</b>
<b>1. INTRODUCTION .....</b>	<b>54</b>
1.1. Result of Permanent Cessation of Screening, Randomization, and Dosing of Atabecestat .....	54
1.2. Background Information on the Disease to be Treated .....	54
1.3. Target Population – Asymptomatic Subjects at Risk for Alzheimer’s Dementia .....	55
1.4. Background Information on Atabecestat .....	57
1.5. Overall Rationale for the Study .....	62
<b>2. OBJECTIVES AND HYPOTHESES .....</b>	<b>64</b>
2.1. Objectives .....	64
2.2. Hypotheses .....	66
<b>3. STUDY DESIGN AND RATIONALE .....</b>	<b>66</b>
3.1. Overview of Study Design .....	66
3.2. Study Design Rationale .....	68
3.2.1. Blinding, Control, Study Phase/Periods, Treatment Groups .....	68
3.2.2. Study Population .....	68
3.2.3. Dose Selection .....	69
3.2.4. Study Duration .....	70
3.2.5. Cognitive and Functional Outcome Measures .....	71
3.2.6. Biomarkers .....	72
3.2.6.1. Determination of Elevated Amyloid Accumulation at Screening .....	73
3.2.6.2. Fluid Biomarkers (Other than CSF A $\beta$ for Screening) .....	73
3.2.6.3. Imaging .....	76
3.2.7. Safety Evaluations .....	77
3.2.8. Pharmacokinetic Evaluations .....	78
3.2.9. Medical Resource Utilization and Health Outcomes .....	78
3.2.10. Interim Analyses .....	78
<b>4. SUBJECT POPULATION .....</b>	<b>79</b>
4.1. Inclusion Criteria .....	79
4.2. Exclusion Criteria .....	81
4.3. Prohibitions and Restrictions .....	85
<b>5. TREATMENT ALLOCATION AND BLINDING .....</b>	<b>86</b>
<b>6. DOSAGE AND ADMINISTRATION .....</b>	<b>87</b>
<b>7. TREATMENT COMPLIANCE .....</b>	<b>88</b>

<b>8. PRESTUDY AND CONCOMITANT THERAPY .....</b>	<b>89</b>
<b>9. STUDY EVALUATIONS .....</b>	<b>90</b>
9.1. Study Procedures.....	90
9.1.1. Overview.....	90
9.1.2. Screening Phase .....	93
9.1.3. Double-blind Treatment Phase.....	97
9.1.4. Posttreatment Phase (Follow-Up) .....	99
9.1.5. Long-Term Extension Study .....	99
9.2. Efficacy.....	99
9.2.1. Primary Efficacy Measure: Preclinical Alzheimer Cognitive Composite.....	99
9.2.2. Secondary Efficacy Measures .....	101
9.2.2.1. Clinical Scales for Cognitive Outcome Measures .....	101
9.2.2.1.1. Repeatable Battery for the Assessment of Neuropsychological Status.....	101
9.2.2.1.2. Neuropsychological Assessment Battery - Daily Living Tests .....	101
9.2.2.2. Clinical Scales for Functional Outcome Measures.....	102
9.2.2.2.1. Cognitive Function Index.....	102
9.2.2.2.2. Cognitive Function Index-acute.....	102
9.2.2.2.3. ADCS Activities of Daily Living – Prevention Instrument .....	102
9.2.2.2.4. Clinical Dementia Rating Scale.....	102
9.3. Efficacy Endpoints.....	103
9.3.1. Primary Endpoint .....	103
9.3.2. Secondary Endpoints.....	103
9.4. Biomarkers .....	104
9.4.1. Fluid Biomarkers.....	104
9.4.1.1. CSF Biomarkers .....	104
9.4.1.2. Plasma Biomarkers .....	105
9.4.2. Imaging Biomarkers.....	105
9.4.2.1. Amyloid Positron Emission Tomography Substudy.....	105
9.4.2.2. Tau Positron Emission Tomography Substudy .....	106
9.4.2.3. Magnetic Resonance Imaging .....	106
9.5. Additional Clinical Scales .....	107
9.5.1. Rosen-modified Hachinski Ischemic Scale.....	107
9.5.2. Geriatric Depression Scale .....	107
9.5.3. Views & Perceptions about Amyloid Imaging .....	107
9.5.4. Concerns about Alzheimer's Disease Dementia .....	107
9.5.5. Impact of Events Scale .....	108
9.5.6. Future Time Perspective Scale .....	108
9.5.7. Assessment of Psychological Well Being.....	108
9.5.8. Columbia Suicide Severity Rating Scale .....	108
9.5.9. Computerized Cognitive Battery.....	109
9.5.10. Financial Capacity Instrument .....	110
9.5.11. Amsterdam IADL Questionnaire .....	110
9.6. Pharmacokinetic Evaluations.....	110
9.6.1. Evaluations .....	110
9.6.2. Analytical Procedures .....	111
9.6.3. Pharmacokinetic Parameters .....	111
9.7. Genomic Evaluations .....	111
9.8. Medical Resource Utilization and Health Outcomes.....	112
9.8.1. Healthcare Resource Utilization Questionnaire.....	112
9.8.2. Short Form-36.....	112
9.8.3. European Quality of Life-5 Dimensions 5-level .....	112
9.9. Safety Evaluations .....	113
9.9.1. Adverse Events.....	113
9.9.2. Vital Signs.....	113
9.9.3. Electrocardiogram.....	113
9.9.4. Physical and Neurological Examinations.....	113
9.9.5. Dermatological Examination.....	114

9.9.6.	Clinical Laboratory Tests .....	114
9.10.	Sample Collection and Handling .....	116
<b>10.</b>	<b>SUBJECT COMPLETION/WITHDRAWAL .....</b>	<b>117</b>
10.1.	Completion .....	117
10.2.	Discontinuation of Study Treatment .....	117
10.3.	Withdrawal From the Study .....	118
<b>11.</b>	<b>STATISTICAL METHODS .....</b>	<b>118</b>
11.1.	Subject Information .....	119
11.2.	Sample Size Determinations .....	119
11.2.1.	Primary Cognitive Endpoint .....	119
11.3.	Efficacy Analyses .....	119
11.3.1.	Analysis of the Primary Endpoint .....	119
11.3.2.	Analysis of the Secondary Endpoints .....	120
11.3.3.	Multiple Comparison Adjustment .....	121
11.3.4.	Handling of Missing Data .....	121
11.3.5.	Subgroup Analyses .....	121
11.4.	Potential Study Design Modifications .....	121
11.4.1.	Blinded Sample Size Adjustment .....	121
11.4.2.	Potential Design Modifications Based on External Data .....	121
11.4.3.	Unblinded Interim Analyses to Assess Futility .....	122
11.5.	Pharmacokinetic Analyses .....	123
11.6.	Pharmacokinetic/Pharmacodynamic Analyses .....	123
11.7.	Biomarker Analyses .....	124
11.8.	Pharmacogenomic and Gene Expression Analyses .....	124
11.9.	Medical Resource Utilization and Health Outcome Analyses .....	124
11.10.	Safety Analyses .....	124
11.11.	Data Monitoring Committee .....	126
<b>12.</b>	<b>ADVERSE EVENT REPORTING .....</b>	<b>126</b>
12.1.	Definitions .....	127
12.1.1.	Adverse Event Definitions and Classifications .....	127
12.1.2.	Attribution Definitions .....	128
12.1.3.	Severity Criteria .....	128
12.2.	Special Reporting Situations .....	129
12.3.	Procedures .....	129
12.3.1.	All Adverse Events .....	129
12.3.2.	Serious Adverse Events .....	130
12.3.3.	Adverse Events of Special Interest .....	131
12.3.4.	Adverse Drug Reactions .....	131
12.3.5.	Pregnancy .....	132
12.4.	Contacting Sponsor Regarding Safety .....	132
<b>13.</b>	<b>PRODUCT QUALITY COMPLAINT HANDLING .....</b>	<b>132</b>
13.1.	Procedures .....	132
13.2.	Contacting Sponsor Regarding Product Quality .....	133
<b>14.</b>	<b>STUDY DRUG INFORMATION .....</b>	<b>133</b>
14.1.	Physical Description of Study Drug .....	133
14.2.	Packaging .....	133
14.3.	Labeling .....	133
14.4.	Preparation, Handling, and Storage .....	133
14.5.	Drug Accountability .....	133
<b>15.</b>	<b>STUDY-SPECIFIC MATERIALS .....</b>	<b>134</b>
<b>16.</b>	<b>ETHICAL ASPECTS .....</b>	<b>135</b>
16.1.	Study-Specific Design Considerations .....	135

16.2.	Regulatory Ethics Compliance .....	136
16.2.1.	Investigator Responsibilities .....	136
16.2.2.	Independent Ethics Committee or Institutional Review Board .....	136
16.2.3.	Informed Consent .....	138
16.2.4.	Privacy of Personal Data .....	139
16.2.5.	Long-Term Retention of Samples for Additional Future Research .....	140
16.2.6.	Country Selection .....	140
<b>17.</b>	<b>ADMINISTRATIVE REQUIREMENTS .....</b>	<b>140</b>
17.1.	Protocol Amendments .....	140
17.2.	Regulatory Documentation .....	141
17.2.1.	Regulatory Approval/Notification .....	141
17.2.2.	Required Prestudy Documentation .....	141
17.3.	Subject Identification, Enrollment, and Screening Logs .....	142
17.4.	Source Documentation .....	142
17.5.	Case Report Form Completion .....	143
17.6.	Data Quality Assurance/Quality Control .....	143
17.7.	Record Retention .....	144
17.8.	Monitoring .....	144
17.9.	Study Completion/Termination .....	145
17.9.1.	Study Completion .....	145
17.9.2.	Study Termination .....	145
17.10.	On-Site Audits .....	145
17.11.	Use of Information and Publication .....	145
<b>REFERENCES</b> .....		<b>148</b>
<b>INVESTIGATOR AGREEMENT</b> .....		<b>163</b>

## LIST OF ATTACHMENTS

Attachment 1:	Anticipated Events .....	155
Attachment 2:	Adverse Events of Special Interest .....	156
Attachment 3:	Evaluation of Increased Liver Enzymes: .....	157
Attachment 4:	The Immunological Basis of Drug-Induced Liver Injury .....	160

## LIST OF IN-TEXT TABLES AND FIGURES

### TABLES

Table 1:	Staging Categories for Preclinical Alzheimer Disease Research .....	56
Table 2:	Volume of Blood to be Collected From Each Subject .....	93
Table 3:	Minimum Schedule for Follow-Up Blood Sampling and Contact with Medical Monitor .....	158

### FIGURES

Figure 1:	Progression to Clinical Dementia Rating Scale Score of At Least 0.5 - Symptomatic Alzheimer's Disease by Preclinical Alzheimer's Disease Stage .....	56
Figure 2:	Schematic Overview of Design for Study 54861911ALZ2003 .....	67
Figure 3:	Modeling of CSF A $\beta$ <sub>1-40</sub> Reduction (graph) and Population Predicted Percentiles of CSF A $\beta$ <sub>1-40</sub> Reduction at Steady State (table) in Subjects in the Early Alzheimer's Disease Spectrum (Preliminary Data from Study 54861911ALZ1005) .....	69
Figure 4:	Pharmacokinetic/Pharmacodynamic Modeling of QTcF Prolongation Based on Expected Exposures and Observed QTcF Values from Study 54861911ALZ1007 .....	70
Figure 5:	Screening Steps .....	94

## PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	28 Apr 2015
Amendment 1	26 Jun 2015
Amendment 2	21 July 2015
Amendment 3	02 Mar 2016
Amendment 4	24 Mar 2017
Amendment 5	19 Dec 2017
Amendment 6	25 May 2018

Amendments below are listed beginning with the most recent amendment.

### **Amendment 6** (25 May 2018)

**The overall reason for the amendment:** 1) Cessation of screening, randomization, and dosing, 2) JNJ-54861911 changed to atabecestat, and 3) other minor editorial updates.

Applicable Section(s)	Description of Change(s)
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**Rationale:** Frequent hepatic enzyme elevations have been observed in subjects receiving JNJ-54861911 (atabecestat). After a thorough evaluation of all available hepatic safety data and in consultation with external experts, the sponsor has concluded that the benefit-risk is no longer favorable to continue development of atabecestat in individuals with preclinical sporadic Alzheimer's disease (AD). The sponsor requested on 17 May 2018 that study sites permanently stop all screening, randomization, and dosing with atabecestat immediately in Study 54861911ALZ2003.

Synopsis; Section 1.1 Result of Permanent Cessation of Screening, Randomization, and Dosing of Atabecestat	A description of cessation of screening, randomization, and dosing of atabecestat has been added. It was noted that subjects will be followed for approximately 3 to 6 months from cessation of dosing.
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**Rationale:** Drug name now available for JNJ-54861911.

Throughout the document	JNJ-54861911 changed to atabecestat globally with the exception of the title of the study and previous protocol amendment summaries.
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**Rationale:** Minor errors were noted.

Throughout the protocol	Minor grammatical, formatting, and spelling changes were made.
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### **Amendment 5** (19 December 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:** 1) To add an additional blood draw in an optional substudy to characterize the T-cell response to study drug as a possible mechanism of drug-induced hepatic enzyme elevation. This substudy will be conducted in a limited set of subjects who experienced hepatic enzyme elevations. 2) To update and clarify 2 exclusion criteria, 3) To broaden criteria for medical professional permitted to perform skin examination, 4) To add the definition of the primary estimand to reflect the recent draft International Conference on Harmonisation (ICH) E9 addendum and the feedback received from health authorities, and 5) Other minor clarifications.

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> To remove unaligned protocol text relating to the definition of intent-to-treat, and include additional clarification on the populations and the analysis of the primary estimand.	
Synopsis; Section 11.3.1 Analysis of the Primary Endpoint	The definition of intent-to-treat set was updated to include all randomized subjects. Components of the primary estimand were added consistent with the draft ICH E9 addendum. A clarification of which posttreatment observations will be included in the primary analysis, depending on treatment discontinuation reason, was added.
<b>Rationale:</b> A footnote was clarified to ensure sites understand that oral dosing (self-administration) at the site is only done on the visits with check boxes and not on all visits.	
Time and Events Schedule- Double-Blind Treatment and Follow-Up Phases	“During scheduled visits” was updated to “At visits specified in the table”.
<b>Rationale:</b> Some subjects with elevated hepatic enzymes will be asked to provide an additional blood sample in an optional substudy. T-cells will be isolated from this blood specimen and tested to determine whether immune based mechanisms may be a cause of the elevation of hepatic enzymes.	
Time and Events Schedule- Double-Blind Treatment and Follow-Up Phases; 3.2.6 Biomarkers; 3.2.6.2 Fluid Biomarkers (Other than CSR Aβ for Screening); 9.4.1.2 Plasma Biomarkers; 9.10 Sample Collection and Handling; Attachment 3; Attachment 4	Text was added to Section 3.2.6.2 regarding additional blood draws for subjects in an optional immunologic substudy to characterize the T-cell response in subjects who experienced hepatic enzyme elevations. Cross references were added in the other protocol sections referring to Section 3.2.6.2. A new attachment was added (Attachment 4) to describe the proposed immunological basis of drug-induced liver injury.
<b>Rationale:</b> Updated for accuracy.	
1.3 Background Information on JNJ-54861911	Multidrug and toxin extrusion protein 2 (MATE-2) was updated to MATE-2K.
<b>Rationale:</b> The level of elevation of ULN was updated for consistency with the rest of the protocol.	
3.2.7 Safety Evaluations	Monitoring cases for elevated liver enzymes was updated from > to $\geq 3 \times$ ULN (ie, the “greater than” symbol was changed to the “greater than or equal to” symbol).
<b>Rationale:</b> To clarify that all cases of vitiligo are excluded. Other small, stable hypopigmented lesions may be allowed. Vitiligo tends to progress and it may be difficult to differentiate study drug effects from progression of vitiligo even if lesions are small at baseline.	
4.2 Exclusion Criteria	Exclusion Criterion 14 was updated to indicate that small localized lesions other than vitiligo are allowed in the study.

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Applicable Section(s) Description of Change(s)

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**Rationale:** Based on Goldenberg et al. 2006<sup>41</sup>, a prolonged QTc for males is >450 msec and for females >470 msec.

**TABLE 2**  
Suggested Bazett-Corrected QTc Values for Diagnosing QT Prolongation

Rating	1–15 years (msec)	Adult Male (msec)	Adult Female (msec)
Normal	<440	<430	<450
Borderline	440–460	430–450	450–470
Prolonged	>460	>450	>470

We have been excluding males and females with QTc >450msec. Since females have higher average QTc than males, we are excluding borderline and prolonged female cases rather than just prolonged. There is no rationale for this differential entry criteria for females than males.

We have evidence from a thorough QT study that 50 mg JNJ-54861911 produces only a small and nonsignificant (per ICH E14 guidelines) increase in QTc (6.6 msec [90% CI: 4.02, 9.12]). Currently the maximum dose in this study is 25 mg and modeled data from the TQT study suggested lack of significant increase in QTc. Therefore, there should be no safety consequence to allowing females with borderline QTc to participate in this study. With respect to attributing any treatment-emergent QTc prolongation to JNJ-54861911 versus baseline prolonged QT syndrome, we need to use equivalent cut-offs for females as males to ensure our analyses are consistent.

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Synopsis; 4.2 Exclusion Criteria	Exclusion Criterion 17 was updated to increase the threshold of QTcF to 470 msec in females (instead of 450 msec in both females and males). A summary of the major exclusions in the synopsis was updated to align with the change in Exclusion Criterion 17.
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**Rationale:** Based on Goldenberg et al. 2006<sup>41</sup>, a prolonged QTc for males is >450 msec and for females >470 msec. The analysis of QTcF interval was updated to align with the revised criterion for male and female QTcF interval as noted above.

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11.10 Safety Analyses	Description of the statistics of the QTcF interval was updated to include different summary ranges for males and females.
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**Rationale:** Table 2 was updated to include the optional immunologic sample added to the study.

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9.1.1 Overview Table 2	An additional sample was added for peripheral blood mononuclear cells (PBMC) sampling for immunology.
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**Rationale:** The footnote was updated to match the schedule of assessments and to help clarify that this is not the same subset that will be in the optional immunologic substudy.

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9.1.1 Overview Table 2	Footnote c was updated from “only for subset of subjects who participate in PBMC sampling” to “only at sites capable of processing PBMC samples”.
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**Rationale:** The timing of the results of the magnetic resonance imaging (MRI) was clarified to ensure the results were available and reviewed prior to subjects undergoing amyloid testing. This will help avoid premature communication of amyloid status in patients who cannot participate due to MRI findings, a potential ethical concern.

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Synopsis; 9.1.2 Screening Phase; Time and Events Schedule-Screening Phase	Text was updated stating that the MRI results must be available and reviewed prior to amyloid testing. Figure 5 (and replicated figure in the synopsis) for the screening steps was also updated to align with the change in text from a bidirectional to a unidirectional arrow between Step III and Step IV. The sentence and footnote pertaining to the amyloid disclosure visit was updated to remove the option for it to be performed prior to Step III assessments.
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Applicable Section(s)	Description of Change(s)
	<b>Rationale:</b> To eliminate further amyloid-positive screen failures due to skin findings identified after amyloid status (ie, melanoma, vitiligo). Similar to MRI, some patients are having amyloid status communicated only to later screen fail due to skin findings, leading to potential ethical concerns.
Time and Event Schedule - Screening Phase;	A footnote was updated to clarify the dermatology examination should preferably be done before Step III, but must be performed before amyloid testing (Step IV), rather than at any time during screening.
	<b>Rationale:</b> Clarification was added to provide a definition of “dermatologist” for the sites.
9.1.2 Screening Phase	The following definition of dermatologist was added: Medical Doctor/Doctor of Osteopathic Medicine dermatology specialist or a non-physician medical specialist such as an advanced practice nurse with extensive clinical experience in dermatology, certified to conduct independent dermatological examinations, and approved by the sponsor’s medical monitor.
	<b>Rationale:</b> Updated for consistency in the protocol.
Time and Event Schedule - Screening Phase; Time and Events Schedule- Double-Blind Treatment and Follow-Up Phases; 9.9.5 Dermatological Examination	A cross-reference to Section 9.1.2 was added to align with the updated definition of dermatologist.
	<b>Rationale:</b> To add clarity for the sites for what constitutes a subjects’ history.
9.1.2 Screening Phase	Examples of information to gather for subject history was added, as well as requesting this be done prior to other study activities.
	<b>Rationale:</b> To allow flexibility on the timing of the analyses in case of any delays during the analysis.
Synopsis; 11.4.3. Unblinded Interim Analyses to Assess Futility	The words “at least” were added prior to “60 subjects” and “168 subjects” in reference to the timing of interim analyses (IA).
	<b>Rationale:</b> The CSF IA may not be needed if the long-term CSF data from other sources demonstrates continued robust pharmacodynamic effects of JNJ-54861911 at 12 months or more.
Synopsis	“Will” was updated to “may” in regard to an unblinded IA being performed on CSF A $\beta$ <sub>1-40</sub> .
	<b>Rationale:</b> Personnel change at the sponsor company (ie, at Janssen Research and Development).
Investigator Agreement	The name of the sponsor’s responsible medical officer was updated.
	<b>Rationale:</b> Minor errors were noted.
Throughout the protocol	Minor grammatical, formatting, and spelling changes were made.

**Amendment 4** (24 March 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, to remove previously prohibited concomitant medications, to remove the stated-choice preference study, to update the frequency of the Alzheimer's Disease Cooperative Study - Activities of Daily Living-Prevention Instrument (ADCS-ADL-PI), Cognitive Function Index-acute (CFI-a), and Columbia Suicide Severity Rating Scale's administration, to provide additional information on adverse events of special interest (AESI), and to provide new guidelines for rescreening subjects.

Applicable Section(s)	Description of Change(s)
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	<p><b>Rationale:</b> The results of clinical drug-drug interaction (DDI) study 54861911ALZ1012 showed no clinically significant DDI between JNJ-54861911 at a dose of 25 mg and the substrates of the transporters breast cancer resistance protein (BCRP), multidrug and toxin extrusion protein 1 (MATE1), multidrug and toxin extrusion protein 2-K (MATE-2K), and organic cation transporter 2 (OCT-2). As a result, no specific precaution in relation to the exposure needs to be taken when co-administering JNJ-54861911 with substrates of the transporters BCRP, MATE1, MATE-2K, and OCT-2.</p>
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Abbreviations;	Additional text describing the DDI study and its clinical relevance was added.
1.3 Background Information on JNJ-54861911;	The prohibited concomitant medications were removed in the text and the corresponding attachment of known substrates was removed.
3.2.2 Study Population;	
8 Prestudy and Concomitant Therapy;	
Attachment 1 List of Known Substrates for Transporters	

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> The stated-choice preference study was removed to reduce subject burden.	
Synopsis; Time and Event Schedule - Screening Phase; 2.1 Objectives; 3.2.9 Medical Resource Utilization and Health Outcomes; 9.1.2 Screening Phase; 9.8 Medical Resource Utilization and Health Outcomes; 9.8.4 Stated-Choice Preference Study; 11.9 Medical Resource Utilization and Health Outcome Analyses; 15 Study-Specific Materials; References	The stated-choice preference study was removed from the protocol.
<b>Rationale:</b> Per FDA's August 2012 Draft Guidance for Industry, suicidal ideation and behavior assessments should be performed at all planned visits during which other clinical assessments are to be carried out.	
Time and Events Schedule- Double-Blind Treatment and Follow-Up Phases; 9.5.8 Columbia Suicide Severity Rating Scale	Columbia Suicide Severity Rating Scale (C-SSRS) assessments were added to week 2, Month (M)1+2 weeks, M2, M2+2 weeks, M4, M5, M8, and M10 visits during the double-blind treatment phase. Language updated to clarify the C-SSRS assessments will occur once during screening and at each visit during the double-blind phase.
<b>Rationale:</b> A new safety report of drug-induced hepatotoxicity for JNJ-54861911 was identified.	
Time and Events Schedule- Double-Blind Treatment and Follow-Up Phases; 1.3 Background Information on JNJ-54861911; 3.2.7 Safety Evaluations; 9.1.1 Overview; 9.1.3 Double-blind Treatment Phase; 10.2 Discontinuation of Study Treatment	Additional safety labs (hematology and chemistry) are to be drawn approximately 2 weeks after randomization, approximately 2 weeks after the Month 1 visit and approximately 2 weeks after the Month 2 visit. Therefore, visits Week 2, Month 1+2 weeks, and Month 2+2 weeks were added to the Time and Events Schedule-Double-Blind Treatment and Follow-Up Phases. Columbia Suicide Severity Rating Scale assessments were also added to these new visits to be consistent with the FDA's August 2012 Draft Guidance for Industry. Additional background information was added for the recent clinical cases with elevations in liver enzymes. A statement was added to Section 3.2.7 to mention the additional monitoring for elevated liver enzymes. Description of the visit timing was updated in Section 9.1.1 and Section 9.1.3. The volume of blood collected was updated to account for the increased blood sampling in Section 9.1.1. Section 10.2 was updated to have discontinuation of study treatment rules separated for the first 3 months, and after 3 months of treatment.

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> Text updated for clarity.	
Synopsis; 11.3.1 Analysis of the Primary Endpoint	The use of Wald statistics was removed and was replaced with appropriate contrasts based on the mixed effect model for repeated measurement (MMRM).
<b>Rationale:</b> The frequency of administration of the CFI-a and the ADCS-ADL-PI have been increased to address FDA's point that annual collection of data may be insufficient to capture significant changes that may occur between visits.	
Time and Events Schedule- Double-Blind Treatment and Follow-Up Phases	The frequency of administration of ADCS-ADL-PI and CFI-a was increased, such that they both are administered every 3 months during the double-blind period.
<b>Rationale:</b> An additional exploratory biomarker was added.	
3.2.6.2 Fluid Biomarkers (Other than CSF A $\beta$ for Screening)	Neurofilament light chains (NFLs) were added to the list of biomarkers.
<b>Rationale:</b> Additional information on AESIs were added for clarity.	
3.2.7 Safety Evaluation; 12.3.1 All Adverse Events; 12.3.3 Adverse Events of Special Interest; Attachment 2	Additional information on AESIs was added for lightening of skin, lightening of hair, and ophthalmological adverse events (AEs).
<b>Rationale:</b> A sentence was deleted describing the order of assessments being detailed in a separate manual, as there is no separate manual.	
3.2.5 Cognitive and Functional Outcome Measures	The following sentence was deleted "Additional details of the various cognitive tests and functional outcome measures, versions and alternate forms, and their sequence of performance are described in a separate manual."
<b>Rationale:</b> A word was updated as the criteria is mandatory.	
Synopsis; 4 Subject Population	The word "should" was changed to "must" in the following sentence: "To be considered for screening, subjects <del>should</del> <b>must</b> meet the following criteria: <ul style="list-style-type: none"> <li>Subjects 60 to 64 years of age must have 1 of the following additional key risk factors: a previously known APOE <math>\epsilon</math>4 genotype, a positive family history for dementia (minimum of 1 first degree relative), or a previously known biomarker status demonstrating elevated amyloid accumulation in CSF or by PET.</li> <li>For subjects 65 years of age or older, age is a sufficient risk factor to be considered for screening."</li> </ul>
<b>Rationale:</b> Occasional use of cannabinoids may not be contraindicated for the study.	
4.2 Exclusion Criteria; 9.9.6 Clinical Laboratory Tests	Cannabinoids were removed Exclusion criterion 25, and subsequently from the required drug screen.

Applicable Section(s)	Description of Change(s)
	<b>Rationale:</b> A reference to a drug packaging/blister card was added as a tool for treatment compliance, as this was not described previously in the protocol.
7 Treatment Compliance	A reference to a drug packaging/blister card was added.
	<b>Rationale:</b> A definition of overdose was added, based on doses exceeding the existing experience with the compound from Phase 1.
7 Treatment Compliance	Overdose was described in more detail adding in the number of tablets per day, and per month that would be considered a potential overdose. A rationale for the number of tablets chosen was also added.
	<b>Rationale:</b> No separate manual is being used in this study so it was removed and updated.
9.1.1 Overview	Language was updated from “separate manual” to “site training” and details on the information provided in the separate manual was deleted.
	<b>Rationale:</b> An MRI read before amyloid testing would prevent amyloid-positive subjects from eventually not being randomized because of MRI. Amyloid testing/disclosure for subjects that will not be allowed to participate in the study for other reasons (eg. pathologic MRI) should be prevented.
Screening; 9.1.2 Screening Phase	A statement that it is preferred that the investigator review the magnetic resonance imaging (MRI) results before the subject undergoes amyloid testing.
	<b>Rationale:</b> Updates were made to clarify the dermatological examination.
Time and Events Schedule-Screening Phase;	It was clarified that the examination is performed by a dermatologist and photographs are collected by the dermatologist or assigned designee in Section 9.1.2, and the Time and Events Schedule-Screening Phase.
Time and Events Schedule-Double-Blind Treatment and Follow-Up Phases;	The bolded words were added to Section 9.9.5 “Whenever a skin lesion not previously documented is reported by the study subject, informant, investigator, or study personnel, <b>and if deemed medically relevant, subject should undergo a dermatologic exam by a dermatologist. In addition,</b> digital images of the lesion will be acquired <b>by the dermatologist or qualified designee</b> at the time the lesion is discovered and at follow-up visits with a frequency which is deemed appropriate by the sponsor. <b>As skin lesions may be temporary, the site personnel may consider documenting immediately at site with a photograph in addition to referring the subject to the dermatologist.</b> ”
9.1.2 Screening Phase;	
9.9.5 Dermatological Examination	A corresponding footnote was added to the Time and Events Schedule-Double-Blind Treatment and Follow-Up Phases.
	<b>Rationale:</b> Rescreening criteria were added to allow more flexibility for those who were screen failures yet remain likely to qualify for study enrollment.
9.1.2 Screening Phase	Conditions were added to describe in what cases a screen failed subject can be rescreened.
	<b>Rationale:</b> The Time and Events Schedule-Screening Phase was updated to correct errors and to ensure consistency with other updates throughout the protocol.
Time and Events Schedule-Screening Phase	Added a footnote for informed consent: “The Informant should sign an ICF or equivalent document prior to completing any study procedures. Added “and photography” to the dermatological examination in the table and added “performed by a dermatologist with photography (taken by dermatologist or qualified designee)” to the footnote. Footnote “I” was removed from the Financial Capacity Instrument (FCI) as this footnote was not applicable to FCI.

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> The timing of the Cognitive Function Index (CFI), CFI-a, and ADCS-ADL-PI was updated as these assessments were erroneously moved in Amendment 3.	
Time and Events Schedule-Screening Phase; 9.1.2 Screening Phase	CFI, CFI-a, and ADCS-ADL-PI assessments were moved from the “Amyloid Status Disclosure Conversation Visit” column to the “Baseline Cognitive Measures” column, and the text in Section 9.1.2 was updated to match the Time and Events Schedule-Screening Phase.
<b>Rationale:</b> The Time and Events Schedule-Double-Blind Treatment and Follow-up Phases was updated to correct errors and to ensure consistency with other updates throughout the protocol.	
Time and Events Schedule- Double-Blind Treatment and Follow-Up Phases	Added “and photography” to the row title for Dermatological Examination in the table. Additional detail was added to the footnote “h”. The footnote letter for Amsterdam IADL questionnaire (A-IADL-Q) (informant) was corrected. The footnote order was corrected for amyloid positron emission tomography (PET) and tau PET. Additional information was added to the amyloid PET footnote to take into account local rules or regulations. Footnote “r” was reworded. Footnote “t” was removed.
<b>Rationale:</b> The fasting requirement was removed to reduce subject burden.	
Time and Events Schedule-Screening Phase; Time and Events Schedule- Double-Blind Treatment and Follow-Up Phases; 9.9.6 Clinical Laboratory Tests	The requirement for fasting before clinical laboratory tests was removed.
<b>Rationale:</b> An incorrect sentence was deleted.	
9.1.1 Overview	The following was deleted: “All visit-specific, patient-reported outcome assessments should be performed before any tests (including cognitive tests), procedures, or other consultations for that visit to prevent influencing subject perceptions.”
<b>Rationale:</b> Additional wording was added to ensure investigators are aware that the examinations during the double-blind treatment phase included a dermatologic examination.	
9.1.3 Double-blind Treatment Phase	Dermatologic examination was added for clarity.
<b>Rationale:</b> Confirmation with the medical monitor was added to ensure subjects’ treatment is not interrupted for non-significant events.	
Synopsis; 9.1.3 Double-blind Treatment Phase	A sentence was updated with the text in bold “Interruption of treatment should be limited to significant events, <b>and confirmed with the medical monitor</b> ”.

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> Assessment for cognitive functional ability is not planned for posttreatment phase. The telephone contact location was moved from posttreatment procedures to long-term extension as it only relates to subjects not participating in the long-term extension study.	
9.1.4 Posttreatment Phase (Follow-Up); 9.1.5 Long-Term Extension Study	Text regarding telephone contact was moved and updated from Section 9.1.4 to Section 9.1.5. Section 9.1.5 heading changed from Long-Term Extension to Long-Term Extension Study. Cognitive functional ability was removed.
<b>Rationale:</b> The previous description was for a different version of the ADCS-ADL-PI.	
9.2.2.2.3 ADCS Activities of Daily Living – Prevention Instrument	The description of the ADCS-ADL-PI was updated.
<b>Rationale:</b> Text not deleted during a previous amendment has now been deleted, as it was not applicable in the updated context.	
9.4.1.1 CSF Biomarkers	The following was deleted “and safety information, including glucose levels, and cell counts.”
<b>Rationale:</b> Additional text adds flexibility with amyloid PET scan internal protocols across countries.	
9.4.2.1 Amyloid Positron Emission Tomography Substudy	Language was added to allow for the effect of local regulations on PET scans and the priority of the Month 24 scan.
<b>Rationale:</b> Additional text clarifies MRI reports for investigators.	
9.4.2.3 Magnetic Resonance Imaging	Additional text was added to describe the process in the event of an MRI report indicating “not eligible” or “for further consultation”.
<b>Rationale:</b> The Behavioral Pattern Separation Object Task was deleted as it will not be used in this study.	
9.5.9 Computerized Cognitive Battery	The Behavioral Pattern Separation Object Task and its description were removed.
<b>Rationale:</b> Additional text was added for the management of increased liver enzymes to guide investigators and ensure subject safety.	
9.9.6 Clinical Laboratory Tests	The following text was added: “The investigator’s review of laboratory results should address the exclusion criteria, particularly criterion 18. The investigator should use clinical judgment and provide documented evidence when deemed necessary by the medical monitoring team that the subject does not have “ongoing hepatic, renal, cardiac, vascular, pulmonary, gastrointestinal, endocrine, hematologic, rheumatologic, psychiatric, or metabolic conditions” that are significant in the clinical trial setting. Abnormal laboratory results may be repeated to rule out worsening abnormalities and, in consultation with the sponsor’s medical monitor, to establish subject eligibility prior to amyloid testing. In the case of hepatic enzyme elevations, attempts should be made to establish an etiology of an underlying condition and demonstrate normalization. The sponsor’s medical monitor may request additional evaluation (see Attachment 3).”
<b>Rationale:</b> Clarifications were made to the presentation of Section 10.2.	
10.2 Discontinuation of Study Treatment	Reporting instructions were added. Updated “liver function tests” to “liver enzymes”. Bullet points were rearranged and additional text was added to clarify that re-initiation is related to QT interval not liver enzymes, and to reference Attachment 3 for liver enzymes.

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> Reporting requirements should not have been presented in the statistical analysis section.	
11.10 Safety Analyses	A subheading was added for Adverse Events of Special Interest. The sentence regarding reporting was removed.
<b>Rationale:</b> Text updated to reflect change from hierarchical hypothesis testing procedure to gatekeeping strategy.	
Synopsis; Section 2.2 Hypotheses; 11.3.1 Analysis of the Primary Endpoint	The hypothesis was updated from using language “the high dose regimen” to “either dose regimen”.
<b>Rationale:</b> Text revised to clarify that all randomized subjects are included in primary efficacy analysis set.	
Synopsis; 11.3.1 Analysis of the Primary Endpoint; 11.3.2 Analysis of the Secondary Endpoints	The analysis population was updated from a “modified intent-to-treat population” to “intent-to-treat analysis set.”
<b>Rationale:</b> The description of the statistical analyses for CFI-a was moved, as it is not medical resource utilization.	
Synopsis; 11.9 Medical Resource Utilization, and Health Outcomes and Stated-Choice Preferences Analyses; 11.3.2 Analysis of the Secondary Endpoints	The description of the statistical analyses for CFI-a was moved from Medical Resource Utilization and Health Outcome Analyses (Section 11.9) into the section describing secondary endpoints (Section 11.3.2).
<b>Rationale:</b> A subsection on Adverse Drug Reactions (ADRs) was added to ensure the information on elevated liver enzymes was easy to find.	
12.3.4 Adverse Drug Reactions	A subsection for ADRs was added.
<b>Rationale:</b> Prohibition 3 related to alcohol consumption was removed, as it would be hard to ensure subjects follow this criterion and doing so will not adversely affect the quality of the study or the safety of the subjects.	
4.3 Prohibitions and Restrictions	Prohibition 3 was removed.
<b>Rationale:</b> Text was updated to ensure consistency within the protocol.	
9.1.2 Screening Phase; 9.1.1 Overview; 9.1.3 Double-blind Treatment Phase	The following was updated for consistency with the language in the rest of the protocol: “up to 90 days” was replaced with “approximately 90 days” in Section 9.1.2, and the word “about” was updated to “approximately” in Section 9.1.1 and Section 9.1.3.
<b>Rationale:</b> The text was updated to match the Time and Events Schedule.	
9.1.3 Double-blind Treatment Phase	The description of regular visit intervals was updated to match the Time and Events Schedule.



Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> Subsection was moved up so that the description of CFI-a followed immediately after the description of CFI.	
9.5.10 Cognitive Function Index-acute; 9.2.2.2.2 Cognitive Function Index-acute	Previous Section 9.5.10 was moved to become Section <a href="#">9.2.2.2.2</a> .
<b>Rationale:</b> The protocol text was updated for consistency with the Time and Events Schedule.	
9.8.1 Healthcare Resource Utilization Questionnaire	The word “all” was removed and updated to “specified” in the statement “at all visits during the double-blind treatment phase...”
<b>Rationale:</b> To clarify that reporting also applies to AESIs.	
9.9.1 Adverse Events	The phrase “including AESI” was added.
<b>Rationale:</b> An attachment was added to describe the evaluation of increased liver enzymes and the procedures that the investigator should follow.	
Attachment 3	Detailed description of the procedures the investigator should follow when alanine aminotransferase (ALT) or AST are $\geq 3 \times \text{ULN}$ .
<b>Rationale:</b> The term substudy was removed for instances other than the amyloid PET for clarity.	
3.2.8 Pharmacokinetic Evaluations; 9.1.3 Double-blind Treatment Phase; 9.4.1.1 CSF Biomarkers	Removed “substudy” and reworded the sentences appropriately.
<b>Rationale:</b> Added a sentence to clarify that some amyloid PET scans are part of a substudy.	
9.4.2.1 Amyloid Positron Emission Tomography Substudy	Added the following sentence: “Amyloid PET scans will be collected for amyloid screening as well as longitudinally from the subset of subjects with baseline/screening amyloid PET scans.”
<b>Rationale:</b> Text revised to reflect updated sample sizes for biomarker interim analyses with justification based on futility criteria. Relocated to Interim Analysis (IA) section because justification is directly related to the IAs.	
Synopsis; 11.2.2 Amyloid Positron Emission Tomography; 11.2.3 Cerebrospinal Fluid; 11.2.4 Tau Positron Emission Tomography; 11.4.3 Unblinded Interim Analyses to Assess Futility	The description of sample size determination for potential IAs and sample size determination for maintenance of pharmacodynamics effect was removed from the Synopsis as the corresponding text was consolidated and moved in the main text. The subsections for amyloid PET, CSF, and tau PET were removed, the text was updated, consolidated and moved to Section <a href="#">11.4.3</a> .

Applicable Section(s)	Description of Change(s)
	<b>Rationale:</b> Multiple comparison procedure changed from hierarchical procedure to gatekeeping strategy to lessen reliance on a dose-response assumption and allow testing on key secondary efficacy endpoint if only 1 dose is superior to placebo on the primary efficacy endpoint.
Synopsis; 11.3.3 Multiple Comparison Adjustment	The multiple comparison adjustment was updated.
	<b>Rationale:</b> The text was corrected, as it was not accurately correlated to the Time and Events schedule for the study -- the PACC assessment is not conducted at Month 39 (ie, at 3.25 years), but is conducted at Month 42 (ie, at 3.5 years).
Synopsis; 3.2.4 Study Duration; 11.4.2 Potential Design Modifications Based on External Data	In the text describing a potential change to the timing of the primary endpoint (based on interim data analyses of emerging external data) 3.25 years was corrected to 3.5 years.
	<b>Rationale:</b> Amyloid-beta (A $\beta$ ) <sub>1-40</sub> futility decision will be based on CSF result only, not plasma.
11.4.3 Unblinded Interim Analyses to Assess Futility	Removed “and plasma.”
	<b>Rationale:</b> The analytical parameters for MRI have been updated to reflect the best available technology.
11.7 Biomarker Analyses	The parameters of key interest for MRI were updated.
	<b>Rationale:</b> AESI were added into the protocol, which have special reporting requirements.
12.2 Special Reporting Situations	AESI were added.
	<b>Rationale:</b> A clarification was added to the Amendment 3 Description of Changes that the pharmacokinetic (PK) sample at the ET visit was removed from the Time and Events Schedule, as it was not written in detail before.
Amendment 3	The following bolded sentence was added to the Description of Changes for Amendment 3 under the Rationale: “The Time and Events Schedule was updated to correct errors and avoid confusion at the clinical trial sites.” <b>The PK sample at the ET visit was removed.</b>
	<b>Rationale:</b> Additional detail was added for clarity as to which test is being referenced.
15 Study-Specific Materials	PET Imaging was updated to Amyloid PET, and Tau Imaging was updated to tau PET.
	<b>Rationale:</b> Subject diaries are not being provided by the sponsor.
15 Study-Specific Materials	Subject medication diary was removed.
	<b>Rationale:</b> The list of anticipated events was updated after an analysis of anticipated events in the target population.
Attachment 1	“Fractures associated with falls”, and “Falls” were added to the list of anticipated events.
	<b>Rationale:</b> A clause was added to the attachment to be consistent with the body of the protocol.
Attachment 1	The clause “if allowed by local practice/regulations” was added to the sentence regarding expedited reporting.

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Applicable Section(s)	Description of Change(s)
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**Rationale:** Minor errors were noted.

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Throughout the protocol	Minor grammatical, formatting, and spelling changes were made.
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**Amendment 3** (02 March 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, to add additional scales to the study, and other required changes which were relevant to the study.

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Applicable Section(s)	Description of Change(s)
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**Rationale:** A stated-choice preference study was added as an exploratory measure to analyze subjects' willingness to accept tradeoffs between treatment-related benefits and potential adverse events. The purpose is to understand the subjects' perspective on benefits and risks.

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Synopsis; Time and Event Schedule - Screening Phase; 2.1 Objectives; 3.2.9 Medical Resource Utilization and Health Outcomes; 9.1.2 Screening Phase; 9.1.3 Double-Blind Treatment Phase; 9.8 Medical Resource Utilization and Health Outcomes; 9.8.4 Stated-Choice Preference Study; 11.9 Medical Resource Utilization/Health Outcome Analysis; 15 Study-Specific Materials, References	A stated-choice preference study was added and described in Section 9.8.4 in detail, as well as updated in all other appropriate sections.
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Applicable Section(s)	Description of Change(s)
	<p><b>Rationale:</b> A new safety signal for potential liver injury has been identified and is under investigation. There seems to be a possible dose-relationship and it is desirable to increase the likelihood of a clean dose in the trial. The latest modelling data based on patients in the ALZ1005 trial provides a narrower spread of the distribution of the A<math>\beta</math> lowering than before, which makes 5 mg still a suitable dose from an efficacy point of view (median decrease 52%, 95% percentiles 27% to 72%).</p>
Synopsis; 3.1 Overview of Study Design; 6 Dosage and Administration; Throughout the protocol	References to the 10-mg dose were removed and replaced with the updated 5-mg dose. Additionally, the dose reduction alters the treatment group regimens: Treatment group 1 will receive only one 5-mg tablet instead of two 5-mg tablets; Treatment group 2 will receive only one 25-mg tablet instead of a 25-mg tablet and a matching placebo, and Treatment group 3 will receive only 1 matching placebo instead of 2 placebo tablets.
	<p><b>Rationale:</b> Based on the dose reduction from 10 mg to 5 mg, <a href="#">Figure 3</a> was updated to highlight the 5 mg column, and the text was updated to match the figure.</p>
3.2.3 Dose Selection (Figure 3)	Adjustments were made to the text and to the figure on the expected reduction in CSF A $\beta$ based on the dose reduction.
	<p><b>Rationale:</b> A correction was made regarding blood sampling timing. Additionally, the placement of this paragraph was updated for better readability.</p>
9.1.2 Screening Phase	“In Step IV” was deleted and replaced with “during screening” in the following sentence: “ <b>The</b> following blood samples will also be collected <b>during screening</b> ”, The paragraph was moved to later in Section 9.1.2 to be in general screening procedures instead of Step IV procedures.
	<p><b>Rationale:</b> Updates were made to the plasma biomarkers section to specify specific samples which were incorrectly written as being collected in screening, are actually collected at multiple time points in the study.</p>
9.4.1.2 Plasma Biomarkers	The descriptor “screening phase” was deleted from the text after “Time and Events Schedule” in reference to when venous blood samples and RNA blood sample are drawn.
	<p><b>Rationale:</b> A correction was made in the type of sample being collected during screening.</p>
9.4.1.2 Plasma Biomarkers	“PD/biomarker” was deleted and replaced with “platelet-rich” plasma sample. This is a correction in the type of sample being collected.
	<p><b>Rationale:</b> The text changed to give a range of the standard deviation and to add clarity to the assumptions.</p>
Synopsis; 11.2.1 Primary Cognitive Endpoint	Adjustments were made to the power calculation for the primary cognitive endpoint, and the paragraph re-written to add clarification on assumptions of power and attrition.
	<p><b>Rationale:</b> Clarification was made to the total number of enrolled subjects.</p>
Synopsis; 3.1 Overview of Study Design (Figure 2); 4 Subject Population; 11.2.1 Primary Cognitive Endpoint	The current number of subjects listed in the protocol was clarified to be a minimum number of subjects (1,650 subjects, 550/treatment arm), and a maximum number of subjects was added (2,400 subjects, 800/treatment arm).
	<p><b>Rationale:</b> Sentences were added to clarify the assumption for missing data.</p>
Synopsis; 11.3.1 Analysis of Primary Endpoint	Added sentences: All observed data will be included in the analysis. Missing-at-random is assumed for all missing data.

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> Random effects were modified for the analysis of primary and secondary endpoints.	
Synopsis; 11.3.1 Analysis of the Primary Endpoint; 11.3.2 Analysis of the Secondary Endpoints	Stratification factor center/region as a random effect was deleted. Country was added as a fixed effect for the model.
<b>Rationale:</b> The DMC will not be involved with blinded sample size adjustment, as the DMC may be privy to certain unblinded study data.	
Synopsis; 11.4.1 Blinded Sample Size Adjustments; 11.11 Data Monitoring Committee	The following sentence was deleted from the synopsis and Section 11.4.1 “An independent external DMC (see Section 11.11) will make recommendations on sample size adjustment per prespecified decision rules.” Reference to blinded sample size re-estimation was removed from Section 11.11.
<b>Rationale:</b> Three new in vitro p-glycoprotein (P-gp)/multidrug resistance protein 1 (MDR1) inhibition studies were conducted and the results are considered relevant to this clinical study.	
1.3 Background Information on JNJ-54861911	A short description of the 3 in vitro P-gp/MDR1 studies and their results were added into the background information.
<b>Rationale:</b> Because previous nonclinical in vitro data indicated that JNJ-54861911 might be an inhibitor of P-gp, and organic anion-transporting polypeptide 1B1 (OATP1B1) a conservative approach was taken by not permitting digoxin or dabigatran etexilate use during the trial. The new data shows there is no clinically relevant P-gp or OATP1B1 inhibition by JNJ-54861911.	
8 Prestudy and Concomitant Therapy; Attachment 1 List of Known Transporters	Digoxin, dabigatran etexilate, and procainamide were removed from the prohibited concomitant medications, and P-gp and OATP1B1 were removed from the list of transporters.

Applicable Section(s)	Description of Change(s)
	<b>Rationale:</b> A new cognitive function index measure (Cognitive Function Index-acute [CFI-a]) was added to assess cognitive function based on a shorter time scale than the CFI.
Synopsis; 2.1 Objectives; Time and Events Schedule; List of Abbreviations; 3.2.5 Cognitive and Functional Outcome Measures; 9.1.2 Screening Phase; 9.1.3 Double-blind Treatment Phase; 9.5.10 Cognitive Function Index- Acute; 11.9 Medical Resource Utilization, Health Outcomes and Stated-Choice Preferences Analyses; 15 Study-Specific Materials	An exploratory objective was added to evaluate the performance of the CFI-a scale in assessing decline of cognitive function and performance of everyday activities. The description of the scale was added to Section 9.5.10. References to the scale schedule were added throughout the protocol.
	<b>Rationale:</b> A statement was added in protocol and a list added as an attachment to define anticipated adverse events based upon updated FDA guidance. This is in effort to reduce the number of individual case safety reports reported in an expedited manner to the FDA. This is relevant to certain SAEs, that are pre-defined as likely to be manifestations of the underlying disease, commonly occurring in the study population independent of drug exposure, and for which there are few reasons to believe that the drug caused the event.
12.3.1 All Adverse Events; Attachment 2	The sentence “Anticipated adverse events may be recorded and reported based on local rules and regulations.” as well as a reference to an attachment was added within the protocol text. An attachment was added to describe in detail, the events considered anticipated adverse events, as well as their reporting procedures and requirements.
	<b>Rationale:</b> Language was added to allow for changes to the informed consent form, which would allow subjects, especially screen failures to be contacted again for future or other, more appropriate studies.
16.2.3 Informed Consent	Additional wording was added into the consent language regarding re-contacting subjects.
	<b>Rationale:</b> Language was added to state that a subject who has cognitive decline during the study can renew consent or assent in accordance with local law or guidance.
16.2.3 Informed Consent	Additional wording was added to the consent language regarding cognitive decline.
	<b>Rationale:</b> The error in the sentence was removed, and timing was clarified, as Step IV is not the amyloid disclosure visit.
Synopsis; 9.1.2 Screening Phase	The following sentence was corrected for clarity: “the amyloid disclosure visit ‘Step IV, elevated amyloid accumulation”, this was changed to “Step IV assessments”.

Applicable Section(s)	Description of Change(s)
	<b>Rationale:</b> Sentences were added to clarify the statistical analysis of the added instruments, CFI-a and the stated-choice preference study.
Synopsis; 11.9 Medical Resource Utilization, Health Outcomes and Stated-Choice Preferences Analyses	Sentences were added describing the analysis of the stated-choice preference study by summary statistics and regression modeling and the use of descriptive statistics and evaluation of the CFI-a ability to measure change over time for analysis of the data from the CFI-a..
	<b>Rationale:</b> In order to match the footnote which says PACC and RBANS, NAB-DLTs for Memory and Attention, and computerized cognitive battery can be done prior to Step IV procedures, the columns were merged for Steps I through III for these assessments within the table.
Time and Events Schedule-Screening Phase	Table cells were merged for PACC and RBANS, NAB-DLTs for Memory and Attention, and computerized cognitive battery for Screening steps I to III.
	<b>Rationale:</b> The Time and Events Schedule was updated to correct errors and avoid confusion at the clinical trial sites.
Time and Events Schedule-Screening Phase; Time and Events Schedule- Double-Blind Treatment and Follow-Up Phases	Blood sample collection (for <i>APOE</i> genotyping and pharmacogenomics analysis) time point was moved from Step IV to Step I. Table cells were merged for peripheral blood mononuclear cell sample collection in order to clarify that it can occur any time prior to amyloid disclosure. Fluid biomarkers blood collection was updated to “blood collection for plasma and gene expression (RNA). CSF collection was updated to add corresponding plasma sample. A footnote was added to correct the timing of the tau PET: “Tau PET to be performed after amyloid disclosure but before first drug intake at M0.” “subject and informant” was added to CDR to clarify who will complete these measures. Footnote d was moved from D1 of the double-blind treatment phase to the study procedure title to indicate all time points should be collected prior to dosing, not just the first collection. This was done for blood collection for PD markers and for gene expression (RNA), and for CSF collection and corresponding plasma collection. The PK sample at the ET visit was removed.
	<b>Rationale:</b> The amount of CSF was not previously disclosed, this update has specified that it is maximally 12mL, per individual lumbar puncture.
3.2.6 Biomarkers	Specification of maximally 12mL for the CSF collection was added.

Applicable Section(s)	Description of Change(s)
	<b>Rationale:</b> The Amsterdam instrumental activities of daily living Questionnaire (A-IADL-Q) was added to measure difficulties subjects have with complex daily activities. This test was added due to its good construct and content validity, its high internal consistency and high test-re-test reliability.
Synopsis; List of Abbreviations; Time and Events Schedule-Screening Phase; Time and Events Schedule- Double-Blind Treatment and Follow-Up Phases; 2.1 Objectives; 3.2.5 Cognitive and Functional Outcome Measures; 9.1 Study Procedures; 9.5 Additional Clinical Scales	An exploratory objective was added to explore the effect of JNJ-54861911 compared with placebo on instrumental activities of daily living (IADL) as measured by the A-IADL-Q. This scale was added and described in Section 9.5.11 in detail, as well as updated in all other appropriate sections.
	<b>Rationale:</b> A sentence regarding interim analysis (IA) was moved down a few paragraphs within the synopsis for better clarity as it is not related to blinded sample size increases.
Synopsis	The following sentence was moved: “An independent external statistical support group will perform the IAs. The external DMC will review the results of the IAs and make recommendations based on prespecified decision rules. All personnel involved in the conduct of the study will remain blinded throughout the study.”
	<b>Rationale:</b> Minor errors were noted.
Throughout the protocol	Minor grammatical, formatting, and spelling changes were made.
	<b>Rationale:</b> A sentence was added to clarify that the order of administration of procedures will be provided in a separate manual.
9.1.1 Overview	The following sentence was added: “Guidance on the order of administration of scales and procedures will be provided to the sites in a separate manual.”



Applicable Section(s)	Description of Change(s)
	<b>Rationale:</b> The word “and” was updated to “or” in order to clarify that the test will not need to be performed again depending on when the Early Termination (ET) visit occurs. In addition, a sentence was added to clarify that no subject will receive more than 3 amyloid positron emission tomography (PET) scans during the study.
9.4.2.1 Amyloid Positron Emission Tomography Substudy; 9.4.2.2 Tau Positron Emission Tomography Substudy; Time and Events Schedule-Screening Phase; Time and Events Schedule-Double-Blind Treatment and Follow-Up Phases	The word “and” was replaced with “or” in the following sentence: PET imaging for brain amyloid will be performed longitudinally at Months 0, 24, and 48 ( <b>and</b> at the ET visit, if applicable) in the subset of subjects who have a screening/baseline amyloid PET assessment. In addition, the following sentence was added: “Note, no subject will receive more than 3 amyloid PET scans during the study.” This note was also added as a footnote to the Time and Events Schedule.
	<b>Rationale:</b> The phrase “including screening samples” was added to clarify that due to the nature of this study samples from screening are retained.
16.2.5 Long-Term Retention of Samples for Additional Future Research	A sentence was updated to clarify the retention of samples included screening samples. “Samples collected ( <b>including screening samples</b> ) in this study may be stored for up to 15 years (or according to local regulations) for additional research.”
	<b>Rationale:</b> New abbreviations were introduced into the protocol with the addition of new scales and in vitro data.
Abbreviations	The “Abbreviations” section was updated to include the new terms for the in vitro data and scales.
	<b>Rationale:</b> Clarification and corrections were made to the description of the Cognitive Function Index (CFI).
9.2.2.2.1 Cognitive Function Index	Specification was added that out of the 15 questions, only 14 of those questions are scored.
	<b>Rationale:</b> Clarification was made to the EQ-5D that was being used.
Throughout the protocol	The designation “5L” was added after “EQ-5D” (EQ-5D-5L) in order to specify the version being used.
	<b>Rationale:</b> Section 11.4.4 was removed because the option to adapt the endpoint using the unblinded interim data will no longer be considered.
Synopsis; 3.1 Overview of Study Design; 11.4.4 Potential Unblinded Interim Analysis for Design Adaptations	Section 11.4.4 was removed from the text. References within the rest of the protocol to the unblinded interim analyses to optimize the primary endpoint, were removed.
	<b>Rationale:</b> To add consistency the term study partner was updated to informant.
Throughout the protocol	Throughout the protocol the term “study partner” and “informant” were both used. These terms were all updated to informant.

Applicable Section(s)	Description of Change(s)
	<b>Rationale:</b> The term “assay” was removed, the intention is to use a single laboratory, however there is a possibility that the planned assay could change over the course of the study.
3.2.6.1 Determination of Elevated Amyloid Accumulation at Screening	The words “assay and” were deleted from the following sentence “The use of a single assay and laboratory allows for the use of a single threshold and simplifies operational logistics.
	<b>Rationale:</b> A sentence was added to emphasize that dermatologic photography was a requirement of the study.
9.9.5 Dermatological Examination	The following sentence was modified, and a sentence added: “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.”
	<b>Rationale:</b> Updates were made to Table 2 to reflect the changes from the Time and Events Schedule.
9.1.1 Overview (Table 2)	Biomarker sample for plasma and gene expression (RNA) was added as 1, 10 mL sample due to the extra sample being collected at screening. The total blood volume was amended to reflect this change.
	<b>Rationale:</b> The use of ADCS-PACC was updated to PACC. Both versions of the PACC are composed of 4 measures that are weighted towards episodic memory and includes a timed executive function test and a global cognitive screening test. The PACC version used and described here, uses 3 alternate forms for each of the 4 elements and includes minor differences from the ADCS-PACC to allow optimal translation and cultural adaptation of items into multiple country-languages.
9.2.1 Primary Efficacy Measures: Preclinical Alzheimer Cognitive Composite; Synopsis (Figure); List of abbreviations; Throughout the protocol	References to ADCS-PACC were updated to PACC and the differences were described in Section 9.2.1. The figure in the synopsis and Figure 5 were updated to reflect the change from ADCS-PACC to PACC.
	<b>Rationale:</b> To add clarity to the protocol.
Synopsis; 3.1 Overview of Study Design; 3.2.1 Blinding, Control, Study Phase/Periods, Treatment Groups; 5 Treatment Allocation and Blinding	The randomization stratification was updated from study center/region to country.
	<b>Rationale:</b> The completion of 2 additional clinical studies impacted the potential safety profile of this study, therefore they have been added into the protocol background.
1.3 Background Information on JNJ-54861911; 1.4 Overall Rationale for the Study	Two additional clinical studies have been completed and added to the list, as well as the safety information updated according to the results of these studies.

Applicable Section(s)	Description of Change(s)
<b>Rationale:</b> A new safety signal for potential liver injury has been identified and is under investigation. Based on the currently available information extra visits to monitor liver function were added.	
Synopsis; Time and Events Schedule- Double-Blind Treatment and Follow-Up Phases	The number of monthly visits was increased from the first 3 months, to every month for months 1 to 6. Additionally, visits at 8 months and 10 months were added. Four additional visits were added to the time and events schedule for Month 4, Month 5, Month 8, and Month 10. At all of these visits, blood will be collected for hematology and chemistry. Additionally, safety labs (hematology and chemistry) will be collected every 3 months for the rest of the treatment duration, adding 11 safety labs to the time and events schedule. The visit numbers were updated to reflect these additions. A corresponding footnote was added to the time and events schedule and text within Section 9.1.1 to describe the timing of the visits.
<b>Rationale:</b> This level of detail was not included for the other evaluations within the protocol and was therefore removed for consistency.	
Time and Events Schedule- Double-Blind Treatment and Follow-Up Phases	The following footnote was deleted: “ADCS-PACC or RBANS versions at Early Termination visit should be the next version in the series as defined in the cognition manual.
<b>Rationale:</b> To align the table with the updated text within the protocol.	
9.1.1 Overview; Table 2	The maximum amount of blood drawn in the study was increased. Table 2 was updated to align with the additional biomarker sample for plasma and gene expression (RNA) added to the screening samples and the additional hematology and serum chemistry for Months 4, 5, 8, 10, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, and 51.
<b>Rationale:</b> A new safety signal for potential liver injury has been identified and is under investigation. Based on the available information, additional criteria for discontinuation and re-initiation were added for safety.	
10.2 Discontinuation of Study Treatment	An additional reason for discontinuation and re-initiation based on liver function tests was added. The added criteria are: <ul style="list-style-type: none"> <li>• A subject has 1 (or more) of the below described changes in liver function tests. <ul style="list-style-type: none"> <li>• ALT or AST &gt;8×ULN</li> <li>• ALT or AST &gt;5×ULN for more than 2 weeks</li> <li>• ALT or AST &gt;3×ULN and (total bilirubin &gt;2×ULN or INR&gt;1.5)</li> <li>• ALT or AST &gt;3×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (&gt;5%)</li> </ul> </li> </ul> Abnormal liver function tests greater than 3×ULN should be confirmed within 48 to 72 hours. 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.
<b>Rationale:</b> There will be no Type I adjustment for all futility IA.	
11.2.2 Amyloid Positron Emission Tomography; 11.2.3 Cerebrospinal Fluid; 11.2.4 Tau Positron Emission Tomography	The following sentence was added: “This IA sample size might be revised based on the evidence from emerging external research prior to the time of the IA.”

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Applicable Section(s)	Description of Change(s)
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**Rationale:** To add clarity to the protocol.

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11.4.1 Blinded Sample Size Adjustment	The following sentences were updated from: “Blinded interim aggregated study data will be used to estimate the variability of the endpoints. Sample size may be increased to account for increased variability as well as dropout rate.” to “Blinded interim aggregated study data and external data will be used to assess sample size. Sample size may also be increased to account for dropout rate”.
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**Rationale:** To add clarity to the protocol.

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11.4.1 Blinded Sample Size Adjustment; 11.4.2 Potential Design Modifications Based on External Data	The following sentence was added “Full details will be specified in the SAP.”
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**Rationale:** The characteristics of the biomarkers are not definite, and the use of external research data might be taken into account in the IA.

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11.4.3 Unblinded Interim Analyses to Assess Futility	The words “biomarker based” were deleted.
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**Rationale:** To align the description of the label to the updated dosing regimen.

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5 Treatment Allocation and Blinding	The following sentence was updated from “The label will not identify the study dose (0, 10, or 25 mg once daily) in the container.” to “The label will be blinded indicating possible tablets packaged as 5 mg, 25 mg, or placebo.”
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### **Amendment 2** (21 July 2015)

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 an additional adverse event of special interest to Section 11.10.

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Applicable Section(s)	Description of Change(s)
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**Rationale:** Ophthalmologic adverse events were added as adverse events of special interest.

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11.10 Safety Analyses	Per recommendation from the Voluntary Harmonisation Procedure, ophthalmologic adverse events were added to adverse events of special interest. These events will now be recorded and have expedited reporting.
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**Amendment 1** (26 June 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:** The overall reason for the amendment is to add a risk-benefit statement to Section 1.3, amend a secondary endpoint, and remove the listing of anticipated events.

Applicable Section(s)	Description of Change(s)
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**Rationale:** A risk-benefit evaluation of the study was added.

1.3. Overall Rationale	The sponsor's evaluation was added to inform the investigators about potential risks and benefits of JNJ-54861911.
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**Rationale:** One of the other secondary objectives, "To assess the effect of JNJ-54861911 compared with placebo on the Clinical Dementia Rating (CDR) scale," was clarified to include the statement, "including progression from CDR 0 to CDR 0.5 or higher."

Synopsis; 2.1. Objectives	Subjects must have a CDR scale score of 0 at baseline (an inclusion criterion). The new statement clarifies that progression to a CDR score $\geq 0.5$ will be assessed.
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**Rationale:** Attachment 2, "Anticipated Events," and a reference to it in the body of the protocol was removed.

13.3.1. All Adverse Events; Attachment 2	The list contained specific adverse events that were to be excluded from expedited reporting. These anticipated events will be recorded and will be subject to expedited reporting when appropriate.
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**Rationale:** "Should" was changed to "will" in the following statement: "A subject's study treatment **should** be discontinued if the investigator believes that for safety reasons (eg, AE) it is in the best interest of the subject, including for the following reason: QTcF interval of  $>500$  msec if confirmed upon repeat ECG [electrocardiogram], and/or QTcF increase versus baseline of  $>60$  msec if confirmed upon repeat ECG, after consultation with the sponsor's medical monitor."

10.2. Discontinuation of Study Treatment	Because the trial population consists of asymptomatic subjects, a more conservative approach was adopted, and discontinuation of study treatment (including prolongation of the QT interval) is now absolute.
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**Rationale:** A footnote was added to describe the Assessment of Psychological Well Being; lettering of the subsequent footnotes was updated.

Time and Event Schedule - Screening Phase	Footnote d now states, "The Assessment of Psychological Well Being will consist of the State-Trait Anxiety Inventory only at screening, as the GDS [Geriatric Depression Scale] short version will be extracted from the GDS."
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**Rationale:** The abbreviation ADCS-DLT-PI was changed to ADCS-ADL-PI for consistency in the protocol.

Time and Event Schedule – Double-blind Treatment and Follow-up Phases	The abbreviation ADCS-ADL-PI (Alzheimer's Disease Cooperative Study - Activities of Daily Living - Prevention Instrument) is preferred and used throughout the document.
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**Rationale:** The table listing of the volume per sample was updated.

9.1.1. Overview, Table 2, Volume of Blood to be Collected From Each Subject	The volume per sample for biomarkers and peripheral blood mononuclear cells (PBMC) (whole blood sample) was reduced, and a typographical error was corrected (PMBC was changed to PBMC).
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Applicable Section(s)	Description of Change(s)
	<b>Rationale:</b> In the description of the Alzheimer’s Disease Cooperative Study Activities of Daily Living, a correction in the number of questions related to physical functioning was made.
9.2.2.2.2. ADCS Activities of Daily Living	Five questions was reduced to 3 questions.
	<b>Rationale:</b> The description of the Geriatric Depression Scale was corrected.
9.5.2. Geriatric Depression Scale	“Self-reported” was incorrect and was removed.
	<b>Rationale:</b> A correction was made in the description of the Impact of Events Scale.
9.5.5. Impact of Events Scale	“Imaging-related distress” was changed to “disclosure-related stress.”
	<b>Rationale:</b> An explanation of the assessment was added, and the sentence stating that it is a patient-reported outcome was removed.
9.5.7. Assessment of Psychological Well Being	A phrase describing the assessment as “a combination of the GDS (short version) and State-Trait Anxiety Inventory (short version)” was added. The assessment is not a patient-reported outcome measure, so the sentence was deleted.
	<b>Rationale:</b> “Assessment of Well Being” was changed to “Assessment of Psychological Well Being” in several instances throughout the protocol.
Throughout the protocol	“Assessment of Psychological Well Being” is the correct term.
	<b>Rationale:</b> The “Abbreviations” and “Definitions of Terms” sections were updated.
Abbreviations; Definitions of Terms; 1.3. Background Information; 1.4 Overall Rationale	A new abbreviation and a definition of terms were introduced into the protocol with the addition of the risk/benefit evaluation. They were added to the appropriate list.
	<b>Rationale:</b> Minor errors were noted.
Throughout the protocol	Minor grammatical, formatting, and spelling changes were made.

## SYNOPSIS

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

JNJ-54861911 (atabecestat) is a beta-site amyloid precursor protein cleaving enzyme inhibitor (BACEi) that is being developed by Janssen Research and Development (JRD) for the treatment of Alzheimer's disease (AD) by reducing production of amyloid-beta (A $\beta$ ) fragments.

Study 54861911ALZ2003 is a Phase 2b/3 confirmatory registration trial to evaluate the efficacy and safety of atabecestat for slowing cognitive decline in asymptomatic subjects (60 to 85 years of age) who are at risk for developing Alzheimer's dementia due to evidence of elevated amyloid accumulation.

As a result of permanently stopping all screening, randomization, and dosing with atabecestat, the subjects will continue in the double-blind treatment phase without treatment for approximately 3 to 6 months from cessation of dosing. This will permit continued safety monitoring of the subjects per protocol. At the end of the 3 to 6 months, the subjects will undergo an early termination visit as per the protocol.

**EudraCT NUMBER: 2015-000948-42**

## OBJECTIVES AND HYPOTHESES

### Primary Objective

The primary objective of this study is to determine whether treatment with atabecestat slows cognitive decline compared with placebo treatment, as measured by a composite cognitive measure, the Preclinical Alzheimer Cognitive Composite (PACC), in amyloid-positive subjects who are asymptomatic at risk for developing Alzheimer's dementia.

### Secondary Objectives

The key secondary objective of this study is the following:

- To determine if atabecestat will slow the decline of cognitive function and performance of everyday activities, compared with placebo, based on the Cognitive Function Index (CFI).

The other secondary objectives of this study are the following:

- To assess the overall safety and tolerability of atabecestat versus placebo.
- To determine if a decline in activities of daily living can be detected based on the ADCS-Activities of Daily Living-Prevention Instrument (ADCS-ADL-PI) scale, and if so, to assess the effect of atabecestat compared with placebo.
- To compare changes in cognitive performance between atabecestat and placebo based on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).
- To determine if the Neuropsychological Assessment Battery–Daily Living Tests (NAB-DLTs) for Memory and Attention can detect decline in cognitive function, and if so, to assess the effect of atabecestat compared with placebo.
- To assess the effect of atabecestat compared with placebo on the Clinical Dementia Rating (CDR) scale, including progression from CDR 0 to CDR 0.5 or higher.
- To assess the plasma and cerebrospinal fluid (CSF) pharmacokinetics (PK) of atabecestat following chronic treatment using a population PK approach and to explore their relationship with efficacy and safety parameters (including biomarkers).

- To assess the effects of atabecestat on accumulation of cerebral fibrillar amyloid, as measured by amyloid positron emission tomography (PET) imaging.
- To assess the effects of atabecestat on markers of neurodegeneration (eg, tau peptides) in CSF compared with placebo.
- To assess the maintenance of atabecestat effects on markers of A $\beta$  processing in CSF and plasma compared with placebo.

### **Exploratory Objectives**

The exploratory objectives of this study are the following:

- To investigate the effect of atabecestat compared with placebo on brain volume as measured by volumetric magnetic resonance imaging (MRI).
- To investigate the impact of atabecestat compared with placebo on markers of synaptic dysfunction on task-free functional MRI.
- To assess the effects of atabecestat on additional downstream markers of neuronal injury, neurodegeneration, or inflammation in CSF compared with placebo.
- To assess the effects of atabecestat on progression of tau spreading pathology in the brain as measured by tau PET imaging.
- To explore if baseline markers of neurodegeneration (eg, volumetric MRI, CSF t-tau or p-tau, or tau PET) are related to cognitive decline and response to treatment with atabecestat.
- To explore the correlation between the effect of atabecestat on biomarkers (eg, amyloid PET, plasma A $\beta$ , CSF A $\beta$  and t-tau or p-tau, tau PET) and clinical outcomes.
- To explore the impact of disclosure of amyloid status on questionnaires probing subject perception of amyloid imaging and concern about developing AD dementia.
- To investigate the effect of atabecestat compared with placebo on cognition as measured by a computerized cognitive battery.
- To investigate the effect of atabecestat compared with placebo on function as measured by the Financial Capacity Instrument (FCI).
- To investigate the effect of atabecestat compared with placebo on medical resource utilization as measured by the Healthcare Resource Utilization Questionnaire (HRUQ) scale.
- To investigate the effect of atabecestat compared with placebo on health outcomes as measured by the Short Form-36 (SF-36) and European Quality of Life-5 Dimensions 5-level (EQ-5D-5L) scales.
- To explore the ability of the Cognitive Function Index-acute (CFI-a) to measure decline of cognitive function and performance of everyday activities.
- To explore the effect of atabecestat compared with placebo on instrumental activities of daily life (IADL) as measured by the Amsterdam IADL questionnaire (A-IADL-Q).

### **Hypotheses**

The primary hypothesis is that cognitive decline, as measured by the PACC change from baseline at Month 54 (Year 4.5), will be significantly less for subjects treated with either atabecestat dose in comparison to subjects treated with placebo. The key secondary hypothesis is that functional decline, as measured by the CFI change from baseline at Month 54 (Year 4.5), will be significantly less for subjects treated with either atabecestat dose in comparison to subjects treated with placebo.



## OVERVIEW OF STUDY DESIGN

This is a multicenter, double-blind, placebo-controlled, randomized, parallel-group study assessing the efficacy and safety of atabecestat over approximately 4.5 years of treatment in subjects (60 to 85 years of age) who are asymptomatic and at risk for developing Alzheimer's dementia due to evidence of elevated amyloid accumulation based on CSF or amyloid PET imaging. The study will be conducted in an outpatient setting, with a planned recruitment of approximately 1,650 randomized subjects (550 per treatment group). It is planned that a total of 1,155 subjects (385 per group) will complete the Month 54 (Year 4.5) assessments, assuming a 30% attrition rate. The number of subjects randomized can be increased based on blinded sample size re-estimation, but the study enrollment will be capped at 2,400 subjects. Some design elements of this Phase 2b/3 study can be modified during the study based on emerging external data. The potential changes include optimization of the primary endpoint and the timing of the primary analysis. Sample size may be adjusted using blinded aggregated study data. Unblinded interim analyses (IAs) may be performed to assess futility.

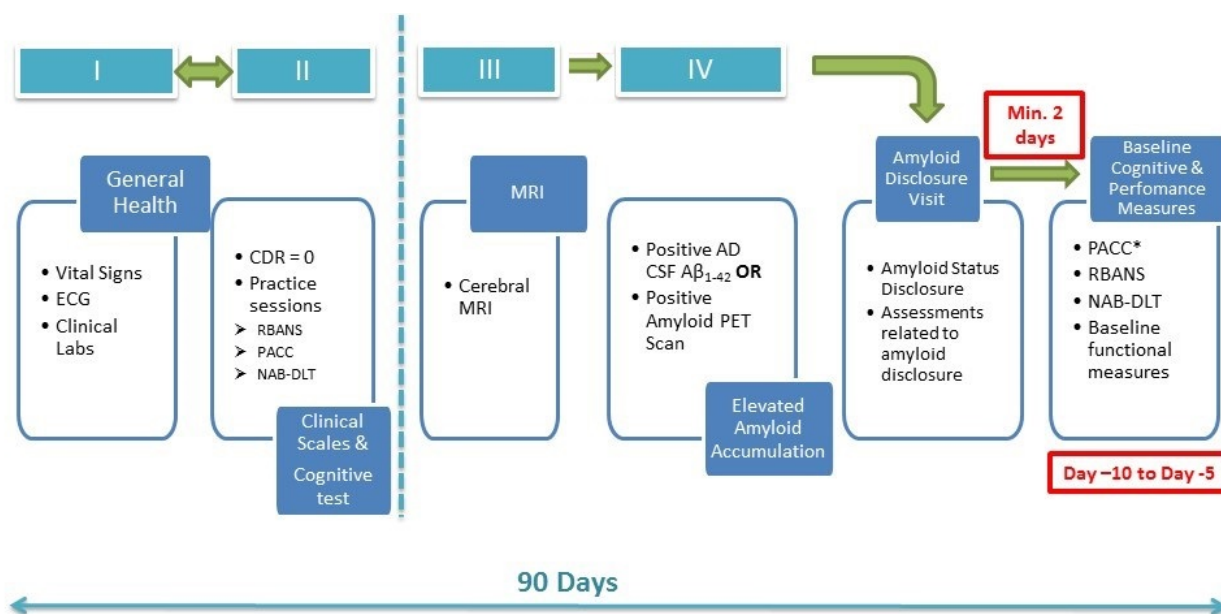
The study will consist of 3 phases: a screening phase of approximately 90 days in which subject eligibility will be assessed; a double-blind treatment phase during which eligible subjects will receive a fixed dose of randomly assigned study drug once daily for up to 4.5 years; and a follow-up phase to be conducted 7 to 28 days after the last dose of study drug (ie, after the last visit of the double-blind treatment phase). In addition to the longitudinal follow-up of subjects' screening biomarker(s) (ie, amyloid PET and/or CSF), subjects will have the opportunity to participate in 1 or more longitudinal pharmacodynamic (PD) substudies: CSF for biomarkers and drug exposure, amyloid PET imaging, and tau PET imaging. When sufficient longitudinal biomarker data has been collected, further collection of biomarker data can be terminated to reduce patient and site burden.

Following screening and baseline evaluations, subjects who meet all of the study inclusion criteria and none of the study exclusion criteria will be assigned randomly to 1 of 2 doses of atabecestat or placebo in a 1:1:1 ratio. Randomization will be stratified by country, and by apolipoprotein E (*APOE*)  $\epsilon$ 4 carrier status (carrier vs noncarrier). The dose levels of atabecestat selected are in the dose range expected to be well tolerated and to achieve a substantial reduction in CSF A $\beta$  at steady-state based on results of single and multiple ascending dose studies in healthy elderly subjects and preliminary results in a population with predementia Alzheimer's disease.

An independent Data Monitoring Committee (DMC) will be commissioned for this study to review safety and other relevant data on an ongoing basis, and to review findings from the potential IAs and make recommendations based on prespecified decision rules.

### Screening Phase

The screening phase consists of 4 primary screening steps as shown below. In addition, part of the baseline cognitive, functional, and medical resource utilization/health outcomes measures will be performed during the screening phase, as described further below. Assessments for **Step III** (MRI) and **Step IV** (Elevated Amyloid Accumulation) may only be performed after the subject is determined to be still eligible for the study after review of results from **Step I** (General Health) and **Step II** (Clinical Scales). **Step III** must be completed before **Step IV**. The investigator must review the MRI results before the subject undergoes amyloid testing. The specific assessments and procedures to be performed during the screening phase are detailed on the Time and Events Schedule-Screening Phase.



\* PACC baseline assessment will be performed on Day 1 predose.

AD=Alzheimer's disease; CDR=Clinical Dementia Rating; CSF=cerebrospinal fluid; ECG=electrocardiogram; Min=minimum; MRI=magnetic resonance imaging; NAB-DLT=Neuropsychological Assessment Battery-Daily Living Test; PACC=Preclinical Alzheimer Cognitive Composite; PET=positron emission tomography; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status.

Evidence of the subject's general health will be assessed in screening **Step I**, while confirmation of the subject's asymptomatic clinical status at baseline, as shown by a CDR global score of 0, will be obtained in screening **Step II**. A practice session with each of the cognitive performance scales (PACC, RBANS, NAB-DLTs for Memory and Attention, and the computerized cognitive battery) will occur during the screening phase and must be completed (1) prior to **Step IV** assessments, and (2) no later than 20 days (ie, Day -20) before the start of dosing. The subject's baseline functional performance will be profiled during screening by means of the CFI, CFI-a, ADCS-ADL-PI, and A-IADL-Q (informant [selected sites only]).

Evidence of any brain disease, other than potential very early signs of AD (eg, mild hippocampal atrophy) or typical age-related changes (eg, mild white matter hyperintensity), will be assessed during screening **Step III** by means of cerebral MRI. In screening **Step IV**, evidence of elevated amyloid accumulation will be assessed by a CSF sample for determination of Aβ<sub>1-42</sub> concentration, or an amyloid PET scan for determination of cerebral fibrillar amyloid, or both. Results of the amyloid pathology assessment will be disclosed to subjects during a separate in-clinic amyloid status disclosure visit. It is sufficient to demonstrate elevated amyloid accumulation by 1 of the 2 markers, but the decision to perform 1 or both needs to be made before either result is available. The amyloid disclosure visit will be performed when both results, if applicable, are available.

Eligible subjects, based on screening assessments, will return to the site during the screening phase to have part of their baseline cognitive and functional measures performed. This visit should be at least 2 days after the amyloid disclosure visit and between Day -10 and Day -5 (inclusive). Baseline measures obtained at this visit will include the CFI, CFI-a, RBANS, NAB-DLTs for Memory and Attention, ADCS-ADL-PI. The computerized cognitive battery, FCI, and A-IADL-Q may be administered at selected sites.

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**Double-blind Treatment Phase**

Subjects who successfully complete the screening assessments will return to the site on Day 1, at which time a series of predose baseline measurements (including the PACC) will be performed.

Following confirmatory review of a subject's eligibility for further participation, eligible subjects will be randomly assigned on Day 1 to 1 of 2 dose levels of atabecestat (5 mg or 25 mg, administered once daily) or matching placebo in a 1:1:1 ratio. Study drug for the double-blind treatment phase will be dispensed on Day 1 and at subsequent visits as listed in the Time and Events Schedule.

Following dosing on Day 1 and during the entire double-blind treatment phase, treatment effects will be evaluated by means of cognitive assessments, functional outcome measures, fluid and imaging biomarkers, PK, assessment of subject concerns about AD, and safety and tolerability at the time points listed in the Time and Events Schedule. During the double-blind treatment phase, subjects will visit the site at monthly intervals for the first 6 months, thereafter at Month 8, Month 9, Month 10, Month 12, and then at 3-month intervals through Month 54.

The treatment effect of atabecestat on slowing cognitive decline will be assessed in all subjects by regular neuropsychological assessments during the double-blind treatment phase, using the PACC, RBANS, and NAB-DLTs for Memory and Attention, and will be explored with a computerized cognitive battery. Functional outcome or performance will be evaluated in all subjects using the CFI, CFI-a, ADCS-ADL-PI, A-IADL-Q (selected sites only) and CDR, and will be explored with the FCI. Medical resource utilization and health outcomes will be explored using the HRUQ, SF-36, and EQ-5D-5L.

Assessment of the potential effects of atabecestat on the pathophysiologic processes underlying AD will be based on fluid biomarkers (CSF, blood [protein, genomic (DNA)], gene expression [RNA]) as well as on imaging biomarkers (MRI, amyloid PET, and tau PET).

Exposure to atabecestat will be determined in plasma samples collected using a sparse sampling approach and may be determined in CSF samples collected longitudinally in subjects with available baseline measurements.

Safety and tolerability will be assessed at regular intervals throughout the double-blind treatment phase.

**Interruption of Treatment**

If a subject has to interrupt treatment due to a significant medical condition or life event, it is possible to re-initiate treatment. Interruption of treatment should be limited to significant events, and confirmed with the medical monitor. Treatment re-initiation should occur as soon as possible and has to be confirmed by the sponsor's medical officer. The re-initiation may include a general safety examination and safety labs.

**End of Treatment or Early Withdrawal**

Every attempt should be made to follow subjects through their final visit of the double-blind treatment phase (Month 54). If a subject discontinues the study prematurely for any reason, he/she will be expected to complete the Early Termination (ET) visit. Subjects who discontinue study medication prematurely but do not withdraw from the study will be asked to complete all regular study visits through the end of the study. To reduce burden on subjects and increase compliance, the focus will be on collecting primary and secondary clinical outcome measures and reducing other assessments in these subjects.

**Posttreatment Phase (Follow-Up)**

After a minimum of 7 days to a maximum of 28 days after the last dose of study drug in the double-blind treatment phase, subjects will return to the site for a follow-up visit (see the Time and Events Schedule for the list of procedures to be completed). Subjects who withdraw prematurely from the study during the double-blind treatment phase will also be asked to complete the posttreatment phase (follow-up visit)

assessments within 7 to 28 days after the last dose of study drug or the ET visit assessments (if performed), whichever comes last.

## SUBJECT POPULATION

Approximately 1,650 subjects who are asymptomatic and at risk for developing Alzheimer's dementia are planned to be randomized in this study. The number of subjects randomized can be increased based on blinded sample size re-estimation, but the study enrollment will be capped at 2,400 subjects. This includes male or female subjects who are 60 to 85 years of age (inclusive), are clinically normal (asymptomatic) at baseline, as defined by the CDR Scale (CDR score=0), with or without subjective memory complaints, and have a typical biomarker pattern for AD indicating elevated amyloid accumulation, as shown by a low CSF A $\beta$ <sub>1-42</sub> level or a positive amyloid PET scan at screening. The key risk factors for elevated amyloid accumulation and development of AD are age (ie, 65 years of age or older), *APOE* genotype, and family history. To be considered for screening, subjects must meet the following criteria:

- Subjects 60 to 64 years of age must have 1 of the following additional key risk factors: a previously known *APOE*  $\epsilon$ 4 genotype, a positive family history for dementia (minimum of 1 first degree relative), or a previously known biomarker status demonstrating elevated amyloid accumulation in CSF or by PET.
- For subjects 65 years of age or older, age is a sufficient risk factor to be considered for screening.

The major exclusion criteria include treatment with acetylcholinesterase inhibitors or memantine during screening or on Day 1 predose; evidence of brain disease other than potential very early signs of AD or typical age-related changes; other abnormalities causing possible cognitive defects; a QT interval corrected for heart rate using the Fridericia formula (QTcF) of >450 msec (males) or >470 msec (females); dementia or brain disease that can cause dementia; and known familial autosomal dominant AD.

## DOSAGE AND ADMINISTRATION

### Dosage for Subjects randomized and medication dispensed prior to Amendment 3

During the double-blind treatment phase, randomly assigned study medication will include atabecestat 10 mg (administered as two 5-mg tablets of atabecestat), atabecestat 25 mg (administered as one 25-mg tablet of atabecestat and 1 matching placebo tablet), or placebo (administered as 2 matching placebo tablets). All study medication tablets will be identical in appearance. Study medication should be self-administered by subjects orally once daily with a glass of noncarbonated water, preferably between 0700 and 1100 hours (7:00-11:00 AM).

### Dosage for Subjects randomized after Amendment 3 and for Subjects with medication re-dispensed after Amendment 3

During the double-blind treatment phase, randomly assigned study medication will include atabecestat 5 mg (administered as one 5-mg tablet of atabecestat), atabecestat 25 mg (administered as one 25-mg tablet of atabecestat), or placebo (administered as 1 matching placebo tablet). All study medication tablets will be identical in appearance. Study medication should be self-administered by subjects orally once daily with a glass of noncarbonated water, preferably between 0700 and 1100 hours (7:00-11:00 AM).

Subjects who started the study under the 2 tablets/day regimen will be informed about the upcoming change to their regimen at the first visit after the implementation of Amendment 3. Once the subject has signed the new informed consent, a switch will be made to the 1 tablet/day regimen.

## EFFICACY EVALUATIONS/ENDPOINTS

The primary efficacy endpoint is the change in the PACC score from baseline at Month 54. The PACC score is the sum of the transformed z-scores for each of the 4 components of this measure (Free and Cued Selective Reminding Test; Delayed Paragraph Recall score on Logical Memory from Wechsler Memory Scale; Coding Subtest from the Wechsler Adult Intelligence Scale IV; and Mini Mental State Examination Total score).

The key secondary efficacy endpoint is the change from baseline in the CFI total score at Month 54. Other secondary efficacy endpoints include the following: the change from baseline in the ADCS-ADL-PI total score at Month 54; the change from baseline in the RBANS total scale score at Month 51; the change from baseline in the NAB-DLTs for Memory and Attention at Month 54; and the change from baseline in the CDR-Sum of Boxes (CDR-SB) at Month 54.

## BIOMARKER EVALUATIONS

### *Biomarkers to Determine Elevated Amyloid Accumulation*

Amyloid PET imaging, or lumbar puncture to collect a cerebrospinal fluid (CSF) sample for determination of  $A\beta_{1-42}$  levels, or both will be performed to assess elevated amyloid accumulation at study entry and to determine eligibility. Elevated amyloid accumulation can be determined by results for either of these biomarkers (CSF  $A\beta_{1-42}$  levels or amyloid PET imaging).

During the double-blind treatment phase, brain amyloid burden by amyloid PET imaging will be measured in those subjects with available baseline measurements. These measurements will evaluate the impact of therapy in brain regions known to accumulate substantial amyloid in AD (eg, frontal, medial temporal, or parietal cortices; anterior and posterior cingulates), as well as a global composite of these regions.

Similarly, longitudinal CSF samples will be collected from those subjects with available baseline measurements. Different  $A\beta$  fragments (eg,  $A\beta_{1-37}$ ,  $A\beta_{1-38}$ ,  $A\beta_{1-40}$ , and  $A\beta_{1-42}$ ) will be measured. The primary CSF biomarker used to confirm atabecestat target engagement is CSF  $A\beta_{1-40}$  as it is the most prevalent.

### *Fluid Biomarker Evaluations (Other than CSF $A\beta$ )*

In the subset of subjects that has CSF collection during screening/baseline and longitudinally during the double-blind treatment phase, the potential impact of atabecestat on markers of the pathophysiological disease process underlying AD will additionally be assessed by measuring levels of p-tau and t-tau, and additional exploratory downstream biomarkers of neuronal injury, inflammation, and synaptic dysfunction. Exploratory analyses for soluble APP-alpha (sAPP $\alpha$ ; cleaved at the alpha-secretase site) and sAPP-beta (sAPP $\beta$ ; cleaved at the BACE/ $\beta$ -secretase site) may be conducted.

Blood samples may also be analyzed in all subjects for  $A\beta$  fragments to confirm atabecestat target engagement by means of  $A\beta_{1-40}$ .

A blood sample will be collected at screening for *APOE* genotyping and for potential exploratory pharmacogenomics (DNA) analysis.

Blood samples will be collected at screening and during the double-blind treatment phase and may be analyzed for gene expression (RNA) profiles. A peripheral blood mononuclear cell (PBMC) sample will be collected at screening to explore the humoral immune response to AD-related proteins (eg, anti-tau antibodies) in a subset of sites. Blood-based evaluations may be used for translational biomarker research related to atabecestat or the diagnosis of AD. Collections may be modified based on local rules and regulations.

### *Imaging Evaluations (Other Than Amyloid PET)*

Brain MRIs will be performed on all subjects for eligibility at screening (read locally and centrally), for safety monitoring during the study, and for brain volumetric and functional analyses.

Brain tau burden by tau PET imaging will be measured longitudinally during the study in a subset of subjects who provide separate informed consent. Baseline brain tau signal will be measured in specific brain regions, including those known to accumulate tau early in the disease process (eg, hippocampus, amygdala, and parahippocampus) to determine the degree of tau pathology at study entry. In addition, brain tau burden by PET in these specified regions and in a global composite will be measured over the course of the study to evaluate the impact of therapy on brain tau burden.

All analyses/data may be used for translational biomarker research related to atabecestat or the diagnosis of AD.

### **PHARMACOKINETIC EVALUATIONS**

Venous blood samples for analysis of atabecestat will be collected from all subjects at the time points indicated in the Time and Events Schedule. CSF samples will be collected from a subset of subjects for a similar analysis.

Population PK modeling of plasma and, if possible, CSF concentrations of atabecestat will be undertaken. Data may be combined with those from select Phase 1 or Phase 2 studies to support a relevant structural model. This model will be used to predict PK parameters which may include trough concentration ( $C_{\text{trough}}$ ) and area under the concentration-time curve over the dosing interval ( $AUC_{\text{tau}}$ ) at steady-state.

### **SAFETY EVALUATIONS**

The safety of atabecestat in the study population will be assessed by monitoring AEs and concomitant medication use; safety laboratory testing (hematology, chemistry, urinalysis); triplicate recording of 12-lead electrocardiograms (ECG) at baseline and at 1 to 4 hours after dosing during the double-blind treatment phase; measurement of vital signs (blood pressure, pulse rate, temperature) and body weight; MRI imaging; and physical, neurological, and dermatological examinations. In addition, suicidality risk will be evaluated using the Columbia Suicide Severity Rating Scale (C-SSRS). Subjects will also complete the Assessment of Psychological Well Being questionnaire.

An independent external Data Monitoring Committee (DMC) will be established to monitor study data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study.

### **OTHER EVALUATIONS**

Other assessments during the double-blind treatment phase will include the Concerns About Alzheimer's Disease Scale, the Future Time Perspective Scale, HRUQ, SF-36, EQ-5D-5L, and CFI-a. The computerized cognitive battery, FCI, and A-IADL-Q may be administered at selected sites.

### **STATISTICAL METHODS**

#### *Sample Size Determination for Primary Endpoint*

The decline in PACC from baseline was assessed using data from clinically normal populations in the Alzheimer's Disease Neuroimaging Initiative (ADNI), Australian Imaging, Biomarkers, and Lifestyle Flagship Study of Aging (AIBL), and ADCS Prevention Initiative studies. The average difference in PACC decline at 36 months in AIBL between subjects with and without elevated brain amyloid was 1.40 units (95% CI: 0.52 to 2.29), and the SD at Week 144 (Month 36) was estimated at 2.44 units. If a similar decline in PACC at Month 54 is seen and the SD is 2.44, then 385 completers per treatment arm would provide 83% power (at the 2-sided alpha of 0.05) to detect a difference from placebo of 0.49. The SD at 54 months will likely be higher. If the SD at month 54 increases by 20% to 2.93, then 555 completers per

groups would be required in order to maintain the same power. The sample size is estimated based on an MMRM model, assuming a constant correlation of 0.5. Under the above assumptions and assuming the attrition is no more than 30%, a total of 1,650 randomized subjects (550/treatment arm) will be required at minimum, and 2,400 subjects (800/treatment arm) at maximum. The treatment difference of 0.49 represents 35% of the 1.40-unit difference, or a 35% slowing of decline in PACC in subjects with elevated brain amyloid. If the average time from amyloid positivity to dementia is 15 years, then, assuming linear decline, a 35% slowing of cognition may translate into approximately a 5-year delay in the onset of dementia. A 5-year delay could lead to a 57% reduction in the number of patients with dementia.

#### *Efficacy Analysis of Primary and Secondary Endpoints*

The primary analysis will be carried out in the intent-to-treat analysis set, which includes all randomized subjects. The analysis of the PACC change score will only include subjects for whom the PACC change score is non-missing at least 1 postbaseline time point.

A mixed effect model for repeated measurement (MMRM) analysis will be performed to assess the treatment effect for the primary efficacy endpoint. The change from baseline in the PACC at each visit that the endpoint is measured will be the dependent variable. The model for the fixed effects will include the following terms: baseline of the endpoint measure, treatment group, visit, treatment-by-visit interaction, age, sex, education, hippocampal volume, country, and *APOE*  $\epsilon$ 4 carrier status.

The null hypothesis is that there is no treatment difference between either dose of atabecestat and placebo for the primary endpoint. The estimated treatment effects at 4.5 years will be compared at a 2-sided 0.05 significance level using the appropriate contrasts based on the MMRM. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. If the unstructured covariance structure matrix results in a lack of convergence, an alternative covariance structure will be used. The details will be specified in the statistical analysis plan (SAP).

The key secondary endpoint is the CFI. Other secondary endpoints include the ADCS-ADL-PI, RBANS, NAB-DLTs for Memory and Attention, and CDR-SB. All secondary endpoint analyses will be performed in the intent-to-treat analysis set. The change from baseline in CFI total score will be analyzed using an MMRM analysis. The change from baseline score at each visit will be the dependent variable. Visits scheduled for the measure will be treated as a categorical variable. An unstructured covariance structure will be assumed. The model for the fixed effects will include the following terms: baseline of the endpoint measure, treatment group, visit, treatment-by-visit interaction, age, sex, education, hippocampal volume, country, and *APOE*  $\epsilon$ 4 carrier status. If the unstructured covariance structure matrix results in a lack of convergence, an alternative covariance structure will be used. For each of the other secondary efficacy endpoints, the change from baseline score will be similarly analyzed as above.

Descriptive statistics and evaluation of the CFI-a ability to measure change over time will be described in the SAP.

Statistical adjustment will be made to account for multiplicity due to multiple dose comparisons for the primary endpoint and the key secondary endpoint. To control the Type I error, the statistical testing for these endpoints will be performed using a 2-stage gatekeeping strategy.

For dropout subjects, every effort will be made to retrieve efficacy data at the study endpoint. The impact of the missing data on the efficacy results will be assessed using sensitivity analyses. The follow-up data from subjects who stop taking study medication prematurely and data from relevant external databases will be incorporated in the sensitivity analyses.

If warranted, the treatment effect will be assessed in various subgroups of the study population.

### *Interim Analyses*

Some study design elements may be modified during the study based on a review of emerging external data. The potential changes include optimization of the primary endpoint (eg, substituting PACC components with corresponding RBANS-PACC components or alternative weighting of the PACC components), or timing of the primary endpoint (eg, changing from 4.5 years to 3.5 years). Since any of the above changes would be done based on external information without any knowledge of unblinded study data, there will be no Type I error adjustments.

Sample size may potentially be increased based on review of blinded aggregated study data. There will be no Type I error adjustment for such a sample size increase.

An unblinded IA may be performed on CSF  $A\beta_{1-40}$  to assess futility when at least 60 subjects (20 per group) have a Month 12 CSF  $A\beta_{1-40}$  result. Unblinded IAs may potentially be performed on amyloid PET, CSF tau/p-tau, and tau PET, and depending on these results, potentially on cognitive endpoints, as well, for futility. Interim analyses for the other biomarkers would occur when at least 168 subjects (56 per group) have a Month 24 amyloid PET, a Month 12 CSF tau/p-tau, and a Month 18 tau PET. There will be no Type I error adjustment for the biomarker-based IAs since superiority will not be declared from any of them.

An independent external statistical support group will perform the IAs. The external DMC will review the results of the IAs and make recommendations based on prespecified decision rules. All personnel involved in the conduct of the study will remain blinded throughout the study.

### *Pharmacokinetic Analyses and Pharmacokinetic/Pharmacodynamic Analyses*

For each dosage, descriptive statistics will be calculated for atabecestat plasma and CSF concentrations at each sampling time and for all the estimated atabecestat steady-state PK parameters.

Population PK analysis of concentration-time data of atabecestat will be performed using nonlinear mixed effect modeling. Population PK/PD analysis of biomarkers and/or cognitive markers may also be performed, and a suitable dose- and/or exposure-response model may be developed.

### *Biomarker Analyses*

Statistical analyses will be performed for CSF  $A\beta_{1-40}$  and plasma  $A\beta_{1-40}$ , amyloid PET parameters, CSF p-tau, tau PET, and volumetric and task-free functional MRI parameters. In addition, alternate CSF markers of neurodegeneration will also be analyzed similarly.

### *Medical Resource Utilization and Health Outcome Analyses*

Summary statistics will be provided for the HRUQ, SF-36, A-IADL-Q, and EQ-5D-5L scales. For each of these outcome measures, the scores will be summarized by treatment group at each of the scheduled time points.

### *Safety Analyses*

Safety will be assessed in subjects who received at least 1 dose of study drug. The incidence of AEs will be summarized for each treatment group by body system and preferred term. Changes from baseline in clinical laboratory values, vital signs measurements, body weight, and ECG variables will be presented descriptively. The QT interval corrected for heart rate (ie, QTcF) will be summarized using frequency tabulations. For C-SSRS, the percentage of subjects with a suicide-related outcome will be summarized in incidence and shift tables. Dermatological examination findings, physical and neurological examination findings, and results from the Assessment of Psychological Well Being questionnaire for each scheduled time point will be summarized using frequency tabulations of abnormalities.



**TIME AND EVENTS SCHEDULE – SCREENING PHASE**

Phase	Screening <sup>a</sup>					
Duration	<----- 90 days----->					
Day <sup>a</sup>	Day -90 to Day -1					Day -10 to Day -5
Screening Step/Visit Purpose	I: GH	II: CS	III: MRI	IV: EAmA	Amyloid Status Disclosure Conversation Visit <sup>b</sup>	Baseline Cognitive Measures
Visit Number <sup>a</sup>	1	2	3	4	5	6
<b>Study Procedures</b>						
<b>Screening/Administrative</b>						
Full informed consent process prior to study-specific procedures (subject and informant) <sup>c</sup> (HIPAA Authorization, if applicable)	X					
Inclusion/exclusion criteria	X					
Medical history, demographics, and education level	X					
Prestudy therapy	X					
Preplanned surgery/procedure(s)	X					
<b>Safety Assessments</b>						
Physical examination	X					
Neurological examination	X					
Dermatological examination and photography	X <sup>d</sup>					
Vital signs (supine and standing blood pressure, pulse)	X					
Triplicate 12-lead ECG	X					
Height	X					
Weight	X					
Temperature	X					
Assessment of Psychological Well Being <sup>e</sup>		X				
C-SSRS	X					
<b>Clinical Laboratory Assessments</b>						
Hematology and chemistry	X <sup>f</sup>					
Thyroid function tests (TSH, T3, T4)	X					
Serology	X					
Urinalysis	X					

Phase	Screening <sup>a</sup>					
Duration	<----- 90 days----->					
Day <sup>a</sup>	Day -90 to Day -1					Day -10 to Day -5
Screening Step/Visit Purpose	I: GH	II: CS	III: MRI	IV: EAmA	Amyloid Status Disclosure Conversation Visit <sup>b</sup>	Baseline Cognitive Measures
Visit Number <sup>a</sup>	1	2	3	4	5	6
<b>Study Procedures</b>						
Urine drug screen	X					
<b>Amyloid Disclosure Assessments</b>						
Amyloid status disclosure					X	
Views & Perceptions of Amyloid Imaging Scale <sup>e</sup>		X			X (post disclosure)	
Concerns about Alzheimer’s Disease Dementia Scale		X			X (post disclosure)	
Future Time Perspective Scale		X			X (post disclosure)	
Impact of Events Scale					X <sup>h</sup>	
<b>Cognitive Evaluations</b>						
PACC		X <sup>i</sup>				
RBANS		X <sup>i</sup>				X <sup>j</sup>
<b>Clinical Scales and Functional Outcome Measures</b>						
CDR (subject and informant)		X				
CFI (self and informant)						X
CFI-a (self and informant)						X
ADCS-ADL-PI (self and informant)						X
A-IADL-Q <sup>k</sup> (informant)						X
NAB-DLTs for Memory and Attention		X <sup>i</sup>				X <sup>j</sup>
Computerized cognitive battery <sup>k</sup>		X <sup>i</sup>				X <sup>j</sup>
FCI <sup>k</sup>						X <sup>j</sup>
GDS		X				
HIS		X				
<b>Medical Resource Utilization and Health Outcomes Measures</b>						
HRUQ		X				

Phase	Screening <sup>a</sup>					
Duration	<----- 90 days----->					
Day <sup>a</sup>	Day -90 to Day -1					Day -10 to Day -5
Screening Step/Visit Purpose	I: GH	II: CS	III: MRI	IV: EAmA	Amyloid Status Disclosure Conversation Visit <sup>b</sup>	Baseline Cognitive Measures
Visit Number <sup>a</sup>	1	2	3	4	5	6
Study Procedures						
SF-36		X				
EQ-5D-5L		X				
Genomics						
Blood sample collection (for <i>APOE</i> genotyping and pharmacogenomic analysis)	X					
Fluid Biomarkers						
Blood collection for plasma and gene expression (RNA)	X					
CSF collection and corresponding plasma sample				X <sup>l</sup>		
Peripheral blood mononuclear cell sample collection	X <sup>m</sup>					
Imaging						
MRI			X <sup>n,o</sup>			
Amyloid PET <sup>p</sup>				X <sup>l,n</sup>		
Ongoing Subject Review						
Concomitant therapy	<-----Continuous----->					
Adverse events	<-----Continuous----->					
<b>Abbreviations:</b> ADCS-ADL-PI=Alzheimer’s Disease Cooperative Study - Activities of Daily Living - Prevention Instrument; A-IADL-Q=Amsterdam instrumental activities of daily living questionnaire; <i>APOE</i> =apolipoprotein E; CDR=Clinical Dementia Rating Scale; CFI=Cognitive Function Index; CFI-a=Cognitive Function Index-acute; CS=clinical scales; CSF=cerebrospinal fluid; C-SSRS=Columbia Suicide Severity Rating Scale; EAmA=elevated amyloid accumulation; ECG=electrocardiogram; EQ-5D-5L=European Quality of Life-5 Dimensions 5-level; FCI=Financial Capacity Instrument; GDS=Geriatric Depression Scale; GH=general health; HIPAA=Health Insurance Portability and Accountability Act; HIS=Rosen-modified Hachinski Ischemic Scale; HRUQ=Healthcare Resource Utilization Questionnaire; ICF=informed consent form; MRI=magnetic resonance imaging; NAB-DLT=Neuropsychological Assessment Battery - Daily Living Test; PACC= Preclinical Alzheimer Cognitive Composite; PET=positron emission tomography; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; SF-36=Short Form-36; T3=tri-iodothyronine; T4=thyroxine; TSH=thyroid stimulating hormone.						

## Footnotes:

- <sup>a</sup> Screening assessments may be performed over multiple visits over a period of 90 days prior to dosing, with the determination of inclusion and exclusion criteria occurring over Visits 1 through 5. If needed for biomarker collection or interpretation, or for logistical reasons, this period can be prolonged with written approval from the sponsor. Steps III and IV assessments may only be performed after Steps I and II assessments relevant for determination of eligibility are done and if, based on the results, the subject is eligible for continued participation. The order of individual assessments within a step is not fixed, unless indicated otherwise. Different screening assessments associated with each step may be performed on a single visit day or spread over multiple visit days. Eligible subjects based on Steps I to IV assessments will return during the screening phase to the site to have part of their baseline cognitive and functional measures performed between Day -10 and Day -5 and at least 2 days post amyloid disclosure. Although visit numbers are specified, fewer or additional visits can occur based on the above, and the numbering is considered guidance.
- <sup>b</sup> This visit will be performed once Step IV results are available and must take place at least 2 days prior to the baseline cognitive assessments.
- <sup>c</sup> The Informant should sign an ICF or equivalent document prior to completing any informant related study procedures.
- <sup>d</sup> Dermatological examination performed by a dermatologist (as defined in Section 9.1.2) with photography (taken by dermatologist or qualified designee) it is preferred that the dermatology exam be conducted before Step III, but it must be conducted before amyloid testing
- <sup>e</sup> The Assessment of Psychological Well Being will consist of the State-Trait Anxiety Inventory only at screening, as the GDS short version will be extracted from the GDS.
- <sup>f</sup> Including coagulation, vitamin B12, and folic acid.
- <sup>g</sup> Only for those subjects having a PET scan performed to assess eligibility.
- <sup>h</sup> Administered by phone (or at a visit) within 3 days post amyloid disclosure visit.
- <sup>i</sup> In order to assess for and mitigate practice effects, the PACC, RBANS, NAB-DLTs for Memory and Attention, and computerized cognitive battery must be performed once during the screening period but (1) prior to Step IV assessments, (2) no later than Day -20.
- <sup>j</sup> Serves as baseline assessment and will be performed between Day -10 and Day -5 and at least 2 days after the amyloid disclosure visit.
- <sup>k</sup> At selected centers only.
- <sup>l</sup> Amyloid PET imaging or lumbar puncture to collect a CSF sample for determination of A $\beta$ <sub>1-42</sub> levels, or both, will be performed to assess elevated amyloid accumulation at study entry and to determine eligibility. Elevated amyloid accumulation can be determined by results for either of these biomarker evaluations, but the decision on which tests are going to be done must be made before either result is available. The amyloid disclosure visit will be performed when both results, if applicable, are available.
- <sup>m</sup> Only at sites capable of processing PBMC samples.
- <sup>n</sup> MRI and PET collection can be performed at the same visit based on-site preference, and results must be available during screening phase to confirm subject eligibility.
- <sup>o</sup> For safety; both volumetric and task-free functional MRI.
- <sup>p</sup> No subjects will receive more than 3 amyloid PET scans during the study.



Phase	Double-blind Treatment Phase																												Early Termination	Follow up Visit <sup>c</sup>	
	Month (M) <sup>a</sup>	M0 (D1)	W2*	M 1	M1 +2W	M 2	M2 +2W	M 3	M 4	M 5	M 6	M 8	M 9	M 10	M 12	M 15	M 18	M 21	M 24	M 27	M 30	M 33	M 36	M 39	M 42	M 45	M 48	M 51			M 54
Visit Window (± days)	0	± 2	± 4	± 2	± 4	± 2	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12		
Visit Number	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34		35	
<b>Study Procedures</b>																															
Vital signs (supine and standing blood pressure, pulse)	X <sup>d</sup>						X			X		X		X		X		X		X		X		X		X		X	X	X	
Triplicate 12-lead ECG <sup>i</sup>	X <sup>d</sup>		X				X			X				X		X		X		X		X		X		X		X	X	X <sup>f</sup>	
Height																												X	X		
Weight	X <sup>d</sup>									X				X		X		X		X		X		X		X		X	X	X	
Temperature	X <sup>d</sup>						X			X		X		X		X		X		X		X		X		X		X	X	X <sup>f</sup>	
Assessment of Psychological Well Being	X						X					X			X		X		X		X		X		X		X	X	X	X	
C-SSRS (since last visit)	X <sup>d</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
<b>Clinical Laboratory Assessments</b>																															
Hematology and chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>f</sup>
Urinalysis													X						X					X			X	X	X <sup>f</sup>		
<b>Amyloid Disclosure Assessments</b>																															
Future Time Perspective Scale			X				X					X					X								X			X	X		
Concerns about Alzheimer's Disease Dementia Scale			X				X					X					X								X			X	X		
<b>Cognitive Evaluations</b>																															
PACC	X <sup>d</sup>									X				X <sup>j</sup>		X		X		X		X <sup>j</sup>		X		X		X	X <sup>k</sup>		
RBANS							X				X			X		X		X		X		X		X		X		X	X <sup>k</sup>		

Phase	Double-blind Treatment Phase																												Early Termination	Follow up Visit <sup>c</sup>
	Month (M) <sup>a</sup>	M0 (D1)	W2*	M 1	M +2W 2	M +2W 3	M 4	M 5	M 6	M 8	M 9	M 10	M 12	M 15	M 18	M 21	M 24	M 27	M 30	M 33	M 36	M 39	M 42	M 45	M 48	M 51	M 54			
Visit Window (± days)	0	± 2	± 4	± 2	± 4	± 2	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12			
Visit Number	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34		35
<b>Study Procedures</b>																														
<b>Clinical Scales and Functional Outcome Measures</b>																														
CDR (subject and informant)														X					X							X		X	X	
CFI (self and informant)														X					X							X		X	X <sup>k</sup>	
CFI-a (self and informant)							X			X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>k</sup>	
ADCS-ADL-PI (self and informant)							X			X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>k</sup>		
A-IADL-Q (informant) <sup>l</sup>														X					X						X		X	X <sup>k</sup>		
Computerized cognitive battery <sup>l</sup>									X				X		X			X		X			X		X		X	X		
FCI <sup>l</sup>														X					X					X		X		X	X <sup>k</sup>	
NAB-DLTs for Memory and Attention												X						X					X			X		X	X <sup>k</sup>	
<b>Medical Resource Utilization and Health Outcomes Measures</b>																														
HRUQ			X		X		X			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
SF-36														X						X					X			X	X	
EQ-5D-5L														X					X					X			X	X		

Phase	Double-blind Treatment Phase																												Early Termination	Follow up Visit <sup>c</sup>
	Month (M) <sup>a</sup>	M0 (D1)	W2*	M1	M1 +2W	M2	M2 +2W	M3	M4	M5	M6	M8	M9	M10	M12	M15	M18	M21	M24	M27	M30	M33	M36	M39	M42	M45	M48	M51		
Visit Window (± days)	0	± 2	± 4	± 2	± 4	± 2	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	Visit (ET) <sup>b</sup>
Visit Number	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34		35
<b>Study Procedures</b>																														
<b>Pharmacokinetics</b>																														
Blood sample collection	X <sup>d</sup>						X <sup>m</sup>			X <sup>m</sup>				X <sup>m</sup>		X <sup>m</sup>		X <sup>m</sup>		X <sup>m</sup>		X <sup>m</sup>		X <sup>m</sup>		X <sup>m</sup>		X <sup>m</sup>		
CSF collection <sup>d</sup>	See Biomarkers- CSF																													
<b>Fluid and Imaging Biomarkers</b>																														
Blood collection for PD markers <sup>d</sup>	X						X			X				X		X		X		X		X		X		X		X	X	
CSF collection and corresponding plasma collection <sup>d,n</sup>	X <sup>o</sup>													X <sup>p</sup>									X						X <sup>k</sup>	
Blood collection for gene expression (RNA) <sup>d</sup>	X													X						X						X		X	X	
Optional Immunologic Sample <sup>q</sup>	-----X----->																													
MRI										X				X					X									X	X <sup>k</sup>	
Amyloid PET <sup>r</sup>	X <sup>d,o</sup>																		X								X		X	
Tau PET <sup>s</sup>	X <sup>d,t</sup>															X								X					X <sup>k</sup>	
<b>Ongoing Subject Review</b>																														
Concomitant therapy	-----Continuous----->																													
Adverse events	-----Continuous----->																													



Phase	Double-blind Treatment Phase																												Early Termination	Follow up Visit <sup>c</sup>
	Month (M) <sup>a</sup>	M0 (D1)	W2*	M 1	M1 +2W	M 2	M2 +2W	M 3	M 4	M 5	M 6	M 8	M 9	M 10	M 12	M 15	M 18	M 21	M 24	M 27	M 30	M 33	M 36	M 39	M 42	M 45	M 48	M 51		
Visit Window (± days)	0	± 2	± 4	± 2	± 4	± 2	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	± 12	Visit (ET) <sup>b</sup>
Visit Number	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34		35

**Study Procedures**

**Abbreviations:** ADCS-ADL-PI=Alzheimer's Disease Cooperative Study - Activities of Daily Living - Prevention Instrument; AESI=adverse event of special interest; A-IADL-Q=Amsterdam instrumental activities of daily living questionnaire ; BL=Baseline; CDR=Clinical Dementia Rating Scale; CFI=Cognitive Function Index; CFI-a=Cognitive Function Index-acute; CSF=cerebrospinal fluid; C-SSRS=Columbia Suicide Severity Rating Scale; D=day; ECG=electrocardiogram; EQ-5D-5L=European Quality of Life-5 Dimensions 5-level; FCI=Financial Capacity Instrument; HRUQ=Healthcare Resource Utilization Questionnaire; MRI=magnetic resonance imaging; NAB-DLT=Neuropsychological Assessment Battery - Daily Living Test; PACC= Preclinical Alzheimer Cognitive Composite; PD=pharmacodynamics; PET=positron emission tomography; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; RNA=ribonucleic acid; SF-36=Short Form-36; Trt=treatment; W=week.

**Footnotes:**

\* Note this visit is to occur approximately 2 weeks after randomization.

<sup>a</sup> Timing of all study visits postbaseline should be calculated based on the difference in time from the baseline visit, not from the prior study visit. During this phase, subjects will visit the site approximately every 2 weeks for the first 3 months (visit 2W=2 weeks post-D1, visit M1=4 weeks post-D1, visit M1+2 weeks=6 weeks post-D1, M2=8 weeks post-D1, M2+2weeks=10 weeks post D1, M3=13 weeks post-D1), at monthly intervals from 3 months to 6 months (M4=17 weeks post-D1, M5=21 weeks post-D1, M6=26 weeks post-D1), additional visits at Month 8, Month 9, Month 10, and Month 12 (M8=34 weeks pose dose-D1, M9=39 weeks post-D1, M10=43 weeks post-D1, M12=52 weeks post-D1, and then at 3-month (13-week) intervals through Month 54 (eg, visit M15=65 weeks post-D1, M54=234 weeks post-D1).

<sup>b</sup> If a subject is withdrawn from the study, he/she will be asked to have the Early Termination Visit assessments performed. The subject will complete the posttreatment phase (follow-up visit) within 7 to 28 days following the last dose of study drug or the Early Termination Visit assessments (if performed), whichever comes last. Subjects who discontinue study treatment but elect to remain in the study will continue to have study assessments performed through Month 54; the focus will be on collecting primary and secondary clinical outcome measures and reducing other assessments. In both cases (withdrawal from the study or discontinuation of study treatment but remaining in the study), the disposition status should be completed for the subject.

<sup>c</sup> Follow-up Visit assessments to be performed 7 to 28 days after last dose of study drug.

<sup>d</sup> Predose.

<sup>e</sup> Between 7:00 and 11:00 AM daily, subjects should self-administer study drug (atabecestat/placebo) with a glass (200 mL) of noncarbonated water. On Day 1, the first dose of study drug can take place at any time during the day provided all predose assessments have been performed. At visits specified in the table, , subjects should self-administer the study drug on-site (at the study center/clinic).

<sup>f</sup> Only if any clinically significant abnormalities observed on previous occasion.

<sup>g</sup> Whenever a skin lesion not previously documented is reported by the subject or the investigator, in addition to a dermatological exam performed by a dermatologist (as defined in Section 9.1.2), digital images of the lesion will be acquired at the time (taken by dermatologist or assigned designee) the lesion is discovered and at follow-up visits with a frequency that 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.

<sup>h</sup> To be done at Early Termination visit only if not performed at Month 12. Note: If a subject discontinues study treatment before completion of the double-blind treatment phase or is withdrawn during the double-blind treatment phase, the subject will be asked to complete this at the Early Termination visit if early termination is before Month 12.

- <sup>i</sup> Triplicate ECG recordings to be obtained 1 to 4 hours postdose. The 3 individual ECG tracings are to be obtained as close as possible in succession, but no more than 2 minutes apart, and the full set of triplicate recordings are to be completed in less than 4 minutes.
- <sup>j</sup> Must be performed prior to lumbar puncture.
- <sup>k</sup> Only if assessment not performed during previous visit as scheduled (eg, for PACC and RBANS, perform assessment that was not performed at the last visit per the alternating pattern of these assessments).
- <sup>l</sup> At selected centers only.
- <sup>m</sup> Blood samples for plasma PK determinations will be collected predose and between 1 to 4 hours postdose.
- <sup>n</sup> CSF collection should be done after all other assessments (eg, safety, cognitive, functional, clinical, medical resource utilization/health outcomes).
- <sup>o</sup> May be collected during the screening period upon confirmation of eligibility based on the Steps I to IV screening assessments.
- <sup>p</sup> Flexible CSF time point which may be rescheduled to any time point during the double-blind treatment phase, following interim review of the biomarker data.
- <sup>q</sup> In subjects who experience significant increase in hepatic enzymes, an additional blood draw may be drawn in an optional immunologic substudy (see Section 3.2.6.2).
- <sup>r</sup> No subject will receive more than 3 amyloid PET scans during the study. If mandated by local rules or regulation (eg, exposure limits for radiation), the number of follow-up scans can be adjusted.
- <sup>s</sup> Subjects will provide separate informed consent prior to participation.
- <sup>t</sup> Tau PET to be performed after amyloid disclosure but before first drug intake at M0.

**ABBREVIATIONS**

A4	Anti-Amyloid Treatment in Asymptomatic Alzheimer's study
A $\beta$	Amyloid-beta
A $\beta$ +	Amyloid-beta positive
AChE	acetylcholinesterase
AD	Alzheimer's disease
ADCS	Alzheimer's Disease Cooperative Study
ADCS-ADL-PI	Alzheimer's Disease Cooperative Study - Activities of Daily Living-Prevention Instrument
ADCS-PACC	Alzheimer's Disease Cooperative Study - Preclinical Alzheimer's Cognitive Composite
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
A-IADL-Q	Amsterdam IADL questionnaire
AIBL	Australian Imaging, Biomarkers and Lifestyle Flagship Study of Aging
ALT	alanine aminotransferase
<i>APOE</i>	apolipoprotein E
<i>APOE</i> $\epsilon$ 4	apolipoprotein E, $\epsilon$ 4 allele
APP	amyloid precursor protein
ARAD	asymptomatic at risk for Alzheimer dementia
ARC	Anticipated Event Review Committee
ARIA-E	amyloid-related imaging abnormalities – edema or effusion
AST	aspartate aminotransferase
BACE	beta-site amyloid precursor protein cleaving enzyme (types 1 and 2)
BACEi	beta-site amyloid precursor protein cleaving enzyme inhibitor
BCRP	breast cancer resistance protein
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
CFI-a	Cognitive Function Index-acute
CI	confidence interval
CNS	central nervous system
COPD	Chronic obstructive pulmonary disease
CSF	cerebrospinal fluid
CYP	cytochrome P450
DAT	dementia of Alzheimer's type
DDI	drug-drug interaction
DIAT	Diaminothiazine
DMC	Data Monitoring Committee
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTI	diffusion tensor imaging
DWI	diffusion weighted imaging
eCRF	electronic case report form
ECG	electrocardiogram
eDC	electronic data capture
ET	early termination
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-5L	European Quality of Life-5 Dimensions 5-level
EQ VAS	European Quality Visual Analogue Scale
FCI	Financial Capacity Instrument
FCSRT	Free and Cued Selective Reminding Test
FDG	fluorodeoxyglucose ( <sup>18</sup> F)
FTP	Future Time Perspective Scale
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
HBsAg	hepatitis B surface antigen

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HIS	Hachinski Ischemic Scale
HIV	human immunodeficiency virus
HRUQ	Healthcare Resource Utilization Questionnaire
IA	interim analysis
IADL	instrumental activities of daily living
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IES	Impact of Events Scale
INR	International Normalized Ratio
IRB	Institutional Review Board
IWRS	interactive web response system
JRD	Janssen Research and Development
LC-MS/MS	liquid chromatography/tandem mass spectrometry
LOQ	limit of quantitation
MAD	multiple ascending dose
MATE1	multidrug and toxin extrusion protein 1
MATE-2K	multidrug and toxin extrusion protein 2-K
MCI	mild cognitive impairment
MDR1	multidrug resistance protein 1
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed effect model for repeated measurement
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
NAB-DLT	Neuropsychological Assessment Battery–Daily Living Test
NFLs	neurofilament light chains
NOAEL	no observable adverse effect level
OATP1B1	organic anion-transporting polypeptide B1
OCT2	organic cation transporter 2
PACC	Preclinical Alzheimer Cognitive Composite
pAD	prodromal Alzheimer’s Disease
PD	pharmacodynamics
PET	positron emission tomography
P-gp	p-glycoprotein
PK	pharmacokinetics
PBMC	peripheral blood mononuclear cell
PopPK	population PK
PQC	product quality complaint
p-tau	phosphorylated tau
QTc	QT interval corrected
QTcF	QT interval corrected for heart rate according to Fridericia
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RBC	red blood cell
ROI	region of interest
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
sAPP	soluble amyloid precursor protein (alpha and beta forms)
SD	standard deviation
SF-36	Short Form-36 Scale
SOP	standard operating procedure
SSG	statistical support group
SUSAR	suspected unexpected serious adverse reaction
SUVr	standard uptake value ratio
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
WAIS	Wechsler Adult Intelligence Scale

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WAIS-IV	Wechsler Adult Intelligence Scale, version IV
WBC	white blood cell
WMS	Wechsler Memory Scale
WMS-IV	Wechsler Memory Scale, version IV

## DEFINITIONS OF TERMS

AUC	area under the plasma concentration curve
$AUC_{\infty}$	area under the plasma concentration curve extrapolated to infinity
$AUC_{last}$	area under the plasma concentration curve observed from administration to the last measurable concentration
$AUC_{\tau}$	area under the plasma or CSF concentration-time curve from 0 to tau hours post dosing (time tau is the dosing interval)
$C_{max}$	maximum plasma or CSF concentration (during a dosing interval)
$C_{trough}$	trough plasma or CSF concentration, ie, the concentration that is just prior to the beginning of, or at the end of, a dosing interval
$t_{1/2}$	terminal (apparent elimination) half-life
$t_{max}$	time to maximum plasma concentration

## 1. INTRODUCTION

### 1.1. Result of Permanent Cessation of Screening, Randomization, and Dosing of Atabecestat

As a result of permanently stopping all screening, randomization, and dosing with atabecestat, the subjects will continue in the double-blind treatment phase without treatment (as in Section 10.2) for approximately 3 to 6 months from cessation of dosing. This will permit continued safety monitoring of the subjects per protocol. At the end of the 3 to 6 months, the subjects will undergo an early termination visit as per the protocol.

### 1.2. Background Information on the Disease to be Treated

Alzheimer's disease (AD) is a fatal neurodegenerative disease that is manifested by progressive cognitive deficits and memory loss, as well as by behavioral problems such as anxiety. With the increasing number of elderly in the population, AD is a growing medical concern. No treatment is currently available that targets the underlying cause of these symptoms.

The hallmark pathologic features of AD are neurofibrillary tangles, which consist of hyperphosphorylated tau protein and amyloid plaques, whose main constituent is amyloid-beta ( $A\beta$ ). In amyloid plaques,  $A\beta_{1-42}$  peptide is overrepresented relative to other forms of  $A\beta$  (eg,  $A\beta_{1-40}$ ).  $A\beta_{1-42}$  has a high tendency to aggregate, forming oligomers and fibrils as well as amyloid plaques. The oligomers and fibrils of  $A\beta$  formed immediately after amyloid precursor protein (APP) cleavage have been demonstrated to be neurotoxic.<sup>50,111</sup>  $A\beta$  accumulation and amyloid deposition are thought to be early, potentially initiating events in the pathogenesis of AD, formulated as the amyloid cascade hypothesis.<sup>50</sup>

Convergent data from positron emission tomography (PET) amyloid imaging and cerebrospinal fluid (CSF) markers in both genetic and sporadic forms of AD suggest that the pathophysiological process begins many years prior to the onset of dementia.<sup>104,123</sup> The accumulation of  $A\beta$  in particular is thought to be a very early event that may trigger and accelerate neurodegeneration and lead to cognitive decline. Thus, very early intervention with an anti-amyloid agent may hold the greatest promise for slowing the inexorable disease progression of AD.<sup>116</sup>

Agents that prevent the formation of  $A\beta$  overall, or  $A\beta_{1-42}$  specifically, have been proposed as potentially disease-modifying agents for the treatment of AD.  $A\beta$  is generated from the APP as mentioned above. The N-terminus of  $A\beta$  is cleaved by the  $\beta$ -site amyloid precursor protein cleaving enzyme 1 (BACE1), and then  $\gamma$ -secretase cleaves the C-terminal end. BACE1 cleavage is the first and rate-limiting step. As such, it is hypothesized that BACE1 inhibition can reduce the production of toxic amyloid forms and impact the progression of AD. The observed correlation between the catalytic efficiency of BACE1 for its substrate APP and the occurrence of AD supports this hypothesis. The Swedish APP mutant (KM670/671NL), which is a more efficient substrate for BACE1 ( $\pm 10x$ ), causes a rare familial form of AD that is inherited in a dominant Mendelian fashion. At the other end of the spectrum, an allelic variant of APP

(A673T), which is a less efficient substrate for BACE1 ( $\pm 0.5\times$ ), is protective against sporadic AD in the wider population.<sup>61</sup>

Atabecestat is an orally administered BACE inhibitor (BACEi) being developed for the treatment of AD. Atabecestat reduces production of A $\beta$  fragments by inhibiting BACE1 processing of APP, with the aim of reducing amyloid plaque formation.

### 1.3. Target Population – Asymptomatic Subjects at Risk for Alzheimer’s Dementia

In recent years the United States (US) National Institute for Aging and the International Working Group have proposed guidelines to better define the preclinical (asymptomatic) stages of AD.<sup>30,116</sup> These working groups developed a hypothetical model for the pathophysiological process of AD that closely parallels the hypothetical biomarker model put forth by Jack et al.<sup>57</sup> These models postulate that A $\beta$  accumulation begins many years before the onset of overt clinical impairment. The key risk factors for elevated amyloid accumulation and development of AD are age (ie, 65 years or older), apolipoprotein E (*APOE*) genotype, and family history. Approximately one third of clinically normal older individuals over 75 years of age demonstrate evidence of A $\beta$  accumulation on PET amyloid imaging studies<sup>40,59,62,84,107,123</sup> or based upon CSF measurements.<sup>22,33</sup> Similar findings are seen in large autopsy studies.<sup>3,8,88</sup> These amyloid-positive (A $\beta$ +) clinically normal individuals consistently demonstrate evidence of an “AD-like endophenotype” on other biomarkers, including elevations in CSF tau and phosphorylated tau (p-tau),<sup>22,23,24,33,48</sup> disrupted functional network activity in both functional magnetic resonance imaging (MRI) and resting state connectivity,<sup>52,55,65,85,113</sup> fluorodeoxyglucose (<sup>18</sup>F) (FDG) hypometabolism,<sup>7,58</sup> cortical thinning, and accelerated rates of atrophy.<sup>6,14,24,25,60,108,110</sup> Multiple studies have now reported that higher A $\beta$  burden in clinically normal individuals is associated with evidence of subtle decreases in cognitive performance over time with changes that can be detected even within the range of “normal” values.<sup>14,28,51,62,77,91,93,98,99,105,115</sup> The accumulating longitudinal data also strongly suggests that A $\beta$  clinically normal individuals are at increased risk for cognitive decline and progression to mild cognitive impairment (MCI) and AD dementia.<sup>21,29,60,75,112,122</sup> Several published studies from the Alzheimer’s Disease Neuroimaging Initiative (ADNI), Australian Imaging Biomarker and Lifestyle (AIBL), and Mayo Clinic have confirmed a faster rate of cognitive decline in A $\beta$  clinically normal individuals.<sup>68,71,76,77,124</sup> The Alzheimer’s scientific community is of the consensus that these A $\beta$  clinically normal individuals represent an early stage in the continuum of AD pathology.

Recent publications have outlined 3 stages in the continuum of preclinical AD,<sup>116</sup> representing the full spectrum of asymptomatic, at risk subjects (Table 1).

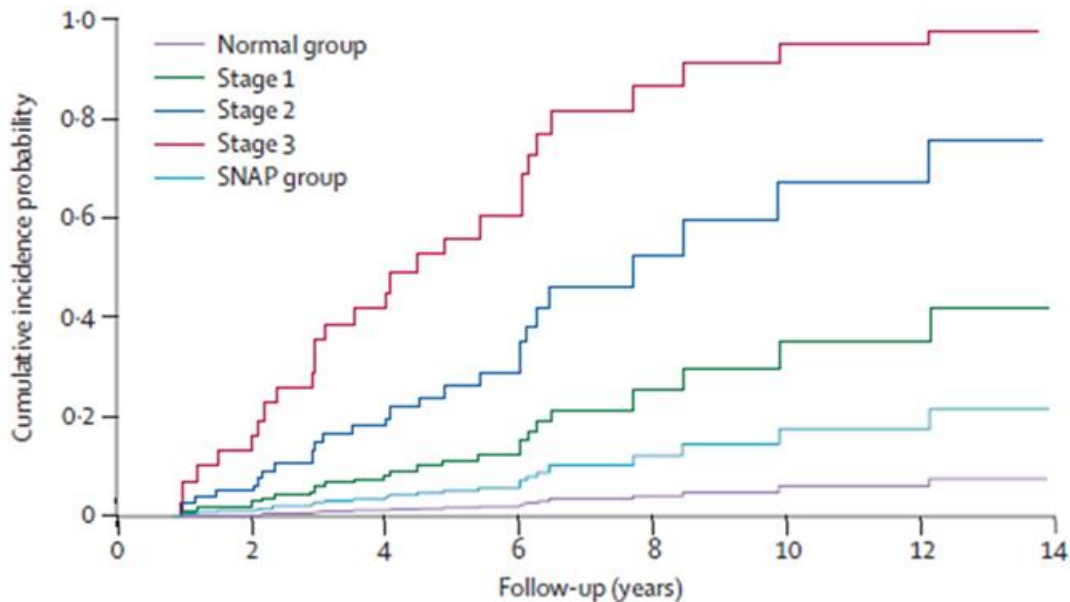
**Table 1: Staging Categories for Preclinical Alzheimer Disease Research**

Stage	Description	A $\beta$ (PET or CSF)	Markers of neuronal injury (tau, FDG, sMRI)	Evidence of subtle cognitive change
Stage 1	Asymptomatic cerebral amyloidosis	Positive	Negative	Negative
Stage 2	Asymptomatic amyloidosis +“downstream” neurodegeneration	Positive	Positive	Negative
Stage 3	Amyloidosis +neuronal injury +subtle cognitive/behavioral decline	Positive	Positive	Positive

Sperling et al.<sup>116</sup>

Abbreviations: A $\beta$ =amyloid-beta; PET=positron emission tomography; CSF=cerebrospinal fluid; FDG=fluorodeoxyglucose (<sup>18</sup>F); sMRI=structural magnetic resonance imaging.

These publications demonstrated that all 3 stages characterized in [Table 1](#) progress, and the progression is more rapid in Stage 3 relative to Stage 2, and similarly in Stage 2 relative to Stage 1 ([Figure 1](#)).

**Figure 1: Progression to Clinical Dementia Rating Scale Score of At Least 0.5 - Symptomatic Alzheimer’s Disease by Preclinical Alzheimer’s Disease Stage**Adapted from Vos et al.<sup>124</sup>

Abbreviation: SNAP: suspected non-Alzheimer’s pathology.

Janssen Research and Development’s (JRD) intention for the present Phase 2b/3 study is to investigate the effect of atabecestat in the population of individuals (60 to 85 years of age) who are asymptomatic and at risk of developing Alzheimer’s dementia due to evidence of elevated amyloid accumulation (ie, Stages 1, 2, or 3 of preclinical AD; see [Table 1](#)).



#### 1.4. Background Information on Atabecestat

Following is a summary of key nonclinical and clinical information on atabecestat. For a comprehensive report of nonclinical and clinical information, refer to the latest version of the Investigator's Brochure.

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.

##### Nonclinical

Repeated-dose toxicity studies up to 6 months duration in the rat and up to 9 months duration in the dog were performed; additionally a 6-month carcinogenicity study in the transgenic Tg.rasH2 mouse was performed. In general, repeated dosing of atabecestat was well tolerated in all species. Target organs were limited and were mostly only affected at high doses.

Discoloration of the fur, ie, from dark-brown to paler cream or grey, was observed in the 6-month carcinogenicity study in the Tg.rasH2 mouse from approximately 3 months of dosing at dose levels of  $\geq 100$  mg/kg/day. Rochin et al. (2013)<sup>104</sup> described the role of BACE-2 in melanogenesis with similar fur discoloration (depigmentation) in dark-colored mice. Therefore, it is likely that the discoloration, which showed at least partial recovery during a 3-month drug-free period, can be ascribed to BACE-2 inhibition by atabecestat. Standard histopathologic evaluation of the skin and of the pigmented parts of the eye (iris, retina), as well as ophthalmologic examination of the eye, did not reveal any relevant changes in this 6-month study. Similar changes cannot be detected in typically used albino animals (rats and mice), but in dog studies (eg, beagle dogs with colored fur), no change in fur color, no histological changes of the skin, and no changes of the pigmented parts of the eye were seen at either ophthalmologic or histopathologic examination at any dose level tested.

Based on the in vitro and in vivo safety pharmacology studies conducted, atabecestat has the potential to induce QTc prolongation and an increase in heart rate with an in vivo safety margin of approximately 9-fold (no observed effect level of 1,850 ng/mL after an oral dose of 10 mg/kg in the telemetered conscious dog Good Laboratory Practice [GLP] study) versus the exposure at a dose of 25 mg/day in humans (210 ng/mL at steady-state). Therefore an early thorough QT study was performed in the clinical program (see Clinical section below).

Atabecestat widely distributes in the whole body, with highest levels reached in pigmented tissue (eye and skin), adrenal gland cortex, liver, Harderian gland, preputial gland, and hypophysis. Two major routes of metabolism were observed in rat and dog in vivo and in human liver preparations in vitro: cytochrome P450 (CYP) 3A-mediated glutathione addition and amide hydrolysis to form the metabolite diaminothiazine (DIAT). In vitro data suggests the amide hydrolysis to form DIAT is not CYP-mediated.

Nonclinical in vitro data indicates that atabecestat is an inhibitor of certain drug transporters at anticipated steady-state drug concentrations achieved after a 25 mg once daily dose in humans,

namely breast cancer resistance protein (BCRP), organic cation transporter 2 (OCT2), or multidrug and toxin extrusion protein 1 or protein 2-K (MATE1 or MATE-2K, respectively).

A clinically relevant interaction between atabecestat at the highest investigated clinical dose (25 mg/day) and these transporters was excluded.

Three recent in vitro p-glycoprotein (P-gp)/multidrug resistance protein 1 (MDR1) inhibition studies have excluded clinically relevant P-gp inhibition by atabecestat per FDA and European Medicines Agency guidance documents.

Three in vitro P-gp/MDR1 inhibition studies were conducted with atabecestat. The initial single concentration screening in vitro P-gp-MDR1 inhibition study in LLC-PK1 cells (DMPK-2009-MTS-0385896A-07) presented 50% inhibition at the single concentration of 10  $\mu$ M tested, suggesting an IC<sub>50</sub> value of 10  $\mu$ M and a corresponding estimated K<sub>i</sub> value. Meanwhile a comprehensive in vitro P-gp/MDR1 inhibition study in LLC-PK1 cells (FK11041) was performed replacing the screening study. Study FK11041 presented an IC<sub>50</sub> value of 60.2  $\mu$ M, and, as the digoxin P-gp substrate concentration used was well below K<sub>m</sub>, an identical K<sub>i</sub> value. Furthermore, P-gp/MDR1 inhibition was examined in an alternative comprehensive in vitro P-gp/MDR1 inhibition study (FK10783). This study (FK10783) showed no inhibition up to the highest concentration of 100  $\mu$ M tested, implying an IC<sub>50</sub> value >100  $\mu$ M and a corresponding estimated K<sub>i</sub> value >50  $\mu$ M.

A clinically relevant P-gp inhibition by atabecestat at the highest investigated clinical dose (25 mg/day) was excluded.

### Clinical

JRD has completed a number of Phase 1 studies with atabecestat, including a proof of mechanism study in subjects with early AD (54861911ALZ1005) (treatment phase complete), and a proof of mechanism study in Japanese subjects (54861911ALZ1008). Several Phase 1 and Phase 2 studies are ongoing, including a bioavailability/food effect study with a 25 mg tablet (54861911ALZ1011), and a 6-month safety study in subjects with early AD (54861911ALZ2002). An extension study for subjects who have completed any Phase 2 study (54861911ALZ2004) will be conducted. A total of approximately 269 subjects have been exposed to atabecestat in the following completed single and multiple dose Phase 1 studies:

- 54861911ALZ1001 (single ascending dose [SAD], 1-150 mg, 42 received atabecestat)
- 54861911ALZ1002 (multiple ascending dose [MAD] [7-14 days exposure], 5-150 mg, 52 received atabecestat)
- 54861911ALZ1003 (single dose bioavailability/food effect, 25 mg, 12 received atabecestat)
- 54861911ALZ1005 (4 week dosing in subjects with prodromal AD (pAD) or asymptomatic at risk for Alzheimer dementia (ARAD), 10, 50 mg, 31 received atabecestat) (clinically complete)
- 54861911ALZ1006 (single ascending dose in Japanese subjects, 25, 50, 100 mg, 18 received atabecestat)

- 54861911ALZ1007 (multiple dose thorough QT study [7 days exposure], 50 mg and 150 mg, 64 received atabecestat)
- 54861911ALZ1008 (4week dosing in Japanese ARAD subjects 10, 50 mg, 12 received atabecestat)
- 54861911ALZ1009 (single dose CYP3A4 drug-drug interaction study, 25 mg, 13 received atabecestat)
- 54861911ALZ1010 (multiple dose CYP3A4, CYP2C9, and CYP1A2 cocktail drug-drug interaction study [8 days exposure], 50 mg, 16 subjects received atabecestat)
- 54861911ALZ1012 (single dose drug-drug interaction study for substrates of the transporters BCRP, MATE-1, MATE-2K, and OCT-2)

### *Safety*

In general, atabecestat has been well tolerated in the 9 clinical studies that have completed the treatment phase. Even the most common side effects were in the range of 1% to 6% (constipation, diarrhea, vomiting, fatigue, musculoskeletal stiffness, paresthesia, and somnolence), and these were considered as either not related or doubtfully related to atabecestat. Headache was seen in up to 20% to 30% of participants and back pain in up to 3% to 36% of subjects, but most likely related to CSF sampling procedures, as a known side effect of this procedure. Overall, the conclusion of these studies is that atabecestat was safe and well tolerated for the treatment durations studied.

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 atabecestat dose of 50 mg/day as well as a suprathreshold dose of 150 mg/day, and including moxifloxacin 400 mg to confirm assay sensitivity. The 150 mg dose showed a prolongation of the corrected QT interval (QTc) as defined by the International Council for Harmonisation (ICH) E14 guidance,<sup>a</sup> ie, the maximum mean difference (90% confidence intervals [CI]) between atabecestat 150 mg and placebo was 15.5 msec (12.92, 18.06) at Day 7, 1 hour 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 to 4 hours after dosing. The observed peak concentrations ( $C_{max}$ ) in the thorough QT trial (fasted drug administration) in healthy young subjects were slightly higher than those observed when the compound was given with food in Phase 1 studies in elderly healthy subjects. See Section 3.2.3 for QTc modeling information related to dose selection.

Magnetic resonance imaging findings consistent with cerebral vasogenic edema have been reported in clinical trials of amyloid-lowering compounds in AD. These amyloid-related imaging abnormalities – edema or effusion (ARIA-E) have been seen mainly with immunotherapy, less

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<sup>a</sup> ICH E14 Guidance for Industry: Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-arrhythmic drugs. US Department of Health and Human Services; Food and Drug Administration; Oct 2005.

frequently with other drugs, and occasionally on placebo and spontaneously. No cases of ARIA-E have been observed to date in trials of atabecestat, but they may be expected in all large amyloid-lowering trials of AD since they occur on placebo.

A 6-month Phase 2a safety study with atabecestat (54861911ALZ2002) in subjects who have early AD (predementia) was initiated in December 2014, and this study will be followed by a long-term extension study (54861911ALZ2004). Both studies will provide information on the safety of atabecestat 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 towards normal, and there were no lasting effects. The further investigation of this signal is continuing, but there is potential that atabecestat can cause injury to the liver and therefore more frequent monitoring of these liver tests has been included in this study. To date (17 March 2017), more than 200 subjects have received atabecestat 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  $>3 \times$  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 this Study 54861911ALZ2003, 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 atabecestat. As this subject's increase in ALT and AST were observed in Month 1, increased monitoring in the first 3 months of dosing has been introduced.

Based upon these cases, the protocol has been modified to include more frequent monitoring of serum chemistry and hematology (indicated in the Time and Events Schedule), guidelines for discontinuation of treatment due to abnormal liver enzymes (Section 10.2), and guidelines for evaluation and management of such cases (Attachment 3).

#### Pharmacokinetics, Metabolism, and Pharmacodynamics

Multiple dose pharmacokinetic results from Study 54861911ALZ1002 showed steady-state drug plasma levels were reached by Day 5, steady-state plasma  $C_{\max}$  and area under the concentration-time curve from 0 to tau hours postdosing ( $AUC_{\tau}$ ) were approximately dose proportional across the doses studied, and median time to maximum plasma concentration ( $t_{\max}$ ) was 2 to 4 hours. On Day 14, the mean terminal (apparent elimination) half-life ( $t_{1/2}$ ) ranged from 14.4 to 18.5 hours across doses, and mean accumulation ratios for steady-state  $C_{\max}$  and  $AUC_{\tau}$  ranged from 1.27 to 1.73 and 1.34 to 2.17, respectively.

Only minor metabolites were observed in human plasma from Study 54861911ALZ1002, and none of them were human specific. In Studies 54861911ALZ1001 and 54861911ALZ1002, the area under the plasma concentration curve (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.

For assessable doses in Study 54861911ALZ1001, atabecestat plasma exposure was similar between males and females, with male:female ratios for  $C_{\max}$  of 0.987 and 0.820, and for area

under the plasma concentration curve observed from administration to the last measurable concentration ( $AUC_{last}$ ) of 0.814 and 0.667 for the 30- and 150-mg dose groups, respectively.

Study 54861911ALZ1003 showed food had little effect on exposure to a atabecestat tablet formulation following a high fat/high calorie meal. In the fed state, median  $t_{max}$  was delayed by 1.5 hours compared to the fasted state.

Results from Phase 1 studies with atabecestat have confirmed observations in animal models (see Investigator's Brochure) in showing that this compound results in profound reductions in  $A\beta$  levels in the central nervous system. In the completed Phase 1 single- and multiple-ascending dose studies with atabecestat in healthy elderly subjects (SAD Study 54861911ALZ1001 and MAD Study 54861911ALZ1002), dose-dependent reductions in plasma and CSF  $A\beta_{1-40}$  were observed. The onset of inhibition was rapid (maximum reduction in plasma during first 4 hours postdose). The onset of  $A\beta$  reduction in CSF was delayed by about 6 hours, paralleling the expected time course of newly produced, brain-derived  $A\beta$ . In the MAD study, the reduction in CSF  $A\beta_{1-40}$  with atabecestat was between 85% and 90% with 30 mg/day and approximately 90% at doses of 50 mg/day or higher. In both studies, the decreases in plasma and CSF levels were relatively stable during the 36-hour postdose period. Preliminary analyses of a proof-of-mechanism study in a population with early AD (preclinical) (54861911ALZ1005) also showed dose-dependent reductions in  $A\beta_{1-40}$  in plasma and CSF following oral atabecestat administration parallel to the reductions seen in healthy volunteers. See Section 3.2.3 for  $A\beta_{1-40}$  modeling information from this study related to dose selection.

#### Drug-Drug Interactions

The effect of once daily administration of 200 mg itraconazole, a strong inhibitor of CYP3A4 activity, on the pharmacokinetics of atabecestat was evaluated in a clinical drug-drug interaction (DDI) study (Study 54861911ALZ1009). The results indicated that in the presence of itraconazole 200 mg once daily, JNJ54681911  $C_{max}$  and area under the plasma concentration curve extrapolated to infinity ( $AUC_{\infty}$ ) increased by 13% and 82% respectively, which is not considered clinically significant.

Results from a clinical DDI study to evaluate the interaction potential of atabecestat as perpetrator when co-administered with a drug cocktail of CYP3A4, CYP1A2, and CYP2C9 substrates (Study 54861911ALZ1010) did not show a clinically relevant effect of atabecestat on the activity of CYP3A4, CYP1A2, or CYP2C9.

Results from a clinical DDI study, to evaluate atabecestat 25 mg dosed once daily, demonstrated that atabecestat did not affect the single-dose PK of rosuvastatin (10 mg), a probe substrate for BCRP, and of metformin (500 mg), a probe substrate for MATE-1, MATE-2K, and OCT-2, thus showing there is no clinically significant drug-drug interaction between atabecestat and the substrates of the transporters BCRP, MATE-1, MATE-2K, and OCT-2.

## 1.5. Overall Rationale for the Study

The amyloid cascade hypothesis postulates that accumulating amyloid aggregates trigger a pathophysiological cascade (including acceleration of tau pathology) that leads to progressive neurodegeneration, neuronal loss, and cognitive impairment. Thus, it has been argued that intervention with a therapeutic agent that decreases A $\beta$  production is likely to be more effective if started at a disease stage before widespread neurodegeneration has occurred.<sup>64</sup> A number of sponsors are currently testing BACE inhibition at the stage of dementia or in prodromal AD. However, by the time individuals are symptomatic, there are already large pools of both soluble and insoluble forms of A $\beta$ , as well as widespread neuritic injury and irreversible neuronal loss, which are likely to make it more difficult to slow degeneration and preserve function.

The present Phase 2b/3 confirmatory registration study (54861911ALZ2003) is a multicenter, double-blind, placebo-controlled, randomized, parallel-group study designed to assess the efficacy and safety of once daily, oral administration of 2 doses of atabecestat (5 and 25 mg) over approximately 4.5 years treatment in amyloid-positive subjects (60 to 85 years of age) who are asymptomatic at enrollment and therefore at risk for development of AD. See Sections 3.1 and 4 for additional details on the study design and subject population.

The efficacy of atabecestat will be assessed in Study 54861911ALZ2003 using both cognitive and functional outcome endpoints. The persistence of the pharmacodynamic (PD) effect of atabecestat on A $\beta$  will be evaluated by measuring relevant biomarkers in plasma and CSF. Plasma and CSF A $\beta$  provide a direct read out of target engagement by atabecestat. Additional biomarkers to understand downstream effects and biological relevance include brain imaging (PET) to measure fibrillar amyloid and tau deposition, as well as markers of neurodegeneration in CSF. Safety assessments will include, but are not limited to, AEs, laboratory measures (hematology and clinical chemistry), vital signs, triplicate 12-lead electrocardiograms (ECG), physical, neurological, and dermatological examinations, suicidality risk, and MRIs.

Ongoing collection of safety data from Study 54861911ALZ2002 and 54861911ALZ2004 (extension study) will be monitored by a Data Monitoring Committee (DMC) and provided to the DMC of Study 54861911ALZ2003. This will help to develop a safety database and detect any potential safety issues early.

### **Risk-Benefit Evaluation of Study 54861911ALZ2003**

No clinical benefit of treatment with atabecestat has been demonstrated to date, but the mechanism of action and demonstrated pharmacodynamic effect (dose-dependent reduction of central A $\beta$ ) indicate a potential for a clinical meaningful effect for subjects treated in Study 54861911ALZ2003.

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

During the screening process, subjects will be informed of their personal biomarker status, which will involve the discussion of potential risks of developing cognitive deficits or symptoms of AD. Only subjects who are willing and capable of participating in this disclosure process are eligible for participation.

In addition to the above described signal on potential liver injury (Section 1.4), based on the preclinical data, 3 potential risks of atabecestat administration in humans have been identified: QT prolongation, progressive lightening of hair or skin, and seizure.

Preclinical data indicated the potential for QT interval prolongation. A thorough QT trial, Study 54861911ALZ1007, has been performed in 64 healthy subjects. The suprathreshold 150-mg dose showed a prolongation of the QTc interval, with a maximum mean difference and 90% CIs between atabecestat 150 mg and placebo of 15.5 msec (12.92, 18.06). The 50-mg dose showed a maximum mean difference from placebo of 6.6 msec (90% CI: 4.02, 9.12). At 50 mg, none of the subjects showed an increase of >30 msec or a QTcF value >480 msec. In both groups, the observed changes were most apparent 1 to 4 hours after dosing. Pharmacokinetic/pharmacodynamic modeling was performed to assess the relationship between atabecestat plasma concentrations and effect on QTcF prolongation. Results of this modeling activity showed that at a once-daily dose of 25 mg, the median changes in the QTcF, as well as the 90% population interval, are expected to remain well below 5 msec.

Additionally, in a 6-month carcinogenicity study in Tg.rasH2 mice, fur discoloration (progressive lightening) was observed from Day 85 onwards in animals dosed at 100 mg/kg/day or higher. 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, nor were ophthalmologic changes seen. Note that fur discoloration was, however, not seen in acute or chronic studies in beagle dogs. The no observable adverse effect level (NOAEL) for fur discoloration at 30 mg/kg/day has a safety margin of 9.9- (♂) to 15.3-fold (♀) (AUC) versus the 25-mg dose.

Preclinical data also suggested 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 100 mg/kg/day ( $C_{max}$  5.78 [♂] and 7.98 µg/mL [♀]). In a 9-month dog study, no CNS effects were observed up to the highest dose tested, ie, 60 mg/kg/day ( $C_{max}$  3.55 [♂] and 5.35 µg/mL [♀]). The highest dose in this clinical study will be 25 mg/day. Plasma drug concentrations in human subjects dosed 25 mg/day are expected to be approximately 16.9- to 25.5-fold lower than the NOAEL in the 9-month dog study.

In Study 54861911ALZ1009, once-daily administration of 200 mg itraconazole, a strong CYP3A4 inhibitor, increased the  $C_{max}$  and  $AUC_{\infty}$  of JNJ54681911 by 13% and 82%, respectively. As a result, even with this increase in  $C_{max}$ , no clinically relevant prolongation of QTc is expected with the 25-mg dose. Preliminary results of Study 54861911ALZ1010 indicate that atabecestat does not have a clinically relevant effect on plasma concentrations of the substrates of CYP3A4, CYP1A2, or CYP2C9. Based on these studies, it is recommended that

drugs that are moderate to strong inhibitors of CYP3A4 should be taken with an assumption that a moderate increase of atabecestat could be seen.

In addition to the potential compound-related risks, there are study procedure-related risks. All of these procedures (eg, blood draw, lumbar puncture [if applicable], ECG, MRI, and PET) are standard clinical assessments with limited associated risks for the subject and are described in the respective parts of this clinical study protocol.

An independent DMC will be commissioned for this study to review safety and other relevant data on an ongoing basis.

A placebo arm is necessary to allow for an accurate assessment of safety and tolerability, as well as the potential beneficial effect on cognition and function. Because there is at the moment no treatment available for subjects at risk for Alzheimer's dementia, the use of placebo is warranted. Initiation of approved symptomatic treatment is possible during the course of the study, if that is deemed necessary by the subject and the respective treating physician. Throughout the course of the study, the sponsor will have the option, based on recommendations by the DMC or on newly emerging safety, biomarker, or efficacy data from ongoing or completed atabecestat studies, to revise the dose levels in this study.

## **2. OBJECTIVES AND HYPOTHESES**

### **2.1. Objectives**

#### **Primary Objective**

- The primary objective of this study is to determine whether treatment with atabecestat slows cognitive decline compared with placebo treatment, as measured by a composite cognitive measure, the Preclinical Alzheimer Cognitive Composite (PACC), in amyloid-positive subjects who are asymptomatic at risk for developing Alzheimer's dementia.

#### **Secondary Objectives**

The key secondary objective of this study is the following:

- To determine if atabecestat will slow the decline of cognitive function and performance of everyday activities, compared with placebo, based on the Cognitive Function Index (CFI).

The other secondary objectives of this study are the following:

- To assess the overall safety and tolerability of atabecestat versus placebo.
- To determine if a decline in activities of daily living can be detected based on the ADCS-Activities of Daily Living-Prevention Instrument (ADCS-ADL-PI) scale, and if so, to assess the effect of atabecestat compared with placebo.
- To compare changes in cognitive performance between atabecestat and placebo based on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).



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- To determine if the Neuropsychological Assessment Battery–Daily Living Tests (NAB-DLTs) for Memory and Attention can detect decline in cognitive function, and if so, to assess the effect of atabecestat compared with placebo.
  - To assess the effect of atabecestat compared with placebo on the Clinical Dementia Rating (CDR) scale, including progression from CDR 0 to CDR 0.5 or higher.
  - To assess the plasma and CSF pharmacokinetics (PK) of atabecestat following chronic treatment using a population PK approach and to explore their relationship with efficacy and safety parameters (including biomarkers).
  - To assess the effects of atabecestat on accumulation of cerebral fibrillar amyloid, as measured by amyloid PET imaging.
  - To assess the effects of atabecestat on markers of neurodegeneration (eg, tau peptides) in CSF compared with placebo.
  - To assess the maintenance of atabecestat effects on markers of A $\beta$  processing in CSF and plasma compared with placebo.

### Exploratory Objectives

The exploratory objectives of this study are the following:

- To investigate the effect of atabecestat compared with placebo on brain volume as measured by volumetric MRI.
- To investigate the impact of atabecestat compared with placebo on markers of synaptic dysfunction on task-free functional MRI.
- To assess the effects of atabecestat on additional downstream markers of neuronal injury, neurodegeneration, or inflammation in CSF compared with placebo.
- To assess the effects of atabecestat on progression of tau spreading pathology in the brain as measured by tau PET imaging.
- To explore if baseline markers of neurodegeneration (eg, volumetric MRI, CSF t-tau or p-tau, or tau PET) are related to cognitive decline and response to treatment with atabecestat.
- To explore the correlation between the effect of atabecestat on biomarkers (eg, amyloid PET, plasma A $\beta$ , CSF A $\beta$  and t-tau or p-tau, tau PET) and clinical outcomes.
- To explore the impact of disclosure of amyloid status on questionnaires probing subject perception of amyloid imaging and concern about developing AD dementia.
- To investigate the effect of atabecestat compared with placebo on cognition as measured by a computerized cognitive battery.
- To investigate the effect of atabecestat compared with placebo on function as measured by the Financial Capacity Instrument (FCI).
- To investigate the effect of atabecestat compared with placebo on medical resource utilization as measured by the Healthcare Resource Utilization Questionnaire (HRUQ) scale.

- To investigate the effect of atabecestat compared with placebo on health outcomes as measured by the Short Form-36 (SF-36) and European Quality of Life-5 Dimensions 5-level (EQ-5D-5L) scales.
- To explore the ability of the Cognitive Function Index-acute (CFI-a) to measure decline of cognitive function and performance of everyday activities.
- To explore the effect of atabecestat compared with placebo on instrumental activities of daily life (IADL) as measured by the Amsterdam IADL questionnaire (A-IADL-Q).

## **2.2. Hypotheses**

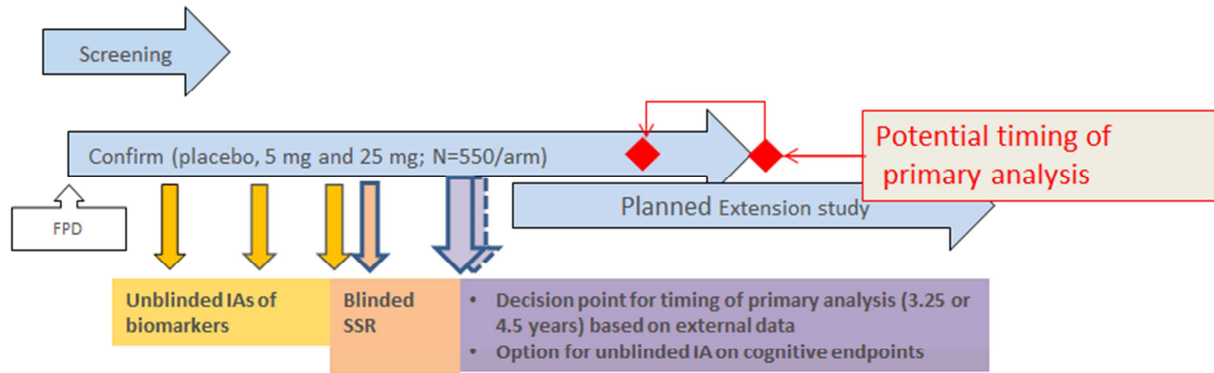
The primary hypothesis is that cognitive decline, as measured by the PACC change from baseline at Month 54 (Year 4.5), will be significantly less for subjects treated with either atabecestat dose in comparison to subjects treated with placebo. The key secondary hypothesis is that functional decline, as measured by the CFI change from baseline at Month 54 (Year 4.5), will be significantly less for subjects treated with either atabecestat dose in comparison to subjects treated with placebo.

## **3. STUDY DESIGN AND RATIONALE**

### **3.1. Overview of Study Design**

This is a multi-center, double-blind, placebo-controlled, randomized, parallel-group study assessing the efficacy and safety of atabecestat over approximately 4.5 years of treatment in subjects (60 to 85 years of age) who are asymptomatic and at risk for developing Alzheimer's dementia due to evidence of elevated amyloid accumulation based on CSF or amyloid PET imaging (see Section 3.2.2 and complete definition of study population in Section 4).

The study will consist of 3 phases: a screening phase of approximately 90 days during which subject eligibility will be assessed; a fixed dose, double-blind treatment phase during which eligible subjects will receive randomly assigned study drug once daily for up to 4.5 years; and a follow-up phase to be conducted 7 to 28 days after the last dose of study drug. This study will be conducted in an outpatient setting. The maximum study duration for a subject will be 58 months (3-month screening phase + 54-month double-blind treatment phase +1-month follow-up phase). A diagram of the study design is provided in [Figure 2](#).

**Figure 2: Schematic Overview of Design for Study 54861911ALZ2003**

### Continuous safety monitoring by DMC + Interim biomarker analyses

DMC=Data Monitoring Committee; FPD=first patient date; IA=interim analysis; SSR=sample size re-estimation.

Subjects who meet all of the study inclusion criteria (Section 4.1) and none of the study exclusion criteria (Section 4.2) will be assigned randomly to 1 of 3 treatment groups in a 1:1:1 ratio at the start of the double-blind treatment phase: atabecestat 5 mg, atabecestat 25 mg, or placebo (see Section 3.2.3 for dose selection rationale). Approximately 1,650 subjects (550 per treatment group) will be randomized in order to achieve a total of 1,155 subjects (385 per treatment group) who complete the Month 54 (Year 4.5) assessments (assumed 30% attrition rate per treatment group), as outlined in Section 11.2. The number of subjects randomized can be increased based on blinded sample size re-estimation, but the study enrollment will be capped at 2,400 subjects. At randomization, subjects will be stratified by country, and by apolipoprotein E (*APOE*)  $\epsilon 4$  carrier status (carrier vs noncarrier) (see Section 5).

In addition to longitudinal follow-up of subjects' screening biomarker(s) (ie, amyloid PET and/or CSF), subjects will have the opportunity to participate in 1 or more longitudinal PD substudies: CSF for biomarkers and drug exposure, amyloid PET imaging, and tau PET imaging (see Section 3.2.6). Longitudinal tau PET imaging will be open to all subjects enrolled at sites having access to this technology, and subjects who elect to undergo these assessments will provide separate informed consent for this procedure. When sufficient longitudinal biomarker data has been collected, further collection of biomarker data can be terminated to reduce patient and site burden.

An informant (eg, relative, partner, or friend) will be used in this study (see Section 4.1, Inclusion Criterion 7). The informant will provide subject information on clinical scales, and may help with handling and dispensing of study drug, or reporting of AEs. Because of the informant's critical role for several endpoints, a second, replacement informant should be identified, preferably prior to Day 1.

Some design elements of this Phase 2b/3 study can be modified during the trial based on emerging external data. The potential changes include optimization of the primary endpoint and

the timing of the primary analysis. Sample size may be adjusted based on review of blinded aggregated study data. Unblinded interim analyses (IAs) may be performed to assess futility.

An independent DMC will be commissioned for this study to review safety and other relevant data on an ongoing basis, and to review findings from the potential IAs and make recommendations based on prespecified decision rules. (see Section 11.11).

### **3.2. Study Design Rationale**

#### **3.2.1. Blinding, Control, Study Phase/Periods, Treatment Groups**

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment. Central randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints and AEs.

Stratification of subjects (see Section 5) by country and *APOE* ε4 carrier status will be used to prevent disproportionate representation in any treatment group. In particular, *APOE* ε4 carrier status could influence treatment effects as it may be associated with a more extensive amyloid deposition pattern.

#### **3.2.2. Study Population**

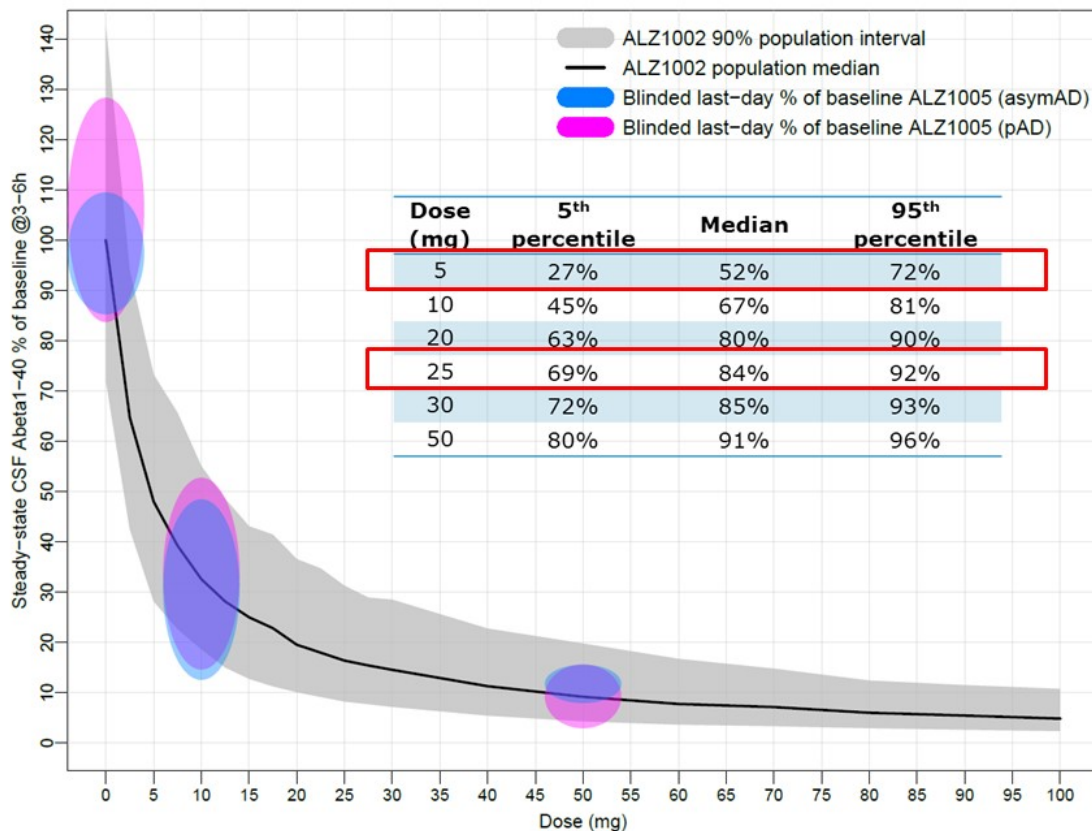
The target population for Study 54861911ALZ2003 will consist of amyloid-positive individuals without apparent cognitive deficits (preclinical stage) who are 60 to 85 years of age, inclusive. Specifically, subjects in this study will be defined as those individuals with evidence of elevated cerebral amyloid accumulation at screening as indicated by low CSF Aβ<sub>1-42</sub> levels or high amyloid brain burden as shown on an amyloid PET scan, and showing no clinically evident cognitive impairment at screening and functionally normal, as demonstrated by a CDR score of 0. Individuals meeting these criteria are considered to be in the preclinical stage of AD,<sup>116</sup> demonstrating evidence of elevated amyloid accumulation and often early signs of neurodegeneration but without widespread, irreversible neuronal loss. The preclinical stage of AD may precede MCI by several years, and represents an important stage for potential early intervention aimed at slowing the pathophysiological process and delaying the appearance of the clinical manifestation of AD. As discussed in Section 1.3, such individuals are at a particularly high risk for cognitive decline and progression to MCI and Alzheimer's dementia.

The age range for subjects in this study is 60 to 85 years inclusive at the start of screening. The key risk factors for elevated amyloid accumulation and development of AD are age (ie, 65 years or older), *APOE* genotype, and family history.

### 3.2.3. Dose Selection

The optimal level of therapeutic A $\beta$  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. Data from completed SAD and MAD studies in healthy older subjects and from preliminary analyses of a proof-of-mechanism study in a population with early AD (preclinical) (54861911ALZ1005) showed dose-dependent reductions in A $\beta_{1-40}$  in plasma and CSF following oral atabecestat administration (Section 1.4). PK/PD modeling of preliminary data (Figure 3) from the proof-of-mechanism study (54861911ALZ1005) shows that the median reduction from baseline (averaged over 24 hours, at steady-state) in CSF A $\beta_{1-40}$  with a 25 mg/day dose would be about 84%. Doubling the dose to 50 mg/day would further reduce this by only about 7% (ie, to 91%). At the lower dose of 5 mg/day, the subjects in this study are expected to have about a 50% reduction from baseline in CSF A $\beta_{1-40}$ .

**Figure 3: Modeling of CSF A $\beta_{1-40}$  Reduction (graph) and Population Predicted Percentiles of CSF A $\beta_{1-40}$  Reduction at Steady State (table) in Subjects in the Early Alzheimer's Disease Spectrum (Preliminary Data from Study 54861911ALZ1005)**

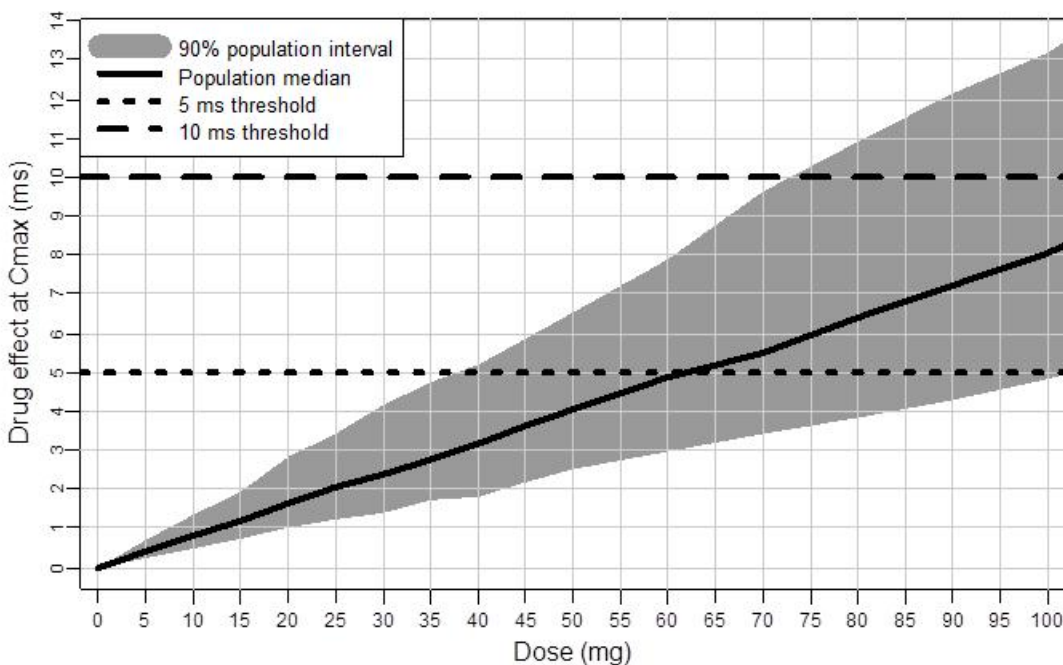


Embedded chart shows population percentiles of steady-state mean CSF A $\beta_{1-40}$  percent of baseline values versus atabecestat dose. 50th refers to the median values, while '95th' and '5th' refer to the high and low borders of the population interval, respectively.

Abeta=amyloid-beta; CSF=cerebrospinal fluid; pct=percentage.

PK/PD modeling was also performed to assess the relationship between atabecestat plasma concentrations and effect on QT interval corrected for heart rate according to Fridericia (QTcF) prolongation, using data from Study 54861911ALZ1007 (Figure 4). The PK profiles were then simulated from a previous population PK model based on Study 54861911ALZ1002 (healthy elderly subjects, fed state), and the distribution of the drug's effect on QTcF prolongation was evaluated at the maximum plasma concentration of the simulations for each dose level. Results of this modeling activity showed that at a dose of 25 mg once daily, the median change in the QTcF and 90% population interval are expected to be well below 5 msec.

**Figure 4: Pharmacokinetic/Pharmacodynamic Modeling of QTcF Prolongation Based on Expected Exposures and Observed QTcF Values from Study 54861911ALZ1007**



$C_{max}$ =peak concentration; ms=millisecond.

Based on the available clinical data for atabecestat, doses of 5 and 25 mg once daily were selected for evaluation in Study 54861911ALZ2003. These doses have not been associated with significant safety signals in early clinical trials and are expected to be well tolerated and to achieve substantial reductions in CSF  $A\beta_{1-40}$  and  $A\beta_{1-42}$  at steady-state.

### 3.2.4. Study Duration

Evidence from observational studies such as ADNI and AIBL indicates that, over 3 years, subjects with elevated amyloid accumulation demonstrate a decline in episodic memory that is measurably greater compared with individuals without biomarker evidence of AD.<sup>26,122,123</sup> In these subjects with preclinical AD, progression from normal cognition to cognitive impairment occurs in 10% to 50% of individuals over 2 to 5 years.<sup>26,120,123,124</sup> The variance in progression was accounted for, in part, by a greater decline in individuals with evidence of neuronal degeneration in addition to amyloid burden.

If the study hypothesis is correct, namely that the decrease in amyloid burden with atabecestat treatment has a positive downstream effect on cognition, it is likely that additional time will elapse between the initial reduction in cerebral A $\beta$  and detection of a cognitive effect. Based on these considerations, a treatment period of approximately 4.5 years is believed to be an appropriate duration to evaluate the efficacy of atabecestat compared to placebo in slowing cognitive decline in subjects. The treatment period and timing of the primary analysis may be shortened to 3.5 years if supported by external data on the rate of decline in placebo-treated subjects (see Section 11.4.2).

### 3.2.5. Cognitive and Functional Outcome Measures

Clinical endpoints in this study include both cognitive tests (PACC, RBANS, NAB-DLTs for Memory and Attention, and computerized cognitive battery [selected centers only]) and other clinically relevant functional outcome measures (CFI, CFI-a, ADCS-ADL-PI, CDR, A-IADL-Q [selected centers only] and FCI [selected centers only]), which will be administered at the time points indicated in the Time and Events Schedule. The selected tests are included to evaluate the cognitive and functional decline among subjects and to determine which of these assessments are most sensitive to disease progression.

Cognitive decline is the earliest measurable clinical manifestation of AD; however, different cognitive domains have been shown to progress at different rates,<sup>118</sup> with episodic memory, executive function, and orientation showing change early in the course of the disease.<sup>26,43,120</sup> The primary outcome measure selected for the current Phase 2b/3 study is the PACC, a retrospectively validated composite that is weighted towards episodic memory and includes a timed executive function test and a global cognitive screening test. The PACC composite is composed of the following (see also Section 9.2.1): (1) the Free and Cued Selective Reminding Test (FCSRT)<sup>34,44,45</sup> for list learning (episodic memory); (2) the Delayed Paragraph Recall Score<sup>129</sup> for memory of written language; (3) the Coding Subtest from the Wechsler Adult Intelligence Scale-IV (WAIS-IV)<sup>128</sup> for timed executive function; and (4) the Mini Mental State Examination (MMSE)<sup>35</sup> for a global screening test that emphasizes orientation.

The PACC is designed to serve as the primary outcome measure for trials conducted in the asymptomatic phase of AD, with a sufficient range to detect an early decline in the preclinical stages of AD. As described in Section 3.2.4, retrospective analyses of data from observational studies in populations with preclinical AD (ADNI, ADCS, and AIBL) suggested that the PACC is sufficiently sensitive to cognitive decline in the preclinical AD population to be used in a prospective clinical trial for detecting a slowing of cognitive decline.<sup>26</sup> Although experience with the PACC is still limited, longitudinal and interventional data for the included elements is more extensive than for other candidate measures for the study of asymptomatic subjects at risk of Alzheimer's dementia, and the PACC is currently being used in another large clinical trial of preclinical AD (ie, ADCS A4 Study2). For these reasons, the PACC is identified as the primary efficacy measure for this Phase 2b/3 study of atabecestat.

The RBANS is a widely-used measure to differentiate healthy normal individuals from those with MCI or AD, is predictive of functional status,<sup>4</sup> and correlates with the CDR,<sup>53</sup> biomarkers,<sup>36,131</sup> and cognition.<sup>31</sup>

The CFI, CFI-a, and ADCS-ADL-PI are instruments used to track early changes in function such as the ability to perform high-level activities of daily living and individuals' perception of their own ability to perform cognitively demanding functional tasks. These measures demonstrated significant decline in individuals who progressed to MCI in the ADCS-Prevention Instrument study.<sup>26</sup>

The A-IADL-Q is a computerized questionnaire aimed at measuring difficulties with complex daily activities. It is completed by the informant of the subject.

The CDR is a global scale with 'face' validity, in that it assesses the influence of cognitive loss on the ability to conduct every day activities.<sup>89</sup> The CDR is well-established for staging AD and has been used extensively in trials of MCI and AD.<sup>101</sup> Only minimal changes in this score are expected over 4.5 years in individuals who are not functionally impaired at baseline.

In addition to the cognitive and functional measures described above, the NAB-DLTs for Memory and Attention will be administered in Study 54861911ALZ2003, as listed in the Time and Events Schedule. These are objective measures of performance on clinically relevant tasks in specific domains. Positive results on these tests would provide further evidence that any treatment effects for atabecestat on other cognitive endpoints are clinically relevant.

The computerized cognitive battery provides rapid, sensitive, and valid measurements of distinct cognitive function. The tests use novel visual and verbal stimuli to ensure assessments are independent of any cultural context. Additionally, the battery is designed for repeated administration with minimal practice or learning effects and is easy to administer. The battery has demonstrated sensitivity to individual cognitive change subsequent to administration of a wide variety of pharmacological agents and in a wide variety of populations and indications.

Issues of financial capacity are frequently seen in subjects with AD, and recent studies have shown that the ability to manage financial affairs may be 1 of the first functional changes to occur in the course of Alzheimer's dementia.<sup>80</sup> The FCI is a validated instrument that can potentially measure these early functional changes.

### **3.2.6. Biomarkers**

Fluid biomarker assessments (CSF [maximally 12 mL sample], blood [protein, genomic (DNA)], and gene expression [RNA], peripheral blood mononuclear cell [PBMC]) and imaging biomarker assessments (MRI, PET) will be performed during screening to assess the baseline status for these biomarkers as well as during the double-blind treatment phase (except PBMC). This biomarker data may be used for translational biomarker research related to atabecestat or the diagnosis of AD. Collections may be modified based on local rules and regulations. See also Section 3.2.6.2 for additional blood tests.



### 3.2.6.1. Determination of Elevated Amyloid Accumulation at Screening

At screening, amyloid status will be evaluated in all subjects using either CSF A $\beta$ <sub>1-42</sub> concentrations as measured using a validated assay, or brain amyloid burden by PET imaging, or both. Study eligibility will be determined by a positive result showing evidence of elevated amyloid accumulation on either evaluation.

Each of the 2 biomarkers has been shown to identify cognitively normal individuals who are at risk of developing cognitive decline and progression to MCI and/or Alzheimer's dementia.<sup>68,71,77,87</sup> Further, either of these measures is considered appropriate for this use since both have been shown to yield sufficiently concordant results.<sup>72,91,92</sup> Allowing either biomarker to establish the amyloid positivity of subjects at enrollment permits utilization of regional and center-specific common practices, expertise, and preferences for measurement of 1 biomarker versus the other.

For amyloid screening by CSF, a CSF A $\beta$ <sub>1-42</sub> assay performed at a single laboratory with demonstrated high sensitivity and specificity will be used. The use of a single laboratory allows for the use of a single threshold and simplifies operational logistics. Similarly, a single imaging agent will be used for amyloid PET imaging to simplify operational logistics and allow for the standardized analyses of the PET scans.

If alternative CSF assays or amyloid PET agents would demonstrate sufficient clinical validation, those could be used as additional or alternative agents. The procedures will be documented in the laboratory manual and imaging manual/charter, respectively.

### 3.2.6.2. Fluid Biomarkers (Other than CSF A $\beta$ for Screening)

CSF and blood samples (protein, genomic [DNA], and gene expression [RNA], PBMC) will be collected during the study to allow for the evaluation of whether the PD effects of atabecestat are consistent with the putative effects of BACE inhibition, to allow for the evaluation of the effect on markers of disease expression, and to potentially aid evaluation of the drug-clinical response relationship. See also subsection below (Peripheral Blood Mononuclear Cell Sampling) for additional blood tests.

#### CSF Biomarkers

Longitudinal CSF samples will be collected from subjects with available baseline measurements for evaluation of treatment effects on CSF markers of target engagement and downstream biomarkers of neurodegeneration and/or other disease processes.

#### *CSF A $\beta$ profiling*

A $\beta$  fragments of different length are produced by cleavage of the APP by BACE and the  $\gamma$ -secretase complex in the brain and excreted into CSF. BACE cleavage initiates the A $\beta$  production at the N-terminal end of the A $\beta$  fragment, which then is further processed at the C-terminal end by the  $\gamma$ -secretase complex, while cleavage by  $\alpha$ -secretase prevents A $\beta$  fragment formation.

As A $\beta$  turnover rates are rapid, inhibition of BACE results in a reduction of all A $\beta$  fragments in CSF over the course of several hours. Reduction in CSF A $\beta$  over the duration of treatment will confirm persistence of activity of atabecestat based on its mechanism of action and demonstrate maintenance of therapeutic effect. Different A $\beta$  fragments (eg, A $\beta$ <sub>1-37</sub>, A $\beta$ <sub>1-38</sub>, A $\beta$ <sub>1-40</sub>, and A $\beta$ <sub>1-42</sub>) will be measured. The primary CSF biomarker used to confirm atabecestat target engagement in CSF is A $\beta$ <sub>1-40</sub> as it is the most prevalent. CSF A $\beta$ <sub>1-42</sub> will be used to confirm study eligibility (see Section 4).

Exploratory analyses for soluble APP-alpha (sAPP $\alpha$ ; cleaved at the alpha-secretase site) and sAPP-beta (sAPP $\beta$ ; cleaved at the BACE/ $\beta$ -secretase site) may be conducted. Measures of APP processing (sAPP $\alpha$  and total sAPP) may be used to assess potential amyloid accumulation and related safety aspects.

### ***CSF Biomarkers (Other than CSF A $\beta$ )***

CSF tau protein levels will be examined in a subset of subjects. Tau proteins are normally associated with tubulin polymers to stabilize the microtubule system essential for normal neuronal function.<sup>74</sup> However, tau is hyperphosphorylated in AD and is the main component in paired helical filaments, which then associate to form neurofibrillary tangles in the cytoplasm of many neurons.<sup>18,19,20,38,39,46</sup> An elevation in levels of tau is indicative of axonal injury and neurodegeneration downstream of the initiating pathology.

The increase in hyperphosphorylated tau in CSF is relatively specific to AD and therefore distinguishes AD from other neurodegenerative disorders.<sup>47</sup> As the change in CSF p-tau levels is a marker for neurodegeneration, it is believed to be predictive of changes in cognition over time. In the asymptomatic population at risk for developing Alzheimer's dementia, tau pathology may only be starting to develop and as such not detectable in all subjects. Thus, prevention of CSF tau accumulation may be indicative of an impact of therapy on a downstream neurodegenerative process.

Other exploratory measures that may be evaluated in this study include additional downstream biomarkers of neuronal injury (eg, visinin like protein 1 [VILIP-1], neurofilament light chains [NFLs]<sup>119</sup>), inflammation (eg, YKL-40<sup>17</sup>), and synaptic components involved in memory and cognition with potential utility as biomarkers of synaptic dysfunction (eg, neurogranin<sup>70</sup> and GAP43<sup>95</sup>). These exploratory biomarkers may further extend the understanding of the effect of atabecestat and of the disease in the study population.

### **Plasma A $\beta$ Sampling**

Pharmacodynamic markers in blood samples will be evaluated. A $\beta$  fragments can be measured in plasma, similar to CSF, although concentrations are typically lower and more difficult to quantify due to interference with other plasma proteins. It is the intention to measure various A $\beta$  fragments in plasma (primary: A $\beta$ <sub>1-40</sub>; exploratory: eg, A $\beta$ <sub>1-37</sub>, A $\beta$ <sub>1-38</sub>, and A $\beta$ <sub>1-42</sub>). Additional exploratory measures in plasma may include, but are not limited to, sAPP fragments (sAPP $\alpha$ , sAPP $\beta$ , total sAPP).

## Genomic and Gene Expression Markers

Genetic variation can be an important contributory factor to inter-individual differences in drug distribution and response, and can also serve as a marker for disease susceptibility and prognosis. Genetic factors may help to explain inter-individual variability in clinical outcomes and may help identify population subgroups that respond differently to a drug. For example, rare variants in the APP gene have been shown to be protective via reduced BACE cleavage activity.<sup>61</sup> The goals of the genomic component are to conduct *APOE* genotyping for screening and to collect DNA to allow for the identification of genetic factors that may influence the PK, PD, safety, or tolerability of atabecestat or pathways related to AD and A $\beta$  processing/metabolism, as needed.

For all subjects, the *APOE* genotype will be determined and utilized as a stratification variable (see Section 5). *APOE* is involved in several key A $\beta$ -mediated processes associated with AD, including the distribution, clearance and/or metabolism of A $\beta$ , altered lipid-binding properties leading to an augmentation of A $\beta$ -mediated toxicity (eg, disruption of lysosomal storage), and formation of aggregates that may promote A $\beta$  nucleation and plaque formation. The *APOE*  $\epsilon$ 4 gene product also has a preference to bind with large, triglyceride rich lower density lipoproteins. In addition, *APOE*  $\epsilon$ 4 is indicated to be less effective at the transport of high density lipoproteins (cholesterol-rich) required for neuronal maintenance and repair.<sup>11,121</sup> The *APOE*  $\epsilon$ 4 allele is considered the most significant genetic risk factor for AD and is associated with a decreased age of onset of the disease.<sup>121</sup> Increasing *APOE*  $\epsilon$ 4 allele dosage (0, 1, 2 alleles) has been shown to be associated with greater brain amyloid burden and greater rate of brain amyloid accumulation,<sup>40</sup> and has been suggested to influence cognitive decline.<sup>121</sup> In addition, response to treatment for AD might differ with different *APOE* genotypes.<sup>109</sup>

The blood sample will also allow for potential exploratory pharmacogenomic analysis. For all subjects, blood samples for plasma and RNA will also be collected to analyze gene expression profiles to allow for translational biomarker research related to atabecestat. Collections may be modified based on local rules and regulations.

## Peripheral Blood Mononuclear Cell Sampling

A PBMC sample (and concomitant platelet-rich plasma sample) will be collected at screening from all subjects at sites capable of processing PBMC samples to explore the humoral immune response to AD-related proteins in subjects who are asymptomatic and at risk for developing Alzheimer's dementia. It is anticipated that individuals in the early (predementia) AD spectrum may have a more matured anti-tau immune response and/or a response of greater magnitude relative to healthy control individuals (subjects without elevated amyloid accumulation) due to longer-term exposure to the altered forms of tau that accumulate in the brain during AD.

Subjects who experienced significant hepatic enzyme elevations may be asked to volunteer for a specialized immunologic substudy to determine possible mechanisms for hepatic enzyme elevation. This will require an additional blood draw of 120 mL (see Attachment 4 for details). The decision to take this blood draw must take into account other blood draws that have been taken for the subject. No subject should donate more than 450 mL in any 3-month period based on American Red Cross guidelines.

### 3.2.6.3. Imaging

#### MRI

A brain MRI will be performed at screening to assess study eligibility, for safety monitoring during the trial, and for brain volumetric and functional analyses. The screening eligibility brain MRI will be performed to document that there is no other clinically relevant disease that could impair the subject's cognitive status independent of the AD-related elevated amyloid accumulation.

Ongoing brain MRI monitoring will be performed during the trial for routine safety assessments and to monitor for potentially treatment-related radiological safety events that have been reported with other AD therapies (see Section 1.4).<sup>114</sup> Brain volume (global and regional) measurements will be performed to better understand how brain volumes change in the study population and in relation to therapy and clinical outcomes. Brain atrophy and ventricular enlargement are well described phenomena in AD, and reflect cumulative neuronal and synaptic loss and the extent of neurofibrillary pathology.<sup>1,130</sup> Prior studies have shown significant correlations between rates of brain atrophy and cognitive decline.<sup>59,100</sup> Brain atrophy begins, and is most severe, in the medial temporal lobe, particularly the entorhinal cortex and hippocampus. This neurodegenerative atrophy spreads to adjacent and higher multi-modal association cortices, and is associated with progressive dementia which is due to neuronal dysfunction.

Functional neuroimaging techniques, which have the potential to elucidate the neural underpinnings of the cognitive impairment in AD, and to serve as important biomarkers of therapeutic effect and disease progression, will also be included. Functional MRI may provide useful information about the functional integrity of brain networks supporting memory and other cognitive domains, including the neural correlates of specific behavioral events. Diffusion tensor imaging (DTI) measurements will be included as these reflect brain axonal integrity and white matter connectivity.

#### Amyloid PET Substudy

Brain amyloid burden by PET imaging will be measured longitudinally in a subset of subjects, including all those who select this biomarker as a criterion for study entry. High abnormal brain amyloid burden is a key hallmark of AD,<sup>67,111</sup> and it is possible to detect brain amyloid burden in vivo without the need to rely on postmortem neuropathologic confirmation of an in-life clinical diagnosis of probable AD.<sup>82,83</sup> It is now recognized that amyloid accumulation in the brain is an early event in the disease process and initiates decades prior to the onset of AD dementia.<sup>5,60,123</sup> Amyloid PET imaging is an in vivo method to measure brain amyloid burden. An amyloid PET scan is 1 of the 2 methods by which elevated amyloid accumulation will be determined for enrollment eligibility. In addition, brain amyloid burden by PET in brain regions known to accumulate amyloid in AD (eg, frontal, medial temporal, or parietal cortices; anterior and posterior cingulates) as well as a global composite will be measured over the course of the study to evaluate the impact of therapy on brain amyloid burden.

## Tau PET Substudy

Brain tau burden by tau PET imaging will be measured longitudinally in a subset of subjects only at those sites with the technical capabilities to do so. In addition to the hallmark pathological feature of brain amyloidosis, AD is also characterized by the downstream neuropathological feature of neurofibrillary tangles consisting mainly of hyperphosphorylated tau proteins, with properties that enable fibril formation. The work of Braak<sup>9</sup> and others have shown the progressive increase and spread of pathological brain tau in AD using postmortem immunohistochemical methods. In addition, neurofibrillary (tau) tangles are linked to the duration and severity of AD.<sup>56</sup> Tau PET imaging is an in vivo method to measure brain tau burden and can track accumulation. Early results with [<sup>18</sup>F]-T807 PET suggest that signal intensity and spread are linked to the severity of the cognitive impairment,<sup>15,16</sup> which parallels earlier pathology-based observations by others.

The baseline tau signal in specified brain regions, including those known to accumulate tau early in the disease process (eg, hippocampus, amygdala, and parahippocampus) will be measured to determine the degree of tau pathology at study entry. In addition, pathological tau burden by PET in these specified regions and in a global composite will be measured over the course of the study to evaluate the impact of therapy on pathological tau burden.

### 3.2.7. Safety Evaluations

During the double-blind treatment phase, regular safety assessments will be performed as listed in the Time and Events Schedule. These safety assessments include but are not limited to AE and concomitant medication monitoring; clinical laboratory test determinations (hematology, clinical chemistry, urinalysis); vital sign measurements; physical and neurological examinations; and assessment of suicidality risk using the Columbia Suicide Severity Rating Scale (C-SSRS; see Section 9.5.8). Triplicate ECGs will also be routinely recorded postdose at the time point corresponding to anticipated greatest changes in QTc as indicated by the results of the thorough QT study 54861911ALZ1007 (see Section 1.4 and Section 3.2.3) (ie, 1 to 4 hours postdose) for evaluation of potential for QTc prolongation with daily doses of 5 or 25 mg atabecestat. For those subjects with PK sampling during the same interval, the ECG should be performed close to collection of the blood sample for PK determination (ie, both ECG and PK within a 20 minute window).

In addition to these standard safety assessments, brain MRI including fluid attenuated inversion recovery (FLAIR) and gradient echo sequences read both locally and centrally, and a comprehensive dermatologic evaluation with photography of the upper face will be performed as part of the safety assessments. MRI evaluations are included as safety assessments to monitor for amyloid-related imaging abnormalities (ARIA).<sup>114</sup> The inclusion of dermatologic evaluations in Study 54861911ALZ2003 was based on the reported findings for knockout animals or other BACE inhibitors in development as well as the observed findings of fur discoloration at 100 mg/kg dose level in the 6-month carcinogenicity study in transgenic mice (see Section 1.4 and the latest version of Investigator's Brochure for detailed description of these findings). Note that cases of lightening of skin, lightening of hair or ophthalmological AEs are considered AESIs

and are subject to reporting timelines as described in Section 12.3.3. Additional monitoring for cases with elevated liver enzymes is described in Attachment 3 (ALT/AST  $\geq 3 \times$ ULN).

Each subject's concern about developing AD and his/her views and perceptions of amyloid imaging, as well as perception of future time, will be assessed via questionnaires (Views & Perception of Amyloid Imaging Scale, Concerns about Alzheimer's Disease Scale, Future Time Perspective Scale). The Assessment of Psychological Well Being will be used to monitor subjects for anxiety and depression. The results of these assessments must be reviewed prior to scheduling any amyloid biomarker measurement to ensure that the subject is willing to receive a pathological biomarker result and that, in the judgment of the investigator, disclosure would not constitute a significant risk for the subject.

### **3.2.8. Pharmacokinetic Evaluations**

Plasma and, potentially, CSF concentration-time data will allow for estimation of individual PK parameters for atabecestat using a population PK (popPK) modeling approach, possibly in combination with data from Phase 1 or Phase 2 studies. These data will also help to understand potential PK differences between healthy subjects and subjects who are asymptomatic and at risk for developing Alzheimer's dementia. The specific time points for measurement of atabecestat plasma and CSF concentrations were chosen to gather maximal information about the PK properties of atabecestat through sparse sampling while minimizing subject burden regarding blood and CSF sampling.

CSF samples for measuring atabecestat will be obtained in the subset of subjects in which CSF will be collected. Assessment of CSF drug concentration in this subset of subjects may help to infer the relationship between steady-state exposure (eg, trough PK) in the central nervous system and PD effects such as CSF A $\beta$  reduction.

### **3.2.9. Medical Resource Utilization and Health Outcomes**

The HRUQ allows tracking of the utilization of health care resources during the study, which is a key metric in understanding the burden of AD.

The SF-36 measures general health. The concepts measured by the instrument are not specific to any age, disease, or treatment group, allowing comparison of relative burden of different diseases and the relative benefit of different treatments.<sup>126</sup>

The EQ-5D-5L is a standardized measure of health status developed by the EuroQoL Group to provide a simple, generic measure of health for clinical and economic appraisal.<sup>32</sup> The EQ-5D-5L is applicable to a wide range of health conditions and treatments.

### **3.2.10. Interim Analyses**

An overview and description of potential interim analyses and potential design modifications of this study are provided in Section 11.4.

## 4. SUBJECT POPULATION

Approximately 1,650 subjects who are asymptomatic at enrollment and at risk for developing Alzheimer's dementia due to evidence of elevated amyloid accumulation will be enrolled in this study (550 subjects per treatment arm). The number of subjects randomized can be increased based on blinded sample size re-estimation, but the study enrollment will be capped at 2,400 subjects. For a discussion of the statistical considerations of sample size determination, refer to Section 11.2. The sample size for this study may be adjusted based on blinded sample size re-estimation (see Section 11.4.1).

Screening for eligible subjects will be performed within the 90-day interval prior to the first dose of study drug. If needed (eg, for biomarker collection or interpretation or for logistical reasons), the period for screening can be prolonged with written approval of the sponsor. Subjects can participate in both CSF sampling and amyloid PET imaging assessments, but this needs to be decided up front before either result is available. Eligibility will be based on at least 1 of these biomarkers confirming elevated amyloid accumulation with the following provisions:

- Subjects with negative results for both biomarker tests of elevated amyloid accumulation cannot be rescreened.
- Subjects who elect up front to be tested on only 1 of the biomarkers cannot be screened for the other if their results are negative, unless the decision is made before either result is available.

Limited re-testing of other abnormal screening laboratory or ECG values will be allowed once, especially if the abnormality is the result of an acute medical condition that is not exclusionary; rescreening for such abnormalities can occur after the medical condition has resolved or is appropriately treated.

The key risk factors for elevated amyloid accumulation and development of AD are age (ie, 65 years of age or older), *APOE* genotype, and family history. To be considered for screening, subjects must meet the following criteria:

- Subjects 60 to 64 years of age must have 1 of the following additional key risk factors: a previously known *APOE*  $\epsilon 4$  genotype, a positive family history for dementia (minimum of 1 first degree relative), or a previously known biomarker status demonstrating elevated amyloid accumulation in CSF or by PET.
- For subjects 65 years of age or older, age is a sufficient risk factor to be considered for screening.

The inclusion and exclusion criteria for enrolling subjects in this study are described in Section 4.1 and Section 4.2. 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.

### 4.1. Inclusion Criteria

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

1. Subject must be a man or woman 60 to 85 years of age, inclusive, at time of informed consent. Subjects 60 to 64 years of age must also have 1 of the following 3 conditions:
  - a. A positive family history for dementia (minimum of 1 first degree relative)
  - b. A previously known *APOE*  $\epsilon$ 4 genotype
  - c. A previously known biomarker status demonstrating elevated amyloid accumulation in CSF or PET
2. Subjects must have a global CDR score of 0 at screening.
3. Subjects must be able to read and write and must have adequate hearing and visual acuity to complete the psychometric tests. The legally acceptable representative must also be able to read and write.
4. Subjects must have evidence of elevated amyloid accumulation by means of either:
  - a. Low CSF  $A\beta_{1-42}$  levels at screening
  - b. A positive amyloid PET scan at screening (depending on the site's PET capability)

*Note: The cut-off value for CSF  $A\beta_{1-42}$  will be based on the value established by the central CSF screening laboratory and specified in a separate laboratory manual. Screening amyloid PET scans will be assessed centrally by a qualified reader for inclusion based on predefined criteria as documented in the imaging manual.*
5. Subjects must be otherwise healthy for their age group or medically stable with or without medication on the basis of physical examination, medical history, vital signs, and 12-lead ECG performed at screening or at baseline.
6. Subjects must be otherwise healthy or medically stable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel, hormones (thyroid tests), hematology, or urinalysis are outside the normal reference ranges, the subject may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant, to be appropriate and reasonable for the population under study, and not to be a potential cause of cognitive impairment. For low vitamin B12 and abnormal thyroid hormone tests, enrollment requires written approval from the sponsor's medical monitor.
7. Subjects must have a reliable informant (relative, partner, or friend). The informant must be willing to participate as a source of information and must have 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 believes he/she will provide consistent, accurate, and meaningful information on clinical scales (eg, CDR and CFI). An alternate informant meeting these criteria who can replace the primary informant should be identified, preferably prior to randomization.
8. Subject must be able to swallow drug as a whole and to be compliant with self-administration of medication.



9. Subject must reside at a permanent address other than a nursing facility.
10. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.
11. Subject must sign an informed consent form (ICF) indicating that he/she understands the purpose of and procedures required for the study and is willing to participate in the study. The subject's informant must also sign a separate ICF indicating that he/she understands the study requirements and is willing to participate in the study.
12. A woman must not be of childbearing potential: postmenopausal ( $\geq 60$  years of age with amenorrhea for at least 12 months; permanently sterilized [eg, bilateral tubal occlusion (which includes tubal ligation procedures as consistent with local regulations), hysterectomy, bilateral salpingectomy, bilateral oophorectomy]); or otherwise be incapable of pregnancy. In case of questionable status qualified personnel of the sponsor should be consulted to decide on the potential for inclusion of the subject.
13. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control, eg, 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, and all men must also agree not to donate sperm during the study and for 3 months after receiving the last dose of study drug. In addition, their female partners, if of childbearing potential, should also use an appropriate method of birth control for at least the same duration. Effective methods of birth control include prescription oral contraceptives, contraceptive injections, intrauterine device, double barrier method, and contraceptive patch.

#### **4.2. Exclusion Criteria**

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

1. Subject is receiving an acetylcholinesterase (AChE) inhibitor and/or memantine at any time during screening or Day 1 predose.
2. Subject has evidence of any brain disease other than potential very early signs of AD (eg, mild hippocampal atrophy) or typical age-related changes (eg, mild white matter hyperintensity on MRI). The screening MRI scan shall be interpreted by a local radiologist and a central radiologist for exclusionary findings prior to enrolling the subject. Both local and central interpretations shall be reviewed by the investigator; in case of disagreement, the central radiology report will be used to determine subject eligibility in consultation with the sponsor's medical monitor.

3. Subject has any other abnormality that could cause a possible cognitive deficit (including, but not limited to, vascular encephalopathy or large strokes [as imaged by cerebral MRI]).
4. Subject has any contraindications for MRI (eg, prostheses, implants, claustrophobia, pacemaker)
5. Subject has met criteria for dementia or has a brain disorder that can cause dementia.
6. Subject has evidence of familial autosomal dominant AD (mutation identified in the family and/or subject prior to randomization).
7. Subject has a history of or current thyroid disease or thyroid dysfunction, which is currently uncontrolled, unevaluated, or untreated. Subjects treated for thyroid disease may be enrolled following review of their diagnostic and treatment history records by the investigator and with written concurrence by the sponsor's medical monitor to ensure disease/treatment stability and compliance.
8. Subject has a vitamin B12 or folic acid deficiency. A low vitamin B12 level is exclusionary unless follow-up labs (homocysteine and methylmalonic acid) indicate that the value is not physiologically significant. Subjects treated with vitamin B12 or folic acid may be enrolled following review of their diagnostic and treatment history records by the investigator and with written concurrence by the sponsor's medical monitor to ensure disease/treatment stability and compliance.
9. Subject has chromosome 21 trisomy (Down syndrome).
10. Subject has a history within the past 2 years or current diagnosis of significant psychiatric illness, per the most current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM) (including but not limited to major depressive disorders and anxiety disorders) (subjects who are symptom free or with minimal limited symptoms may be included); or the subject has a current diagnosis or history of schizophrenia or bipolar disorder.
11. Subject has a relevant history of or current neurological disease other than preclinical AD, which may make interpretation of possible new neurological signs or symptoms difficult.
12. Subject has had a history within the last 5 years of a serious infectious disease affecting the brain (including neurosyphilis, meningitis, or encephalitis) or head trauma resulting in protracted loss of consciousness.
13. Subject has a history of epilepsy. Subject has a history of fits or unexplained black-outs other than vasovagal syncope within 10 years before screening.

14. Criterion modified per Amendment 5
  - 14.1 Subject has a hypopigmentation abnormality of the skin such as vitiligo at screening dermatological exam. Small localized lesions other than vitiligo are allowed.
15. Subject has any amyloid-related imaging abnormalities – edema or effusion (ARIA-E) at screening.
16. Subject has a clinically significant abnormal physical or neurological examination or vital signs at screening or baseline (Day 1 predose), which in the opinion of the investigator is not appropriate and reasonable for the population under study.
17. Criterion modified per Amendment 5
  - 17.1 Subject has, in the opinion of the investigator, a clinically significant 12-lead ECG abnormality (including left bundle branch block, atrioventricular [AV] block of second degree or higher, permanent pacemaker or implantable cardioverter defibrillator) at screening or baseline (Day 1 predose). The screening QTcF must be evaluated and must not exceed 450 msec in males or 470 msec in females. For triplicate ECGs, 2 of the 3 tracings must be below 450 msec in males or 470 msec in females. ECG recordings may be repeated once, and in the case of a question, a cardiologist and sponsor medical monitor should be consulted.
18. 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).
19. Subject has a history of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that, in the opinion of the investigator with written concurrence by the sponsor's medical monitor obtained prior to subject randomization by site, is considered cured with minimal risk of recurrence).
20. Subject has current, clinically relevant anemia.
21. Subject has donated 1 or more units (approximately 450 mL) of blood or had an acute loss of an equivalent amount of blood within 90 days prior to study drug administration.
22. Subject has a history of positive tests for hepatitis B surface antigen (HBsAg) or hepatitis C virus antibody, or other clinically active liver disease, or tests positive for HBsAg or anti-hepatitis C virus at screening.

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23. Subject has a history of a positive test for human immunodeficiency virus (HIV) antibody, or tests positive for HIV at screening.
24. Subject has a current or recent history of clinically significant suicidal ideation within the past 6 months, corresponding to a score of 4 (active suicidal ideation with some intent to act, without specific plan) or 5 (active suicidal ideation with specific plan and intent) for ideation on the C-SSRS, or a history of suicidal behavior within the past year, as validated by the C-SSRS at screening.

Subjects with a prior suicide attempt of any sort, or prior serious suicidal ideation/plan within the last 10 years, should be carefully screened for current suicidal ideation and only included after documented assessment by the investigator.

25. Criterion modified per Amendment 4
- 25.1 Subject has a history of drug or alcohol abuse according to most current version of the DSM criteria within the past 5 years before screening or positive test result(s) for other drugs of abuse (including barbiturates, opiates, cocaine, amphetamines and benzodiazepines) at screening (except if related to current treatment, eg, benzodiazepines).
26. Subject has taken any disallowed therapies as noted in Section 8, Prestudy and Concomitant Therapy before the planned first dose of study drug.
27. Subject has known allergies, hypersensitivity, or intolerance to atabecestat or its excipients (see current Investigator's Brochure).
28. Subject has received an investigational drug (including vaccines), including atabecestat, or used an investigational medical device within 3 months before the planned start of study or is currently enrolled in an interventional study with an active drug component.
29. Subject has received an anti-amyloid therapy within 12 months before the planned start of study. Subjects who have received an anti-amyloid vaccine at any time are excluded.
30. Subject has had major surgery (eg, requiring general anesthesia) within 8 weeks before screening, or will not have fully recovered from surgery, or has major surgery planned during the time the subject is expected to participate in the study.

*Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate.*

31. Subject is generally frail, or has any (medical) condition that, in view of the investigator or the sponsor's responsible medical officer, is likely to prohibit or limit further participation in the study or performance of study-specific assessments during the duration of the study.
32. Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
33. Subject is unable to comply with the study-specific requirements.
34. Subject is an employee of the investigator or study site with direct involvement in the proposed study or other studies under the direction of that investigator or study site, or is a family member of an employee or the investigator.
35. Subject has signs of increased intracranial pressure, eg, based on clinical or MRI examination.

For subjects having amyloid or tau PET scans performed, the additional exclusion criterion applies:

36. Subject has past or planned exposure to ionizing radiation that in combination with the planned administration of study amyloid and tau PET ligand would result in a cumulative exposure that exceeds local recommended exposure limits.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4 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 (ie, final follow-up visit) of the study.
2. For prohibitions or restrictions related to concomitant medication see also Section 8.
3. Criterion deleted per Amendment 4.

## 5. TREATMENT ALLOCATION AND BLINDING

### Treatment Allocation

A stratified permuted block randomization will be used in this study. There will be 2 stratification factors, country and *APOE* ε4 carrier status (yes/no). Subjects will be assigned to 1 of 3 treatment groups in a 1:1:1 ratio. The randomization scheme will be implemented in the interactive web response system (IWRS). The IWRS will assign a unique treatment code for each subject, which will dictate the treatment assignment and matching study drug kit(s) for that subject.

### Blinding

To maintain the study blind, the study drug container will have a label containing the study name, study drug number, and reference number. The label will be blinded indicating possible tablets packaged as 5 mg, 25 mg or placebo. However, if it is necessary for a subject's safety, the study blind may be broken and the identity of the study drug ascertained. The study drug number will be entered in the electronic case report form (eCRF) when the study drug is dispensed. The study drugs will be identical in appearance and will be packaged in identical containers.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS which has the functionality to allow the investigator to break the blind for an individual subject.

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

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the blind should be broken only if a specific emergency treatment or course of action would be dictated by knowing the treatment status of the subject. If possible, the investigator should attempt to contact the sponsor or its designee first 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 an emergency the investigator may determine the identity of the treatment by contacting the IWRS (see IWRS manual). 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 in the source document, IWRS, and/or in the appropriate section of the eCRF. 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 should continue to return for scheduled evaluations.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, if an IA is specified, the randomization codes and, if required, the translation of randomization codes into treatment and control groups will be disclosed to those authorized and only for those subjects included in the IA.

## 6. DOSAGE AND ADMINISTRATION

Active study medication will be provided as tablets for oral administration containing atabecestat 5 mg or atabecestat 25 mg. Matching placebo tablets for the 5-mg and 25-mg atabecestat tablets will also be provided. All study medication tablets will be physically identical in appearance to maintain the blind, and will be packaged in blisters.

A study site investigational product manual (pharmacy 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.

On Day 1, eligible subjects will be randomized to 1 of 2 dose levels of atabecestat or matching placebo and receive the following:

- For Subjects randomized and medication dispensed prior to Amendment 3
  - Treatment Group 1: 10 mg once daily (n=550). Subjects will receive 2 atabecestat 5-mg tablets.
  - Treatment Group 2: 25 mg once daily (n=550). Subjects will receive 1 atabecestat 25-mg tablet and 1 matching placebo tablet.
  - Treatment Group 3: placebo once daily (n=550). Subjects will receive 2 matching placebo tablets.
- For Subjects randomized after Amendment 3 and for Subjects with medication re-dispensed after Amendment 3
  - Treatment Group 1: 5 mg once daily (n=550). Subjects will receive 1 atabecestat 5-mg tablet.
  - Treatment Group 2: 25 mg once daily (n=550). Subjects will receive 1 atabecestat 25-mg tablet.
  - Treatment Group 3: placebo once daily (n=550). Subjects will receive 1 matching placebo tablet.

Subjects who started the study under the 2 tablets/day regimen will be informed about the upcoming change to their regimen at the first visit after the implementation of Amendment 3. Once the subject has signed the new informed consent, a switch will be made to the 1 tablet/day regimen.

On Day 1, prior to administration of the first dose of study drug, subjects will be dispensed a sufficient number of tablets of the appropriate study medication for a 12-week treatment period.

Re-dispensing of study medication will occur at 12-week intervals throughout the double-blind treatment phase.

During the entire double-blind treatment phase, subjects should self-administer study drug (atabecestat/placebo) on a once daily schedule with a glass of noncarbonated water (approximately 200 mL) preferably in the morning between the hours of 0700 and 1100 (7:00-11:00 AM), according to the instructions provided by the investigator. The first dose of study drug should be self-administered by the subject at the site as described above, and at all subsequent scheduled visits, subjects should self-administer their study medication on-site. Subjects having difficulties reaching the site during morning hours will be permitted to administer drug later during the day (eg, with lunch), but every attempt should be made to ensure consistency in the time of study drug administration during the course of the study.

Subjects who forget to take their daily dose in the morning as directed will be instructed to take their daily dose later that day, as long as it is before 1600 hours (4:00 PM). Subjects who forget to take their morning dose of study drug and cannot take their daily dose of study drug before 1600 hours (4:00 PM) will be instructed not to take any dose during that day and to resume dosing the following day.

Subjects who are no longer capable of ensuring compliance with their daily medication schedule, in the judgment of the investigator (eg, due to progression to dementia), will be required to have support in the handling and administration of study drug (eg, study informant, partner, caregiver, or nurse practitioner).

## **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 should be self-administered by subjects. As such, the number of study drug tablets dispensed will be recorded and compared with the number returned before the subject leaves the clinic, based on the drug packaging/blister cards. If study diaries are used to record this information, they should also be checked. At study visits, study drug should be self-administered on-site, which will be witnessed by designated study-site personnel.

Subjects will receive instructions on compliance with study drug administration when study medication is 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. See Section 9.1.3 (Interruption of Treatment) for information on subjects who have to interrupt treatment during the study. For this study, overdose will be defined as ingestion by a subject of any dose greater than 6 tablets on any day or cumulatively more than 60 tablets in a month, as this could exceed the maximum exposures tested in earlier clinical studies (maximum daily exposure 150 mg, maximum exposure in 1 month 1.5 g [30 days × 50 mg]). The limits of 6 tablets per day/60 tablets per month were chosen to cover the high dose group in this study (ie, 25 mg). In other words, since >6 tablets per day at



the 25 mg dose would equal >150 mg/day and >60 tablets per month at 25 mg dose would equal >1.5 g/month). This should be reported as in Section 12.2. There is no specific precaution or measure that would be taken if a subject takes an overdose.

## 8. PRESTUDY AND CONCOMITANT THERAPY

All prestudy therapies administered up to 30 days before the start of screening must be recorded at screening.

All concomitant therapies must be recorded throughout the study beginning with signing of the initial ICF until the end-of-study visit (follow-up visit). Specifically, any therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; nonpharmacologic therapies such as electrical nerve stimulation, acupuncture, special diets, exercise regimens) different from the study drug must be recorded in the subject's source record and entered into the eCRF.

Concomitant therapies should also be recorded beyond this time in conjunction with new or worsening AEs until resolution of the event. Subjects will be instructed to consult the investigator or other appropriate study personnel at the site before initiation of any new medications or supplements and before changing dose of any current concomitant medications or supplements.

Information on use of specific concomitant medications of special interest (ie, AChE inhibitors, memantine, benzodiazepines, and antidepressants) will be collected separately in the eCRF, including dose and route of administration, dates of administration, and indication for use.

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

Any symptomatic AD treatment used in association with progression of AD symptoms will be documented until the end-of-study visit (follow-up visit).

Modification of an effective preexisting therapy must not be made for the explicit purpose of enrolling a subject into the study.

Treatment of stable medical conditions, which might be frequent in an older population, is permitted, provided a subject is on a stable medication(s) for at least 6 weeks prior to the start of study drug dosing. The subject should remain on the stable medication(s), if possible, for the duration of the study. Changes or additions of medications are permitted only if clinically indicated and have to be documented in the concomitant medication section of the eCRF.

Treatment with cognitive enhancers (eg, AChE inhibitors) or drugs intended for the treatment of cognitive deficits is exclusionary at enrollment into the study. Subjects who experience cognitive decline during the study are allowed to receive approved AD therapies, but these new therapies or therapy adaptations that are expected to have an impact on cognitive performance (eg, AChE inhibitors or memantine) will not be permitted without explicit permission by the sponsor based

on medical necessity. Before a subject starts, stops, or changes the dose of a therapy expected to have an impact on cognition, the sponsor's medical monitor must be contacted to determine if the subject should continue in the study or not, and whether or not clinical outcome measures should be performed.

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

Other concomitant medications that affect central nervous system (CNS) function may be given if the dose is intended to remain unchanged throughout the study. Doses of these compounds should remain constant beginning from 6 weeks prior to randomization. To avoid effects on cognitive assessments, the following apply, except in cases of documented medical necessity, discussed with the sponsor's medical monitor:

- A subject receiving a stable dose of a medication(s) that affects CNS function for at least 6 weeks prior to randomization should not stop administration of this medication(s) during the study and should not change the dose of this medication.
- A subject should not add any medication(s) that affect CNS function during the study period.

In the case of any unforeseen start, stop, or change to stable doses of a therapy that affect CNS function during the study, the sponsor's medical monitor must be contacted to determine if the subject should continue in the study and whether clinical outcome measures should be performed.

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

## **9. STUDY EVALUATIONS**

### **9.1. Study Procedures**

#### **9.1.1. Overview**

The Time and Events Schedule summarizes the timing of efficacy, PK, biomarker, genomic, and safety measurements applicable to this study.

The Time and Events Schedule lists the month associated with each visit during the double-blind treatment phase. During this phase, subjects will visit the site at approximately every 2 weeks for the first 3 months (visit 2 weeks=2 weeks post-Day 1, visit Month 1=4 weeks post-Day 1, visit Month 1+2 weeks=6 weeks post-Day 1, Month 2=8 weeks post-Day 1, Month 2+2weeks=10

weeks post-Day 1, Month 3=13 weeks post-Day 1), monthly intervals from 3 months to 6 months (visit Month 4=17 weeks post-Day 1, Month 5=21 weeks post-Day 1, Month 6=26 weeks post-Day 1), with additional visits at Month 8, Month 9, Month 10, and Month 12 (Month 8=34 weeks post Dose-Day 1, Month 9=39 weeks post-Day 1, Month 10=43 weeks post-Day 1, Month 12=52 weeks post-Day 1), and then at 3-month (13-week) intervals through Month 54 (eg, visit Month 15=65 weeks post-Day 1, Month 54=234 weeks post-Day 1). A visit window of  $\pm 4$  calendar days will be allowed for visits at Months 1 and 2 of the double-blind treatment phase, while a visit window of  $\pm 12$  calendar days will be allowed for subsequent visits during this phase. All visits of the double-blind treatment phase are in principle single day visits, however, they may be performed over multiple days within the allowed visit window in the case of logistical issues or subject preference. The date of the visit should always be calculated from the baseline visit, not from the prior visit.

The time points for safety measures, PK measures, and biomarker measures may be changed by the sponsor (with or without affecting the overall frequency of these assessments) prior to and during the study based on newly obtained data (eg, IA results) to optimize evaluation of the safety, PK, and PK/PD profile of the study drug. These modifications may result in a change in the overall frequency of the safety measures or sample collections. The maximal total blood volume collected per subject will not be exceeded. In general, such modifications to the time points for key study parameters, where performed only to optimize evaluation of the actual safety, PK, or PK/PD profile of atabecestat will be documented in a note to file and included in the next following protocol amendment.

If possible, cognitive testing should always be performed before any medical procedure(s) that could be stressful for the subjects (eg, blood draws, CSF collection, imaging scans). Guidance on the order of administration of scales and procedures will be provided to the sites through site training. See Section 8 for details regarding concomitant use of sedating medication and timing of study assessments/procedures with respect to concomitant medication use. Additionally, all neuropsychological testing and CSF collections should be performed at approximately the same time on each day they are performed. All cognitive evaluations, clinical scales, functional outcome measures, and medical resource utilization/health outcomes scales should be administered by the same rater to reduce potential variability (ie, the same rater for any particular scale, but different raters can be used across the scales). Adequate breaks should be incorporated between the different cognitive tests administered at the same visit to ensure optimal performance.

Information regarding handling, shipment, and labeling of biological samples (including samples for safety laboratory measures) will be provided in a separate laboratory manual. For CSF sampling, local site standard operating procedures (SOPs) may be applied for performing the actual lumbar puncture (not the CSF collection). Separate imaging manuals and charters will be also provided, describing the MRI and PET imaging procedures, data acquisition, and handling. Any changes to the laboratory manual and imaging manuals/charters will not result in a protocol amendment.

Venous blood will be collected for all blood-based analyses. When assessments occur at the same time point, the blood sample for PK and biomarker (including RNA) 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 the specified time points, if needed. Actual dates and times of assessments will be recorded in the source documentation, on the laboratory requisition form, and/or in the eCRF.

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.

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 source documentation, on the laboratory requisition form, and/or in the eCRF. The order of multiple assessments within 1 protocol time point should be the same throughout the study. The volume of blood to be collected from each subject is summarized in [Table 2](#). For each subject, the maximum amount of blood drawn in this study will not exceed 480 mL. Note: Blood taken will not exceed 450 mL in any 3 month period, and the majority of subjects will not have blood draws exceeding 360 mL (see [Table 2](#)).

**Table 2: Volume of Blood to be Collected From Each Subject**

Type of Sample	Volume per Sample (mL)	No. of Samples per Subject	Total Volume of Blood (mL) <sup>a</sup>
Safety (including screening and posttreatment assessments)			
Hematology and serum chemistry	4.5	29	130.5
Screening folate, homocysteine, coagulation, methylmalonic acid, vitamin B12	11.3	1	11.3
Thyroid function	3.5	1	3.5
Serology (HIV, hepatitis)	5	1	5
Pharmacokinetic sample	3	21	63
PD sample for A $\beta$ <sub>1-40</sub> and A $\beta$ <sub>1-42</sub>	6	12	72
Biomarker sample associated with CSF collection <sup>b</sup>	6	3	18
Biomarker sample for plasma and gene expression (RNA)	10	1	10
Sample for gene expression (RNA)	2.5	7	17.5
Sample for <i>APOE</i> genotyping and pharmacogenomics (DNA)	10	1	10
Blood sample for PBMC (whole blood) <sup>c</sup>	10	1	10
Corresponding plasma sample <sup>c</sup>	8	1	8
Blood sample for PBMC (whole blood) for subset of subjects with hepatic enzyme elevation <sup>c</sup>	120	1	120
Approximate Total <sup>d</sup>	NA	80	478.8

<sup>a</sup> Calculated as number of samples multiplied by amount of blood per sample.

<sup>b</sup> Only for subjects who have CSF samples collected (eg, amyloid screening by CSF).

<sup>c</sup> Only at sites capable of processing PBMC samples.

<sup>d</sup> Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.

<sup>e</sup> Only for subjects participating in an optional immunologic substudy (see Section 3.2.6.2). Blood taken will not exceed 450 mL in any 3 month period.

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

Abbreviations: A $\beta$ =amyloid-beta; *APOE*=apolipoprotein E; CSF=cerebrospinal fluid; HIV=human immunodeficiency virus; NA=not applicable; PBMC= peripheral blood mononuclear cell; PD=pharmacodynamic.

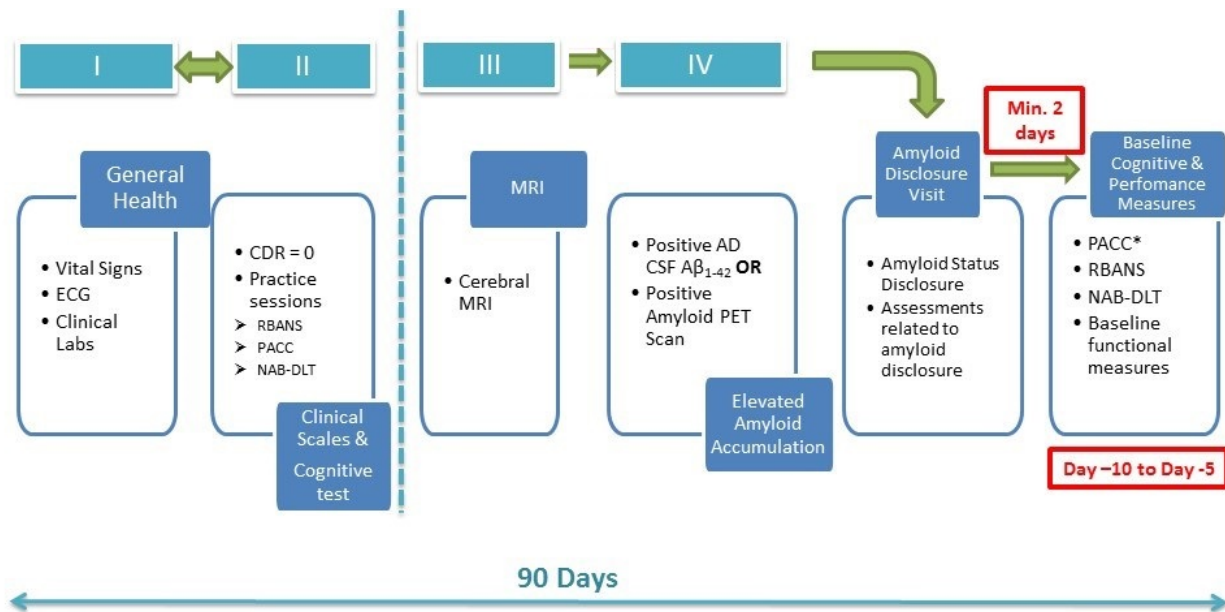
### 9.1.2. Screening Phase

After providing written informed consent, subjects may be screened over a period of approximately 90 days to assess their eligibility for the study according to the inclusion and exclusion criteria defined for this study (see Section 4). If needed for biomarker collection, data interpretation, or logistical reasons, this period can be prolonged with written approval of the sponsor.

During screening, 4 primary screening steps will be assessed as shown in Figure 5. In addition, part of the baseline cognitive, functional, performance, and medical resource utilization/health outcomes measures will be performed during the screening period, as described further below. The complete list of assessments is noted in the Time and Events Schedule. Assessments for **Step III** (MRI) and **Step IV** (Elevated Amyloid Accumulation) may only be performed after the subject is determined to be still eligible for the study after review of results from **Step I** (General Health) and **Step II** (Clinical Scales). Step I and II can occur in any order, however, a subjects' history should be obtained before all other study activities. The history should include questions to ensure appropriateness to participate in the study (eg, availability of study partner, current symptomatic AD treatments, unstable medical illness, extended travel or upcoming surgeries, etc.). **Step III** must be completed before **Step IV**. The investigator must review the MRI results before the subject undergoes amyloid testing. The order of individual assessments within a step

is not fixed, unless otherwise indicated, and may differ by site depending on logistical aspects and subject preferences, provided the defined visit windows are maintained.

**Figure 5: Screening Steps**



\*PACC baseline assessment will be performed on Day 1 predose.

AD=Alzheimer's disease; CDR=Clinical Dementia Rating; CSF=cerebrospinal fluid; ECG=electrocardiogram; Min=minimum; MRI=magnetic resonance imaging; NAB-DLT=Neuropsychological Assessment Battery–Daily Living Test; PACC= Preclinical Alzheimer Cognitive Composite; PET=positron emission tomography; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status.

During screening, the subject's **general health (Step I)** will be assessed according to the specific safety assessments listed in the Time and Events Schedule. Subjects will complete the C-SSRS to assess suicidal ideation and behavior in Step I of screening.

The subject's **clinical scales (Step II)** assessment will include the CDR (baseline assessment). In order to perform the CDR, each subject needs to be accompanied by the specified informant. The CDR global score is a standardized global clinical measure (for additional details on this test, see Section 9.2.2.2.4). Subjects with a CDR global rating score higher than 0 will be excluded from further participation. The CDR must be completed prior to proceeding to the Step III and IV screening assessments. In addition, in Step II of screening, the following scales will be completed for all subjects: (1) Rosen-modified Hachinski Ischemic Scale (HIS) to collect information relevant to risks for vascular cognitive impairment, (2) Geriatric Depression Scale (GDS) to collect information related to depressive symptoms; (3) Assessment of Psychological Well Being to monitor for anxiety and depression; (4) HRUQ scale to collect information on resource utilization; and (5) SF-36 and EQ-5D-5L to assess general health. Each subject's concern about developing AD and his/her views and perceptions of amyloid imaging, as well as perception of future time, will be assessed via questionnaires during Step II (Views & Perception of Amyloid Imaging Scale, Concerns about Alzheimer's Disease Dementia Scale, Future Time Perspective Scale). The results of these assessments as well as the Assessment of Psychological Well Being must be reviewed prior to scheduling any amyloid biomarker measurement to ensure

that the subject is willing to receive a report of a pathological biomarker result and that, in the judgment of the investigator, the disclosure would not constitute a significant risk for the subject. As discussed below, these same questionnaires are also to be completed following disclosure of the subject's amyloid status in Step IV.

Subjects will have a single practice session during the screening phase for the PACC, RBANS, NAB-DLTs for Memory and Attention, and computerized cognitive battery. These practice sessions will be done to assess and mitigate potential practice effects. Practice sessions can occur at any time during screening but must be completed (1) prior to Step IV assessments, and (2) no later than 20 days (ie, Day -20) before the start of dosing.

**Evidence of any brain disease (Step III), other than potential very early clinical signs of AD** (eg, mild hippocampal atrophy) or typical age-related changes (eg, mild white matter hyperintensity on MRI), will be assessed during screening by means of cerebral MRI. Screening MRI results that demonstrate any relevant other pathology that by itself is likely to result in decline of cognitive function are exclusionary (see Section 4.2). Central and local review of the MRI will be performed, and where discrepancies are noted, the central read will be viewed as the primary source of information for eligibility determination in consultation with the sponsor's medical monitor.

**Evidence of elevated amyloid accumulation (Step IV)** will be assessed by either (1) a CSF sample for determination of A $\beta$ <sub>1-42</sub> concentration or (2) an amyloid PET scan for determination of cerebral fibrillar amyloid. Subjects can have both CSF collection and amyloid imaging performed (the aim is that approximately 20% of subjects will have both screening biomarker evaluations to better understand concordance of the biomarkers in screening and treatment). Amyloid status for study entry will be based on at least 1 of these biomarkers confirming elevated amyloid accumulation. It is sufficient to demonstrate elevated amyloid accumulation by 1 of the 2 markers, but the decision to perform 1 or both needs to be made before either result is available. The amyloid disclosure visit will be performed when both results, if applicable, are available. Subjects with negative results for both biomarker tests of elevated amyloid accumulation cannot be rescreened. Subjects who elect up front to be tested on only 1 of the biomarkers cannot be screened for the other if their results are negative, unless the decision is made before either result is available.

All subjects who undergo the **Step IV** amyloid burden assessment will have their results disclosed during a separate in-clinic **amyloid status disclosure visit** conducted during the screening period by a clinical investigator approved for this role. This visit must take place at least 2 days prior to the baseline cognitive assessments. Disclosure of the amyloid accumulation results will be per local laws and regulations. Informant attendance is not required at this visit, but may be permitted if the subject agrees. Subject concern about developing AD and his/her views and perceptions of amyloid imaging, as well as perception of future time, will be repeated following disclosure of amyloid status using the questionnaires specified above for Step I. The Impact of Events Scale (IES) will be administered over the phone (or at a visit) within 3 days following the amyloid status disclosure visit.

Eligible subjects based on screening assessments will return during the screening period to the site to have part of their baseline cognitive and performance measures performed at least 2 days after the amyloid disclosure visit and between Day -10 and Day -5 (inclusive). Baseline measures obtained at this visit will include the CFI, CFI-a, ADCS-ADL-PI, RBANS, NAB-DLTs for Memory and Attention, computerized cognitive battery (selected sites only), and FCI (selected sites only).

Some assessments of the screening process may also be performed by screening centers in close collaboration and agreement with sites and sponsor to facilitate the screening process at these sites.

The following blood samples will also be collected during screening: DNA blood sample from all subjects for *APOE* genotyping; venous blood sample from all subjects for the analysis of A $\beta$  fragments and additional exploratory markers; RNA blood samples from all subjects; and PBMC sample from all subjects at sites capable of processing them.

The comprehensive skin examination should be performed by a dermatologist (Medical Doctor/Doctor of Osteopathic Medicine dermatology specialist or a non-physician medical specialist such as an advanced practice nurse with extensive clinical experience in dermatology, certified to conduct independent dermatological examinations, and approved by the sponsor's medical monitor). Photographs collected by the dermatologist or assigned designee will be included in the general health assessments. It is preferred that the examination be conducted before Step III, but it must be performed before amyloid testing (Step IV).

In some cases, subjects who screen fail for reasons that are subsequently addressed may be considered for rescreening after approval by the sponsor's medical monitor. Scenarios to be considered include: previous 54861911ALZ2003 screening was not completed within protocol time windows, delay in obtaining past medical history, mild or asymptomatic medical conditions that required further evaluation to demonstrate stability, and medications that had not been stable for 6 months prior to randomization. Individuals previously excluded for not meeting inclusion criterion 4 (biomarker amyloid status) or exclusion criterion 2 (MRI ineligibility) cannot be rescreened.

Subjects approved for rescreening must sign a new ICF, and undergo appropriate screening evaluation according to the Time and Events Schedule, confirmed by the sponsor's medical monitor. This will include interim medical history, safety assessments, clinical laboratory assessments, and ECG. If MRI was completed within 6 months of randomization, it would not need to be repeated in most cases. If tests for amyloid accumulation (CSF, amyloid-PET or both), genomics and fluid biomarkers were completed and valid, they would not need to be repeated. Screening cognitive and other endpoint evaluations should follow the Time and Events Schedule; if screening cognitive evaluations were completed previously then testing in rescreening should be conducted 3 months or more after the prior testing.



### 9.1.3. Double-blind Treatment Phase

Subjects participating in the double-blind treatment phase will visit the site at regular intervals (approximately every 2 weeks for the first 3 months, monthly from 3 months to 6 months with additional visits at Month 8, Month 9, Month 10, and Month 12, and then every 3 months thereafter; see Time and Events Schedule- Double-Blind Treatment and Follow-up Phases).

#### Day 1/Day of Randomization

Subjects who successfully complete the screening assessments will return to the site on Day 1, at which time a series of predose baseline measurements (including PACC) will be performed (as listed in the Time and Events Schedule).

Following confirmatory review of a subject's eligibility for further participation based on the inclusion criteria and exclusion criteria (see Section 4), eligible subjects will be randomly assigned on Day 1 to 1 of 2 dose levels of atabecestat (5 mg or 25 mg once daily) or matching placebo in a 1:1:1 ratio. As described in Section 5, randomization will be stratified by country and *APOE*  $\epsilon$ 4 carrier status.

Study drug for the double-blind treatment phase will be dispensed on Day 1 and at each regular visit thereafter (except Month 54), as listed in the Time and Events Schedule. Instructions for intake will be provided to the subjects when the study drug is dispensed, or more frequently when needed. Subjects should self-administer single daily doses of study medication (once daily) from Day 1 until Month 54, inclusive as described in Section 6.

#### Double-blind Treatment Phase

Following dosing on Day 1 and during the entire double-blind treatment phase, treatment effects will be evaluated by means of cognitive assessments, functional outcome measures, fluid and imaging biomarkers, PK, assessment of concerns about AD, medical resource utilization/health outcomes measures, and safety and tolerability at the time points listed in the Time and Events Schedule.

The treatment effect of atabecestat on slowing cognitive decline will be assessed in all subjects by neuropsychological assessments during the double-blind treatment phase, using the PACC (see Section 9.2.1), RBANS (see Section 9.2.2.1.1), and NAB-DLTs for Memory and Attention (9.2.2.1.2), and will be explored with the computerized cognitive battery (selected centers only). Functional outcome or performance will be evaluated in all subjects using the CFI, CFI-a, ADCS-ADL-PI, A-IADL-Q (selected centers only), and CDR, and will be explored with the FCI (selected centers only). Additional details on the cognitive and functional outcome assessments are presented in Section 9.2.2.1, Section 9.2.2.2, and Section 9.5.

The potential effects of atabecestat on the pathophysiologic processes underlying AD will be assessed based on fluid biomarkers (CSF [subset of subjects with baseline measurements] and plasma [all subjects]), imaging biomarkers (MRI [all subjects], amyloid PET [subset of subjects with baseline measurements], and tau PET [subset of subjects electing to participate in

substudy]). Details on these evaluations are presented in Section 9.4, while the collection time points are specified in the Time and Events Schedule.

For all subjects, RNA blood samples will be collected to allow for analysis of gene expression profiles for translational biomarker research related to atabecestat at time points during the double-blind treatment phase as indicated in the Time and Events schedule. Collections may be modified based on local rules and regulations.

Blood samples for determination of atabecestat concentrations in plasma will be collected prior to dosing and at 1 to 4 hours postdose using a sparse sampling approach at the time points indicated in the Time and Events Schedule. In addition, atabecestat concentrations in CSF samples may be analyzed. Additional details concerning the evaluation of PK parameters are provided in Section 9.6.

Medical resource utilization and health outcomes will be explored with the HRUQ, SF-36, and EQ-5D-5L (see Section 9.8).

Safety (ECG, vital signs, safety labs, MRI, physical, neurological and dermatologic examination, and C-SSRS), and tolerability (AEs and Assessment of Psychological Well Being) will be assessed at regular intervals during the double-blind treatment phase, as listed per the Time and Events Schedule, and described in Sections 9.5.7, 9.5.8, and 9.9). Most of these safety assessments (except for the MRI, ECG, and Assessment of Psychological Well Being) will be done predose at the specified visit. Questionnaires assessing a subject's concern about AD and his/her perception of future time will be repeated at regular intervals during the double-blind treatment phase as indicated on the Time and Events Schedule (see also Sections 9.5.4 and 9.5.6). A comprehensive skin examination by a dermatologist will be repeated at Month 12 of the double-blind treatment phase, or at the Early Termination (ET) visit for any subject who withdraws from the study prior to Month 12.

### **Interruption of Treatment**

If a subject has to interrupt treatment due to a significant medical condition or life event, it is possible to re-initiate treatment. Interruption of treatment should be limited to significant events, and confirmed with the medical monitor. Treatment re-initiation should occur as soon as possible and has to be confirmed by a medical officer of the sponsor. The re-initiation may include a general safety examination and safety labs.

### **End of Treatment or Early Withdrawal**

Every attempt should be made to follow subjects through their final visit of the double-blind treatment phase (Month 54), including subjects who prematurely discontinue study medication but do not withdraw from the study. For subjects who prematurely discontinue study medication, the focus will be on collecting primary and secondary clinical outcome measures and reducing other assessments. In the event that a subject prematurely discontinues from the study for any reason, an ET visit should be completed (see Section 10.3 for criteria for treatment

discontinuation or drop-outs). Assessments and procedures to be completed at the ET visit are listed in the Time and Events Schedule.

Disposition status should be recorded for subjects who withdraw from the study, discontinue study medication but continue in the study, and complete the study.

If a subject drops out of the study due to an AE, every reasonable attempt will be made to follow the subject until the AE resolves or until the investigator, in conjunction with the sponsor, deems the AE to be chronic or stable. All serious adverse events (SAEs) will continue to be followed as instructed in Section 12.3.2.

#### **9.1.4. Posttreatment Phase (Follow-Up)**

After a minimum of 7 days to a maximum of 28 days after the last dose of study drug in the double-blind treatment phase (ie, after the last visit of the double-blind treatment phase), subjects will return to the site for a follow-up visit. The procedures to be completed during the follow-up visit are listed in the Time and Events Schedule. Subjects who withdraw prematurely from the study during the double-blind treatment phase will also be expected to complete the posttreatment phase (follow-up visit) assessments within 7 to 28 days after the last dose of study drug, or the ET visit assessments (if performed), whichever comes last.

If the subject has died, the date and cause of death will be collected and documented on the eCRF. Investigators may recontact the subject or informant to obtain long-term follow-up information to determine safety or survival status (refer to Section 16.2.3).

#### **9.1.5. Long-Term Extension Study**

Subjects who complete the double-blind treatment phase may be eligible to participate in a long-term extension study if enrollment criteria are met for the extension study. Subjects participating in a long-term extension study will receive study medication during the course of that study after all assessments for Study 54861911ALZ2003 are completed. The availability, design, and implementation of such a long-term extension study will be established prior to the last study visit of the double-blind treatment phase in Study 54861911ALZ2003 for the first subject enrolled.

For subjects completing the double-blind treatment period, but deciding not to participate in the long-term extension study, telephone contact will be made to determine subjects' general clinical status. The availability, design, and implementation of such a long-term follow-up will be established prior to the last study visit of the double-blind treatment phase in Study 54861911ALZ2003 for the first subject enrolled.

### **9.2. Efficacy**

#### **9.2.1. Primary Efficacy Measure: Preclinical Alzheimer Cognitive Composite**

The primary efficacy measure for this study, the PACC, version used in this study, is similar to the Alzheimer's Disease Cooperative Study - Preclinical Alzheimer's Cognitive Composite (ADCS-PACC), a theoretically derived composite that was designed to be a sensitive measure of

early cognitive changes attributable to cerebral amyloid effects in asymptomatic individuals (see Section 3.2.5). Both versions of the PACC are composed of 4 measures that are weighted towards episodic memory and includes a timed executive function test and a global cognitive screening test. The PACC version used and described here, uses 3 alternate forms for each of the 4 elements and includes minor differences from the ADCS-PACC to allow optimal translation and cultural adaptation of items into multiple country-languages. The administration of the PACC should be recorded (audio) for quality review purposes according to locally applicable laws and regulations. The PACC, version used in this study, will be completed at Day 1 and at 6-month intervals beginning at Month 6 through Month 54, or at the ET visit; the PACC will also be administered in a practice session during the screening phase (see Section 9.1.2). Three alternate forms of the PACC, version used in this study, will be administered in an alternating manner during the study, including once during screening prior to the baseline administration. These versions are functionally and psychometrically equivalent, but have different list learning sections. Components of the PACC include the following:

- **Free and Cued Selective Reminding Test (FCSRT).** The FCSRT<sup>34,35,43,45</sup> is a test of associative learning using 16 items presented visually as figures and auditorily as words. Semantic cuing is used to facilitate encoding and retrieval. Higher scores indicate better performance.
- **Delayed Paragraph Recall (Logical Memory test, Wechsler Memory Scale [WMS]).** Immediate and Delayed Paragraph Recall tests episodic memory.<sup>129</sup> Free recall of a short story that consists of 25 items of information will be elicited immediately after it is read aloud to the subject and again after approximately a 30-minute delay. The total number of items of information from the story that are recalled immediately (maximum score=25) and after the delay interval (maximum score=25) are recorded. Higher scores indicate better performance. The delay score (0-25 story units) will be used in the composite.
- **Wechsler Adult Intelligence Scale (WAIS)-IV Coding.** The WAIS-IV Coding (previously WAIS-III Digit Symbol; WAIS-R Digit Symbol Substitution Test) is a subtest of the larger WAIS-IV battery and takes less than 5 minutes to complete.<sup>128</sup> Coding involves multiple cognitive domains including attention/concentration, visuospatial motor coordination, psychomotor speed, and executive functioning. In this subtest the participant copies symbols that are paired with numbers as quickly as possible for 120 seconds. Specifically, the top of the page has a ‘key’ containing boxes with the numbers 1 to 9 paired with random symbols. The remainder of the page contains boxes with the numbers with blank boxes below these numbers. The participants are directed to fill in the appropriate symbols corresponding to the numbers in these blank boxes as quickly as possible working from left to right without skipping numbers or rows. The maximum possible score is 135 points. The total raw score is the number of correctly drawn symbols completed in 120 seconds; the number correct in 90 seconds will also be recorded as a secondary score. Higher scores indicate better performance.
- **MMSE Total Score.** The MMSE<sup>35</sup> is a brief, frequently used screening instrument used for dementia including AD. The MMSE scale evaluates orientation, memory, attention, concentration, naming, repetition, comprehension, and ability to create a sentence and to copy 2 overlapping pentagons. The MMSE is scored as the number of correctly completed

items with a lower score indicative of poorer performance and greater cognitive impairment. The total score ranges from 0 (worse) to 30 (perfect performance).

Slight differences in the PACC, version used in this study, from the ADCS-PACC include changes to some of the figures and text of the FCSRT to facilitate cultural adaptation and translations to other languages, inclusion of a different Logical Memory paragraph for administration during screening, and use of serial sevens in the MMSE instead of spelling “world” backwards.

Each component score will be transformed into z-scores. These z-scores will then be summed to form the composite.<sup>26</sup> A decrease of 1 baseline standard deviation (SD) on each component would result in a 4-point decrease in the composite.

## **9.2.2. Secondary Efficacy Measures**

### **9.2.2.1. Clinical Scales for Cognitive Outcome Measures**

Cognitive outcome/performance will be evaluated in all subjects using the RBANS and NAB-DLTs for Memory and Attention. These will be evaluated at the time points outlined in the Time and Events Schedule.

#### **9.2.2.1.1. 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 for neuropsychological screening for younger patients.<sup>97</sup> The time needed to administer this battery is dependent on disease severity, but is shorter if the participant is more impaired. The RBANS will be completed at 6-month intervals at Month 3 through Month 51, or at the ET visit; the RBANS will also be administered in a practice session during the screening phase (see Section 9.1.2).

The RBANS includes 12 subtests that measure the following 5 indices: (1) Attention Index, composed of Digit Span and Coding; (2) the Language Index, consisting of Picture Naming and Semantic Fluency subtests; (3) the Visuospatial/Construction Index, made up of Figure Copy and Line Orientation subtests; (4) the Immediate Memory Index, composed of List Learning and Story Memory subtests, and (5) the Delayed Memory Index, consisting of List Recall, List Recognition, Story Recall, and Figure Recall subtests. The RBANS is administered face-to-face, is available in over 30 languages, and has been used in multinational clinical trials, including AD trials.<sup>63,69,96</sup> Completion of the RBANS yields 5 index scores based on participant performance on the various subtests, as well as a composite Total Index score for the battery. Index scores range from 40 to 160, and are normalized to a mean of 100 and standard deviation of 15. Higher scores indicate less impairment.

#### **9.2.2.1.2. Neuropsychological Assessment Battery - Daily Living Tests**

The NAB-DLTs represent a series of performance-based measures covering 5 domains (Attention, Memory, Language, Spatial, and Executive function).<sup>117</sup> These are valid, clinically meaningful measures that objectively assess functional deficits. Participant performance scores on the NAB subtests are summed, and then normalized to yield an index score. Index scores can

range from  $\leq 55$  to  $\geq 145$ , and are normalized to a mean of 100 and standard deviation of 15. Higher scores indicate less impairment. Positive results on these tests would provide further evidence that any treatment effects on other cognitive endpoints were clinically relevant.

### **9.2.2.2. Clinical Scales for Functional Outcome Measures**

Functional outcome/performance will be evaluated in all subjects using the CFI, ADCS-ADL-PI, and CDR. These will be evaluated at the time points outlined in the Time and Events Schedule.

#### **9.2.2.2.1. Cognitive Function Index**

The CFI is a modified version of the Mail-in Cognitive Function Screening Instrument,<sup>125</sup> a subject- and informant-reported outcome measure developed by the ADCS. This assessment includes 15 questions (14 of which contribute to the total score, and 1 additional unscored item) that assess the subject's perceived ability to perform high-level functional tasks in daily-life and sense of overall cognitive functional ability. Study subjects and their informants independently rate the subject's abilities. Total scores range from 0 to 14 (yes=1; no=0; maybe=0.5 for each question) with higher scores indicating greater impairment.

#### **9.2.2.2.2. Cognitive Function Index-acute**

The CFI-a is a modified version of the CFI, a subject and informant-reported outcome measure developed by Janssen. This assessment includes 14 questions similar to those in the CFI that evaluate the subject's perceived ability to perform high-level functional tasks in daily-life and sense of overall cognitive functional ability. Study subjects and their informants independently rate the subject's abilities based on their current or most recent experience. The scale uses frequency (never, rarely, sometimes, often, or always) to measure impairment, with always indicating greatest impairment.

#### **9.2.2.2.3. ADCS Activities of Daily Living – Prevention Instrument**

The ADCS-ADL-PI was developed in the ADCS Prevention Instruments Trial and is a functional measure composed of 18 items that includes 15 activities of daily living rated on a 4-point scale and 3 high-level function items.<sup>37</sup> Study subjects and their informants independently rate the subject's level of ability. Informants are additionally asked to evaluate whether activities were completed less often, required more time to complete, and if any errors were made performing the task. High-level function items are rated as "yes" or "no". Total scores range from 0 to 45 with higher scores indicating less impairment.

#### **9.2.2.2.4. Clinical Dementia Rating Scale**

The CDR is a global clinical scale with established diagnostic and severity-ranking utility that is widely used in clinical trials. It does not directly rely on psychometric tests, thereby avoiding learning effects. The CDR assesses 3 domains of cognition (memory, orientation, judgment/problem solving) and 3 domains of function (community affairs, home/hobbies, personal care) using semi-structured interviews of both the study subject and an informant carried out by a trained rater. The CDR is 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, ie, “CDR Global” score ranging from 0 to 3, with 0 indicating no signs of clinically apparent cognitive impairment or dementia and 3 indicating severe dementia.

Scores for the 6 domains (ranging from 0 to 3) can additionally be summed to obtain the CDR Sum of Boxes (CDR-SB) score with scores ranging from 0 to 18. The CDR-SB scores can be used to stage patients.<sup>13,90</sup> Higher scores indicate greater impairment.

The CDR assessment will be audiotaped. In case of any discrepancy between the CDR global score and the subject’s performance in neurocognitive tests, a review process will be initiated to explain or resolve discrepancies for the assessment that determines study eligibility during screening.

### **9.3. Efficacy Endpoints**

#### **9.3.1. Primary Endpoint**

The primary endpoint of Study 54861911ALZ2003 is the change from baseline at Month 54 (Year 4.5) in the PACC score.

The change from baseline in PACC is the sum of the following 4 z-score changes:

- Change from baseline in -PACC =  $Z1 + Z2 + Z3 + Z4$ ,

where  $Z1$  = the change from baseline in the sum of the Total + Free Recall scores from the FCSRT divided by SD, where SD is the standard deviation associated with the baseline sum of the Total + Free Recall scores from the FCSRT in the analysis population.

$Z2$ ,  $Z3$ , and  $Z4$  are similarly calculated z-score changes for the Delayed Paragraph Recall score, WAIS-IV Coding score, and MMSE score, respectively.

#### **9.3.2. Secondary Endpoints**

The key secondary efficacy endpoint in this Phase 2b/3 study is the following:

- Change from baseline at Month 54 on CFI (total score)

Other secondary efficacy endpoints are the following:

- Change from baseline at Month 54 in ADCS-ADL-PI score (total score)
- Change from baseline at Month 51 on RBANS (total scale score)
- Change from baseline at Month 54 on CDR-SB
- Change from baseline at Month 54 on NAB-DLTs for Memory and Attention

## 9.4. Biomarkers

### 9.4.1. Fluid Biomarkers

#### 9.4.1.1. CSF Biomarkers

CSF samples will be collected for amyloid screening as well as longitudinally from the subset of subjects with baseline CSF collection for measuring different A $\beta$  fragments and exploratory PD markers.

For amyloid screening by CSF, a CSF A $\beta_{1-42}$  assay performed at a single accredited laboratory with demonstrated high sensitivity and specificity will be used. This selected CSF A $\beta_{1-42}$  assay has demonstrated high sensitivity and specificity in identifying subjects with MCI or normal cognition who will decline cognitively or progress to AD dementia.<sup>12,49,81,124</sup>

CSF samples will be collected at baseline (predose on Day 1) and prior to dosing at Month 12 and Month 36 (and at the ET visit, if applicable) to assess the following: levels of p-tau, t-tau, A $\beta_{1-40}$ , A $\beta_{1-42}$ , and other biomarkers for PD endpoints; levels of atabecestat (see Section 9.6). The corresponding blood sample will be collected for additional analytes. In cases where a screening CSF sample is collected to confirm elevated amyloid accumulation, the screening CSF sample will replace the baseline sample to be collected on Day 1 predose.

The baseline and Month 36 CSF sampling time points are fixed. The Month 12 CSF sampling time point is considered flexible and may be shifted during the course of the study to any time point between Day 1 and Month 36, following an interim review by the DMC of the biomarker data (CSF A $\beta_{1-40}$  and CSF p-tau or an alternate biomarker of neurodegeneration; see Section 11.4.3). In addition, a blood sample for PD biomarkers will be collected at the same visit. It is recommended that the blood samples be obtained before performing the lumbar puncture.

Multiple sampling time points for CSF collection will permit an assessment over time of when changes in CSF p-tau levels or additional downstream markers of neurodegeneration occur and their respective time courses. The primary CSF biomarker to assess and predict a potential therapeutic effect of atabecestat is CSF p-tau, while the primary CSF biomarker to confirm engagement of atabecestat at the intended target site is CSF A $\beta_{1-40}$ . See Section 3.2.6.2 for a discussion of biomarkers to be measured in CSF samples.

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



### 9.4.1.2. Plasma Biomarkers

Venous blood samples will be collected from all subjects for the analysis of A $\beta$  fragments and additional exploratory markers (see Section 3.2.6.2) at the time points indicated on the Time and Events Schedule.

A PBMC sample and platelet-rich plasma sample will be collected at screening from all subjects at sites capable of processing PBMC samples (see Time and Events Schedule - Screening Phase). See Section 3.2.6.2 for additional blood tests for an optional immunologic substudy to characterize T-cell response. Additional details will be provided in a laboratory manual if such samples need to be collected (see also Attachment 4).

An RNA blood sample will be collected from all subjects at the time points indicated in the Time and Events Schedule.

A DNA blood sample will be collected for *APOE* genotyping and pharmacogenomic research from all subjects at the time point indicated in the Time and Events Schedule - Screening Phase.

### 9.4.2. Imaging Biomarkers

#### 9.4.2.1. Amyloid Positron Emission Tomography Substudy

Amyloid PET scans will be collected for amyloid screening as well as longitudinally from the subset of subjects with baseline/screening amyloid PET scans.

Amyloid PET scans will be performed to detect and measure fibrillar A $\beta$  amyloid in the brain (parenchymal A $\beta$  plaques and vessel wall deposits). PET imaging for brain amyloid will be performed longitudinally at Months 0, 24, and 48 (or at the ET visit, if applicable) in the subset of subjects who have a screening/baseline amyloid PET assessment. In cases where a screening amyloid PET scan was performed to confirm elevated amyloid accumulation, this scan will replace the baseline scan to be done at Month 0. Note, no subject will receive more than 3 amyloid PET scans during the study. If mandated by local rules or regulation (eg, exposure limits for radiation), the number of follow-up scans can be adjusted. If only 1 of the 2 follow-up scans (Month 24 and Month 48) can be performed for this reason, priority shall be given to the scan at Month 24.

While there are currently multiple amyloid PET imaging agents approved for use in the US and Europe, a single approved agent will be used at screening and throughout the study for estimating  $\beta$  amyloid burden in the brain. Tracer retention in different brain regions known to accumulate substantial amyloid in AD (eg, regions of interest [ROIs], including but not limited to the frontal, medial temporal, or parietal cortices; anterior and posterior cingulates) and different ROIs for reference (eg, pons and cerebellum) will be determined.

Details of the amyloid PET imaging procedures, including the particular tracer that will be used, tracer administration, image acquisition, image pre- and post-processing, and image analysis will be provided in a separate imaging manual/charter. In addition, instructions for reading of amyloid PET scans and rater training will be included. All PET scans will be sent to a core

imaging laboratory for central review for quality control purposes, determination of the amyloid status of each PET scan (positive or negative) by trained readers, and for data management, data analysis, and archiving, as defined in the manual/charter. For the screening eligibility scan, predefined criteria for eligibility will be documented in the imaging manual/charter.

#### **9.4.2.2. Tau Positron Emission Tomography Substudy**

Tau PET scans will be performed in those subjects who agree to participate in the assessment of brain tau burden (ie, sign a separate ICF for this substudy). PET imaging for pathological tau will be performed at Months 0, 18, and 39 (or at the ET visit, if applicable).

A single tau imaging radiotracer will be used in all tau PET scans conducted during the study. Tracer retention in different brain regions (eg, ROIs including but not limited to the amygdala, hippocampus, and parahippocampus) will be determined.

Details of the tau PET imaging procedures, including information on the tracer and its administration, image acquisition, image pre- and post-processing, and image analysis will be provided in a separate imaging manual/charter. All PET scans will be sent to a core imaging laboratory for central review for quality control purposes and for data management, data analysis, and archiving, as defined in the manual/charter.

#### **9.4.2.3. Magnetic Resonance Imaging**

All subjects will receive MRI imaging at screening to assess eligibility (Step III). In addition, MRI imaging will be conducted in all subjects during the double-blind treatment period at the time points indicated on the Time and Events Schedule to assess safety and potential treatment effects. Imaging sequences for all prespecified MRI studies comprise an identical set of pulse sequences, as described in the MRI imaging manual/charter.

Global and regional brain volumes and regional cortical thickness will be derived from the volumetric MRI sequence (3DT1) and will include both cross-sectional absolute measurements and longitudinal volume change. Most of 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 and some selected regions known not to be affected by AD to act as controls.

Task-free functional MRI imaging and DTI will only be obtained at sites that have MRI scanners capable of performing these sequences. For sites that cannot obtain DTI, diffusion weighted imaging (DWI [3 orthogonal directions only]) sequences will include fractional anisotropy and apparent diffusion coefficient in regions of subcortical white matter that are reported to be affected in preclinical AD.<sup>66</sup>

All MRI data collected (screening and on treatment) will be sent to a core imaging laboratory for quality control purposes and for data management, image processing, image analysis, and archiving, as defined in the imaging manual/charter. MRI image evaluation will be performed by a core imaging laboratory. Enrollment in the study will require central review (see Exclusion Criterion 2 in Section 4.2). If the central MRI report indicates “not eligible” or “for further

consultation,” additional screening procedures should not be performed until eligibility is resolved in consultation with the sponsor’s medical monitor.

## **9.5. Additional Clinical Scales**

In addition to the clinical scales described under secondary efficacy measures above (Section 9.2.2), other clinical scales are included in this study for screening purposes, to assess safety or tolerability, or to provide additional patient-reported outcome information. Details on these additional clinical scales are provided below.

### **9.5.1. Rosen-modified Hachinski Ischemic Scale**

The HIS is a clinical questionnaire that collects information relevant for the differentiation between the most common dementia types: Dementia of Alzheimer’s Type (DAT) and Vascular Dementia. Its utility has been validated by meta-analysis in pathologically verified patients with dementia. Scores range from 0 to 18. A cut-off score  $\leq 4$  for DAT and  $\geq 7$  for Vascular Dementia has a sensitivity of 89% and a specificity of 89%.<sup>86</sup> The Modified HIS calculates the likelihood dementia is due to vascular causes.<sup>106</sup> The Modified HIS is completed for all subjects at screening (see Section 9.1.2).

### **9.5.2. Geriatric Depression Scale**

The GDS is a simple 30-item measure used to identify depression in elderly individuals.<sup>132</sup> The simplicity of the GDS (questions are answered only by “yes” or “no”) enables the scale to be used with ill or moderately cognitively impaired individuals. One point is assigned to each answer and the cumulative score is rated on a scoring grid. The grid sets a range of 0 to 9 as ‘normal’, 10 to 19 as ‘mildly depressed’, and 20 to 30 as ‘severely depressed’. The GDS is completed for all subjects at screening (see Section 9.1.2).

### **9.5.3. Views & Perceptions about Amyloid Imaging**

Views & Perceptions about Amyloid Imaging is an instrument that assesses an individual’s perceptions about amyloid imaging and reasons for obtaining an amyloid scan (adapted from Roberts and Connell<sup>102</sup>). The questionnaire asks subjects to rate 9 reasons for seeking results of amyloid PET imaging, based on importance to them, with ratings that range from 1 (not at all important) to 5 (extremely important). The questionnaire will be completed by all subjects undergoing amyloid PET imaging to determine study eligibility, and will be administered prior to as well as after disclosure of amyloid status during the screening phase (see Section 9.1.2).

### **9.5.4. Concerns about Alzheimer's Disease Dementia**

Concerns about Alzheimer’s Disease Dementia is a short self-report instrument that assesses an individual’s concern about developing Alzheimer’s disease dementia (adapted from Roberts et al.<sup>102</sup>). The questionnaire asks subjects to rate their agreement with 6 statements related to concerns about AD dementia with ratings that range from 1 (strongly disagree) to 5 (strongly agree). This questionnaire will be completed by all subjects prior to and after disclosure of amyloid status during the screening phase, as well as at regular intervals during the double-blind treatment phase or at the ET visit (see Time and Events Schedule).

**9.5.5. Impact of Events Scale**

The IES is a 15-item self-report measure that assesses 2 common responses related to a specific stressful life event: intrusion and avoidance.<sup>54</sup> It is a reliable scale that can be anchored to any specific life event and permits assessment of individuals over time, comparison of the degree of distress among subgroups, and comparison of the impact of various events. The IES has been anchored to test-related distress in previous genetic testing studies and has been adapted for amyloid disclosure-related distress. The instrument asks subjects to respond to statements related to the stressful event (ie, disclosure of amyloid results) with ratings of 0 (not at all) to 5 (often). The IES will be administered by study staff to all subjects by telephone within 3 days after disclosure of amyloid status during the screening phase.

**9.5.6. Future Time Perspective Scale**

The Future Time Perspective (FTP) Scale measures an individual's perception of the time remaining in life which, in turn, has been shown to explain the priority of specific goals.<sup>73,103</sup> The assessment of FTP relates to an individual's perception of time rather than to actual physical time. The instrument asks subjects to rate their agreement with 10 statements related to perception of time with ratings that range from 1 (very untrue) to 7 (very true). The FTP will be completed by all subjects prior to and after disclosure of amyloid status during the screening phase, as well as at regular intervals during the double-blind treatment phase or at the ET visit (see Time and Events Schedule), to assess if disclosure of amyloid status at screening had an impact on subject's perspective over time.

**9.5.7. Assessment of Psychological Well Being**

The Assessment of Psychological Well Being, which is a combination of the GDS (short version) and State-Trait Anxiety Inventory (short version), will be used to monitor for anxiety and depression and will be completed for all subjects as part of the screening evaluations (see Section 9.1.2) as well as during the double-blind treatment phase, ET visit, and follow-up phase (see Time and Events Schedule). The screening assessment must be reviewed prior to scheduling any amyloid biomarker measurement and disclosure of amyloid result by a physician (see Section 9.1.2).

**9.5.8. Columbia Suicide Severity Rating Scale**

Consistent with regulatory guidance,<sup>a</sup> the potential occurrence of suicide-related ideation and behaviors will be assessed in this Phase 2b/3 study using the C-SSRS once during screening, at each visit during the double-blind phase, and at the ET and Follow-up visits (see Time and Events Schedule).

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<sup>a</sup> United States Food and Drug Administration. Guidance for Industry. Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials [draft guidance], August 2012. Available at: <http://www.fda.gov/downloads/Drugs/Guidances/UCM225130.pdf>. Accessed 27March2015.

The C-SSRS is a measure of the spectrum of suicidal ideation and behavior and 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.<sup>94</sup> The C-SSRS consists of a clinical interview that can be administered during any evaluation or risk assessment to identify the occurrence and intensity of suicidal thoughts and 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.

Data from the C-SSRS will be included as part of the ongoing monitoring by the DMC.

### **9.5.9. Computerized Cognitive Battery**

The computerized cognitive battery in this study includes tasks that use playing cards as stimuli: detection, identification, one card learning, and one back. For each, the test software measures the speed and accuracy of the subject's responses. The **detection** task is a measure of information processing speed and uses a well-validated simple reaction time paradigm. In this task, the playing cards are all jokers. The subject is asked to press the "yes" key as soon as the card in the center of the screen turns face up. The **identification** task is a measure of visual attention and uses a well-validated choice reaction time paradigm. In this task, the playing cards are all either red or black jokers. The subject is asked whether the card currently being presented in the center of the screen is red. The subject responds by pressing the "yes" key when the joker card is red and "no" when it is black. The **one card learning** task is a measure of visual recognition memory and uses a well-validated pattern separation paradigm. In this task, the subject is asked whether the playing card presented in the center of the screen was seen previously in this task. The subject responds by pressing the "yes" or "no" key. Because no card has been presented yet, the first response is always "no". The **one back** task is a measure of working memory and uses a well-validated n-back paradigm. In this task, the subject is asked whether the playing card being presented is the same as the one presented immediately previously. The subject responds by pressing the "yes" or "no" key. Because no card has been presented yet, the first response is always "no".

In addition to the 4 elements of the computerized cognitive battery above, computerized testing will include the Face Name Associative Memory Exam<sup>98</sup>. The **Face Name Associative Memory Exam** begins with an exposure in which the subject is shown 16 faces, one at a time, for 2 seconds in a random order. For each face the subject is asked to decide whether "the name goes with that face". Once this is completed, each of the 16 faces is then presented again. For each face the subject must recall the name that was associated with that face on the initial trial and indicate this by typing the name into the computer. The correct number of face-name pairs is recorded as an initial learning score. After a delay the subject is shown each face in turn with 3 names given beneath that face. The subject must select the name that was initially paired with the face.

### **9.5.10. Financial Capacity Instrument**

The FCI will be administered at selected centers only during screening and at regular visits during the double-blind treatment phase (and ET visit, if applicable). The FCI is a psychometric instrument that measures financial capacity using 14 tasks of financial ability and comprises 6 domains of financial activity: basic monetary skills (score range 0-79), financial conceptual knowledge (score range 0-41), cash transactions (score range 0-48), checkbook management (score range 0-62), bank statement management (score range 0-40), and financial judgment (score range 0-37).<sup>79</sup> It represents a clinically meaningful, valid functional measure. Higher scores indicate less impairment. Capacity outcome status on the FCI domains (capable, marginally capable, and incapable) were set based on normal controls (capable to marginally capable=1.5 SDs below control mean; marginally capable to incapable=2.5 SDs below control mean).

### **9.5.11. Amsterdam IADL Questionnaire**

The A-IADL-Q will be administered at selected centers only during screening and at regular visits during the double-blind treatment phase (and ET visit, if applicable). The A-IADL-Q is a computerized questionnaire aimed at measuring difficulties with complex daily activities. It is completed by the informant of the subject. The A-IADL-Q consists of 70 items and for each item difficulty is rated on a 5-point scale. To optimize individual differences in premorbid IADL activities, items are tailored to individual responses. If the patient had not performed the main activity, more detailed items on that activity are skipped. The total score is calculated using an item response theory method of scoring. Item response theory assumes that ordered-categorical item responses represent an underlying construct. In this case, the construct is IADL functioning, ranging from disability to ability. The total score is normally distributed, with higher scores indicating better functioning.<sup>69</sup>

## **9.6. Pharmacokinetic Evaluations**

### **9.6.1. Evaluations**

Venous blood samples for determination of atabecestat in plasma will be collected from all subjects at the time points indicated in the Time and Events Schedule. Blood samples will be used to evaluate the plasma PK of atabecestat.

For subjects with CSF collection (see Section 9.4.1.1), assessment of the CSF concentrations of atabecestat is also allowed.

The exact dates and times of blood and CSF sampling will be recorded in the source documentation, on the laboratory requisition form, and/or in the eCRF. In addition, the exact date and time of the last administration of study drug before the visit, as well as the date and time of the dosage at the visit, will be noted in the source documentation, on the laboratory requisition form, and/or in the eCRF.

Every attempt should be made to collect samples at the protocol-specified times. The actual sample times will be recorded to the nearest minute in the source documentation, on the

laboratory requisition form, and/or in the eCRF. The samples will be shipped to and stored by the central laboratory and will subsequently be distributed to and analyzed by reference laboratories.

### 9.6.2. Analytical Procedures

Plasma will be analyzed to determine concentrations of atabecestat using a validated, specific, and sensitive liquid chromatography/tandem mass spectrometry (LC-MS/MS) method by or under the supervision of the sponsor. If required, atabecestat concentrations will be analyzed in CSF (only postdose 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. In addition, plasma and CSF samples may be stored and used for future analysis of protein binding and metabolite profile.

### 9.6.3. Pharmacokinetic Parameters

PK analyses of plasma (and, if required, CSF) concentrations of atabecestat will be undertaken to estimate systemic exposure of atabecestat. Based on the individual plasma and CSF concentration-time data, if sufficient data is available, the following PK parameters of atabecestat will be estimated at steady-state in subjects receiving a dose of atabecestat using population PK modeling:

- $C_{\text{trough}}$ : trough plasma or CSF concentration ie, the concentration at the end of a dosing interval
- $AUC_{\text{tau}}$ : area under the plasma or CSF concentration-time curve from 0 to tau hours post dosing (time tau is the dosing interval)

Baseline covariates (eg, body weight, age, sex, creatinine clearance, and race) may be included in the model, if relevant.

CSF-related parameters will only be estimated if allowed by the model, as very sparse CSF sampling is planned to be performed. Additional analyses may be conducted if required.

## 9.7. Genomic Evaluations

A blood sample for *APOE* genotyping and additional pharmacogenomic analysis will be collected from all subjects at screening. The sample will be shipped to and analyzed by a reference laboratory designated by the sponsor. Instructions for handling, processing, and shipping of DNA samples are detailed in the laboratory manual.

Subject randomization will be stratified for *APOE*  $\epsilon 4$  allele status (see Section 5), and additional analysis may be conducted if it is hypothesized that this may help resolve issues with the clinical data. Information on a subject's *APOE* genotype will be sent to the IWRS for randomization stratification purposes, and neither the subject nor the site will be informed of the genotype results.

Pharmacogenomic research may consist of the analysis of 1 or more candidate genes or analysis of genetic markers throughout the genome or entire genome (as appropriate) in relation to

atabecestat, a clinical endpoint(s), or AD pathways. The analysis plan and results will be summarized separately from the main study results.

## **9.8. Medical Resource Utilization and Health Outcomes**

### **9.8.1. Healthcare Resource Utilization Questionnaire**

The HRUQ questionnaire tracks utilization of healthcare resources (excluding scheduled study visits) throughout the course of the study, and will be administered at screening and at specified visits during the double-blind treatment phase (and at ET visit, if applicable). The baseline measure captures resources utilized within the previous 6 months. The study visit measure captures resources used since the last study visit. The items measured in both versions include hospitalizations, emergency room visits, day hospitalizations, use of adult day centers, outpatient treatment, daily living arrangements, and productivity.

### **9.8.2. Short Form-36**

The SF-36 health survey questionnaire was developed as part of the Rand Health Insurance Experiment and will be administered during screening and at regular visits during the double-blind treatment phase (and ET visit, if applicable). It consists of 8 multi-item scales: (1) limitations in physical functioning due to health problems; (2) limitations in usual role activities due to physical health problems; (3) bodily pain; (4) general mental health (psychological distress and well-being); (5) limitations in usual role activities due to personal or emotional problems; (6) limitations in social functioning due to physical or mental health problems; (7) vitality (energy and fatigue); and (8) general health perception. This scale is scored from 0 to 100 with higher scores indicating better health. Another algorithm yields 2 summary scores, the Physical Component Score (PCS) and Mental Component Score (MCS). These summary scores are also scaled with higher scores indicating better health.<sup>127</sup>

### **9.8.3. European Quality of Life-5 Dimensions 5-level**

The EQ-5D-5L essentially consists of 2 elements: the European Quality of Life-5 Dimensions (EQ-5D) descriptive system and the EQ visual analogue scale (EQ VAS). It will be administered during screening and at regular visits during the double-blind treatment phase (and ET visit, if applicable). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems. The respondent is asked to indicate his/her health state by ticking the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for the 5 dimensions can be combined in a 5-digit number describing the respondent's health state which can be converted into a single summary index (EQ-5D index) by applying a formula that attaches values to each of the levels in each dimension. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled 'Best imaginable health state' and 'Worst imaginable health state'. The EQ VAS can be used as a quantitative measure of health outcome as judged by the individual respondents.



## 9.9. Safety Evaluations

Safety assessments will be performed during the screening and double-blind treatment phase as specified in the Time and Events Schedule. Safety assessments will include, but are not limited to, AEs, laboratory measures (hematology and clinical chemistry), vital signs, ECG, physical and neurological examinations, dermatological examination, MRI (see Section 9.4.2.3), suicidality risk as assessed by C-SSRS (see Section 9.5.8), and evaluation of well-being (see Section 9.5.7).

### 9.9.1. Adverse Events

Adverse events, including AESIs, reported by the subject (or, when appropriate, by a study informant, partner, caregiver, or the subject's legally acceptable representative) will be monitored for the duration of the study, as specified in Section 12.

### 9.9.2. Vital Signs

Vital signs (body temperature, pulse rate, blood pressure) will be collected at the time points indicated in the Time and Events Schedule. Blood pressure and pulse rate measurements will be assessed supine and standing with a completely automated device. Manual techniques will be used only if an automated device is not available. Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

### 9.9.3. Electrocardiogram

Twelve-lead ECGs will be collected at the time points listed in the Time and Events Schedule, and at all time points will be recorded 1 to 4 hours after administration of study drug. During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. For those subjects with PK sampling during the same interval, the ECG should be performed close to the collection of the PK sample (ie, both ECG and PK within a 20 minute window).

At all time points, triplicate ECGs are required, ie, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicate recordings 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 (ie, 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.

### 9.9.4. Physical and Neurological Examinations

The study investigator, or other authorized and appropriately qualified designee, will perform the physical and neurological examinations at the time points listed in the Time and Events Schedule.

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

Height and body weight will be measured per the Time and Events schedule.

#### **9.9.5. Dermatological Examination**

All subjects will undergo a comprehensive skin examination performed by a dermatologist (as defined in Section 9.1.2) during screening and again at Month 12 (or at the ET visit if subject withdraws from study or discontinues treatment prior to Month 12 assessment) to exclude the presence of skin lesions or depigmentation. A digital photograph of the frontal scalp, open eyes, and eyebrows will be collected by the dermatologist or a qualified designee to document changes noted by the dermatologist to monitor for dermatological safety. 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, informant, investigator, or study personnel, and if deemed medically relevant, subject should undergo a dermatologic exam by a dermatologist. In addition digital images of the lesion will be acquired by the dermatologist or qualified designee at the time the lesion is discovered and at follow-up visits with a frequency which is deemed appropriate by the sponsor. As skin lesions may be temporary, the site personnel may consider documenting immediately at the site with a photograph in addition to referring the subject to the dermatologist. Duration of follow-up of newly documented skin lesions or depigmentation might extend beyond the double-blind treatment phase, as judged adequate by the sponsor to ensure the safety of participants in this study.

Lightening of hair and lightening of skin are AESIs in this study based on nonclinical studies conducted with atabecestat or reported findings for BACE knockout animals or other BACE inhibitors in development (see Section 12.3.1).

#### **9.9.6. Clinical Laboratory Tests**

Blood samples for serum chemistry and hematology and urine samples (random) for urinalysis and urine drug screening will be collected at the time points specified in the Time and Events Schedule. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

The investigator's review of laboratory results should address the exclusion criteria, particularly criterion 18. The investigator should use clinical judgment and provide documented evidence when deemed necessary by the medical monitoring team that the subject does not have "ongoing hepatic, renal, cardiac, vascular, pulmonary, gastrointestinal, endocrine, hematologic, rheumatologic, psychiatric, or metabolic conditions" that are significant in the clinical trial setting. Abnormal laboratory results may be repeated to rule out worsening abnormalities and, in

consultation with the sponsor's medical monitor, to establish subject eligibility prior to amyloid testing. The sponsor's medical monitor may request additional evaluation (see Attachment 3).

In the case of hepatic enzyme elevations, attempts should be made to establish an etiology of an underlying condition and demonstrate normalization. The sponsor's medical monitor may request additional evaluation (see Attachment 3).

The following tests will be performed by the central laboratory:

### **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
- creatinine
- glucose
- aspartate aminotransferase
- alanine aminotransferase
- gamma-glutamyltransferase
- total bilirubin
- folic acid (screening only)
- alkaline phosphatase
- creatine phosphokinase
- lactic acid dehydrogenase
- uric acid
- calcium
- phosphate
- albumin
- total protein
- cholesterol
- triglycerides
- magnesium
- Vitamin B12 (screening only)

### **Thyroid Hormones (screening only)**

- thyroid stimulating hormone (TSH)
- thyroxine (T4)
- tri-iodothyronine (T3)

### **Coagulation (screening only)**

- prothrombin time
- activated partial thromboplastin time

**Urinalysis**

Dipstick	Flow Cytometry
-specific gravity	-RBC
-pH	-WBC
-glucose	-epithelial cells
-protein	
-blood	
-ketones	Sediment
-bilirubin	-crystals
-urobilinogen	-casts
-nitrite	-bacteria
-leukocyte esterase	

Dipstick and flow cytometric analysis of the urine samples will be performed in parallel, ie, in the same sample at the same time. If there is discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically.

**Serology (screening only)**

-HIV antibody	-hepatitis C virus antibody
-HBsAg	

**Urine Drug Screen** (opiates [including methadone], cocaine, amphetamines, methamphetamines, barbiturates, and benzodiazepines)

**9.10. Sample Collection and Handling**

The PK, PD (biomarker), and genomic sampling times and sampling volumes can be adapted without protocol amendment provided that the specified maximal volume collected per subject will not be exceeded. Refer to the Time and Events Schedule for the timing and frequency of all sample collections.

The actual dates and times of blood and CSF sample collection will be recorded to the nearest minute in the source documentation, on the laboratory requisition form, and/or in the eCRF. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. If a mandarin (obturator) is used, blood loss due to discard is not expected.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual. Additional details for the optional immunologic substudy for T-cell response will be provided in a laboratory manual.

## 10. SUBJECT COMPLETION/WITHDRAWAL

### 10.1. Completion

A subject will be considered to have completed the treatment phase of the study if he or she has completed assessments at Month 54 of the double-blind treatment phase. Subjects who prematurely discontinue study treatment for any reason before completion of the double-blind treatment phase will not be 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.

Subjects who discontinue study treatment prematurely will be asked to complete all regular study visits through the end of the study. To reduce burden on subjects and increase compliance, the focus will be on collecting primary and secondary clinical outcome measures and reducing other assessments in these subjects.

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

A subject's study treatment will be discontinued if the investigator believes that for safety reasons (eg, AE) it is in the best interest of the subject.

For subjects during the first 3 months of treatment with study drug, treatment must be discontinued if any of the following occurs (for details see Attachment 3):

- ALT or AST  $>5 \times \text{ULN}$
- ALT or AST  $>3 \times \text{ULN}$  and total bilirubin  $>2 \times \text{ULN}$  or International Normalized Ratio (INR)  $>1.5$
- ALT or AST  $>3 \times \text{ULN}$  with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia  $>5\%$

For subjects that have completed 3 months of treatment with study drug, treatment must be discontinued if any of the following occurs (for details see Attachment 3):

- ALT or AST  $>8 \times \text{ULN}$
- ALT or AST  $>5 \times \text{ULN}$  for more than 2 weeks
- ALT or AST  $>3 \times \text{ULN}$  and (total bilirubin  $>2 \times \text{ULN}$  or INR  $>1.5$ )
- ALT or AST  $>3 \times \text{ULN}$  with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ( $>5\%$ )

Note: Abnormal liver enzymes greater than  $3 \times \text{ULN}$  at any time during the treatment phase should be confirmed within 24-72 hours (See Attachment 3).

If the subject has a QTcF interval of >500 msec and/or QTcF increase versus baseline of >60 msec, confirmed upon repeat ECG, after consultation with the sponsor's medical monitor, treatment must be discontinued.

Re-initiation of study treatment for subjects with the above described changes in QTcF interval 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 discontinues study treatment before the end of the double-blind treatment phase and decides not to complete the study procedures, ET and posttreatment assessments should be obtained.

### **10.3. Withdrawal From the Study**

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

- Lost to follow-up
- Withdrawal of consent
- 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 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 eCRF 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.

For subjects who have cognitive decline during the study, see Section [16.2.3](#).

### **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](#)). 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**

Statistical analysis will be performed by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the SAP.

## 11.1. Subject Information

For all subjects who are randomly assigned to study drug and receive at least 1 dose of study drug, descriptive statistics will be provided.

## 11.2. Sample Size Determinations

### 11.2.1. Primary Cognitive Endpoint

The decline in PACC from baseline was assessed using data from clinically normal populations in the Alzheimer's Disease Neuroimaging Initiative (ADNI), Australian Imaging, Biomarkers, and Lifestyle Flagship Study of Aging (AIBL), and ADCS Prevention Initiative studies. The average difference in PACC decline at 36 months in AIBL between subjects with and without elevated brain amyloid was 1.40 units (95% CI: 0.52 to 2.29), and the SD at Week 144 (Month 36) was estimated at 2.44 units. If a similar decline in PACC at Month 54 is seen and the SD is 2.44, then 385 completers per treatment arm would provide 83% power (at the 2-sided alpha of 0.05) to detect a difference from placebo of 0.49. The SD at 54 months will likely be higher. If the SD at month 54 increases by 20% to 2.93, then 555 completers per groups would be required in order to maintain the same power. The sample size is estimated based on an MMRM model,<sup>78</sup> assuming a constant correlation of 0.5. Under the above assumptions and assuming the attrition is no more than 30%, a total of 1,650 randomized subjects (550/treatment arm) will be required at minimum, and 2,400 subjects (800/treatment arm) at maximum. The treatment difference of 0.49 represents 35% of the 1.40-unit difference, or a 35% slowing of decline in PACC in subjects with elevated brain amyloid. If the average time from amyloid positivity to dementia is 15 years,<sup>107</sup> then, assuming linear decline, a 35% slowing of cognition may translate into approximately a 5-year delay in the onset of dementia. A 5-year delay could lead to a 57% reduction in the number of patients with dementia.<sup>116</sup>

## 11.3. Efficacy Analyses

### 11.3.1. Analysis of the Primary Endpoint

The primary objective of this study is to test the hypothesis that either dose regimen evaluated for atabecestat will slow cognitive decline compared with placebo, as measured by the primary endpoint of the PACC change from baseline at Month 54 (see Section 9.3.1).

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the difference in means versus placebo for the primary endpoint in the specified population under the following postrandomization measure of intervention:

- **Population:** amyloid-positive subjects who are asymptomatic at risk for developing Alzheimer's dementia
- **Endpoint:** The Month 54 (Year 4.5) PACC change score (as defined in Section 9.3.1)
- **Measure of Intervention:** the effect of the initially randomized treatment regardless of treatment compliance or initiation of any Alzheimer adjunctive therapy.

The primary analysis will be based on the intent-to-treat analysis set, which includes all randomized subjects. The analysis of the PACC change score will only include subjects for whom the PACC change score is non-missing at least 1 postbaseline time point. Measurements collected after initiation of any Alzheimer adjunctive therapy will be included in the analysis for the primary estimand. Measurements collected after treatment discontinuations due to reasons potentially related to treatment (eg, treatment-related adverse events or lack of efficacy) will also be included in the analysis of the primary estimand. However, measurements collected after treatment discontinuations due to events that are clearly not treatment-related (eg, life events such as relocation, loss of transportation, loss of informant) will not be included in the analysis of the primary estimand.

A mixed effect model for repeated measurement (MMRM) analysis will be performed to assess the treatment effect. The change from baseline in PACC at each visit that the endpoint is measured will be the dependent variable. Visits scheduled for the measure will be treated as a categorical variable with values equal to the visit numbers. An unstructured covariance structure will be assumed. The model for the fixed effects will include the following terms: baseline of the endpoint measure, treatment group, visit, treatment-by-visit interaction, age, sex, education, hippocampal volume, country, and *APOE*  $\epsilon 4$  carrier status.

The null hypothesis is that there is no treatment difference between either dose of atabecestat and placebo for the primary endpoint. The estimated treatment effects at 4.5 years will be compared using the appropriate contrasts based on the MMRM at a 2-sided 0.05 significance level. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. If the unstructured covariance structure matrix results in a lack of convergence, an alternative covariance structure will be used. The details will be specified in the SAP.

Supplementary analyses may be performed to further characterize the treatment effect on the primary endpoint.

### **11.3.2. Analysis of the Secondary Endpoints**

The secondary endpoints are defined in Section 9.3.2. The key secondary endpoint in this study is the CFI. Other secondary endpoints include ADCS-ADL-PI, RBANS, CDR-SB, and NAB-DLTs for Memory and Attention.

All secondary endpoint analyses will be performed in the intent-to-treat analysis set. The change from baseline in CFI total score will be analyzed using an MMRM analysis. The change from baseline score at each visit will be the dependent variable. Visits scheduled for the measure will be treated as a categorical variable. An unstructured covariance structure will be assumed. The model for the fixed effects will include the following terms: baseline of the endpoint measure, treatment group, visit, treatment-by-visit interaction, age, sex, education, hippocampal volume, country and *APOE*  $\epsilon 4$  carrier status. If the unstructured covariance structure matrix results in a lack of convergence, an alternative covariance structure will be used.

For each of the other secondary efficacy endpoints, the change from baseline score will be similarly analyzed as above.



Descriptive statistics and evaluation of the CFI-a's ability to measure change over time will be described in the SAP.

Supplementary analyses may be performed to further characterize the treatment effect on the secondary endpoints. Data from the other clinical scales will generally be summarized descriptively by treatment group. Additional details will be provided in the SAP.

### **11.3.3. Multiple Comparison Adjustment**

Statistical adjustment will be made to account for multiplicity due to multiple dose comparisons for the primary endpoint and the key secondary endpoint (Section 11.3.1 and Section 11.3.2). To control the Type I error a 2-stage gatekeeping strategy will be employed.<sup>26</sup> In the first stage, the atabecestat dose arms will be compared with placebo on the primary efficacy endpoint using a truncated Hochberg procedure with a 2-sided  $\alpha = 0.05$  and truncation parameter  $\lambda = 0.5$ . If both arms are superior to placebo, both arms will be compared with placebo on the key secondary efficacy endpoint using the usual Hochberg procedure with a 2-sided  $\alpha = 0.05$ . If neither arm is superior to placebo on the primary efficacy endpoint, the procedure will stop and the comparison of each atabecestat arm to placebo on the key secondary endpoint will also be ruled not statistically significant. If 1 of the 2 arms is superior to placebo on the primary efficacy endpoint, that arm will be compared with placebo on the secondary efficacy endpoint using a 2-sided  $\alpha = 0.0125$ . The details of the final multiple comparison procedure will be specified in the SAP.

### **11.3.4. Handling of Missing Data**

The impact of the missing data on the efficacy results will be assessed using sensitivity analyses. The follow-up data from subjects who stop taking study medication prematurely and data from relevant external databases will be incorporated in the sensitivity analyses. Methods of missing-data sensitivity analyses will be specified in the SAP.

### **11.3.5. Subgroup Analyses**

If warranted, the treatment effect will be assessed in various subgroups of the study population. The subgroup analyses will be specified in the SAP.

## **11.4. Potential Study Design Modifications**

Some of the study design elements may be modified during the study based on a review of emerging external data, blinded interim aggregated study data, or unblinded interim data.

### **11.4.1. Blinded Sample Size Adjustment**

Blinded interim aggregated study data and external data will be used to assess sample size. Sample size may also be increased to account for dropout rate. There will be no Type I error adjustment for this design modification. Full details will be specified in the SAP.

### **11.4.2. Potential Design Modifications Based on External Data**

Emerging external data (including natural history studies of preclinical AD and available placebo data from interventional trials in preclinical AD) will be analyzed as follows:

- a) The RBANS-PACC components may have superior measurement characteristics in the target population as compared to corresponding PACC components. If supported by external data, PACC components may be substituted for 1 or more of the corresponding RBANS-PACC components in the primary endpoint for this study.
- b) Alternative weighting of the PACC components might improve the sensitivity of the PACC to AD-related cognitive decline. If supported by external evidence, the weighting of the PACC components may be modified to increase sensitivity of the PACC to AD-related cognitive decline.
- c) The timing of the primary endpoint could be moved to 3.5 years. Emerging external data (including natural history studies of preclinical AD and available placebo data from interventional trials in preclinical AD) will be analyzed to determine whether there is already a sufficient decline at 3.5 years. If supported by external data, the time point of the primary endpoint may be changed to 3.5 years.

The DMC will not be involved with any of these modifications, as the DMC may have access to the unblinded study data. Since all of the above potential changes will be carried out in a blinded manner without any knowledge of unblinded study data, there will be no Type I error adjustments. Full details will be specified in the SAP.

#### **11.4.3. Unblinded Interim Analyses to Assess Futility**

The following are the futility IAs, or potential IAs that may lead to a futility IA:

- Futility IA of CSF  $A\beta_{1-40}$
- IAs that may lead to a futility IA of the cognitive endpoints:
  - IA of amyloid PET
  - IA of CSF tau/p-tau
  - IA of tau PET
- Futility IA of cognitive endpoints

$A\beta_{1-40}$  in CSF is expected to be reduced with atabecestat treatment by 50% to 90% at steady-state in a dose dependent manner with an SD of 20%. The DMC may recommend stopping the study if the difference in percentage reduction of CSF  $A\beta_{1-40}$  between the atabecestat 25 mg dose and placebo is <50% at Month 12. Assuming an SD of 20% and 20 subjects per group, there is less than 5% chance of continuing the study if the true percentage reduction at the 25 mg dose is  $\leq 40\%$  and less than a 5% chance of stopping the study if the true percentage reduction at the 25 mg dose is  $\geq 60\%$ .

The DMC may recommend an IA of cognitive endpoints if the percentage amyloid accumulation slowdown (difference in change between placebo and atabecestat dose divided by placebo change) is <10% in the most relevant biomarker (among amyloid PET, CSF tau/p-tau, and tau PET) for both atabecestat dose arms.

Assuming amyloid PET accumulation in 24 months, tau PET accumulation in 18 months and CSF p-tau increase in 12 months in the study population are similar to the amyloid accumulation

data in the ADNI study, a total of at least 168 subjects in the IA analysis set for a given biomarker (56 subjects per group) is expected to provide adequate control of false positive and false negative error for the interim analysis. If the true accumulation slowdown for atabecestat is  $\geq 60\%$ , the probability of a false negative is approximately 10%. If the true accumulation slowdown is  $< 5\%$ , the probability of a false positive is approximately 40%.

There will be no Type I error adjustment for the IAs since no superiority will be declared from any of them. An independent external DMC (see Section 11.11) will review the IA data and make recommendations per prespecified IA decision rules.

### 11.5. Pharmacokinetic Analyses

Data will be listed for all subjects with available plasma concentrations per treatment. All concentrations below the limit of quantification (LOQ) or missing data will be labeled as such in the concentration data listings. Concentrations below the LOQ will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented. Per visit, scheduled time, and dose summary tables of atabecestat plasma concentrations will be presented including descriptive statistics. Actual and/or dose-normalized plasma concentrations will be graphically displayed as a function of dose in order to explore dose proportionality. No formal statistical comparison between doses is planned. The plasma drug concentration-time data collected during the study will be presented graphically as concentrations versus time after the previous dose.

Population PK analysis of plasma concentration-time data of atabecestat will be performed using nonlinear mixed-effects modeling. Data may be combined with those from a selection of Phase 1 or Phase 2 studies in order to support a relevant structural model. Available subject characteristics (eg, demographics, laboratory variables, genotypes) will be tested as potential covariates affecting PK parameters. Descriptive statistics will be used to summarize atabecestat plasma concentrations at each sampling time point and the following PK parameters of atabecestat (estimated using popPK modeling):  $C_{\text{trough}}$  and  $AUC_{\text{tau}}$ . Other PK parameters, if calculated, will also be summarized. Details of the popPK analysis will be provided in a popPK analysis plan and results will be presented in a separate report.

The parameter of interest for the statistical analysis will be the log-transformed estimated dose normalized  $AUC_{\text{tau}}$ . 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 scale with the corresponding 90% CIs.

### 11.6. Pharmacokinetic/Pharmacodynamic Analyses

Modeling of clinical scores (eg, PACC) may be performed using population PK/PD or disease progression models. If PK/PD modeling of clinical scores is performed, possible covariates of disease progression and/or treatment effect will be investigated. PK/PD modeling may also be performed to assess exposure- and dose-response relationships of key biomarkers, such as CSF  $A\beta_{1-40}$  concentrations, amyloid, and/or tau PET imaging results. Other biomarkers may be

explored if required. Details of the PK/PD analyses will be described in a population PK/PD analysis plan and results will be presented in a separate report.

### **11.7. Biomarker Analyses**

Statistical analyses will be performed on the following:

- CSF A $\beta_{1-40}$  and plasma A $\beta_{1-40}$
- Amyloid PET parameters
- CSF p-tau
- Tau PET
- Volumetric and task-free functional MRI parameters

In addition to CSF A $\beta_{1-40}$  and CSF p-tau, alternate CSF markers of neurodegeneration will also be analyzed similarly. CSF analyses will be performed using the CSF analysis population.

For amyloid PET, the parameters of key interest will be the global composite ROI SUVR (eg, frontal, medial temporal, or parietal cortices; anterior and posterior cingulates) and regional SUVR (eg, cortical and subcortical ROIs). Amyloid PET analysis will be performed using the amyloid PET analysis population.

For tau PET, the parameters of key interest will be tau PET signal (SUVR) in ROI(s) known to accumulate substantial tau. The analyses will be performed using the tau PET analysis population.

For MRI, the parameters of key interest will be brain volumes of the cortical and sub-cortical regions.

The treatment effect will be estimated and compared with placebo. Details of the statistical methods will be provided in the SAP.

### **11.8. Pharmacogenomic and Gene Expression Analyses**

Details of the analysis plans and summaries of results from both pharmacogenomics (DNA) and gene expression (RNA) analyses, if performed, will be reported separately.

### **11.9. Medical Resource Utilization and Health Outcome Analyses**

Summary statistics will be provided for the HRUQ, SF-36, and EQ-5D-5L scales.

For each of the outcome measures, the scores will be summarized by treatment group at each of the scheduled time points.

### **11.10. Safety Analyses**

All subjects receiving at least 1 dose of study drug will be included in the safety analysis. Descriptive statistics will be computed.

## **Adverse Events**

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs with an onset during the double-blind treatment phase and AEs that have worsened in intensity since baseline (ie, treatment-emergent adverse events [TEAEs]) will be included in the analysis. For each TEAE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe or serious AE.

## **Adverse Events of Special Interest**

Lightening of hair, lightening of skin, and ophthalmologic adverse events are AESIs. Subjects with AESIs may be counted or listed.

## **Clinical Laboratory Tests**

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results will be presented in pre- versus posttreatment cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the abnormalities will be made. A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

## **Electrocardiogram**

Electrocardiogram data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. These tables will include observed values and changes from baseline values. Frequency tabulations of the abnormalities will be made. The ECG variables that will be tabulated are heart rate, PR interval, QRS interval, QT interval, and QTcF interval.

Descriptive statistics of QTcF intervals and changes from baseline will be summarized by treatment group at each scheduled time point. The percentage of male subjects with a QTc interval >450 msec, >480 msec, or >500 msec, and the percentage of female subjects with a QTc interval >470 msec or >500 msec will be summarized separately for QTcF for each treatment group, as will the percentage of subjects with an increase in the QTcF interval from baseline of  $\leq 30$  msec, 30 to  $\leq 60$  msec, or >60 msec.

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

**Vital Signs**

Descriptive statistics of temperature, pulse rate, and blood pressure (systolic and diastolic, supine and standing values) will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized.

**Physical and Neurological Examinations**

Physical and neurological examination findings will be summarized at each scheduled time point using frequency tabulations of abnormalities.

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

**Dermatological Examinations**

Dermatological examination findings will be summarized at each scheduled time point using frequency tabulations of abnormalities.

**Suicidality Ideation and Behavior**

Suicide-related thoughts and behaviors based on the C-SSRS will be summarized by treatment group in incidence and shift tables.

**Assessment of Psychological Well Being**

Results from the Assessment of Psychological Well Being questionnaire for each scheduled time point will be summarized using frequency tabulations of abnormalities.

**11.11. Data Monitoring Committee**

An independent external DMC will be established and will be supported by an independent external statistical support group (SSG). The DMC will consist of medical experts in AD and at least 1 biostatistician. The DMC and SSG responsibilities, authorities, and procedures will be specified in its charter. The DMC will be responsible for the following:

- Monitor study data on an ongoing basis to ensure the continuing safety of study subjects
- Review the results of the IAs described in Section 11.4.3. Make recommendations per prespecified decision rules

The DMC and SSG will not be involved in any of the activities related to study conduct beyond the scope of the charter. In particular, the DMC and SSG will not be involved with any of the design changes that only rely on knowledge of external data (see Section 11.4.2).

**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 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 AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or noninvestigational) product, whether or not related to that medicinal (investigational or noninvestigational) product. (Definition per International Council for Harmonisation [ICH]).

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

Note: The sponsor collects AEs starting with the signing of the ICF (refer to Section 12.3.1).

#### Serious Adverse Event

An SAE based on ICH and European Union 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 1 of the other outcomes listed in the definition above. These should usually be considered serious. Progression of symptoms associated with AD should not be recorded as an AE unless it is considered to be accelerated in the opinion of the investigator.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must

be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

### **Unlisted (Unexpected) Adverse Event/Reference Safety Information**

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For atabecestat, the expectedness of an AE will be determined by whether or not it is listed in the Reference Safety Information section of the Investigator's Brochure.

### **Adverse Event Associated With the Use of the Drug**

An AE 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 AE that is not related to the use of the drug.

##### **Doubtful**

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

##### **Possible**

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

##### **Probable**

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

##### **Very Likely**

An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, 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 (eg, 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 or 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 exposure to the sponsor study drug, eg, name confusion)
- AESI (see Section 12.3.3)

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the Serious Adverse Event Form of the eCRF.

## 12.3. Procedures

### 12.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety). SAEs, 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.

Progression of symptoms associated with AD should not be recorded as an AE unless they are considered to be accelerated in the opinion of the investigator.

Adverse events of special interest ie, lightening of skin, lightening of hair and ophthalmologic AEs will be recorded on the AE eCRF page with a mark for AESI. For additional information on the reporting of AESIs refer to Attachment 2.

Anticipated adverse events may be recorded and reported based on local rules and regulations. A list of events considered anticipated events for the purposes of this study, and their reporting requirements can be found in Attachment 1.

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

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

Subjects will 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 SAEs 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 SAEs 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 an SAE should be made by facsimile (fax).

All SAEs 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)

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. 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 an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

The cause of death of a subject in this study within 30 days of the last dose of study drug, whether or not the event is expected or associated with the study drug, is considered an SAE. Any death occurring more than 30 days after the last dose of study drug requires expedited reporting within 24 hours only if it is assessed as possibly, probably, or definitely related to the study drug.

### **12.3.3. Adverse Events of Special Interest**

The following events are considered to be events of special interest in this study based on nonclinical studies conducted with atabecestat on reported findings for BACE knockout animals or other BACE inhibitors in development.

- Lightening of skin
- Lightening of hair
- Ophthalmologic AEs

All initial reports of treatment-emergent 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. For additional information on the reporting of AESIs refer to Attachment 2.

### **12.3.4. Adverse Drug Reactions**

Elevated liver enzymes have been identified as an adverse drug reaction (ADR) (see Investigator Brochure). The procedures for reporting these ADRs are described in detail in Attachment 3.

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 (Section 12.3.2).

### **12.3.5. Pregnancy**

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form. If a subject becomes pregnant during the study, a determination regarding study drug discontinuation must be made by the investigator in consultation with the sponsor.

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.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

### **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, ie, 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 within 24 hours after being made aware of the event.

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.3.2). 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**

The active study drug supplied for this study is a solid dosage formulation and will be supplied as 5 mg and 25 mg film-coated tablets, which are identical in appearance. These are round, white to off-white tablets, containing 5 mg or 25 mg of atabecestat. It will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a full list of excipients.

The atabecestat placebo tablets will be supplied as film-coated tablets, matching visually to the active tablets. These are round, white to off-white tablets, containing compendial grade of D-mannitol, microcrystalline cellulose, magnesium stearate triethyl citrate, and Opadry 03A48081.

### **14.2. Packaging**

All study drug and matching placebo tablets will be dispensed in child-resistant packaging.

### **14.3. Labeling**

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

### **14.4. Preparation, Handling, and Storage**

All study drug must be stored at controlled room temperatures ranging from 15°C to 30°C.

Refer to the pharmacy manual/study site investigational product manual for additional guidance on study drug preparation, handling, and storage.

### **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, or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study drug. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

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. Whenever a subject brings his or her study drug to the study site for pill count, this is not seen as a return of supplies. 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 the following supplies:

- Investigator's Brochure
- Pharmacy manual/study site investigational product manual
- Amyloid PET Imaging manual/charter
- Tau PET Imaging manual/charter
- MRI manual/charter
- Laboratory manual
- National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (current version)
- Clinical Scales and patient-reported outcomes (PRO) questionnaires and user manuals
  - Cognition:
    - PACC composed of the following: (1) FCSRT, (2) WMS-IV Logical Memory subtest, (3) WAIS-IV Coding subtest, (4) MMSE
    - RBANS
    - NAB-DLTs for Memory and Attention
    - Computerized cognitive battery
  - Mood: GDS
  - Function:
    - CFI
    - CFI-a
    - CDR

- ADCS-ADL-PI
- A-IADL-Q
- FCI
- Rosen-modified HIS
- PRO Measures:
  - Views & Perception of Amyloid Imaging Scale
  - Concerns about Alzheimer’s Disease Dementia Scale
  - IES
  - The Future Time Perspective Scale
- Medical Resource Utilization and Health Outcome Scales:
  - HRUQ
  - SF-36
  - EQ-5D-5L
- IWRS manual
- eCRF completion guidelines
- Sample ICF

## **16. ETHICAL ASPECTS**

### **16.1. Study-Specific Design Considerations**

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 AEs of the study, and provide their consent voluntarily will be enrolled. During the study, subjects will not be denied treatment for AD with available drugs, if that becomes medically appropriate. A long-term extension study will also be available for subjects, if they meet entry criteria, to provide longer-term access to atabecestat.

When referring to the signing of the ICF, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the subject with authority to authorize participation in research. For each subject, his or her legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. For the purposes of this study, all references to subjects who have provided consent refers to the subjects and the subject's legal guardian(s) or legally acceptable representative(s) who have provided consent according to this process.

If the status in regard to a subject's capacity to consent changes or worsens, a new ICF should be collected, reflecting the current status.

The use of a placebo control in this study is ethically justified as there is currently no treatment for reversing or changing the disease course in patients at risk of developing Alzheimer's dementia. Further, there is only limited information on the time course for natural progression of the development of cognitive deficits in asymptomatic patients exhibiting elevated amyloid accumulation.

The total blood volume to be collected from each subject over the course of this study ([Table 2](#)) is considered to be within the normal range allowed for this subject population over the time period (4.5 years) proposed for this study, and is within the range of Red Cross blood donations.

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

## **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.

Good Clinical Practice 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/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 must give written consent according to local requirements after the nature of the study has been fully explained. Each informant must also sign a separate ICF indicating that he/she understands the study requirements and is willing to participate in the study. 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.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects or their legally acceptable representatives 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 from their physician. Subjects will be told of alternative approaches that will be available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a 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 or legally acceptable representative 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. Additionally, subjects will be asked if they are interested to be contacted for further studies, based on the data collected during the screening process. This is especially relevant for subjects who do not qualify for this specific protocol due to their cognitive or biomarker results, but may qualify for a similar or related study.

The subject or legally acceptable representative 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.

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

Subjects who are unable to comprehend the information provided can be enrolled only after obtaining consent of a legally acceptable representative.

When prior consent of the subject is not possible and the subject's legally acceptable representative is not available, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or legally acceptable representative must be informed about the study as soon as possible and give consent to continue.

A subject who has cognitive decline during the study to the point of clinical dementia may go through the consenting process to give renewed consent or assent 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 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 is 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 DNA and biomarker 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 (including screening samples) 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 atabecestat, to understand AD, to understand differential drug responders, and to develop tests/assays related to atabecestat and AD. The research may begin at any time during the study or the poststudy 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 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.

## **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 nonacceptance, 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 eCRF 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 (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

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

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

### **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 eCRF: 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 AEs and follow-up of AEs; 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.

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).

Patient-reported outcome data and investigator completed scales and assessments may be recorded on paper or directly into an electronic device and will be considered source data.

The minimum source documentation requirements for Sections 4.1 and 4.2 that specify a need for documented medical history are as follows:

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

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

## 17.5. Case Report Form Completion

Case report forms are provided for each subject in an 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 eCRF, 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 eCRF.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in eCRFs prepared by the sponsor. Data must be entered into eCRFs 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 (eg, PACC 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 eCRFs 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.

If corrections to an eCRF are needed after the initial entry into the eCRF, 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, and direct transmission of data from all outside vendors into the study database. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review eCRFs 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 into the study database, data 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 eCRFs 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 postinitiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRFs 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 eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF is consistent with the original source data. Findings from this review of eCRFs 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 the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended 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 eCRFs. 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 atabecestat or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker

research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of atabecestat, 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 eCRF 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 may 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 is 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: Anticipated Events****Anticipated Event**

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease-related) or background regimen.

For the purposes of this study the following events will be considered anticipated events:

- Fatal and non-fatal myocardial infarction
- Angina pectoris
- Fatal and non-fatal stroke
- Transient ischemic attack
- Chronic obstructive pulmonary disease (COPD), COPD exacerbation and chronic bronchitis
- Fractures associated with falls
- Falls

**Reporting of Anticipated Events**

These events will be captured on the CRF and in the database, and will be reported to the sponsor as described in Section 12.3.1, All adverse events. Any event that meets serious adverse event criteria will be reported to the sponsor within the appropriate timeline as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities, if allowed by local practice/regulations. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the sponsor will report these events in an expedited manner.

**Anticipated Event Review Committee (ARC)**

An Anticipated Event Review Committee (ARC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The ARC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The ARC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study drug.

**Statistical Analysis**

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan.

**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 (AEs)

Cases of lightening of skin or lightening of hair should result in dermatological consultation with digital photography of the findings either by the dermatologist or a qualified designee.

For all initial reports of ophthalmologic AEs investigational sites should contact the sponsor's medical monitor for further follow-up.

All initial reports of treatment-emergent 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.

If these are deemed AEs, the site is to record these events on the AE eCRF page checked as AESI. If determined to be a serious adverse event (SAE) follow reporting as outlined in Section [12.3.2](#).

**Attachment 3: Evaluation of Increased Liver Enzymes:**

The following process should be followed whenever assessments for a given subject indicate an elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST)  $\geq 3\times$  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 meds including acetaminophen, NSAIDs and OTC 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 3) and close contact with the medical monitor with a minimal contact frequency (as outlined in the table) is also expected.

**Table 3: Minimum Schedule for Follow-Up Blood Sampling and Contact with Medical Monitor**

	AST or ALT Levels From Most Recent Laboratory Values			
	$\geq 5 \times \text{ULN}$	$\geq 3, < 5 \times \text{ULN}$	$> 1, < 3 \times \text{ULN}$	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  $\geq 8 \times \text{ULN}$
- AST or ALT  $\geq 3 \times \text{ULN}$  with symptoms
- AST or ALT  $\geq 3 \times \text{ULN}$  and total bilirubin  $\geq 2$  mg/dL
- AST or ALT  $\geq 5 \times \text{ULN}$  persists for  $> 1$  week
- AST or ALT  $\geq 3 \times \text{ULN}$  persists for  $> 2$  weeks

## 4. Discontinuation of Study Treatment:

For subjects during the first 3 months of treatment with study drug, treatment must be discontinued if any of the following occurs:

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

For subjects that have completed 3 months of treatment with study drug, treatment must be discontinued if any of the following occurs:

- ALT or AST  $> 8 \times \text{ULN}$

- ALT or AST  $> 5 \times \text{ULN}$  for more than 2 weeks
- ALT or AST  $> 3 \times \text{ULN}$  and total bilirubin  $> 2 \times \text{ULN}$  or INR  $> 1.5$
- ALT or AST  $> 3 \times \text{ULN}$  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 3.

For subjects resuming treatment after an interruption of less than 7 days, the blood sampling schedule in Table 3 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 3 should be followed. Dosages should be at the same level as before the interruption.

7. Characterization of T-cell Response in Subjects Previously Treated with atabecestat

Additional blood draws of 120 mL may be taken from subjects with elevated hepatic enzymes for PBMCs to be isolated and used in an optional immunologic sub study (see Attachment 4).

**Attachment 4: The Immunological Basis of Drug-Induced Liver Injury**

Recent work by the United States Drug-Induced Liver Injury Network has shown that most idiosyncratic, non-dose related, and unpredictable drug-induced liver injury (DILI) are due to host immune responses to the causative drugs or other agents.<sup>2,8,9</sup> The precise mechanism of DILI is still the subject of discussion and research, although Maria and Victorino<sup>6</sup> have described lymphocyte proliferative responses to drugs in over 50% of patients with DILI. More recent data point to human leukocyte antigen (HLA) alleles as risk factors for DILI (eg, flucloxacillin [B\*57:01]<sup>1</sup>, ximelagatran [DRB1\*07:01]<sup>10</sup>, lumiracoxib [DRB1\*15:01]<sup>5</sup>), lending support to an immune mechanism in DILI.

In an overview of drug-specific T-cells in human DILI, Kim and co-workers<sup>4</sup> as well as Monshi and co-workers<sup>7</sup>, showed the involvement or otherwise activation of peripheral blood mononuclear cell (PBMC), T-cell clones, antigen specificity, phenotype, HLA restriction, and cytotoxicity on flucloxacillin- and co amoxiclav-induced DILI. The drug specific T-cell tests planned for use will be conducted at the Liverpool laboratory of Kim, Monshi and Naisbitt.

*The Lymphocyte Proliferation Assay (LPA)*

The lymphocytes of most subjects can be stimulated to proliferate nonspecifically by stimulating them in vitro with the mitogens phytohemagglutinin or pokeweed mitogen, or an antibody anti-CD3. However, these substances provide strong stimuli that are not antigen specific, and usually do not discriminate as well as antigens in reflecting different levels of immunodeficiency. Antigen-specific T-cell proliferation can be measured in vitro using such antigens as cytomegalovirus antigen, tetanus toxoid, varicella zoster virus antigen, and various drugs, if an individual has been previously exposed to these agents.

The LPA allows an assessment of the role of immunological reactions in drug-induced adverse reactions. The assay allows a measurement of the ability of lymphocytes placed in short-term tissue culture to undergo a clonal proliferation when stimulated in vitro by a foreign molecule, antigen or mitogen. Several studies have shown that CD4+ lymphocytes proliferate in response to antigenic peptides in association with Class II major histocompatibility complex (MHC) molecules on antigen-presenting cells.<sup>1</sup> This proliferative response of lymphocytes to antigen in vitro occurs only if the patient has been immunized to that antigen, either by having recovered from an infection with the microorganism containing that antigen, or by having been vaccinated. Therefore, some normal individuals may not respond to a given antigen, but most people will respond to at least one of several common microbial antigens.

Study will be conducted to determine whether subjects who had elevated liver enzymes while on atabecostat have a atabecostat or atabecostat metabolite specific LPA response.

*T-cell Receptor (TCR) Sequencing Studies*

A study<sup>3</sup> using sequencing of the TCRVb CDR3 region to compare the array of T-cell receptor (TCR) sequences present (TCR repertoire) with those in the peripheral blood of the same subject was performed to correlate these factors in order to generate a predictive model for determining which subjects would benefit from dendritic cell vaccination. Examination of the TCR repertoire has previously been used to characterize the immune response to systemic, nonspecific immunotherapies, such as cluster of differentiation 152 (CTLA-4) and programmed cell death protein 1 (PD-1) blockade.

In a study to characterize the functionality of drug-responsive CD8+ T-cell clones generated from HLA-B\*57:01+ drug-naïve subjects and to explore the relationship between abacavir accumulation in



antigen presenting cells and the T-cell response, Bell and co-workers<sup>2</sup> showed that 74 CD8+ clones expressing different V $\beta$  receptors proliferated and killed target cells via different mechanisms when exposed to abacavir. Certain clones were activated with abacavir in the absence of antigen presenting cells. Analysis of the remaining clones revealed 2 pathways of drug dependent T-cell activation.

Studies will be conducted to determine specific T-cell activation pathways in subjects who had elevated liver enzymes while on atacecestat.

### **Sample Collection**

The collection of PBMCs is via a standard blood collection procedure using BD Vacutainer® Cell Preparation Tubes with Sodium Heparin (CPT™) that permit the simple isolation and transport of cells that retain function.

Blood samples will be collected via venipuncture directly into BD Vacutainer CPT tubes. In order to collect 120 mL of blood, 15 CPT tubes of 8 mL will be filled per subject.

Detailed description of the isolation of PBMCs from blood in CPT tubes, freezing and shipping to laboratories are provided in a laboratory manual. Frozen PBMCs are to be sent to Liverpool CDSS for drug specific immune response studies (see below) and to Beerse for TCR sequencing.

### **Activities at Liverpool CDSS**

The overall objective is to define the key immunological events involved in DILI. The project is divided into 2 parts. In Part 1, drug-specific immune responses in subjects with an elevation in liver enzymes and corresponding control subjects will be analyzed. In Part 2 the phenotype and function of drug-responsive T-cells will be characterized. The objectives, main deliverables, and methodological approaches for each part of the study are described in the following sections.

#### **Part 1: Drug-Specific Immune Response**

**Specific objective:** To characterize the drug-specific stimulation of PBMCs from subjects with atacecestat-associated elevation in liver enzymes.

**Deliverables:** (1) Diagnosis of DILI using biological tests; (2) characterization of drug-specific PBMC responses in subjects with atacecestat-associated elevation in liver enzymes and tolerant controls.

**Brief description of work:** PBMC samples from subjects will be analyzed to determine whether study drug stimulates lymphocytes to proliferate and/or secrete cytokines. Methods: To define the role of functional antigen-specific T-cell subsets (T helper [Th]1, Th2, Th17, Th22, CD8+) in DILI, the T-cell stimulatory capacity of the parent drug, metabolites, and structurally-related compounds will be profiled using the lymphocyte transformation test (endpoint [3H] thymidine) and enzyme-linked immunospot (ELISPOT) for monitoring effector T-cell responses. The mitogen phytohemagglutinin and recall antigen tetanus toxoid will be used as positive controls to confirm the proliferative activity of the PBMCs. The negative control will be cell culture medium containing the same quantity of solvent used to dissolve the drug. If the frequency of drug-specific T-cells is too low to detect a T-cell response directly, PBMC from certain subjects will be cultured with drug for up to 4 weeks to generate drug-responsive T-cell clones before analysis of antigen specificity.

## Part 2: Phenotype and Function of Drug-Responsive T-Cells

**Specific objective:** To define the phenotype and function of drug-specific T-cells.

**Deliverables:** (1) Generation and expansion of drug-specific T-cell clones; (2) characterization of the phenotype, function and cross-reactivity with structurally related compounds of T-cell clones; (3) define mechanistic pathways of drug presentation to T-cells.

**Brief description of work:** T-cells will be cloned from subjects and characterized in terms of antigen specificity, phenotype, and function (proliferation, cytolytic activity, cytokine secretion, and tissue homing characteristics). The involvement of the major histocompatibility complex in drug presentation will be assessed using (1) human leukocyte antigen (HLA) blocking antibodies and (2) mismatched or partially HLA-matched antigen presenting cells. Multiplex cytokine analysis and ELISpot will be used to analyze cytokine and effector molecule (eg, perforin, granzyme B, FasL) secretion. The requirement for processing in antigen presentation will be measured by assessing the kinetics of T-cell receptor internalization and through the use of inhibitors of antigen processing. Chemokine receptors expressed on clones will be profiled using flow cytometry.

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### INVESTIGATOR AGREEMENT

JNJ-54861911 (atabecestat)

Clinical Protocol 54861911ALZ2003 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): Panna Sanga, MD

Institution: Janssen Research & Development

Signature: \_\_\_\_\_ Date: 25 MAY 2018

(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.

Approved, 25 May 2018