Title: A Double Blind, Randomized, Placebo Controlled, Parallel Group Study to Simultaneously Qualify a Biomarker Algorithm for Prognosis of Risk of Developing Mild Cognitive Impairment due to Alzheimer's Disease (MCI due to AD) and to Test the Safety and Efficacy of Pioglitazone (AD-4833 SR 0.8 mg QD) to Delay the Onset of MCI due to AD in Cognitively Normal Subjects

NCT Number: NCT01931566

Protocol Approve Date: 27 September 2016

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

PROTOCOL

A Double Blind, Randomized, Placebo Controlled, Parallel Group Study to Simultaneously Qualify a Biomarker Algorithm for Prognosis of Risk of Developing Mild Cognitive Impairment due to Alzheimer's Disease (MCI due to AD) and to Test the Safety and Efficacy of Pioglitazone (AD-4833 SR 0.8 mg QD) to Delay the Onset of MCI due to AD in Cognitively Normal Subjects

Biomarker Qualification for Risk of MCI due to AD and Safety and Efficacy Evaluation of Pioglitazone (AD-4833 SR 0.8 mg QD) in Delaying its Onset

Sponsor: Takeda Development Center Americas, Inc.
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Study Number: AD-4833/TOMM40_301

IND Number: 112,403 **EudraCT Number:** 2012-003111-58

Compound: AD-4833

Date: 27 September 2016 **Amendment Number:** 6

Amendment History:

Date	Amendment Number	Amendment Type	Region
07 February 2013	Initial Protocol	Not applicable	Global
09 April 2013	1	Substantial	Global
19 March 2014	2	Substantial	Global
10 November 2014	3	Substantial	Global
15 April 2015	4	Substantial	Local-Russia
24 July 2015	5	Substantial	Global
27 September 2016	6	Substantial	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

TDC sponsored European and Asian Pacific investigators will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Issue	North America Contact	European Contact	Australia Contact
Serious adverse event and pregnancy reporting	PPD		
Medical Monitor (medical advice on protocol, compound, and medical management of subjects)			
Responsible Medical Officer (carries overall responsibility for the conduct of the study)			

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

PPD

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix B – Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State)

Location of Facility (Country)

1.3 Protocol Amendment 6 Summary of Changes

This document describes the changes in reference to the Protocol Incorporating Amendment No. 6.

The primary purpose of this amendment is to update the protocol regarding revisions to plans for the Futility Analysis as well as to introduce adjustments to the protocol that will help reduce subject burden. Full details on changes of text are given in Appendix J. The following is a summary of the key changes made in the amendment:

1. The efficacy futility analysis has been revised to occur once 33% of events have accrued, rather than at 50%.

   Justification: This change will reduce the time to an initial assessment of futility, protecting study subjects and the Sponsor from continuation of an ultimately futile study, while keeping the risk of a futility 'false negative' finding at an acceptably low probability. (Pivotal study futility analyses are commonly performed with 25-50% of the final planned number of events.)

2. An "operational futility" analysis has been added. This will enable an assessment of whether the study can feasibly be completed within an acceptable timeframe, based on the accrual rate of adjudicated cases meeting the event definition.

   Justification: Given the low but steady dropout rate projected and observed, a delay in study completion could lead to an overall dropout rate greater than 50%, potentially making interpretation of the study data difficult, even if the formal primary efficacy analysis is positive. In addition, a multi-year delay in study completion increases the risk that the study could yield less relevant results with continued developments in Alzheimer disease (AD) diagnosis and treatment.

3. The timing of required magnetic resonance imaging (MRI) scans has been clarified as well as removing the requirement to perform an MRI scan if a scan has been performed for the study within the preceding 6 months.

   Justification: These changes have been implemented to remove ambiguity over the required timing of MRI scans as well as to eliminate a requirement for unnecessary scans from being performed, thereby reducing burden on sites and subjects.

4. Additional options for the performance of the Comprehensive Medical Follow-Up Visit have been introduced, including the ability to perform assessments during routine Month 6 or Month 12 visits in certain situations and during Home Visits or by telephone (for project partners) in exceptional circumstances.

   Justification: These adjustments have been made to provide greater flexibility to sites and subjects in scheduling these visits. In exceptional circumstances, sites will now have the ability to perform selected assessments at a subject's home or by telephone, with prior

approval of the Sponsor. This modification has been made to help mitigate the risk of critical primary endpoint related data not being collected due to challenges associated with conducting the study with an elderly population in which subjects approaching endpoint are repeatedly triggering which requires additional visits, increasing subject burden and study fatigue.

5. Microscopic urine screens will be standard on all urine sample collections at routine visits rather than as a reflex in the event of abnormalities detected on macroscopic examination.

   Justification: This change has been made to eliminate the need for additional site visits, which will decrease subject burden.

6. Formal limits for assessment of compliance with study drug have been introduced.

   Justification: Limits have been introduced to the protocol to help facilitate consistency in global monitoring and reporting of subjects that are not compliant with administration of study drug.

7. Clarification provided over Adverse Event of Special Interest (AESI) follow-up and reporting of macular degeneration and hypoglycemia.

   Justification: Clarification provided to ensure consistency in follow-up of macular edema and to eliminate ambiguity over reporting of hypoglycemia as an AESI, ensuring consistency across all subjects.

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2.0 STUDY SUMMARY

<table>
<tr><td colspan="2">Name of Sponsor(s):
Takeda Development Center Americas, Inc.</td><td>Compound:
AD-4833</td></tr>
<tr><td>Title of Protocol: A Double Blind, Randomized, Placebo Controlled, Parallel Group Study to Simultaneously Qualify a Biomarker Algorithm for Prognosis of Risk of Developing Mild Cognitive Impairment due to Alzheimer’s Disease (MCI due to AD) and to Test the Safety and Efficacy of Pioglitazone (AD-4833 SR 0.8 mg QD) to Delay the Onset of MCI due to AD in Cognitively Normal Subjects</td><td>IND No.: 112,403</td><td>EudraCT No.:
2012-003111-58</td></tr>
<tr><td colspan="2">Study Number: AD-4833/TOMM40_301</td><td>Phase: 3</td></tr>
<tr><td colspan="3">Study Design:
This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Eligible subjects will be stratified into high- and low-risk groups in terms of risk to develop mild cognitive impairment (MCI) due to Alzheimer disease (AD) over the next 5 years, based upon the results of a biomarker risk algorithm (comprised of TOMM40 rs10524523 genotype, apolipoprotein E [APOE] genotype, and age). High-risk subjects will be randomized to receive either pioglitazone or placebo. All subjects stratified to the low-risk stratum will be assigned to receive placebo. The study duration will be the time needed to accumulate a total of 202 conversions to MCI due to AD diagnosis in the non-Hispanic/Latino Caucasian subjects within the high-risk stratum. The study will recruit internationally from large, diverse, community-based populations. Because the data used to develop the enrichment algorithm was collected in non-Hispanic/Latino Caucasian subjects only, the primary analyses of the study to compare the effects of pioglitazone versus placebo will be within the non-Hispanic/Latino Caucasian high-risk sub-group. Likewise, for the biomarker risk algorithm qualification, only the subjects within the non-Hispanic/Latino Caucasian high-risk sub-group will be included. In addition to their participation in the main Phase 3 study, approximately 300 cognitively normal elderly subjects will participate in a volumetric magnetic resonance imaging (vMRI) substudy at selected sites.</td></tr>
<tr><td colspan="3">Primary Objectives:
For biomarker risk algorithm qualification:
• To qualify the biomarker risk algorithm composed of TOMM40 rs10524523 genotype, APOE genotype, and age for prognosis of the risk of developing MCI due to AD within 5 years.
For efficacy evaluation of pioglitazone:
• To evaluate the efficacy of pioglitazone compared with placebo to delay the onset of MCI due to AD in cognitively-normal subjects who are at high-risk, as identified by the biomarker risk algorithm at enrollment, for developing MCI due to AD within 5 years.</td></tr>
<tr><td colspan="3">Key Secondary Objectives:
• To evaluate the effect of pioglitazone compared with placebo on the progression of cognitive decline.
• To evaluate the effect of pioglitazone compared with placebo on functional decline and instrumental activities of daily living.</td></tr>
<tr><td colspan="3">Safety Objectives:
• To evaluate long-term safety and tolerability of pioglitazone compared with placebo during the course of the treatment.</td></tr>
</table>

Exploratory Objectives:

- CCI
- [redacted]

Subject Population: Open enrollment ages 65-83 (inclusive) male and female subjects who are cognitively normal.

Number of Subjects:	**Number of Sites:**
Approximately 3500 Subjects randomized.	Estimated total: approximately 60 in North America, Europe, Australia
Dose Level(s):	**Route of Administration:**
AD-4833 sustained release (SR) 0.8 mg Tablet once daily (QD) Placebo QD	Oral
Duration of Treatment:	**Period of Evaluation:**
Estimate (event-driven study) is minimum 4 years (48 months)	Up to 125 day Screening period prior to Randomization Minimum 4 year Double-Blind Treatment period

Main Criteria for Inclusion:

- Male or postmenopausal female subject between 65 and 83 years of age, inclusive at the time of the screening visit.
- The subject must be cognitively normal at baseline, scoring as indicated for the following tests:
  - Clinical Dementia Rating (CDR)=0.
  - At least one memory test above -1.5 SD of the demographically corrected normative mean.
- The subject must score ≥25 on the Mini Mental Status Examination (MMSE) at the screening visit after the education and age adjustment referenced in Appendix G.
- All subjects require a project partner who can separately complete an Acknowledgment Form on his/her own behalf and take part in the study to provide information on the cognitive, functional, and behavioral status of the subject and to assist with monitoring of study medication, if needed.
- The subject has the ability and intention to participate in regular study visits, in the opinion of the Investigator.

Main Criteria for Exclusion:

- The subject has a current diagnosis or history of any type of cognitive impairment or dementia, or has a current diagnosis or history of neurological/psychiatric disorder or any other diagnosis that significantly affects cognitive performance (eg, mental retardation, organic mental disorder).
- The subject has a current diagnosis of significant psychiatric illness, per the Diagnostic & Statistical Manual of Mental Disorders, 4th Edition - Text Revision (DSM-IV-TR) (including but not limited to major depressive disorder, anxiety disorders) and is in an acute phase/episode, or the subject has a current diagnosis or history of

schizophrenia or bipolar disorder.

- The subject has glycosylated hemoglobin (HbA1c) >8.0% at the time of baseline or requires treatment with insulin, triple oral antidiabetic therapy or a peroxisome proliferator-activated receptor-gamma (PPARγ) agonist. The subject should be on a stable antidiabetic regimen for at least 3 months prior to enrollment.
- The subject has a clinically significant unstable illness, for example, hepatic impairment or renal insufficiency, or cardiovascular, pulmonary, gastrointestinal (including s/p gastric bypass), endocrine, neurological, rheumatologic, immunologic, infectious, skin and subcutaneous tissue disorders, or metabolic disturbance. History of human immunodeficiency virus (HIV) infection is considered exclusionary for this study.
- The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse/dependence within 2 years prior to the Screening Visit.
- The subject has a history or current diagnosis of macular edema or macular degeneration.
- If female, the subject has a history of postmenopausal fractures with no or minimal trauma (eg, wrist, hip, lumbar or thoracic vertebral fracture).
- The subject has a history or current diagnosis of congestive heart failure (CHF), New York Heart Association Class III-IV.
- The subject has been exposed to cognitive tests performed in this study within 6 months prior to the Screening Visit with the exception of the Mini-Mental State Examination (MMSE).
- The subject's TOMM40 rs10524523 or APOE genotypes or APOE phenotype are known by the subject or the study staff participating in this study.

Main Criteria for Evaluation and Analyses:

Efficacy:

The primary endpoint for the biomarker risk algorithm qualification:

- Time to diagnosis of MCI due to AD for placebo-treated, high-risk subjects versus placebo-treated, low-risk subjects.

The primary endpoint for the efficacy evaluation of pioglitazone:

- Time to diagnosis of MCI due to AD for pioglitazone-treated subjects versus placebo-treated subjects in the high-risk stratum.

Key Secondary endpoints for this study are:

- Change from baseline for cognitive decline on composite score on the cognitive battery for pioglitazone-treated subjects versus placebo-treated subjects in the high-risk stratum.
- Changes from baseline in instrumental activities of daily living (Alzheimer's Disease Cooperative Study Activities of Daily Living - Prevention Instrument [ADCS ADL-PI]) between pioglitazone-treated and placebo-treated groups of the high-risk stratum.

Statistical Considerations:

There are 2 independent null hypotheses in this protocol: 1) that there is no difference in conversion rate between the placebo-treated high-risk and low-risk groups, where risk is defined by the prognostic biomarker test and 2) that there is no difference in conversion rate between the high-risk active- and placebo-treated subjects. The alternate hypotheses are: 1) that there is a difference between the high- and low-risk groups treated with placebo, and 2) that there is a difference between placebo and active treatment in the high-risk group. Time to event analyses will be used to evaluate the conversion rates over time. The other secondary endpoints will be analyzed using analysis of covariance, logistic regression, survival analyses, or chi-squared tests as appropriate to the data. As for the primary analysis, the secondary endpoints will be tested at the alpha = 0.01 level.

Pharmacokinetic Analysis:

Sparse plasma samples from approximately 30% per region of study subjects will be collected to estimate population Pharmacokinetics (PK)/Pharmacodynamics (PD) of pioglitazone, random inter/intra-subject variability, random residual variability associated with PK and PD model parameters, and to identify sources of variability (continuous or categorical covariates) that may influence pioglitazone PK and PD profiles in study subjects. Once approximately 30% per region of study subjects have consented to the PK collection, future subjects will not have PK samples collected.

Sample Size Justification: The sample size for this study is based on the event-driven analysis that is planned for comparing treatment groups within the high-risk stratum. For the purposes of this study, it is assumed that the placebo-treated non-Hispanic/Latino Caucasian subjects in the high-risk stratum will have an event rate of 15% over 5 years. With an expected improvement of a reduction in event rate of 40%, the target event rate for the active treatment group will be 9% over 5 years. Furthermore, the following specifications are used: alpha=0.01, a 2-sided statistical test based on survival analysis, power=90%, annual dropout rate of 12% (or cumulative dropout rate of 47% over 5 years). In order to detect a difference of the specified magnitude (≥40% reduction in conversion rates over 5 years), at least 202 events must be observed during the course of the study in the non-Hispanic/Latino Caucasian subjects in the high risk stratum. Based on these assumptions and the fact that only non-Hispanic/Latino Caucasian subjects will be used for the primary analyses, a total of 2,346 non-Hispanic/Latino Caucasian subjects (1,173 on pioglitazone/1,173 on placebo) will be required in the high-risk stratum for randomization.

All subjects screened into the study at the time of Amendment 5 will be allowed to enroll if they continue to meet all eligibility criteria. Therefore, the total number of subjects to be randomized is estimated at 3,500.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study Responsibilities template. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator/Coordinating Investigator

Takeda Development Center, Inc. (TDC) will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The signatory coordinating investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

AA	Alzheimer's Association
AD	Alzheimer disease
ADAPT	Alzheimer's Disease Anti-inflammatory Prevention Trial
ADAS-cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
ADCS ADL-PI	Alzheimer's Disease Cooperative Study Activities of Daily Living - Prevention Instrument
ADCS-CGIC-MCI	Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change – Mild Cognitive Impairment
ADCS-MCFSI	Alzheimer's Disease Cooperative Study – Prevention Instrument Project – Mail-In Cognitive Function Screening Instrument
ADCS-RUI	Alzheimer's Disease Cooperative Study - Resource Use Inventory
ADRC	Alzheimer's Disease Research Center
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APOE	apolipoprotein E
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BOLD	blood oxygen level-dependent
BVMT-R	Brief Visuospatial Memory Test - Revised
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating – Sum of Boxes
CDT	Clock Drawing Test
CFR	Code of Federal Regulations
CI	confidence interval
CIAC	Cognitive Impairment Adjudication Committee
CGIC	Clinical Global Impression of Change
CHF	congestive heart failure
CMFV	Comprehensive Medical Follow-up Visit
CNS	central nervous system
CRO	contract research organization
C-SSRS	Columbia–Suicide Severity Rating Scale
CT	computerized axial tomography
CVLT-II	California Verbal Learning Test – 2nd Edition
CYP	cytochrome P-450
DNA	deoxyribonucleic acid
DSMB	data safety monitoring board

DSM-IV-TR	Diagnostic & Statistical Manual of Mental Disorders, 4th Edition - Text Revision
ECG	electrocardiogram
(e)CRF	(electronic) case report form
EDC	electronic data capture
EoS	end of study
EMA	European Medicines Agency
EQ-5D	European Quality of life (includes single item measures of: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression)
EW	early withdrawal
FAS	full analysis set
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
GEMS	Ginkgo Evaluation of Memory Study
GGT	γ-glutamyl transferase
GWAS	genome wide association study
HbA1c	glycosylated hemoglobin
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDPE	high density polyethylene
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
INR	international normalized ratio
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
IRB	institutional review board
IVD	in vitro diagnostic device
IVRS	interactive voice response system
IWRS	interactive web response system
K2EDTA	potassium ethylenediamine tetraacetic acid
L	long
LC-MS/MS	liquid chromatographic method with mass spectrometry detection
LD	linkage disequilibrium
LFT	liver function test

MACE	major adverse cardiac event
MAR	missing at random
MCI	mild cognitive impairment
Med ID	medication identification number
MedDRA	Medical Dictionary for Regulatory Activities
MetS	metabolic syndrome
MINT	Multilingual Naming Test
MMRM	mixed models repeated measures
MMSE	Mini-Mental State Examination
MOA	mechanism of action
MRI	magnetic resonance imaging
NIA	National Institute on Aging
NPI-Q	Neuropsychiatric Inventory Questionnaire
NPS	neuropsychiatric symptoms
NPV	negative predictive value
NSAID	non-steroidal anti-inflammatory drug
PD	pharmacodynamics
PGx	pharmacogenomics
PK	pharmacokinetics
PPAR-γ	peroxisome proliferator-activated receptor-gamma
PPV	positive predictive value
PRO	patient reported outcome
PROACTIVE	PROspective pioglitAzone Clinical Trial In macroVascular Events
PTE	pretreatment event
PTH	parathyroid hormone
QD	once daily
rCBF	regional cerebral blood flow
RNA	ribonucleic acid
RPR	rapid plasma reagin
RU	resource utilization
S	short
SAE	serious adverse event
SAP	statistical analysis plan
SF-36	Short Form-36
SR	sustained release
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
T4	thyroxine
TMT	Trail Making Tests

TOMM40	translocase of the outer mitochondrial membrane 40 homolog
TSH	thyroid-stimulating hormone
TZD	thiazolidinedione
ULN	upper limit of normal
VAS	visual analog scale
VL	very long
vMRI	volumetric magnetic resonance imaging
WAIS	Wechsler Adult Intelligence Scale
WHIMS	Women's Health Initiative Memory Study
WHO	World Health Organization

3.4 Corporate Identification

TDC (Asia)	Takeda Development Center Asia Pte Ltd
TDC (Europe)	Takeda Development Centre (Europe) Ltd.
TDC (Americas)	Takeda Development Center Americas, Inc.
TDC	TDC (Asia), TDC (Europe) and/or TDC (Americas), as applicable
TPC	Takeda Pharmaceutical Company Limited
Takeda	Takeda Pharmaceutical Company Limited TDC (Asia), TDC (Americas), TDC (Europe), and/or TPC, as applicable

4.0 INTRODUCTION

4.1 Background

Pioglitazone hydrochloride is a member of a class of oral antidiabetic agents known as thiazolidinediones (TZDs) that are approved for the treatment of type 2 diabetes mellitus (T2DM). Pioglitazone is a potent and highly selective agonist of peroxisome proliferator-activated receptor-gamma (PPAR-γ), which is a ligand-activated transcription factor found in tissues sensitive to insulin action (including adipose tissue, skeletal muscle, liver, and the brain) [1]. The mechanism of action through which PPAR-γ agonists might affect Alzheimer disease (AD) pathophysiology is not established at this time; however, activated PPAR-γ regulates a number of pathways implicated in the etiology of AD, and it has been shown that the drug crosses the blood brain barrier [1]. Numerous studies indicate that pioglitazone regulates glucose and lipid metabolism in neuronal cells [2,3], reduces or prevents neuroinflammation [4,5], has neuroprotective effects [6], and modulates mitochondrial biogenesis and function [7] and thus adenosine triphosphate (ATP) production. It is thought that mitochondrial dysfunction may play a chief role in the cerebral hypometabolism observed in AD and in subjects at risk to develop AD [8,9,11]. Roses et al have postulated that PPAR-γ agonists improve mitochondrial function in AD [12].

The effects of pioglitazone on mitochondrial structure and function and on stimulating neurite outgrowth have been suggested to occur at exposures well below the doses approved for T2DM. Pioglitazone at concentrations of 10 nM to 1 μM induces mitochondrial biogenesis and prevents glucose deprivation–induced neuronal death [7], and also stimulates neurite outgrowth in cultured neuronal cells [13]. Using a different neuronal cell line, Ghosh et al have also demonstrated similar effects on mitochondrial biogenesis with significantly higher concentrations of pioglitazone (10 to 20 μM, decreasing at 40 μM), which is greater than the serum levels achieved with doses used to treat T2DM [2]. Pioglitazone treatment significantly increased mitochondrial number and expression of factors involved in mitochondrial biogenesis, including PPAR-γ coactivator -1α and mitochondrial transcription factor [14].

Pioglitazone has been studied in randomized clinical studies as a treatment for subjects already exhibiting clinical symptoms of either mild cognitive impairment (MCI) or probable AD, with mixed results. Geldmacher et al conducted an 18-month, double-blind, placebo-controlled randomized trial to test long-term safety and tolerability of pioglitazone in a nondiabetic elderly population with AD [15]. Twenty-nine subjects were treated with pioglitazone titrated to 45 mg/day (n=14; mean age = 74.9) or matching placebo (n=15; mean age = 67.0 years). Subjects maintained treatment with cholinesterase inhibitors and could begin memantine therapy when it became available during the study. The primary outcome of this study was the frequency of adverse events (AEs), while secondary outcomes included measures of cognition, activities of daily living, neuropsychiatric symptoms (NPS), and global functioning. Pioglitazone was generally well tolerated in this pilot study, as no serious AEs (SAEs) or unanticipated AEs

occurred, while peripheral edema was the principal AE (28.6% in pioglitazone-treated subjects compared with 0% in placebo-treated subjects). No significant treatment effect was observed on exploratory analysis of clinical efficacy.

Sato et al conducted a 6-month, randomized, open-controlled pilot study of pioglitazone efficacy on cognition, regional cerebral blood flow (rCBF), and plasma Aβ40 and Aβ42 [16]. Study subjects were 42 AD patients with T2DM, half of whom were treated with 15 to 30 mg pioglitazone daily; all subjects continued on their previous T2DM treatment (including sulfonylureas, biguanides, and α-glucosidase inhibitors). Subjects receiving pioglitazone demonstrated significantly improved cognition (Mini-Mental State Examination [MMSE], Alzheimer's Disease Assessment Scale-Cognitive Subscale [ADAS-cog]), Wechsler Memory Scale-revised logical memory-I) and rCBF at 6 months compared to baseline (Visit 2), while untreated subjects did not. Untreated subjects did, however, have increased plasma Aβ40 /Aβ42 ratio, while there was no significant change in pioglitazone-treated subjects.

The National Institute on Aging (NIA) is currently sponsoring a pioglitazone study to investigate novel treatments to delay progression to dementia in patients with MCI and metabolic syndrome (MetS) [17]. Adults aged 55 years or older with both MeTS and MCI at Baseline (Visit 2) are randomized to a 6-month intervention with either (1) treatment with pioglitazone, (2) endurance exercise training, or (3) control (placebo and no exercise). It is proposed that treatment with the TZD pioglitazone or endurance exercise training will improve cognitive function compared to controls, as evidenced by either improvement, stabilization, or lesser decline in performance on cognitive testing.

Pioglitazone is an appropriate therapeutic candidate for use in a study with cognitively normal subjects because it has an established safety profile even at doses considerably higher than the intended dose in the proposed phase 3 study. Over 8500 subjects with T2DM have been treated with pioglitazone in randomized, double-blind, controlled clinical studies, including 2605 subjects with T2DM and macrovascular disease treated with pioglitazone in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROACTIVE) clinical trial [18]. In these studies, over 6000 subjects have been treated with pioglitazone for 6 months or longer, over 4500 subjects have been treated with pioglitazone for one year or longer, and over 3000 subjects have been treated with pioglitazone for at least 2 years. Common adverse events that occurred in these studies at an incidence rate of >5% and more frequently in pioglitazone (monotherapy) than in placebo treatment group were headache (9.1%), sinusitis (6.3%), myalgia (5.4%), and pharyngitis (5.1%).

The results of the PROACTIVE study showed that pioglitazone reduced the risk of secondary macrovascular events in a high-risk patient population with type 2 diabetes and established macrovascular disease.

Since launch in the United States in July 1999, through 31 July 2014, the total patient-years of exposure to pioglitazone (monotherapy) globally is estimated to be approximately 26,682,746 [19]. Clinical experience has not identified differences in effectiveness or safety between the

elderly (≥65 years of age) and younger subjects, although small numbers of subjects ≥75 years of age limit this conclusion.

Few postmarketing reports of new-onset or worsening diabetic macular edema with decreased visual acuity have occurred with TZDs, including pioglitazone. Many of these patients reported concurrent peripheral edema. It is not known whether there is a direct association between pioglitazone and macular edema, but investigators should be alert to the possibility of macular edema. If study participants report disturbances in visual acuity (eg, blurred vision, distortion of images, missing areas, dimming or "graying-out" of vision from loss of contrast sensitivity, and changes in the way color is perceived), they will be evaluated by an ophthalmologist.

There have been postmarketing reports of bone fractures associated with the use of TZDs, including pioglitazone. The majority of the fractures occurred in women with most of the fractures involving upper and lower limbs of the body. Many cases lack any information about history or about risk factors for bone fractures. In cases where information was available, patients had a history of and multiple risk factors for fractures.

Adverse events associated with pioglitazone, listed in the Warnings and Precautions section of the Company Core Data Sheet [20], for subjects with T2DM and at doses considerably higher (15-45 mg) than the intended dose in this clinical development program (sustained release [SR] 0.8 mg) were as follows: congestive heart failure (CHF) and peripheral edema due to dose-related fluid retention, hepatic failure, increased incidence of fractures in female population, hypoglycemia, macular edema, and bladder cancer. A detailed discussion of the safety profile of pioglitazone is provided in the investigator's brochure.

4.2 Rationale for the Proposed Study

Zinfandel Pharmaceuticals, Inc. (Zinfandel) identified a genetic variant, translocase of the outer mitochondrial membrane 40 homolog (TOMM40) rs10524523, which appears to be prognostic of onset of cognitive decline within 5 years when combined with apolipoprotein E (APOE) genotype and age. The biomarker risk algorithm, which is the combination of TOMM40rs 10524523 genotype, APOE and age, is used to categorize subjects as being either high-risk or low-risk to develop MCI due to AD within 5 years.

Zinfandel and Takeda entered into a license agreement pursuant to which Takeda is the exclusive licensee of the biomarker risk algorithm, including its use in evaluating the efficacy of pioglitazone for delaying the onset of MCI due to AD in high-risk individuals identified on the basis of the biomarker risk algorithm.

It has been estimated that delaying AD onset by 1 or 2 years could decrease global disease burden in 2050 by 11.8 million or 22.8 million cases, respectively [21]. Coupled with the failure of multiple treatment trials that have been conducted over the past decade, the focus of AD clinical research has begun to shift to the pursuit of a prevention strategy for AD, as brain

pathology may be too advanced to allow effective treatment of clinical symptoms, or disease modification, once patients are diagnosed with AD dementia.

However, few AD primary prevention studies have been conducted to date, and their results have been disappointing. In large (>2,000 subjects), long-term (planned as ≥5 years), randomized clinical trials of ginkgo biloba extract (GuidAge [22] and Ginkgo Evaluation of Memory Study [GEMS] [23]), hormone replacement therapy in women (Women's Health Initiative Memory Study [WHIMS] [24]), and non-steroidal anti-inflammatory drugs (NSAIDs) (Alzheimer's Disease Anti-inflammatory Prevention Trial [ADAPT] [25]) none of the primary, disease prevention objectives were achieved. Each of these studies employed an enrichment strategy to enroll subjects perceived to be at increased risk of developing AD or cognitive impairment. GEMS targeted the very old (≥75) and did not exclude individuals with MCI or milder cognitive syndromes; ADAPT targeted subjects with Alzheimer-like dementia in a first degree relative; WHIMS targeted postmenopausal women; and GuidAge enrolled individuals who spontaneously complained of memory problems to their general practitioner.

Like previous studies, this phase 3 study, AD-4833/TOMM40_301, will employ a strategy to enrich for at-risk subjects, in this case, those who are at-risk for developing MCI due to AD. The enrichment strategy is provided by the biomarker risk algorithm. The trial, therefore, is designed to pursue two primary objectives independently yet simultaneously: 1) to prospectively qualify the risk algorithm comprised of TOMM40 rs10524523 genotype, APOE genotype, and age as a biomarker for prognosis of an individual's risk of developing MCI due to AD in the next 5 years, and 2) to evaluate the efficacy of pioglitazone to delay the onset of MCI due to AD in cognitively normal subjects who are prognosed to be at high risk of developing MCI due to AD within 5 years. Subjects will be prospectively stratified into high-risk and low-risk groups on the basis of the risk algorithm and randomized to treatment with pioglitazone or placebo in the high-risk stratum or to placebo only in the low-risk stratum.

4.2.1 Genetic Risk Factors for AD

APOE epsilon genotype alone is neither sufficiently sensitive nor specific for clinical diagnosis of AD or prediction of age of onset of disease [26]. Roses et al have identified a second risk locus, in TOMM40, that provides greater resolution to the age of disease onset prediction, and for a greater proportion of the at-large population. Over a dozen genome wide association studies (GWAS) have confirmed the presence of a highly significant AD susceptibility locus within the TOMM40 gene, neighboring and in linkage disequilibrium (LD) with the well-known risk gene, APOE. Due to the LD between the genes, the association signal within TOMM40 has been previously attributed to APOE and thus overlooked.

In 2009, Roses et al. described the association between different lengths (short or S, long or L, and very long or VL) of a polyT locus (ie, the rs10524523 locus) in TOMM40 with ages of AD onset [27]. A phylogenetic analysis of high resolution sequence data from the region containing APOE and TOMM40 revealed the relationships between different alleles of TOMM40

rs10524523 and the APOE epsilon alleles, APOE ε3 and APOE ε4, in non-Hispanic/Latino Caucasian subjects. Long alleles of TOMM40 rs10524523 were nearly always linked to APOE ε4 and associated with greater disease risk. In contrast, APOE ε3 (and APOE ε2) was linked to either short or very long TOMM40 rs10524523 alleles, with the short alleles associated with later disease onset and the very long alleles associated with earlier onset (mean onset ages of 77 years versus 70 years, respectively) in a cohort of autopsy-confirmed AD patients carrying the APOE ε3/4 genotype. The association between APOE ε4 and risk of development of AD, or age of AD onset, first reported by Roses et al in 1993, has been replicated in many case-control and cohort studies. However, only ~ 25% of Caucasians carry an APOE ε4-containing genotype (2% are APOE ε4/4, 20% are APOE ε3/4, and 2% are APOE ε2/4); therefore, this allele is potentially informative for a minority of the at-risk population. Further, APOE ε4 carriage, alone, does not provide sufficient sensitivity, selectivity or predictive power to be used as a diagnostic or prognostic tool for AD [26,28]. While homozygosity for APOE ε4 is informative for AD risk prediction in the clinic, it is rare and therefore not widely useful [29,30]. Stratification of age of onset by TOMM40 rs10524523 genotypes provides information for >97% of the at-risk population, as it addresses age-dependent risk for carriers of APOE ε3, the most common allele, in addition to APOE ε4 (see Figure 4.a [31]).

Figure 4.a Age of Onset of Cognitive Impairment as a Function of TOMM40 rs10524523 Genotype

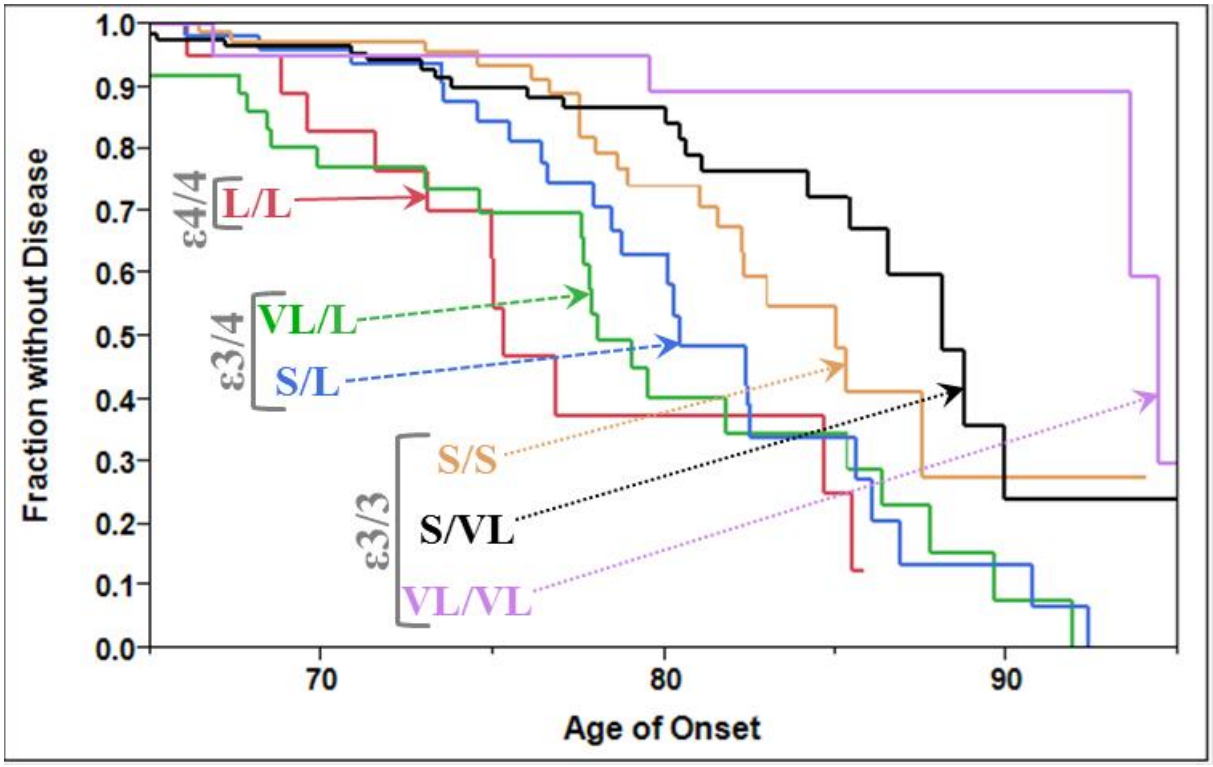


Figure 4.a illustrates that the previously measured age of onset distribution for APOE ε4/4 subjects is identical to the TOMM40 rs10524523 L-L genotype distribution. The APOE ε3/4 curve can be deconvoluted into two curves corresponding to the two different alleles of TOMM40 rs10524523, S and VL, that can be connected to APOE ε3 (and to APOE ε2 alleles). Three TOMM40 rs10524523 age of onset curves, S/S, S/VL, and VL/VL account for the APOE ε3/3 and APOE ε2/3 genotypes. In the entire data set used to develop this figure, only 5 of 70 APOE ε2 allele carriers developed the clinical disease criteria and for the 5 individuals, this occurred after age 75 years on the three different curves (VL/VL, S/VL, and S/S). For the purpose of enrichment in this study, which will enroll subjects aged 65 to 83 years, inclusive, APOE ε2/2 and APOE ε2/3 carriers will be placed in the low risk stratum, while APOE ε2/4 subjects will be stratified to the high-risk stratum because these subjects also carry an APOE ε4 allele. Thus, TOMM40 rs10524523 and APOE genotypes may differentiate subjects at higher and lower age-dependent risk of developing MCI due to AD, and subsequently AD.

4.2.2 Pioglitazone

It has been suggested that PPAR-γ agonists could be effective in treating AD by regulating multiple pathogenic pathways in the central nervous system, including amyloid β homeostasis, insulin sensitivity, energy metabolism, lipid metabolism, and inflammation [32]. PPAR-γ agonists are insulin-sensitizing agents that allow the body to use endogenous insulin efficiently, maintaining the normal physiological feedback mechanisms, and producing minimal hypoglycemia. There is ample documentation that glucose utilization is impaired in brain regions involved in cognition, including memory, in patients with AD. Indeed, it has been demonstrated that subjects at risk of developing AD exhibit impaired cerebral glucose metabolism decades before the typical ages of onset of late onset AD [33,34].

PPAR-γ agonists also play critical roles in energy metabolism due to their direct effects on mitochondrial function and ultimately ATP production and neuronal glucose utilization. Mitochondria may be key players in the cerebral hypometabolism observed in AD, as this organelle plays critical roles in energy metabolism, neuronal apoptosis and the maintenance of synapses. In AD-affected brain, the mitochondria have altered morphology, including an increased proportion of damaged mitochondria, altered distribution within neurons, and there is a decrease in the amounts of enzyme complexes that are essential for ATP production [35]. The effects of PPAR-γ agonists on mitochondria structure and function may be the basis of their beneficial effects on cognition, including memory, in AD subjects [12,36].

A paramount consideration for development of a preventive measure is its safety, set at a particularly high threshold given that the intended study population is cognitively normal. While some side effects may be acceptable to individuals already affected by the devastating symptoms of AD, only few, reversible, and minor adverse drug reactions would be acceptable to cognitively-normal individuals who may or may not decline to AD dementia. Ideally, an active pharmaceutical agent for a delay of MCI due to AD indication would be supported by extensive exposure data gathered through multiple years and in thousands of patients globally. While extensive drug exposure data exist for the two marketed TZDs, pioglitazone is widely considered to be safer than rosiglitazone. The favorable safety profile of pioglitazone was underscored by the meta-analysis presented at the Food and Drug Administration (FDA) Joint Meeting of the Endocrinologic and Metabolic Drug Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting, 2010 [37]. The meta-analysis included 35 trials covering 22,131 patients, of whom 12,213 (55%) were randomized to pioglitazone and 9,918 (45%) to the comparator. Overall, across all trials for pioglitazone, the estimated MACE (major adverse cardiovascular events, defined as cardiovascular death, stroke or myocardial infarction) risk was lower for pioglitazone compared to control (hazard ratio [HR]=0.80; 95% confidence interval [CI]=0.70-0.93).

4.2.3 Mild Cognitive Impairment due to Alzheimer's Disease (MCI due to AD)

In 2011, a workgroup of the NIA and the Alzheimer's Association (AA) published criteria developed to define the predementia symptomatic phase of Alzheimer's disease, referred to as MCI due to AD [38]. The core clinical criteria recommended by the NIA/AA workgroup are applied in this study to define the primary endpoint event of MCI due to AD. It is important to underscore that the primary endpoint in this study is diagnosed using the NIA/AA core clinical criteria for this MCI phenotype without AD biomarker confirmation, since at this time no physical biomarker is validated, or qualified, for diagnosing MCI due to AD [39]. In addition, a recent population-based study confirms prior clinical studies, demonstrating that the development of clinical impairment is associated more with APOE genotype than with amyloid plaque deposition (ie, while amyloid deposition is modestly associated with cognitive performance in a population-based sample of cognitively normal older adults who carry at least one APOE ε4 allele, the relationship between amyloid and cognition is even less apparent in individuals without an APOE ε4) [40].

In clinical practice, the diagnosis of MCI due to AD, like AD dementia, cannot be made solely by laboratory or other tests, but requires the judgment of a clinician who takes into account clinical, cognitive, and functional criteria that define the syndrome. The clinical diagnosis, as defined by the NIA/AA in Albert et al., 2011 [38]:

- Establishes clinical and cognitive criteria:
  - Cognitive concern reflecting a change in cognition reported by subject or informant or clinician (ie, historical or observed evidence of decline over time).
  - Objective evidence of impairment in one or more cognitive domains, typically including memory (ie, formal or bedside testing to establish level of cognitive function in multiple domains).
  - Preservation of independence in functional abilities.
  - Not demented.
- Examines etiology of MCI consistent with AD pathophysiological process:
  - Rule out vascular, traumatic, medical causes of cognitive decline, where possible.
  - Provide evidence of longitudinal decline in cognition, when feasible.
  - Report history consistent with AD genetic factors, were relevant.

A cognitive test battery has been specifically constructed to help study Investigators identify individuals who are beginning to decline in their cognitive status and who can be accurately diagnosed with MCI due to AD. This test battery is summarized in the Table 4.a, and the individual instruments that comprise the battery are described in detail in Section 9.1.15.

Table 4.a Cognitive Test Battery**

Cognitive Domain	Tests
Episodic Memory	California Verbal Learning Test – 2nd Edition (CVLT-II) Brief Visuospatial Memory Test – Revised (BVMT-R)
Executive Function	Trail Making Test (TMT) (Part B) Wechsler Adult Intelligence Scale (WAIS)-III Digit Span Test – backwards span
Language	Multilingual Naming Test (MINT)* Semantic Fluency (animals) Lexical/phonemic fluency (F, A, and S)
Attention	WAIS-III Digit Span Test – forward span TMT (Part A)
Visuospatial	Clock Drawing Test (CDT)* Copy of BVMT figures*

* CDT, BVMT-Copy and the MINT, which do not allow generation of standard z scores, will only be used for diagnostic purposes and will be excluded from the calculation of the composite score.
** There are 12 measures derived from 8 neuropsychological tests in the battery. The CVLT-II test involves 2 primary measures (short delay recall, long delay recall); BVMT-R has 2 measures (copy and recall); Digit Span and Trails both have 2 measures (forward and backward span and Parts A and B, respectively). There is one total score for each test: CDT, MINT, semantic fluency and lexical fluency (F, A, and S).

Study Investigators will use this cognitive test battery to assess subjects' cognitive status and will consider the results of this battery, in combination with the findings from other subject- and project partner-reported instruments of functional change and laboratory findings, to determine further subject flow within the study (ie, send case for adjudication or not).

For the purposes of this clinical trial, the clinical framework described by the NIA/AA [38] publication will be operationalized through the incorporation of objective cutoff points to provide the Investigator's guidance for making a clinical diagnosis of MCI due to AD, as follows:

Table 4.b Operationalized Criteria for MCI due to AD

Establish clinical and cognitive criteria
• Clinical Dementia Rating (CDR) scale score of 0.5 **AND** one or more of the following: – Fails at least one of the two memory tests in the cognitive test battery (failure defined as an individual test score at or below -1.5 SD of the demographically corrected normative mean (a), and the score reflects a decline from baseline). – Fails at least 2 of the cognitive tests from at least 2 different cognitive domains, one of which must be memory (failure defined as an individual test score at or below -1.3 SD (10th percentile) of the demographically corrected normative mean, and the score reflects a decline from baseline).
Examine etiology of MCI consistent with AD pathophysiological process
• Rule out vascular, traumatic, psychiatric, and other proximal medical causes of cognitive decline. • Continued evidence of cognitive impairment or continued decline on 6 month follow-up (ie, 2 consecutive study visits showing impairment). (b)

(a) Normative data will be available per language.
(b) It is not required that the two consecutive visits show an identical profile (ie, meeting any definition of MCI due to AD on two consecutive visits for a subject to be forwarded for adjudication).

The primary endpoint is met only on the second consecutive occurrence when the diagnosis of MCI due to AD is confirmed by the adjudication committee. The adjudicators will look at all the collective information sent by the investigative sites in order to confirm (or not) the diagnosis of MCI due to AD. Subjects who convert directly to an AD dementia diagnosis by the NIA/AA criteria [41] will also be considered toward the numerical count of events that determines the duration of the study.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

For biomarker risk algorithm qualification:

- To qualify the biomarker risk algorithm composed of TOMM40 rs10524523 genotype, APOE genotype, and age for prognosis of the risk of developing MCI due to AD within 5 years.

For efficacy evaluation of pioglitazone:

- To evaluate the efficacy of pioglitazone compared with placebo to delay the onset of MCI due to AD in cognitively-normal subjects who are at high-risk, as identified by the biomarker risk algorithm at enrollment, for developing MCI due to AD within 5 years.

5.1.2 Key Secondary Objectives

- To evaluate the effect of pioglitazone compared with placebo on the progression of cognitive decline.
- To evaluate the effect of pioglitazone compared with placebo on functional decline and instrumental activities of daily living.

5.1.3 Additional Objectives

5.1.3.1 Safety Objectives

- To evaluate long-term safety and tolerability of pioglitazone compared with placebo during the course of the treatment.

5.1.3.2 Exploratory Objectives

- CCI
- [redacted]

- CCI [redacted]
-

5.2 Endpoints

5.2.1 Primary Endpoints

For biomarker risk algorithm qualification:

Time to diagnosis of MCI due to AD for placebo-treated, high-risk, non-Hispanic/Latino Caucasian subjects versus placebo-treated, low-risk, non-Hispanic/Latino Caucasian subjects.

For efficacy evaluation of pioglitazone:

Time to diagnosis of MCI due to AD for pioglitazone-treated, non-Hispanic/Latino Caucasian subjects versus placebo-treated non-Hispanic/Latino, Caucasian subjects in the high-risk stratum.

5.2.2 Key Secondary Endpoints

- Change from baseline for cognitive decline on composite score on the cognitive battery for pioglitazone-treated subjects versus placebo-treated subjects in the high-risk stratum.
- Changes from baseline in instrumental activities of daily living (Alzheimer's Disease Cooperative Study Activities of Daily Living - Prevention Instrument [ADCS ADL-PI]) between pioglitazone-treated and placebo-treated groups of the high-risk stratum.

5.2.3 Additional Endpoints

5.2.3.1 Safety Assessments

- Safety and tolerability: adverse events (including adverse events of special interest [AESIs]), vital signs, body weight, electrocardiogram (ECG), clinical laboratory data, and physical exam findings.

5.2.3.2 Additional Endpoints

- CCI [redacted]

- CCI
- [redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This phase 3 study is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to pursue two primary objectives independently yet simultaneously: (1) to qualify a biomarker risk algorithm composed of TOMM40 rs10524523 genotype, APOE genotype, and age for prognosis of the risk of developing MCI due to AD and (2) to evaluate the efficacy of pioglitazone (AD-4833 SR 0.8 mg once daily [QD)]) to delay the onset of MCI due to AD in cognitively normal subjects who are prognosed to be at high risk of developing MCI due to AD within 5 years.

The study duration will be the time needed to accumulate a total of 202 conversions in non-Hispanic/Latino Caucasian subjects within the high-risk stratum from normal cognition to a diagnosis of MCI due to AD, currently anticipated to be a minimum of 4 years. For the purposes of this study, a Caucasian subject will be defined as a person having origins in any of the original peoples of Europe, the Middle East, or North Africa. Hispanic/Latino will be defined as a person of Cuban, Mexican, Puerto Rican, South or Central American origin, regardless of race. The study will primarily recruit from large community-based populations.

The subjects must be cognitively normal as assessed first by performance on the MMSE at Screening, and then on the CDR scale and the Cognitive Test Battery (Sections 9.1.15.1 and 9.1.15.2) at Baseline (Visit 2). The subject must be between the ages of 65 and 83 years, inclusive, at time of the Screening Visit. The subjects must have a project partner able to complete an Acknowledgement Form on his or her own behalf and take part in the study to provide information on the cognitive, functional, and behavioral status of the subject and to assist with monitoring of study medication, if needed, for as long as the subject is in the study.

Based on statistical requirement, a minimum of 2,793 subjects will be stratified into high- and low-risk (for the development of MCI due to AD over the next 5 years) groups based upon application of the biomarker risk algorithm. Subjects will be randomized via interactive web response system (IWRS) into this study as follows:

- Non-Hispanic/Latino Caucasian subjects. A minimum of 2,660 subjects further divided into:
  - Approximately 2,346 subjects in the high-risk group (pioglitazone, n=1,173; placebo, n=1,173).
  - Approximately 314 subjects in the low-risk group: All subjects stratified to the low-risk stratum will also be randomized to maintain the stratification blind, but all subjects in this stratum will receive placebo.
- Non-Caucasian subjects and Hispanic/Latino Caucasian subjects. Subjects will be allocated to risk strata using the same algorithm as for the non-Hispanic/Latino Caucasian subjects.

Since all subjects screened at the time of Amendment 5 will be allowed to randomize if they continue to meet all eligibility criteria, it is estimated that approximately 3,500 will be randomized with the following groups:

- Non-Hispanic/Latino Caucasian subjects. Estimated 3,330 subjects further divided into:
  - Approximately 2,940 subjects in the high-risk group (pioglitazone, n=1,470; placebo, n=1,470).
  - Approximately 394 subjects in the low-risk group: All subjects stratified to the low-risk stratum will also be randomized to maintain the stratification blind, but all subjects in this stratum will receive placebo.
- Non-Caucasian subjects and Hispanic/Latino Caucasian subjects. Subjects will be allocated to risk strata using the same algorithm as for the non-Hispanic/Latino Caucasian subjects (n=167).

Because the data used to develop the biomarker risk algorithm was collected in non-Hispanic/Latino Caucasian subjects only, biomarker qualification will be based upon non-Hispanic/Latino Caucasian subjects in the placebo arm of the high-risk stratum compared to data from non-Hispanic/Latino Caucasian subjects in the low-risk stratum. Likewise, the primary analyses to evaluate the effects of pioglitazone versus placebo will be within the non-Hispanic/Latino Caucasian high-risk sub-group. Data from non-Caucasian and Hispanic/Latino Caucasian subjects are expected to be limited and will be analyzed as exploratory data to CCI [redacted]

An interactive response system will be used for central randomization. Stratification status and treatment assignment of all study participants will be double-blind.

Subjects in the high-risk stratum will be randomized to pioglitazone and placebo in a 1:1 ratio. Subjects in the low-risk stratum will be randomized only to placebo.

Subjects will be instructed to take the first dose of study medication in the morning on the day following the randomization visit. It is recommended that the site may confirm first dose has occurred through a phone call.

A project partner will be required to participate with the subject in the study visits, including eligibility at Baseline (Visit 2) and follow-up. The project partner is a spouse, adult child, or other person familiar with the participant's health and daily functioning for a minimum of two years prior to the Baseline Visit. Subjects and their project partners are expected to attend study visits every 6 months after randomization, for assessments of safety, efficacy, and treatment compliance. In addition, the subject will be contacted for telephone-based safety checks between visits. In-person participation of the project partner is required at Baseline (Visit 2), Comprehensive Medical Follow-up Visits (CMFV), and EoS Visits. In exceptional cases and with prior approval of the Sponsor, when in-person participation of the project partner is not

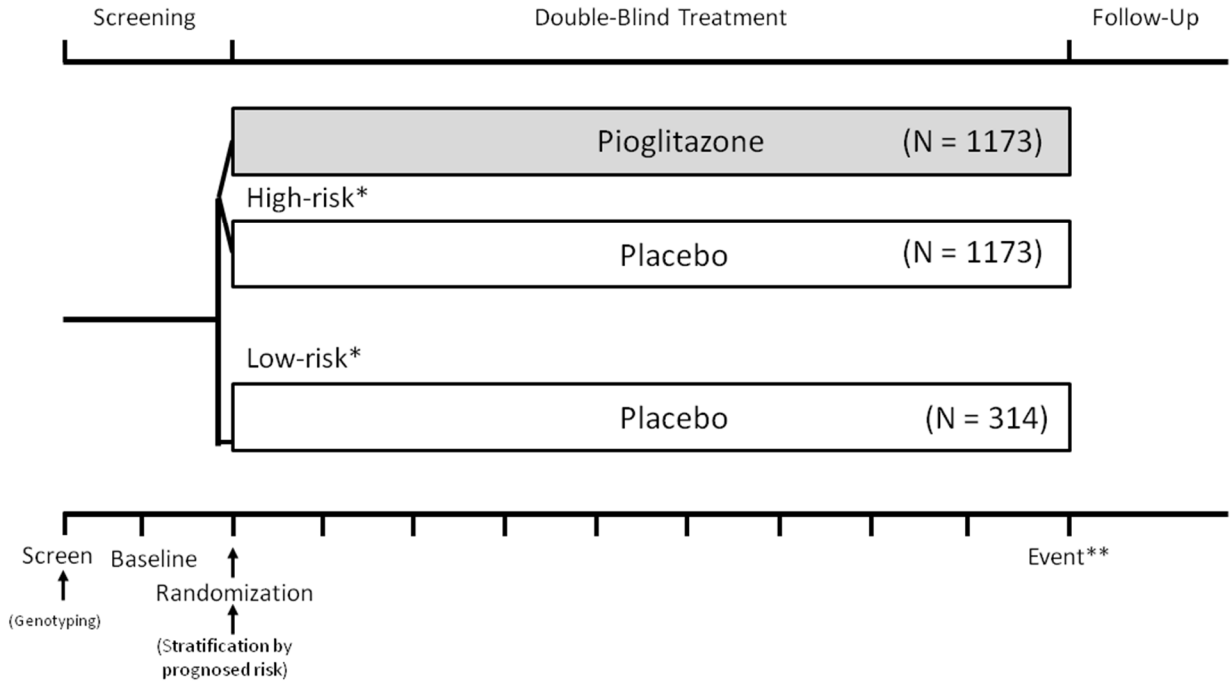
possible for a CMFV or the EoS/EW Visit, assessments may be performed during Home Visits or by telephone (see Section 6.2.4). While in-person participation is also strongly encouraged at all other study visits, telephone assessments for project partners will be acceptable in cases when in-person participation is not possible. If a comprehensive medical follow-up evaluation is needed (see Section 9.1.15) or if a safety issue is suspected, further evaluation of the subject may be required, which may include an unscheduled clinic visit. The project partner should attend unscheduled visits, whenever possible. If the original project partner is not able to continue participation in the study for any reason, he/she may be replaced by a different individual who also meets the criteria described above. The new project partner must sign the acknowledgement form prior to any of the project partner protocol directed procedures being performed.

Two sets of blood samples for deoxyribonucleic acid (DNA) will be collected during the course of this study:

1. CCI
2.

A schematic of the study design is included as Figure 6.a. A schedule of assessments is listed in Appendix A.

Figure 6.a Schematic of Study Design



* Non-Hispanic/Latino Caucasian, Hispanic/Latino Caucasian, and non-Caucasian subjects alike will be stratified into high- and low-risk strata using the same biomarker risk algorithm; however, target sample size for primary endpoint analyses refers to non-Hispanic/Latino Caucasian subjects only.
** As this is an event-driven study, double-blind treatment duration will depend on the time it takes for a total of 202 conversions from cognitively normal status to MCI due to AD dementia to occur in the high-risk non-Hispanic/Latino Caucasian population; conversions from cognitively normal status to AD will also be included in this total. Study visits to the testing center will take place every 6 months after the Randomization Visit.

6.2 Subject Flow based on Neuropsychological and Functional Assessments

6.2.1 Assessments at Screening Visit (Visit 1)

At this visit, after informed consent is given, subjects will be screened for any cognitive impairment using the MMSE. An MMSE score should be ≥25 after the education and age adjustment referenced in Appendix G for a subject to continue with additional procedures (ie, blood draw for genotyping); failure to score at least 25 on the MMSE will make an individual ineligible for the study. All potential subjects passing the MMSE will have a risk stratification blood sample collected to determine their TOMM40 rs1054523 and APOE genotypes. After the results of risk stratification samples are available, those subjects who are still eligible to participate in the study will be asked to attend the Baseline visit (Visit 2), approximately14-18 days after the Screening Visit, unless additional time is required for subject to meet eligibility criteria (for example, subject requires stabilization of medications prior to the

Baseline Visit as per Table 7.a) which could occur up to 90 days after the Screening Visit. The results of the genotype blood test will not be shared with the subject or site.

Sites may choose to conduct the Screening Visit procedures in the subject's home, after appropriate review and approval by the Sponsor of the site's procedures. This allowance only pertains to the Screening Visit.

6.2.2 Assessments at Baseline (Visit 2)

At this visit, in-person participation of both the subject and the project partner is mandatory. The project partner will be asked to sign an acknowledgement form. If the site has opted to use the split informed consent process, subject is required to sign the study entry informed consent at the Baseline Visit. Before being eligible for randomization, subjects' cognitive status will be ascertained using the MMSE, cognitive test battery and the CDR. The cognitive test battery consists of the BVMT-R, CVLT-II, Semantic Fluency, Lexical/Phonemic Fluency, Digit span (forwards and backwards), MINT, TMT Parts A&B, and the CDT (see Section 9.1.15). At this Visit, the results of this assessment are intended to provide the baseline (ie, before study medication) values for each subject on the instruments. The scores from the neuropsychological instruments that are determined as potential triggers for an unscheduled visit/adjudication described above will be converted to a common metric (z-score).

Subjects will be excluded at Baseline (Visit 2) if they meet one or both of the criteria below:

- CDR scale score of >0.
- Fails both memory tests in the cognitive test battery (failure defined as an individual test score at or below -1.5 SD of the demographically corrected normative mean on CVLT-II LONG-delay Free Recall of the CVLT and BVMT-R Delayed Recall).

Also at Baseline (Visit 2), subject and partner-reported questionnaires will be administered as outlined in Appendix A.

6.2.3 Assessments at Randomization (Visit 3)

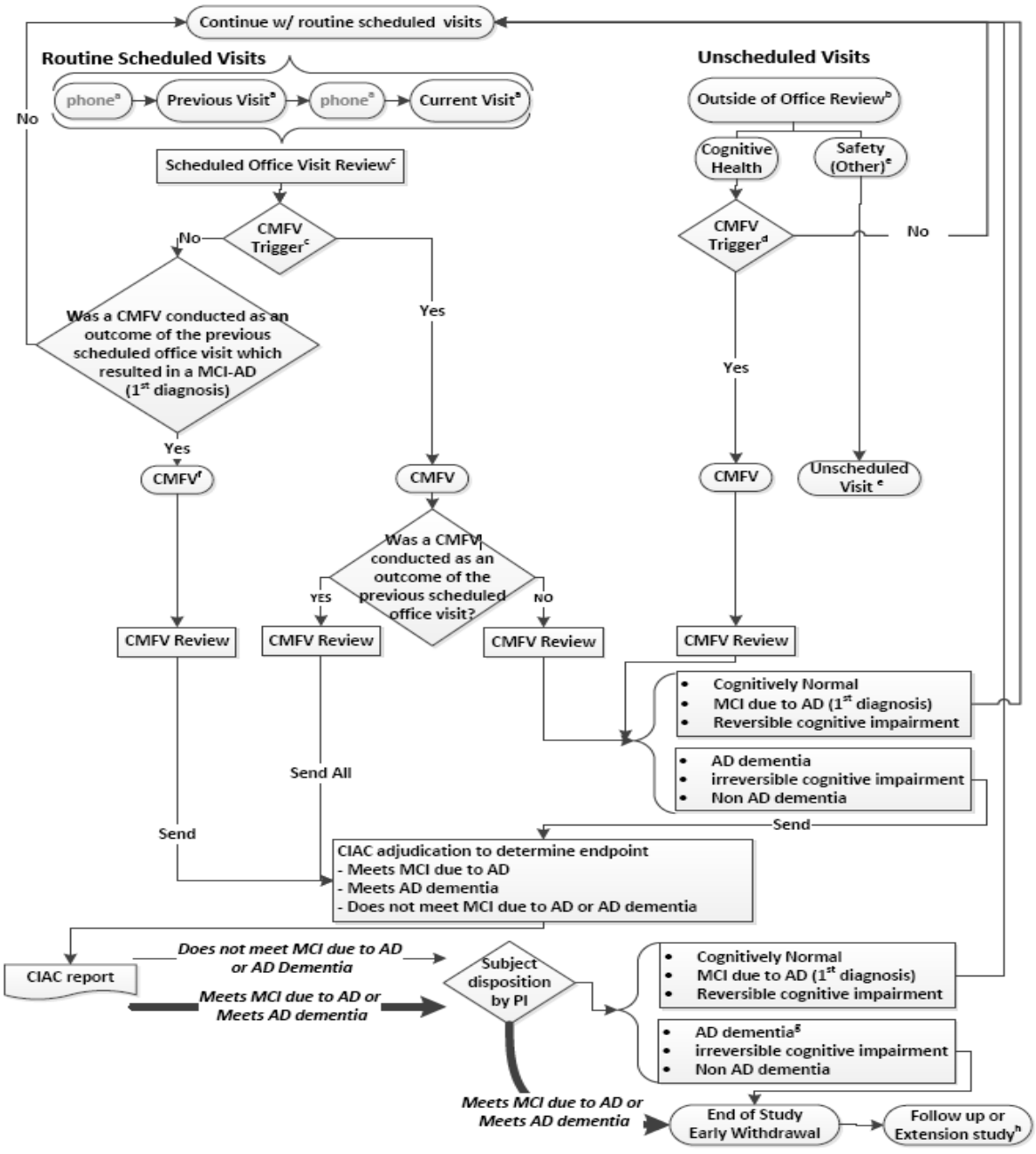
After passing all eligibility criteria and after quality control has been performed on the cognitive battery test results, eligible subjects will return to the testing center for a Randomization Visit (Visit 3) within 35 days of the Baseline Visit (Visit 2). At this Visit, they will receive study medication and have a subject-optional blood sample drawn for PGx.

6.2.4 Assessments after Randomization

Neuropsychological testing and functional assessments (described in Section 9.1.15) will be conducted at each scheduled visit using a broad cognitive test battery and functional measurements (including clinical judgment). Like the Baseline assessment, the scores from each cognitive test will be converted to a common metric (z-score).

The flow of subjects through the visits of this study after Randomization, and how the endpoint adjudication process fits into this flow, are illustrated in Figure 6.b and are described below.

Figure 6.b Subject Flow Chart



Legend:

A: Subjects will be assessed by the site staff after every regularly scheduled Visit (3m, 6m, 9m, 12m)
B: Concern expressed about subject's health to site between regularly scheduled study visits. Concern can be either the subject's cognitive health or safety (other).
C**:** After randomization, at every regularly scheduled visit or between each visit, as applicable, the outcomes listed below will trigger further evaluation:

1. Pre-defined cut-off in cognitive tests:
    a) Fails at least one of the two memory tests in the cognitive test battery (failure defined as an individual test score at or below -1.5 SD of the demographically corrected normative mean, and the score reflects a decline from baseline).
    b) Fails at least 2 of the cognitive tests from at least 2 different cognitive domains, one of which must be memory (failure defined as an individual test score at or below -1.3 SD (10th percentile) of the demographically corrected normative mean, and the score reflects a decline from baseline)
2. Investigator's clinical judgment of cognitive change and/or global deterioration in function based on the following:
    a) Scores on subject-reported questionnaires (eg, ADCS-MCFSI; GDS).
    b) Scores in project partner-reported questionnaires (eg, IQCODE, ADCS ADL-PI).
    c) Subject or project partner expresses concern about the subject's cognitive health to the Investigator or coordinator between regularly scheduled visits.
3. Cognitive impairment diagnosis from non-study clinician (with or without prescription of any cognitive-enhancing drug).

D: Comprehensive medical follow-up at an Unscheduled Visit (ie, a CMFV) may also be required if a subject or his/her project partner expresses their concern about his/her cognitive health to the Investigator or coordinator between regularly scheduled study visits.
E: If a safety issue is suspected, further evaluation of the subject may be required, which may include an unscheduled visit. The Unscheduled visit can result in the Subject remaining in the study or study termination.
F: CMFV. At the discretion of the investigator, the CMFV may be conducted on the same day as a regularly scheduled in-clinic visit (ie, Month 6 or Month 12 of any year) in situations when the CMFV conducted as an outcome of the previous scheduled office visit resulted in a MCI due to AD diagnosis and therefore the next scheduled visit will automatically result in the requirement to perform a CMFV, irrespective of a CMFV trigger being met.
G: If a PI diagnoses AD dementia even after the Cognitive Impairment Adjudication Committee (CIAC) report has determined that the subject does not meet criteria for MCI due to AD or for AD dementia, this will not count toward the total number of primary endpoint events.
H: Extension study is offered to subjects who have completed the current study having received an adjudicated diagnosis of MCI due to AD.

After randomization, at every regularly scheduled visit or between each visit, as applicable, the outcomes listed below will trigger further evaluation:

1. Pre-defined cut-off in cognitive tests:
    a) Fails at least one of the two memory tests in the cognitive test battery (failure defined as an individual test score at or below -1.5 SD of the demographically corrected normative mean, and the score reflects a decline from baseline).
    b) Fails at least 2 of the cognitive tests from at least 2 different cognitive domains, one of which must be memory (failure defined as an individual test score at or below -1.3 SD (10th percentile) of the demographically corrected normative mean, and the score reflects a decline from baseline).
2. Investigator's clinical judgment of cognitive change and/or global deterioration in function based on the following:

a) Scores on subject-reported questionnaires (eg, ADCS-MCFSI; GDS).

b) Scores in project partner-reported questionnaires (eg, IQCODE, ADCS ADL-PI).

c) Subject or project partner expresses concern about the subject's cognitive health to the Investigator or coordinator between regularly scheduled visits.

3. Cognitive impairment diagnosis from non-study clinician (with or without prescription of any cognitive-enhancing drug).

Additional comprehensive medical follow-up assessments will be carried out for any subject who has any of the outcomes above; these assessments will require an Unscheduled Visit, which should take place within approximately 30 days of the routine study Visit when one of these triggers was met. A CMFV should not be conducted on the same day as a regularly scheduled in-clinic visit (ie, Month 6 or Month 12 of any year), except in situations where the CMFV conducted as an outcome of the previous scheduled office visit resulted in an MCI due to AD diagnosis and therefore the next scheduled visit will automatically result in the requirement to perform a CMFV, irrespective of a CMFV trigger being met. In these cases, at the Investigator's discretion, the CMFV assessments may be collected at the routine Month 6 or Month 12 Visit. Any assessments that are scheduled to be performed at both the routine visit and the CMFV do not need to be performed twice when combining visits in this way.

A comprehensive medical follow-up evaluation (which the subject's project partner should make every effort to attend, if possible), triggered by any of the above, at minimum will include the following assessments (refer to Appendix A for a full list of assessments required to be performed at a CMFV):

- Neurological examination (includes information from project partner).
- CDR assessment.
- NPI-Q completed by the project partner.
- Standard blood chemistry and tests used in evaluating cognitively impaired and dementia subjects (eg, thyroid profile, Vitamin B12).
- Cognitive Test Battery (only if beyond 3 months from last study visit; otherwise the neuropsychological outcome battery from the last visit would be used in the evaluation).
- Magnetic resonance imaging (MRI) will be required at a subject's second consecutive comprehensive medical evaluation when other evaluation results corroborate a diagnosis of MCI due to AD in the opinion of the investigator. (Note that this does not need to be the second consecutive investigator diagnosis of MCI due to AD, only the second consecutive CFMV.). This requirement does not preclude the conduct of an MRI on a for-cause basis or to support a potential diagnosis other than MCI due to AD, after discussion with the medical monitor. If an MRI scan has been performed for the study within 6 months of the CMFV, an additional MRI scan will not be required and the existing scan may be used. For subjects who

have contraindications for MRI procedure (such as unremovable ferromagnetic dental work, cardiac pacemakers, etc) a computerized axial tomography (CT) scan may be performed instead.

If a site determines that a subject and/or project partner are unable to return to the clinic for the CMFV within approximately 30 days of the routine study visit, or for the EoS/EW Visit, the following options will be permitted in order to collect the required assessments within the required timeframe:

- Home Visit: with prior approval from Sponsor on a case-by-case basis, qualified site personnel may arrange a visit to the subject or project partner's home in order to perform CMFV or EoS/EW assessments. If necessary (ie, confirmatory rule-out for MCI diagnosis at second of two consecutive CMFVs), the MRI scan will be performed on the subject in-clinic at the earliest opportunity.
- Assessment via telephone: If the project partner is not able to return to the site for the CMFV or EoS/EW Visit, the site may, with prior approval of the Sponsor on a case-by-case basis, conduct the required assessments with the project partner via telephone call. The assessments must be carried out by appropriately qualified personnel in advance of the subject assessments and within a maximum of one day of the subject's visit. Visit assessments of the subject will still be required in clinic.

After the comprehensive medical follow-up evaluation, the Investigator will consider the totality of information collected for the subject and make a clinical assessment which will determine subject flow within the study. The timing of sending a subject's data to the adjudication committee after a first (of any potential two consecutive) CMFVs will depend on the Investigator's clinical assessment.

- If an Investigator's clinical assessment is that the subject is cognitively normal (ie, the comprehensive medical follow-up test results did not support the original trigger concern) or that the subject has a reversible cognitive impairment (eg, depression, hypothyroidism, vitamin B12 deficiency), the subject will continue with routine study visits, and the subject's data **will not be** forwarded to the adjudication committee at this time.
- If an Investigator's clinical assessment is that the subject meets criteria for an MCI due to AD diagnosis for the first time, the subject will also continue with routine study visits, and the subject's data **will not be** forwarded to the adjudication committee at this time.
- If an Investigator's clinical assessment is dementia of any type or an irreversible cognitive impairment not associated with AD, the subject's data **will be** forwarded to the adjudication committee immediately.

At the next regularly-scheduled 6-month visit, the following outcomes can occur:

- If the trigger criteria are not met at the regular 6-month visit and the subject was previously assessed as cognitively normal or as having reversible cognitive impairment, he/she will

continue with routine study visits, and his/her data will not be forwarded to the adjudication committee.

- If the trigger criteria are **not** met at the regular 6-month visit, the subject will still require comprehensive medical follow-up evaluation **only if** he/she met the MCI due to AD criteria at the previous CMFV.
- If the trigger criteria ARE met at the regular 6-month visit, the subject will require comprehensive medical follow-up evaluation.

In cases where a second consecutive comprehensive medical follow-up evaluation is conducted, the Investigator will make another clinical assessment, but regardless of this outcome, the subject's data will be forwarded to the adjudication committee at this time.

When adjudication is required, all pertinent data from the subject will be shared with an adjudication committee, which will be blinded to the subject's risk- and treatment-assignments. The adjudication process will result in one of three possible outcomes (listed below with relevant study dispositions):

1. Meets Criteria for MCI due to AD (primary study endpoint)

   Investigator will be asked to withdraw the subject from the study, the subject will be considered a study completer, will be scheduled for an EoS Visit, and will count toward the total number of events needed for the primary efficacy analysis. The visit at which the initial diagnosis was made will be considered the onset time for the primary endpoint. The subject will be offered the opportunity to continue treatment in an extension study. The operationalized criteria for MCI due to AD are defined in Table 4.b.

2. Meets Criteria for AD dementia [41].

   If probable or possible AD dementia is confirmed, subject will be withdrawn from the study and considered a study completer. Subjects will be scheduled for an EoS Visit, and will count toward the total number of events needed for the primary efficacy analysis. Subjects will stop study treatment and be referred for appropriate standard of care. The operationalized criteria is defined in Appendix I.

3. Does not meet criteria for either MCI due to AD or for AD dementia. Subject disposition will be at the discretion of the Investigator and will be guided by the following possible outcomes:

   a) Cognitively normal, MCI due to AD (first diagnosis), or reversible cognitive impairment: the subject will continue with routine study Visits.

   b) AD dementia, irreversible cognitive impairment (other than MCI due to AD) or non-AD dementia: subject will be scheduled for an EoS Visit. (If a principal investigator [PI] diagnoses AD dementia even after the CIAC report has determined that the subject does

not meet criteria for MCI due to AD or for AD dementia, this will not count toward the total number of primary endpoint events.)

6.3 Justification for Study Design, Dose, and Endpoints

6.3.1 Study Design

The design of this phase 3 study is one that allows for simultaneous co-development of a companion pharmacogenetic test with a therapeutic molecule. While similar studies to date have used enrichment strategies based on demographic and clinical risk factors (such as advanced age or family history), this study will be the first to use genetic information relevant to late-onset AD to enrich a "high-risk" population to increase statistical power for determining the therapeutic molecule's ability to delay onset of cognitive impairment. This enrichment strategy will also allow for calculation of both the positive and negative predictive values of the prognostic marker and potentially provide a means for decreasing the duration of the trial.

The therapeutic goal of this phase 3 study - to delay onset of MCI due to AD in cognitively normal subjects who are at risk for developing MCI due to AD within the next 5 years - reflects the recognition that AD is a continuous process with a clearly identifiable early symptomatic stage (MCI due to AD) that commonly occurs years before the onset of fully expressed dementia. As such: 1) the timeframe for a high-risk elderly individual to decline along the continuum that leads to detectable cognitive impairment is more realistic for a clinical trial than one that leads to diagnosed symptomatic AD dementia; and 2) MCI due to AD is a quantifiable construct indicative of early brain changes of the disease, and well-established, validated neuropsychological and functional instruments that are sensitive to these early changes can be used to detect it.

This study is placebo-controlled, as reliable evaluation of treatments intended for the management of central nervous system disorders is not possible without the use of placebo. Comparison to placebo is also valuable for distinguishing disease manifestations from adverse reactions of the study compound. Furthermore, the use of placebo in subjects at high risk for developing MCI due to AD is justified given the lack of effective therapies available for the delay of onset of cognitive impairment, and subsequently AD dementia (ie, there is no active comparator).

Comparisons between high-risk subjects on placebo with those on active treatment will be used to evaluate the efficacy of pioglitazone to delay the onset of MCI due to AD, whereas comparison between high-risk subjects on placebo with low-risk subjects (all on placebo) will be used for the prospective qualification of the prognostic biomarker risk algorithm within the study.

6.3.2 Study Dose

Because studies for AD prevention require long treatment durations and large study populations, it is not practical to do typical phase 2 studies prior to initiating phase 3 studies. As such a phase 2 program (including dose finding) was not conducted prior to the AD-4833/TOMM40_301 study. Still, there are a number of preclinical studies that indicate that pioglitazone increases mitochondrial numbers, motility and function at very low doses (relative to doses used to treat T2DM) [7]. This effect on mitochondria is hypothesized to be the key mechanism of action (MOA) for pioglitazone's ability to delay the onset of MCI due to AD. In addition to these preclinical studies, an imaging study (using functional magnetic resonance imaging [fMRI] was carried out in cognitively normal elderly subjects). From this study, it was ascertained that pioglitazone has central nervous system (CNS) effects at low doses and that there is a demonstrable blood oxygen level-dependent (BOLD) effect in the left hippocampus during an encoding task for episodic memory. This was a significant factor in dose selection because the intended AD-4833/TOMM40_301 study population is cognitively normal elderly adults, and the overall goal in dose selection was to minimize known dose-dependent adverse events (eg, edema) while ensuring that pioglitazone can still directly influence brain activity. Based on the available literature and the results of the fMRI study, pioglitazone sustained release (SR) 0.8 mg was selected for phase 3.

6.3.3 Study Endpoints

The cognitive test battery proposed in this study has been chosen to be sensitive to early deficits in cognition in the relevant ages and to minimize test-retest (practice or learning) effects that are particularly problematic in repeated measurements designs with cognitively normal individuals. Memory tests are particularly prone to this effect, which may then obscure measurable effects of medications on these domains of function. This study, however, employs a rigorous definition of memory impairment at Baseline and in defining MCI due to AD, as this practice has been shown to result in the highest positive predictive value for later AD outcome in clinical trials of MCI [43] and in a longitudinal study [44]. The assessment also includes measures of instrumental activities of daily living and depression, for determination of functional and mood changes to exclude differential diagnosis associated with impaired cognition. This information, when considered with the neuropsychological performance and other clinical variables, including a clinical diagnosis by the study PI, increases the specificity of the diagnosis of MCI due to AD.

This study acknowledges the importance of both cognitive and functional decline as key assessments in the earliest stage of the AD continuum and includes both of these recommended outcomes as key secondary endpoints. There are precedents for cognitive decline as a secondary endpoint from previous AD prevention studies. Three of the most recently conducted large-scale AD prevention studies (GuidAge, GEMS, and ADAPT) included cognitive decline as a secondary endpoint, while two of them (GuidAge, GEMS) also included functional decline or disability as a secondary endpoint. In addition, in the very early stages of the AD continuum, accelerated decline in multiple cognitive domains can be noted 5 to 6 years before Alzheimer's

Dementia is diagnosed, whereas such decline is usually not observed in elderly individuals who do not eventually develop AD [45]. However, decline in functional abilities is often slower to develop in the early stages of AD and are usually more impactful after a person has already been diagnosed with MCI or AD. Albert et al, 2011 note that one of the core clinical criteria for the MCI due to AD diagnosis is preservation of independence in functional abilities, because while certain activities of daily living may take more time to execute as cognition begins to decline, individuals in this phase of the AD continuum can still usually perform instrumental activities of daily living (such as pay bills, drive, or prepare food) with minimal assistance [38]. Similarly, in a proposal to revise the definition of AD to include both predementia and dementia phases, Dubois et al, [46] describe "prodromal AD" as a stage where episodic memory deficits are present but do not affect instrumental activities of daily living.

6.4 Premature Termination or Suspension of Study or Investigational Site

6.4.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- The independent data and safety monitoring board (DSMB) recommends that the study should be suspended or terminated.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.
- Study-specific criteria for terminating the study (eg, study meets predefined rule for futility) as described in Section 13.2, "Futility Analysis and Criteria for Early Termination".

6.4.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.4.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an institutional review board (IRB)/independent ethics committee (IEC) or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be

provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including any test results, need to be confirmed prior to randomization.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject is able to physically perform the cognitive tests in the opinion of the investigator and is fluent in the language that tests will be administered.
4. The subjects must be cognitively normal at baseline, scoring as indicated for the following tests:
   - CDR=0.
   - At least one memory test above -1.5 SD of the demographically corrected normative mean.
5. The subject must score ≥25 on the MMSE at the screening visit after the education and age adjustment referenced in Appendix G.
6. The subject is male or postmenopausal female between the ages of 65 and 83 years, inclusive, at time of the Screening visit.
7. The subject has the ability and intention to participate in regular study visits, in the opinion of the Investigator.
8. The subject has a project partner able to complete an Acknowledgement Form on his/her own behalf and take part in the study (with the intent to do so as long as the subject is enrolled) to provide information on the cognitive, functional, and behavioral status of the subject and to assist with monitoring of study medication, if needed.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has a current diagnosis or history of any type of cognitive impairment or dementia, or has a current diagnosis or history of neurological/psychiatric disorder or any other diagnosis that significantly affects cognitive performance (eg, mental retardation, organic mental disorder).
2. The subject has a current diagnosis of significant psychiatric illness, per Diagnostic & Statistical Manual of Mental Disorders, 4th Edition - Text Revision (DSM-IV-TR) (or

35DSM-V when published) (including but not limited to major depressive disorder, anxiety disorders) and is in an acute phase/episode, or the subject has a current diagnosis or history of schizophrenia or bipolar disorder.

3. The subject has a glycosylated hemoglobin (HbA1c) >8.0% at the time of baseline or requires treatment with insulin, triple oral antidiabetic therapy or a PPAR-γ agonist. The subject should be on a stable antidiabetic regimen for at least 3 months prior to enrollment.
4. The subject has a clinically significant unstable illness, for example, hepatic impairment or renal insufficiency, or cardiovascular, pulmonary, gastrointestinal (including s/p gastric bypass), endocrine, neurological, rheumatologic, immunologic, infectious, skin and subcutaneous tissue disorders, or metabolic disturbance. History of human immunodeficiency virus (HIV) infection is considered exclusionary for this study.
5. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse/dependence within 2 years prior to the Screening Visit.
6. The subject is an immediate family member, testing center employee, or is in a dependent relationship with a testing center employee who is involved in conduct of this study (eg, spouse, parent, child, and sibling) or may consent under duress.
7. The subject has a history of hypersensitivity or allergies to pioglitazone or related compounds.
8. The subject is required to take excluded medications as specified in the Excluded Medications Section (Section 7.3).
9. The subject had any of the following values at the Baseline Visit (Visit 2):
   a) A serum total bilirubin value >1.5× upper limit of normal (ULN).
   b) A serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >2×ULN.
   c) Unexplained microscopic/macroscopic hematuria on one repeat examination within 2 weeks of the initial assessment.
10. The subject is positive for either Hepatitis B surface antigen (HBsAg) or anti-hepatitis C virus (HCV) antibodies at the Baseline Visit (Visit 2).
11. The subject has a condition or takes medication that, in the opinion of the Investigator, could interfere with the assessments of safety, tolerability, or efficacy, or prevent the subject from adequately participating in the study or continue for the anticipated duration of the study.
12. The subject has received any investigational compound within 30 days prior to screening or 5 half-lives prior to Screening or is currently participating in another study which entails the administration of an investigational or marketed drug, supplement or intervention including, but not limited to diet, exercise, lifestyle or invasive procedure.

13. The subject has a history of any cancer that has been in remission for less than 2 years from the Screening Visit. Subjects with basal cell or stage I squamous cell carcinoma of the skin will be eligible. Subjects with history of bladder cancer are not eligible irrespective of the remission status.
14. The subject has a history or current diagnosis of macular edema or macular degeneration.
15. If female, the subject has a history of postmenopausal fractures with no or minimal trauma (eg, wrist, hip, lumbar or thoracic vertebral fracture).
16. The subject has a history or current diagnosis of CHF, New York Heart Association Class III-IV.
17. The subject has been exposed to the cognitive tests performed in this study within 6 months prior to the Screening Visit, with the exception of the MMSE.
18. The subject's TOMM40 rs10524523 or APOE genotypes or APOE phenotype are known by the subject or the study staff participating in this study.

7.3 Excluded Medications and Treatments

Subjects must be instructed not to take any medication, including over-the-counter products, without first consulting with the Investigator. The medical monitor should be contacted for questions regarding episodic use. Table 7.a describes medications disallowed prior to Baseline and medications disallowed during the course of the study.

Table 7.a Excluded Medications and Treatments

	Use Parameters (Subject Disposition)	
Drug Class	**At Baseline Visit**	**During the Study**
Acetylcholinesterase inhibitors (ie, donepezil, rivastigmine, galantamine, and huperzine)	**Prohibited**, any prior use (Subject not eligible)	**Prohibited**, if initiated (Subject must be discontinued)
Memantine	**Prohibited**, any prior use (Subject not eligible)	**Prohibited**, if initiated (Subject must be discontinued)
Amphetamine and Dextroamphetamine – [Psychostimulants] (eg. Adderal, Concerta, Dexedrine, modafanil)	**Prohibited**, any prior use (Subject not eligible)	**Prohibited**, if initiated (Subject must be discontinued)
Anticholinergic drugs	**Conditional**, if stable dose at least 3 months prior to Baseline (Subject eligible if condition met)	**Conditional**, if initiated, but should be on stable dose at least 3 months prior to next scheduled study Visit (Subject continues if condition met [a])
Antidepressants	**Conditional**, if stable dose at least 3 months prior to Baseline (Subject eligible if condition met)	**Conditional**, if initiated, but should be on stable dose at least 3 months prior to next scheduled study Visit (Subject continues if condition met [a])
Antipsychotic drugs (eg, olanzapine, haloperidol)	**Prohibited,** any prior or concurrent use for treatment of psychosis in subjects with schizophrenia or bipolar disorder **Conditional,** if stable dose for at least 3 months prior to Baseline for conditions other than schizophrenia or bipolar disorder (eg, use in a subject with depression) (Subject eligible if condition met)	**Conditional**, if initiated, but should be on stable dose at least 3 months prior to next scheduled study Visit (Subject continues if condition met [a])
Benzodiazepines and non-benzodiazepines sleep aides (zopiclone, eszopiclone, zolpidem)	**Conditional**, if stable dose at least 3 months prior to Baseline (Subject eligible if condition met) Past episodic use is allowed	**Conditional**, if initiated for chronic use, but should be on stable dose at least 3 months prior to next scheduled study Visit (Subject continues if condition met [a]) Episodic use is allowed
Anticonvulsants	**Conditional**, if stable dose at least 3 months prior to Baseline (Subject eligible if condition met)	**Conditional**, if initiated, but should be on stable dose at least 3 months prior to next scheduled study Visit (Subject continues if condition met [a])
Barbiturates	**Conditional**, if stable dose at least 3 months prior to Baseline (Subject eligible if condition met)	**Prohibited**, if chronic use initiated (Subject must be discontinued)

Footnotes are on last table page.

Table 7.a Excluded Medications and Treatments (continued)

Drug Class	Use Parameters (Subject Disposition)	
	At Baseline Visit	**During the Study**
L-Dopa/carbidopa or any other Parkinson medication for the treatment of Parkinson disease	**Prohibited**, any prior use (Subject not eligible)	**Prohibited**, if initiated (Subject must be discontinued)
Strong CYP2C8 inhibitors (eg, gemfibrozil)	**Conditional**, if prior use was stopped 30 days or 5 half-lives – whichever is longer – prior to Baseline (Subject eligible if condition met)	**Prohibited**, if chronic use initiated (Subject must be discontinued) **Allowed**, if episodic use (Subject continues)
CYP2C8 inducers (eg, rifampin)	**Conditional**, if prior use was stopped 30 days or 5 half-lives – whichever is longer – prior to **Baseline** (Subject eligible if condition met)	**Prohibited**, if chronic use initiated (Subject must be discontinued) **Allowed**, if episodic use (Subject continues)
Insulin	**Prohibited**, if any prior chronic use (Subject not eligible) **Allowed**, if any prior episodic use, eg, to treat nonketotic hyperglycemic coma (Subject eligible)	**Prohibited**, if chronic use initiated (Subject must be discontinued) **Allowed**, if episodic use (Subject continues)
Pioglitazone or any other PPAR-γ agonist	**Conditional**, if prior use was stopped 30 days or 5 half-lives – whichever is longer – prior to **Baseline** (Subject eligible if condition met)	**Prohibited**, if initiated (Subject must be discontinued)
Chemotherapy drugs (b)	No use in the past 2 years before the **Baseline** Visit	**Prohibited**, if initiated (Subject must be discontinued)

CYP= cytochrome P-450.
(a) If condition is not met, neuropsychological battery data for the next scheduled Study Visit may be censured.
(b) Low doses for non cancerous conditions will be allowed on a case-by-case basis followed approval by the medical monitor.

7.4 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study should be recorded in the [electronic] case report form ([e]CRF) using the following categories. For screen or baseline failure subjects, refer to Section 9.1.13.

1. Pretreatment event (PTE) or adverse event (AE). The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE. For guidance on withdrawal criteria due to AESIs please refer to Section 10.2.1.3.

2. Liver Function Test Abnormalities

   Based on local country criteria, subjects in a clinical trial who experience ALT and/or AST >3 ×ULN and total bilirubin >2xULN and satisfy the following two criteria: (1) the liver injury is hepatocellular in nature and there is not a prominent cholestatic component; (2) there is no more likely alternative cause than drug induced liver injury, such as acute viral hepatitis A or B, or other acute liver disease;

   If ALT or AST >3×ULN, laboratory tests should be repeated within a maximum of 7 days, and preferably within 48-72 hours. If the ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions, and this observation cannot be explained by concomitant disease or another alternative etiology, the abnormality should be recorded as an AE. The investigator must contact the Medical Monitor for consideration of immediate discontinuation of study medication, discussion of the relevant subject details and possible alternative etiologies.

   In addition, study medication should be discontinued immediately with appropriate clinical follow-up, including repeat laboratory tests, until a subject's laboratory profile has returned to normal, if the following circumstances occur at any time during study medication treatment:

   - ALT or AST >8 x ULN.
   - ALT or AST >5 x ULN and persists for more than 2 weeks.
   - ALT or AST >3 x ULN in conjunction with elevated total bilirubin >2 x ULN or international normalized ratio (INR) >1.5.
   - ALT or AST >3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

3. Major protocol deviation. The discovery post-randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
4. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
5. Voluntary withdrawal. The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the (electronic) case report form ([e]CRF).

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE or lack of efficacy should not be recorded in the "voluntary withdrawal" category).
6. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
7. Other.

   Note: The specific reasons should be recorded in the "specify" field of the (e)CRF.

7.5 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may terminate a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.4. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded. In addition, efforts should be made to perform all procedures scheduled for the EW Visit. Discontinued or withdrawn subjects will not be replaced.

Subjects who discontinue study medication prematurely should be contacted by the study site every 6 months until the conclusion of the study via telephone to assess the general well-being of the subject as well as to obtain any changes in medications related to cognitive health. In the event the subject is not able to be reached, the subject's caregiver or primary care physician can be contacted to obtain this information.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study medication refers to all or any of the drugs defined below. AD-4833 SR 0.8 mg Tablets and placebo will be provided in high density polyethylene (HDPE) bottles containing a desiccant. The active formulation contains drug substance and excipients and the placebo formulation contains excipients only. These tablets are for oral administration.

8.1.1.1 Investigational drug

AD-4833 Tablets Placebo

AD-4833 tablet placebo is manufactured by Takeda Pharmaceutical Company Limited, Osaka, Japan. The oral administration tablets are pale red plain tablets. Each HDPE bottle contains 100 tablets and a desiccant and has a child resistant cap. The bottles will be labeled with a single panel or booklet label that will contain pertinent study information in local languages.

AD-4833 SR 0.8 mg Tablet

AD-4833 SR 0.8 mg Tablet is manufactured by Takeda Pharmaceutical Company Limited, Osaka, Japan. The oral administration tablets are pale red plain tablets. Each HDPE bottle contains 100 tablets and a desiccant and has a child resistant cap. The bottles will be labeled with a single panel or booklet label that will contain pertinent study information in local languages.

8.1.1.2 Sponsor-Supplied Drug

Sponsor-supplied drugs referenced in other sections of the protocol include the following: AD-4833 tablet placebo and AD-4833 SR 0.8 mg Tablet.

8.1.2 Storage

All clinical trial material must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. All sponsor-supplied drugs must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

This is a placebo-controlled, double-blind, parallel group study comparing AD-4833 SR 0.8 mg Tablet to Placebo. Subjects will be randomized in a blinded fashion to one of the following within the following two subject groups, Non-Hispanic/Latino Caucasian and Non-Caucasian or Hispanic/Latino Caucasian.

Table 8.a describes the dose and tablet count that will be provided to each group.

Table 8.a Sponsor-Supplied Drug

Treatment Group	Dose	Treatment Description	
		Active	**Placebo**
1	Placebo QD	Zero active tablets	One AD-4833 tablet placebo
2	AD-4833 SR 0.8 mg Tablet QD	One AD-4833 SR 0.8 mg tablet	Zero placebo tablets

8.1.4 Overdose

An overdose is defined as a **known** deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated adverse events) will be documented on an Overdose page of the (e)CRF, in order to capture this important safety information consistently in the database. Adverse events associated with an overdose will be documented on AE CRF(s) according to Section 10.0, PTEs and AEs.

Serious adverse events of overdose should be reported according to the procedure outlined in Section 10.2.2, Collection and Reporting of SAEs.

In the event of drug overdose, the subject should be treated symptomatically. In the event of deliberate or accidental drug overdose, general symptomatic and supportive measures should be used.

8.2 Investigational Drug Assignment and Dispensing Procedures

The investigator or investigator's designee will access the IWRS at Screening to obtain the subject study number. The investigator or the investigator's designee will utilize the IWRS to randomize each qualified subject into the study at Visit 3. During this contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at screening.

The investigator or investigator's designee will access the IWRS at each dispensing visit to obtain medication identification numbers (Med IDs) for up to two bottles containing 100 tablets

each of either AD-4833 SR 0.8 mg or placebo based on the subject's randomized treatment arm. Subjects will be instructed to take 1 tablet per day, orally, at the same time of day, preferably in the morning, or as directed. Take with or without food. Study drug is to be kept in the container provided until the dose is to be taken. The first dose is to be taken the morning after the randomization visit. The investigator or investigator's designee will utilize the IWRS for Med ID assignment at every subsequent dispensing visit. If sponsor-supplied drug AD-4833 SR 0.8 mg Tablets or placebo is lost or damaged, the site can request a replacement from the IWRS. (Refer to the IWRS manual provided separately.)

The investigator must maintain records of all sponsor-supplied drug delivery to the site. The site will receive a confirmation email from the IWRS providing the Med ID's assigned at each dispensing visit. The site will print, date and initial the email and file in the subject's file as documentation of correct dispensing. The investigator or designee will maintain records of site inventory, dispensation and use by each subject, and return of investigational medicinal product (IMP) to the sponsor or designee. Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee.

8.3 Randomization Code Creation and Storage

Randomization personnel of the sponsor or designee will generate the randomization schedule and will provide it to the IWRS vendor prior to the start of this study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

Based on statistical requirement, a minimum of 2,793 subjects will be stratified into high- and low-risk groups (for the development of MCI due to AD over the next 5 years) based upon the results of the biomarker risk algorithm. Subjects will be randomized into this study as follows:

- Non-Hispanic/Latino Caucasian subjects. Approximately 2,660 subjects further divided into:
  - Approximately 2,346 subjects in the high-risk group (pioglitazone n=1,173; placebo n=1,173).
  - Approximately 314 subjects in the low-risk group: All subjects stratified to the low-risk stratum will also be randomized to maintain the stratification blind, but all subjects in this stratum will receive placebo.
- Non-Caucasian and Hispanic/Latino Caucasian subjects: Subjects will be allocated to strata using the same algorithm as for the non-Hispanic/Latino Caucasian subjects.

Since all subjects screened at the time of Amendment 5 will be allowed to randomize if they continue to meet all eligibility criteria, it is estimated that approximately 3,500 will be randomized with the following groups:

- Non-Hispanic/Latino Caucasian subjects. Estimated 3,330 subjects further divided into:
  - Approximately 2,940 subjects in the high-risk group (pioglitazone, n=1,470; placebo, n=1,470).

  - Approximately 394 subjects in the low-risk group: All subjects stratified to the low-risk stratum will also be randomized to maintain the stratification blind, but all subjects in this stratum will receive placebo.

- Non-Caucasian subjects and Hispanic/Latino Caucasian subjects. Subjects will be allocated to risk strata using the same algorithm as for the non-Hispanic/Latino Caucasian subjects (n=167).

It is anticipated that at least as many low-risk subjects will be available for screening as high-risk subjects. Since only 314 low-risk subjects are needed, low-risk subjects who pass all other eligibility criteria and are eligible to enter the study will only be randomized into the study if the requirements for a pre-specified allocation scheme are met. This scheme is designed to ensure that low-risk subjects are enrolled throughout the whole duration of the study enrollment period and it is detailed in the IWRS specifications.

8.4 Investigational Drug Blind Maintenance

The investigational drug blind will be maintained using the IWRS.

8.5 Unblinding Procedure

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. In the event of a medical emergency, if possible, the medical monitor should be contacted before the investigational drug blind is broken to discuss the need for unblinding.

For unblinding a subject, the investigational drug blind can be obtained by the investigator, by accessing the interactive voice response system (IVRS)/IWRS.

The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the (e)CRF.

If any site personnel are unblinded, investigational drug must be stopped immediately and the subject must be withdrawn from the study.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee. This includes AD-4833 SR 0.8 mg Tablets and AD-4833 Tablet placebo.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the approved protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug AD-4833 SR 0.8 mg Tablets and AD-4833 Tablet placebo, the investigator must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, the medication is received within the labeled storage conditions, and is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by recording in IWRS. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry/retest date is provided to the investigator.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot (or Medication ID or job number) used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator must record the current inventory of all sponsor-supplied drugs AD-4833 SR 0.8 mg Tablet and AD-4833 Tablet placebo on a sponsor-approved drug accountability log or within IWRS. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiry or retest date and amount dispensed including initials of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform clinical study material accountability and reconciliation before clinical study materials are returned to the sponsor or its designee for destruction. The investigator will retain a copy of the documentation regarding clinical study material accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

On expiry date notification from the sponsor or designee or IWRS, the site must complete if provided, all instructions outlined in the notification, including segregation of expired clinical study material for return to the sponsor or its designee for destruction.

In the event of expiry date extension of supplies already at the study site, supplies may be relabeled with the new expiry date at that site. In such cases, Takeda or its designee will prepare

additional labels, certificates of analyses, and all necessary documentation for completion of the procedure at the sites.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed. This consent will include the risk stratification sample collected to determine their TOMM40 rs10524523 and APOE genotypes. If sites prefer to split the ICF process at Visit 1 and Visit 2 into a screening informed consent and study entry informed consent and have IEC/IRB approval to do so, this is permitted.

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is obtained; this subject number will be used throughout the study.

Study subjects are asked to give informed consent to have their study assessments audio recorded. The study assessments (including the CDR interviews) will be audio-recorded for continuous quality control, training, and calibration purposes. Vendors experienced in providing training and quality control of CDR interviews will review the recordings and provide feedback to the investigative site and sponsor. The recordings may be used by the vendors for internal quality control as part of the training and calibration process for the vendors' clinicians. Only the vendor will have access to the recordings. The recordings will be transferred from investigative sites to the vendor in an encrypted, secure manner with secure protocols: HTTPS, FTPS and SSL. The vendor will store the recordings on a secure, password protected server. Recordings will be deleted one year after the last subject visit.

Pharmacogenomic Informed Consent Procedure

Informed consent pertaining to the PGx sample must be obtained prior to collecting a blood sample for Pharmacogenomic Research for this study. The provision of consent to collect and analyze the PGx sample is independent of consent to the other aspects of the study. Combining the PGx sample informed consent within the main study informed consent form is permitted at sites, if Sponsor/IEC/IRB approval is received.

Project Partner Acknowledgement Form Procedure

The subjects must have a project partner able to complete an Acknowledgement Form on his or her own behalf and take part in the study to provide information on the cognitive, functional, and behavioral status of the subject and to assist with monitoring of study medication, if needed, for as long as the subject is in the study. The Project Partner Acknowledgement Form must be

obtained from the project partner prior to the project partner completing any of the project partner protocol directed procedures. This includes the reported questionnaires and interviews outlined in Section 9.1.15.2. Should the project partner change during the course of the study, an Acknowledgement Form must be obtained from the new project partner prior to any of the project partner protocol directed procedures being performed.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth or age, sex, Hispanic/Latino ethnicity, race as identified by the subject, years of education and academic degrees, bilingualism, years lived in the country/region, occupation, smoking status, and drinking habit of the subject at Screening Visit. In countries that do not allow collection of date of birth, a subject's age will be collected at each post-Baseline Study Visit, Unscheduled Visit (as needed), and at the EoS/EW Visit.

Medical history, including family history of dementia and related conditions, to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.7). Medical history will be collected at screening. Family history will be collected at the first 6 month visit and at the EoS/EW visit.

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 3 months prior to signing of informed consent.

9.1.3 Physical Examination Procedure

A baseline physical and neurological examination (defined as the pretreatment assessment at Baseline (Visit 2) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other. All subsequent physical and neurological examinations should assess clinically significant changes from the baseline examination. Physical examination will be performed at Visit 2 (Baseline), each yearly visit (eg, month 12, 24, 36) of double-blind treatment, Unscheduled Visit, and EoS/EW Visit. Neurological examination will be performed at Visit 2 (Baseline), every 6 month visit during double-blind treatment, Unscheduled Visit, and EoS/EW Visit.

9.1.4 Weight, Height

A subject should have weight and height measured while wearing indoor clothing and with shoes off.

Height will be collected at Visit 2 (Baseline), each yearly visit (eg, month 12, 24, 36), and EoS/EW Visit in centimeters without decimal places.

Weight will be measured at Visit 2 (Baseline), every 6 month visit during double-blind treatment, and EoS/EW Visit. Weight will be collected in kilograms to 1 decimal place.

9.1.5 Vital Sign Procedure

Vital signs will include body temperature (oral or tympanic measurement), sitting blood pressure (5 minutes), and pulse (beats per minute).

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before the scheduled blood draw.

Vital signs will be measured at Visit 2 (Baseline), at each 6 month in clinic visit of double-blind treatment, unscheduled and at the EoS/EW Visit.

9.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Takeda. At each study visit, with the exception of the Visit 1 (Screening), subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the (e)CRF.

9.1.7 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at baseline examination. The condition (ie, diagnosis) should be described.

9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 16 mL, and the approximate total volume of blood for the study is 87 mL. Details of these procedures and required safety monitoring will be given in the laboratory manual. Table 9.a lists the laboratory tests that will be required by the protocol. Laboratory samples will be taken at the time points stipulated in the Schedule of Study Procedures (Appendix A).

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Red blood cells White blood cells count with differentials (Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes) Hemoglobin Hematocrit Platelets HbA1c (b)	Alanine aminotransferase Alkaline phosphatase Aspartate aminotransferase Total bilirubin Direct bilirubin (a) γ-Glutamyl transferase Total protein Albumin Creatinine Blood urea nitrogen Potassium Sodium Glucose Calcium, parathyroid hormone (PTH) Thyroid-stimulating hormone (TSH), free thyroxine (T4) Vitamin B12, folate (c) Rapid plasma reagin (RPR) (c)	pH Specific gravity Protein Glucose Blood Nitrite Microscopic examination (Leucocytes, Erythrocytes, Casts)
Blood		
Hepatitis panel, including HBsAg and anti-HCV (b)		

(a) Assess only if total bilirubin ≥2.0 mg/dL.
(b) To be done at Baseline only.
(c) At Baseline and as part of the comprehensive medical follow-up evaluation to rule out other causes of dementia.

The central laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

A separate contract laboratory will perform the TOMM40 rs10524523 and APOE genotyping. The result of the genotyping will remain blinded to the site, subject, and study team.

Should the subject be excluded from the study due to acute lab exclusions (eg, blood in urine) at Visit 2 that may resolve upon retesting, the subject is permitted to be retested within a window of 2 weeks. Re-testing will only be allowed on safety lab data, not cognitive testing or at Visit 1 for the risk stratification sample. In this situation, sites should not enter that the subject baseline failed into the electronic data capture (EDC) or IVRS until the retest results are completed and verified.

If subjects experience ALT or AST >3 ×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, γ-glutamyl transferase [GGT], and INR) should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was found.

(Please refer to Section 7.4 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests in relation to ALT or AST >3 ×ULN in conjunction with total bilirubin >2 ×ULN.)

If the ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study medication, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3 Reporting of Abnormal Liver Function Tests for reporting requirements).

9.1.9 Pregnancy

Women of childbearing potential will not be included in this study.

9.1.10 ECG Procedure

A standard 12-lead ECG will be recorded. The investigator (or a qualified observer at the investigational site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The following parameters will be recorded on the (e)CRF from the subject's ECG trace: heart rate, QT interval, QRS interval, and QT (corrected). ECG will be recorded at Visit 2 (Baseline), each yearly visit (eg, month 12, 24, 36) of double-blind treatment, and EoS/EW Visit.

9.1.11 Genotyping

9.1.11.1 Risk Stratification Samples (subject enrichment sample)

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[redacted]

9.1.11.2 Pharmacogenomics Samples

There is growing evidence that genetic variation may impact a subject's response to therapy. Variable response to therapy may be due to genetic determinants that affect drug absorption, distribution, metabolism, and excretion, the molecular pathways of drug response, the disease etiology and/or the molecular subtype of the disease being treated, and disease progression (eg, conversion to MCI due to AD). Furthermore, and in accordance with regulatory guidance and white papers, PGx analyses using DNA and/or ribonucleic acid (RNA) collected from trial participants who provide separate consent may support investigation of any unexpected adverse events.

CCI

[redacted]

This information may be used, for example, to develop a better understanding of the safety and efficacy of pioglitazone and other study medications, and for improving the efficiency, design and study methods of future research studies.

When sampling of whole blood for pharmacogenomic analysis occurs, every subject must sign informed consent/be consented in order to participate in the study.

The schedule for this DNA and RNA collection is found in the Study Schedule and identified as Safety/Efficacy PGx (DNA and RNA samples) – subject-optional. See Appendix E for directions on collecting, handling, and storing PGx samples. These samples are optional and should be collected from those subjects who provide independent consent to do so.

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In the event of an unexpected adverse event or the observation of unusual response, DNA or RNA may be isolated from the samples and analyses may be performed to evaluate a genetic or genomic association with response to pioglitazone. These investigations may be limited to a focused candidate gene study or, if appropriate, GWAS may be performed to identify regions of the genome associated with variability in drug response. Samples will only be used for investigations related to disease and adsorption, disposition, metabolism, excretion, or response to drug or class of drugs under study in the context of this clinical program. They will not be used for broad, exploratory, unspecified disease or population genetic analysis.

The DNA sample and the RNA samples will be identified by a unique sample identifier (coded) and stored for up to 15 years after the last subject visit for the study at a facility selected by the Sponsor. The sample and any data generated from it can only be linked back to the subject by clinical site personnel. As with the procedure for the risk stratification sample, PGx data from this sample will not be provided back to the investigator or the subject.

9.1.12 Pharmacokinetic Sample Collection and Analysis

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of study subjects have consented to the PK collection, future subjects will not have PK samples collected.

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Blood sample collection times are listed in Table 9.b.

Subjects will be asked to take their medication at approximately 8:00 AM on the day before the scheduled PK blood draw and the day of the PK blood draw. Subjects will be asked to arrive at the clinic according to their assigned group's time. However, if a patient arrives for a visit outside of their scheduled time period, the PK samples should still be collected. The time of study medication dosing and the drawing of blood samples are critical. For each of the blood sample collections, subjects will be asked to report the dates and times of their last dose of study medication prior to the blood sample collection; this information will be recorded on the appropriate (e)CRF. The exact time of the blood sample collections will also be recorded on the appropriate (e)CRF.

Table 9.b Schedule for Pharmacokinetic Sample Collection

Group	Dosing Time (approximate)	Sample Collection			
			Sample Collection Time Postdose		
		Predose	1-1.5 hr	Start of visit	End of visit
1 (a)	8:00 AM	X	X		
2 (b)	8:00 AM			X	X
3 (c)	8:00 AM			X	X
4 (d)	8:00 AM			X	X

(a) Subjects will arrive at the clinic prior to study drug administration.
(b) Subjects will arrive between 9 AM and noon, one PK sample will be taken at the beginning of the visit and one at the end of the visit.
(c) Subjects will arrive between noon and 3 PM, one PK sample will be taken at the beginning of the visit and one at the end of the visit.
(d) Subjects will arrive after 3 PM, one PK sample will be taken at the beginning of the visit and one at the end of the visit.

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9.1.12.1 Bioanalytical Methods

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9.1.13 Documentation of Screen Failure and Baseline Failure

Investigators must account for all subjects who sign informed consent.

If the subject is found to be not eligible at the Screening Visit or prior to the Baseline Visit, the investigator should complete the (e)CRF. The IWRS should be contacted as a notification of screen failure.

If the subject is found to be not eligible at the Baseline Visit or prior to the Randomization Visit, the Investigator should complete the (e)CRF. The IWRS should be contacted as a notification of baseline failure.

The primary reason for screen failure or baseline failure is recorded in the (e)CRF using the following categories:

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria.
- Major protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal.
- Study termination.
- Other.

Subject numbers assigned to subjects who fail screening should not be reused.

9.1.14 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for failure on the applicable (e)CRF. The IWRS should be contacted as a notification of baseline failure.

9.1.15 Assessments

9.1.15.1 Cognitive Test at Screening

At the Screening Visit, subjects will be tested to determine if their cognitive status qualifies them for entry to the study. The screening instrument will be the MMSE [47]. The MMSE is a measurement of global cognitive function, includes 11 items that assess orientation to time and place, language, verbal registration, memory, and praxis. Scores on this instrument range from zero to 30, with lower scores indicating greater cognitive impairment. At the Screening Visit, MMSE scores should always be adjusted for education and age (Appendix G). Scores ≤24 after age and education adjustment are considered impaired. The MMSE will also be collected at the Baseline Visit, every 6 months after randomization (ie, each Study Visit), and at the EoS/EW Visit.

9.1.15.2 Efficacy Assessments

Cognitive Tests in the Cognitive Test Battery

Neuropsychological testing will be conducted at Baseline (Visit 2) and each scheduled visit (every 6 months) using a broad cognitive test battery (Section 4.2.3). The battery will also be conducted as part of the comprehensive medical follow-up evaluation (at an Unscheduled Visit), if one of the triggers described in Section 6.2 is met and at the EoS/EW Visit, if either of these visits occur greater than 3 months after the previous regularly scheduled visit. The instruments used in the battery are all tools commonly used to evaluate AD in the clinical development setting. It is anticipated the cognitive battery will take approximately 60-90 minutes to administer at each applicable visit. Additional details regarding test administration will be provided in the Training Manual provided by the vendor selected by Takeda.

- Brief Visuospatial Memory Test - Revised (BVMT-R [48]): One of the equivalent alternate forms of the BVMT-R is used to assess immediate and delayed nonverbal memory. The subject is presented with a card depicting six simple designs. After the designs are studied for a brief time period, the card is removed and the subject must immediately draw the designs from memory. Approximately 25 minutes after the initial presentation, the subject is asked to draw the designs again. Immediately thereafter, a yes/no recognition trial is administered. The use of alternate BVMT-R forms will be counterbalanced across visits.
- California Verbal Learning Test – Second Edition (CVLT-II [49]): (list learning and delayed recall). The CVLT-II is a comprehensive and detailed assessment of verbal learning and memory that uses a multiple-trial list-learning task. A list of 16 words (List A), including four words from each of four semantic categories (animals, vegetables, furniture, modes of transportation) is presented and the subject is asked to recall immediately after presentation. A second list of 16 words (List B) is then presented for one trial. This second list contains words drawn from 2 semantic categories of List A (animals, vegetables) and two new categories (musical instruments, parts of a house). After presentation of List B, recall of

List A is assessed with free recall and cued recall procedures. Long term delayed recall and recognition memory of List A are tested 20 minutes later. Indices of learning include total number of words correctly recalled across Trials 1-5. Memory retention is assessed with Short Delay Free Recall, Long Delay Free Recall, and Yes/No Recognition. One alternative form of the CVLT-II is available and will be tested as well. The lists will be alternated between visits according to a pre-determined counterbalance schedule.

- Semantic Fluency [50]: Semantic fluency measures verbal production, semantic memory, and language. Participants are asked to name as many examples of animals as possible in one minute.
- Lexical/Phonemic Fluency [50]**:** For lexical fluency, the participant is asked to produce as many words as possible that begin with a specified letter. Participants will have one minute to produce exemplars for each letter (F, A, and S). The number of words from each letter will be combined for a total score. Verbal fluency letters F, A, and S will vary across languages based upon the frequency of letters in the local language.
- Wechsler Adult Intelligence Scale (WAIS)-III Digit Span Test [51]: The WAIS-III Digit Span subtest is used to assess auditory attention and working memory. Both forward and backward span will be assessed. The forward test consists of 8 pairs of number sequences and backward consists of 7 pairs that the tester reads aloud one at a time. After each sequence is read, the subject must repeat the digits back in the same (forward) or reverse (backward) order.
- Visual naming test from the MINT, [52]. The MINT is a test of confrontation naming ability that was designed to measure this aspect of language in monolingual and in bilingual or multilingual speakers of English, Spanish, Chinese (Mandarin) or Hebrew. The MINT has been validated with oral proficiency interviews for its classification of bilinguals into language dominance groups, and for measuring degree of bilingualism using index scores. Normative data are available for normal older monolingual (English) and bilingual adults (English/Spanish). Preliminary studies support its sensitivity to detecting mild naming deficits [52]. The test is comprised of 32 items that are presented to the participant in increasing order of difficulty. The maximum score is 1.
- Trail Making Test (TMT) A & B [53]: Originally a subtest of the Army Core Battery, the TMT measures visual attention and scanning, motor integration, working memory, and set shifting. For Part A, the participant is required to connect in sequential order numbered circles scattered across a page. Time to complete the task is recorded. Trails B is similar to Trails A but requires connecting numbers and letters scattered on a page by alternating between the two categories in sequential order (1-A, 2-B, 3-C, and so on) and time to completion is recorded.
- Brief Visuospatial Memory Test - Revised (BVMT-R) [48] constructional copy condition: Constructional praxis will be assessed using equivalent alternate forms of the BVMT-R. The

subject is presented with a card depicting six simple designs and asked to copy the figures on the record form. Total score will be calculated based on a point system that codes the overall placement and accuracy of reproduction of the 6 figures.

- Clock Drawing Test (CDT) [54]: The CDT is a test that taps elements of visuospatial analysis, planning, organization, and semantic knowledge. The scoring method evaluates the participant's ability to reproduce three key elements: clock face (2 points), placement of hands (4 points), and placement of numbers (4 points). Total score will be calculated, summing across the three error subtypes, with higher scores indicating better performance [55].

Subject-Reported Outcome Questionnaires

In addition to the cognitive test battery, the following assessments will also be conducted at the time points stipulated in the Schedule of Study Procedures (Appendix A):

- Self-Rating of Memory Functions: Self assessment of memory function will be obtained using the Alzheimer's Disease Cooperative Study Prevention Instrument Project - Mail-In Cognitive Function Screening Instrument (ADCS-MCFSI) [42]: This is a 14-item self administered yes/no questionnaire to assess recent changes (over the last year) in cognition and functional activities which commonly are affected in the development of MCI.
- Geriatric Depression Scale (GDS) [56]: This is a 15-item (short form) self-administered yes/no question test constructed for brief screening of depression in elderly persons.
- Assessment of HRQoL will be done using the EQ-5D [57,58] measure from the EuroQOL Group, and the SF-36 [59]. These assessments will be completed by all subjects enrolled in the study.
- Health care resource utilization during the study period will be measured by the Alzheimer's Disease Cooperative Study - Resource Use Inventory (ADCS-RUI). The ADCS-RUI includes questions pertaining but not limited to hospitalization (all cause), emergency room visits, unscheduled physician office visits, major diagnostic procedures, concomitant medications, use of nonmedical care costs (home health aids, etc), durable medical equipment, caregiver burden. This questionnaire will be completed at Visit 2 (Baseline), every 6 month visit during double-blind treatment, Unscheduled Visit for comprehensive medical follow-up, and EoS/EW Visit. The ADCS-RUI should be completed by the subject and project partner together. The ADCS-RUI will be completed for all subjects enrolled in the study.

Project Partner-Reported Questionnaires

- Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [60]: The IQCODE is a 26-item questionnaire that asks the project partner about changes in an elderly person's everyday cognitive function. The questionnaire aims to assess cognitive decline independent

of pre-morbid ability. Research revealed that it has high reliability, sensitivity, and specificity, and it is very useful in differentiating elderly suffering from dementia from those experiencing normal aging. This questionnaire will be completed at Visit 2 (Baseline), every 6 month visit during double-blind treatment, and EoS/EW Visit.

- Alzheimer's Disease Cooperative Study Instrumental Activities of Daily Living – Prevention Instrument (ADCS ADL-PI) [61]: The ADCS ADL-PI is a functional measure that was specifically designed for standardized administration in long follow-up, AD prevention, clinical trials as a secondary outcome measure. It can be given in the format of an interview, either directly or by phone. Delay of onset and slowed progression therapy should show preserved or slower deterioration on activities of daily living. The ADCS ADL-PI is a 20-item instrument that includes 15 ADL questions plus 5 vision, hearing, and mobility questions. This questionnaire will be completed at Visit 2 (Baseline), every 6 month visit during double-blind treatment, and EoS/EW Visit.
- Neuropsychiatric Inventory Questionnaire (NPI-Q) [62]: The NPI-Q is a brief validated version of the standard NPI [63]. It is designed to assess NPS common in AD and related dementias. The NPI-Q is designed to be a self-administered and queries the presence of symptoms in each of 12 specific domains and is queried over the past 30 days: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, disturbances of sleep, and disturbances of appetite/eating. In special cases when Sponsor permission is given for the project partners to have the CMFV or EoS/EW Visit conducted by telephone, the questionnaire will no longer be self administered but will be conducted aurally over the telephone, more in keeping with the standard NPI, which was designed to be clinician administered with a query question (the items on the NPI-Q) followed by more detailed interviewing. The scale is constructed such that a screening question is asked for each symptom domain. If this item is endorsed, then specific follow up questions are asked to clarify the nature of the symptoms, their frequency, severity, degree of change from premorbid, and treatment. The NPS outcome variable is defined as either the presence or absence of a given NPS domain. The NPI can also be analyzed by dividing into absence of any NPS versus >1 NPS (NPI Total). NPI severity can also be calculated. The physician reviews the form and clarifies the nature and the presence of symptoms endorsed. This questionnaire will be completed at Visit 2 (Baseline), Unscheduled Visit, and EoS/EW Visit.

Investigator-Completed Questionnaire

- Clinical Dementia Rating (CDR) [64]: The CDR is a clinician - completed structured interview with participant and project partner designed to assess an individual's cognitive and functional performance in six areas for purposes of determining the severity of dementia symptoms. The six areas assessed include: memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. A categorical outcome of 0, 0.5, 1, 2, or 3 is generated. Using an algorithm that takes into account the individual domain

scores, a total CDR score can be assigned. A CDR global score of 0 indicates normal function, whereas, a CDR global score of 0.5 indicates questionable dementia and ratings of 1, 2, and 3, indicate progressively more severe impairment, corresponding to mild, moderate, and severe dementia, respectively. More recently, continuous measures on the CDR were introduced by summing the six individual domain scores, resulting in a "sum of boxes" (CDR-SB) score. This continuous measure, which will also be calculated for this study, allows a sensitive measure of cognitive and functional change in early AD progression [65]. The CDR will be completed at Visit 2 (Baseline), Unscheduled Visit, and EoS/EW Visit.

- Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change – Mild Cognitive Impairment (ADCS-CGIC-MCI) [66]: This measure captures the clinician's global impression of the subject. This measure will be completed at Visit 2 (Baseline), every 6 month visit during double-blind treatment, Unscheduled Visit, and EoS/EW Visit.

9.1.16 Assessment of Suicidal Ideation and Behavior

The Columbia–Suicide Severity Rating Scale (C-SSRS; [67]) was developed by researchers at Columbia University as a tool to help systematically assess suicidal ideation and behavior in subjects during participation in a clinical trial. The C-SSRS is composed of 3 questions addressing suicidal behavior and 5 questions addressing suicidal ideation, with subquestions assessing the severity. The tool is administered via interview with the subject. Different versions of the scale are available. In this study, "Baseline" version will be used at Visit 3 (Randomization) and "Since last visit" version at all subsequent visits.

Suicidality Events: A completed suicide is always an SAE based on its fatal outcome. Additionally, for the purpose of this development program, active suicidal behaviors such as "suicidal intention with a definite plan" and "suicide attempt" will also be collected as SAEs. Unless the event meets other serious criteria, suicidal thoughts or suicidal ideations that do not include a definite plan or action will be collected as non-SAEs in accordance with the standard adverse event reporting requirements (eg, if a pre-existing suicidal ideation recorded on the screening C-SSRS got worse during the study, it should be reported as an AE). A subject presenting with self-mutilation or other types of self-injury should be questioned by the investigator to clarify if the action was suicidal in intent. If the event was suicidal in intent, the investigator should include suicidal behavior as part of the verbatim term on the (e)CRF, that is, "slit wrists/suicidal behavior". Such an event will be collected as an SAE. Acts of self-mutilation or self-injury without suicidal intention, ie, self-imposed cigarette burns, will be collected as non-SAEs.

9.1.17 Order of Assessments

Sites should make every attempt to adhere to the assessment schedule in Table 9.c. Should an interruption occur during the visit, the subject, and/or project partner, may return to the site within 2 weeks to complete the assessments. During the Baseline Visit only, sites may elect to administer the CDR prior to the Cognitive Test Battery to evaluate subject eligibility. The ADCS-CGIC-MCI may be administered in parallel with, or before other testing, as long as the tester is blinded to any adverse events or other test results.

Table 9.c Order of Assessments

Cognitive Test/Questionnaire	Visit	Assessor
MMSE	Visit 1, Visit 2, every 6 and 12 month visit after randomization, EoS/EW Visit	Certified tester
Cognitive Test Battery (completed in this order) **1.** CVLT-II: Trials 1-5; Short delay recall trials. **2.** BVMT-R: Learning trials 1-3. **3.** Digit Span Forward. **4.** Digit Span Backward. **5.** Trails A. **6.** Trails B. **7.** CVLT-II: Delayed recall (15-30 minutes should have elapsed from end of short recall and long-delay). **8.** CVLT-II: Recognition trial. **9.** BVMT-R: Delayed recall (15-30 minutes should have elapsed from Trial 3 to delay) **10.** BVMT-R: Recognition trial. **11.** BVMT-R: Copy trial. **12.** MINT. **13.** Semantic fluency (animals). **14.** Lexical fluency. **15.** CDT.	Visit 2, every 6 and 12 month visit after randomization, Unscheduled Visit, EoS/EW Visit	Certified tester
GDS	Visit 2, every 6 and 12 month visit after randomization, EoS/EW Visit	Study Subject

Footnotes are on last table page.

Table 9.c Order of Assessments (continued)

Cognitive Test/Questionnaire	Visit	Assessor
ADCS-MCFSI	Visit 2, every 6 and 12 month visit after randomization, EoS/EW Visit	Study Subject
EQ-5D	Visit 2, Unscheduled Visit, EoS/EW Visit	Study Subject
SF-36	Visit 2, Unscheduled Visit, EoS/EW Visit	Study Subject
IQCODE	Visit 2, every 6 and 12 month visit after randomization, EoS/EW Visit	Project Partner
ADCS ADL-PI	Visit 2, every 6 and 12 month visit after randomization, EoS/EW Visit	Trained Tester
NPI-Q	Visit 2, Unscheduled Visit, EoS/EW Visit	Project Partner
ADCS-RUI	Visit 2, every 6 and 12 month visit after randomization, Unscheduled Visit, EoS/EW Visit	Trained tester
CDR (a)	Visit 2, Unscheduled Visit, EoS/EW Visit	Investigator/ Sub-Investigator (b)
ADCS-CGIC-MCI (c)	Visit 2, every 6 and 12 month visit after randomization, Unscheduled Visit, EoS/EW Visit	Trained tester (b)
AE Assessment	Visit 2, Visit 3, every 6 and 12 month visit after randomization, every 3 and 9 month phone visit, Unscheduled Visit, EoS/EW Visit and follow up visit	Investigator/ Sub-Investigator
C-SSRS	Visit 3, every 6 and 12 month visit after randomization, EoS/EW Visit, and follow up visit	Certified tester

(a) May be administered prior to the Cognitive Test Battery only during the baseline visit.
(b) Sites may utilize the same Investigator/Sub-Investigator tester administering the CDR for the ADCS-CGIC-MCI.
(c) May be administered in parallel with other assessments.

9.1.17.1 Language Considerations

The assessments will be used in local language (ie, language used locally which the subject and investigator are both fluent in; this may include English and is not confined to the language that is native to the subject's race/nationality) versions. Only certified translations provided by TDC (if applicable) are to be used. Some minor differences in test administration may occur in order to make the test results consistent across languages and cultures. For example, verbal fluency letters F, A, and S will vary across languages based upon the frequency of letters in the local language. Language fluency will be captured within the (e)CRF.

9.1.18 Tester Monitoring Management Program

A certified tester at the site will administer the MMSE and cognitive test battery. Additional details and requirements will be provided in the training manual provided by a vendor chosen by Takeda.

9.1.19 Tester Qualification and Certification

In order to ensure satisfactory training of testers and quality execution with regards to data collection, testers assigned to this study will be required to adhere to certain requirements prior to participation in the trial. Furthermore, the trial will include additional steps related to monitoring the quality of tester activity. The training materials and requirements may be adjusted or modified as needed throughout the course of the trial.

All testers will be required to successfully complete the full scope of tester training requirements prior to testing any subjects in this study. Testers who successfully complete all requirements will be approved for participation in the study by Takeda and/or its designee before enrollment may commence at sites. Testers who do not meet all the qualification and training requirements may be prohibited from participating as testers on this trial. Takeda and/or its designee may revoke a tester's certification during the trial.

Investigators completing the CDR will be required to be certified and trained. The investigator who completes the CDR is independent and cannot be the same person who administers the cognitive battery. Sites should make an attempt to use the same investigator to complete the CDR at each assessment.

9.1.20 Health Economics and Outcomes Research Assessments

EQ-5D measure from the EuroQOL Group, and the SF-36 will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information collected with this instrument, proper follow-up with the patient for medical evaluation should be undertaken. Through this follow-up if it is determined that an AE not previously reported has been identified, normal reporting requirements should be applied.

9.1.21 Imaging

Prior to the start of the study, each site should identify a study MRI and CT machine. Each MRI machine will be qualified by the imaging vendor before collection of images in the study. Documentation of qualification will be sent to the site by the imaging vendor, which should be retained in the site's study files as evidence of quality control approval. Each MRI and CT scan will be read by the local radiologist at each site for immediate medical action whenever necessary. The results of the local reading will be recorded in the (e)CRF. Detailed instructions for the processing and shipping of images will be provided separately.

For subjects who have contraindications for MRI procedure (such as unremovable ferromagnetic dental work, cardiac pacemakers, etc) a CT scan may be performed instead.

Imaging will be part of the comprehensive medical follow-up evaluation to rule out other causes of dementia and to provide supplemental information for an adjudicated clinical diagnosis of MCI due to AD during an Unscheduled Visit, as described in Section 6.2.4.

9.1.22 Diet and Exercise Evaluation

All postmenopausal women should be encouraged to employ lifestyle practices that reduce the risk of bone loss and osteoporotic fractures: maintaining a healthy weight, eating a balanced diet, obtaining adequate calcium and vitamin D, participating in appropriate exercise, avoiding excessive alcohol consumption, not smoking. An adequate intake of both calcium and vitamin D is important for bone health and is recognized as an important component of any osteoporosis prevention drug regimen [68]. Although supplementation of a woman's diet with these essential nutrients may be considered, recent guidance from the US Preventive Service Task Force (http://www.uspreventiveservicestaskforce.org/uspstf/uspsvitd.htm) has highlighted the uncertain risk/benefit balance of this approach. Among women age 75 and older, muscle strengthening and balance exercises have been shown to reduce the risk of falls and fall-related injuries by 75% [69]. Weight-bearing exercise can be as simple as brisk walking. Diet and exercise evaluation will be performed at Visit 2 (Baseline), every 6 month visit during double-blind treatment, and EoS/EW Visit.

9.2 Monitoring Subject Treatment Compliance

Subjects will be required to bring study medication containers to each dispensing site visit. The number of pills returned will be captured in the subject's source documentation and (e)CRF. The project partner will also be asked to assess the subject's compliance.

Subjects will be considered to be non-compliant with study medication if they miss >20% of doses required for the visit period, or take more than 100% of the doses for the required visit period. Non-compliance with study medication must be reported in the (e)CRF and subjects should be reminded of the importance of being compliant with dosing instructions. Any detected overdose must be reported on an Overdose page of the (e)CRF.

All subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

During telephone visits that will occur yearly on the 3 month and 9 month interval, treatment compliance should be evaluated during the conversation.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

9.3.1 Screening

Subjects will be screened (Visit 1) prior to Baseline (Visit 2). Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.13 for procedures for documenting screening failures. See Appendix A for list of procedures that will be performed and documented. It is anticipated the Screening visit will be about 45 minutes in length.

9.3.2 Baseline

Prior to the subjects returning to the site for the Baseline visit (Visit 2), the site will receive notification from IWRS to indicate if the Baseline visit should be scheduled based on the blinded risk assessment as determined by the screening visit. Baseline visit will take place prior to Randomization (Visit 3). Sites will complete a pre-randomization eligibility verification form for subjects who meet the baseline requirements. The form will be submitted to the CRO medical monitor for review and confirmation of inclusion/exclusion criteria. See Section 9.1.13 for procedures for documenting baseline failures. See Appendix A for list of procedures that will be performed and documented. It is anticipated the Baseline visit will be about 4 hours in length.

9.3.3 Randomization

Randomization will take place on Day 0 and no more than approximately 35 days after baseline. See Appendix A for list of procedures that will be performed and documented.

If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for randomization, the subject should be randomized using the IVRS/IWRS system, as described in Section 9.1.14. Subjects will be instructed on when to take the first dose of investigational drug as described in Section 6.1. The procedure for documenting Screening and Baseline failures is provided in Section 9.1.13. It is anticipated the Randomization visit will be about 45 minutes in length.

9.3.4 Treatment Phase

See Appendix A for list of procedures that will be performed and documented during the treatment period. Telephone visits will occur yearly on the 3 month and 9 month interval and clinic visits will occur yearly on the 6 month and 12 month interval. It is anticipated the treatment clinic visits will be about 3 to 4 hours in length.

9.3.5 Unscheduled Visit

There are 2 types of Unscheduled Visits in this study: 1) Unscheduled Visits conducted to address any other emerging concerns, including safety, and 2) Unscheduled Visits conducted for Comprehensive Medical Follow-Up after a trigger relating to cognitive status has been met.

9.3.5.1 Unscheduled Visits for Other Concerns (including Safety)

Unscheduled Visits conducted to address any other emerging concerns, including safety, may occur at any time between regularly scheduled in-clinic Study Visits. Depending on the nature of the (non-cognitive) concerns, the Investigator is expected to conduct whatever assessments are necessary to manage the needs of the subject appropriately.

9.3.5.2 Comprehensive Medical Follow-Up

A Comprehensive Medical Follow-Up evaluation (which the subject's project partner should make every effort to attend, if possible, or otherwise complete during a Home Visit or via telephone if appropriate), should be conducted within approximately 30 days of the trigger when one of the triggers described in Section 6.2.4 has been met. This type of Unscheduled Visit will include the assessments noted in Appendix A and Section 6.2.4. If appropriate, the CMFV assessments may be performed during the routine visit if the specific criteria specified in Section 6.2.4 are met. It is anticipated this visit will be about 5 to 6 hours in length, if an MRI is completed during the visit.

9.3.6 Final Visit or Early Termination

The Final visit will be performed once the total number of endpoints are reached, which is expected to occur four years after enrollment ends, or at the EoS/EW Visit for subjects who complete the study or withdraw before the total number of endpoints are reached. See Appendix A for a list of procedures that will be performed and documented.

For all subjects receiving study medication, the investigator must complete the EoS (e)CRF page.

Subjects who discontinue study medication prematurely should attempt to follow the procedures outlined in Section 7.5. It is anticipated the Final visit will be about 4 hours in length.

9.3.7 Follow-up

Subjects will be contacted for a Safety Follow-up call 2 weeks after the EoS/EW Visit. See Appendix A for list of procedures that will be performed and documented.

Follow-up will begin the first day after the EoS/EW Visit and will continue until 2 weeks later. Subjects will be contacted for a Safety Follow-up call, (follow up of any ongoing AEs, new events, new SAEs, and concomitant medications) 2 weeks after the EoS/EW Visit. Subjects who withdraw their consent should still be contacted for a Safety Follow-up call, but the contact

should only be recorded in the medical records (and not the (e)CRF), according to data protection regulations.

The Safety Follow-up call should not occur for those subjects who enter the long-term extension study (AD-4833/TOMM40_303).

9.3.8 Post Study Care

Subject to applicable laws and feasibility, access to the study medication may be available to individual subjects for whom no standard therapy exists, and the subject is at risk of significant morbidity or mortality. The investigator should contact the medical monitor to determine if access is possible.

Subjects who successfully complete this pivotal phase 3 (AD-4833/TOMM40_301) study and have reached the primary endpoint diagnosis of MCI due to AD may be considered for participation in the AD-4833/TOMM40_303 long-term extension study. The safety profile of long-term daily low-dose pioglitazone treatment in the elderly, as well as the efficacy of pioglitazone in slowing the progression of cognitive decline after diagnosis of MCI due to AD will continue to be evaluated in the long-term extension study.

9.4 Biological Sample Retention and Destruction

In this study, specimens for PGx analysis will be collected as described in Section 9.1.11. After extraction and purification, the genetic material will be preserved and retained at CCI for up to but not longer than 15 years or as required by applicable law. The sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

"Stored samples" are defined as samples that are double coded (the samples are stripped of all personal identifying information but a key links the samples to the clinical data collected from the sample donor) and are used in the analysis of investigational drug, related drugs (comparator drug) and the disease state.

Subjects who consented and provided a PGx sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time. Site should notify sponsor of consent withdrawal.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses vs. signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an

intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg, "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs /Serious PTEs:

- If the subject experiences changes in severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as adverse events.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as adverse events.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The principal investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the (e)CRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the (e)CRF.

10.1.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
    - The term "life threatening" refers to an event in which 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.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.

- May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
- Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizures	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 AESIs

An AESI (serious or non-serious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for investigators as to how and when they should be reported to Takeda. AESIs are listed in section 10.2.1.3.

10.1.6 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.7 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Yes:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug can be argued, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
No:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

10.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Yes if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as No.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication (Study Visit 3) or until screen or baseline failure. For subjects who discontinue prior to study medication administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study medication (Study Visit 3). Routine collection of AEs will continue until 2 weeks after completion or withdrawal from the study (safety Follow-up Visit).

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as “How have you been feeling since your last visit?” may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the (e)CRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term.
- Start and stop date.
- Severity.
- Investigator's opinion of the causal relationship between the event and administration of study medication(s) (yes or no) (not completed for PTEs).
- Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
- Action concerning study medication (not applicable for PTEs).
- Outcome of event.
- Seriousness.

10.2.1.3 AESI Reporting

The phase 3 efficacy and safety study will be conducted in cognitively normal elderly subjects. Pioglitazone appears to be safe and well tolerated in the elderly population, based on the available information from healthy volunteers and diabetics in Takeda-sponsored trials or from AD patients in Takeda-supported studies [15,16]. Based on the available safety information in the diabetic population, the following safety procedures will be implemented when specific AESIs are reported during the study. All such AEs will be reported to the Sponsor in an expedited manner irrespective of the event's seriousness or causal relationship:

1. Congestive heart failure (CHF): Subjects and their project partners will be advised to promptly report signs and symptoms of heart failure (eg, excessive, rapid weight gain, dyspnea, and/or edema). Any subject with CHF NYHA class III-IV will be excluded at screening. If a subject develops a new onset CHF or experiences deterioration of pre-existing condition after enrollment, the subject will be withdrawn from the study. Assessment of subjects for signs and symptoms of CHF will take place at every study visit. The diagnosis of CHF can be difficult. Many of the symptoms of heart failure are nondiscriminating and, therefore, of limited diagnostic value. Many of the signs of heart failure result from sodium and water retention and resolve quickly with diuretic therapy, ie, may be absent in patients receiving such treatment. Because the signs and symptoms of heart failure are so non-specific, demonstration of an underlying cardiac cause using diagnostic tests (such as ECG, echocardiogram, chest X-ray, etc) is very important to the diagnosis of heart failure. For

events of heart failure, a CHF eCRF should be completed within 24 hours of the investigator's awareness of the event.

2. Macular edema: All subjects and their project partners will be asked to promptly report symptoms potentially associated with macular edema (eg, blurred vision, distortion of images, missing areas, dimming or "graying-out" of vision from loss of contrast sensitivity, and changes in the way color is perceived). If symptoms are reported, the subject will be evaluated by an ophthalmologist. Subjects diagnosed with macular degeneration during the study will be followed up by an ophthalmologist and have retinal imaging (eg, Optic Coherence Tomography or Heidelberg Confocal Laser Doppler Imaging) performed at least every six months until study completion or early withdrawal to confirm that the condition is stable. Any subject who develops macular edema will stop taking study medication, be withdrawn from the study, and be managed by his or her regular physician using the local standard of care.
3. Hepatic effects: Subjects and their project partners will be advised to promptly report signs and symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. If ALT or AST >3×ULN, laboratory tests should be repeated within a maximum of 7 days, and preferably within 48 to 72 hours. If the ALT or AST remains elevated >3×ULN on these 2 consecutive occasions, and this observation cannot be explained by concomitant disease or another alternative etiology, the abnormality should be recorded on an AE page. The investigator must contact the Medical Monitor for consideration of immediate discontinuation of study medication, discussion of the relevant subject details and possible alternative etiologies.
4. Bone fractures: All female subjects, regardless of their clinical risk factors for osteoporosis, should be encouraged to eat a balanced diet and participate in appropriate exercise, avoid cigarette smoke and excessive alcohol consumption. All postmenopausal women should be encouraged to employ lifestyle practices that reduce the risk of bone loss and osteoporotic fractures: maintaining a healthy weight, eating a balanced diet, obtaining adequate calcium and vitamin D, participating in appropriate exercise, avoiding excessive alcohol consumption, not smoking. An adequate intake of both calcium and vitamin D is important for bone health and is recognized as an important component of any osteoporosis prevention drug regimen [68]. Among women age 75 and older, muscle strengthening and balance exercises have been shown to reduce the risk of falls and fall-related injuries by 75% [69]. Weight-bearing exercise can be as simple as brisk walking. All suspected or confirmed bone fracture will be followed-up for an X-ray confirmation, outcome, and any healing complications. Current standards of care for assessing and maintaining bone health will be applied.
5. Bladder cancer: Subjects and their project partners will be advised to promptly report any signs or symptoms that could be consistent with bladder cancer such as hematuria, urinary urgency, urinary frequency, or dysuria. Any subject with previous or active bladder cancer

will be excluded. All subjects will be screened for evidence of hematuria (macroscopic or microscopic). In the event of unexplained hematuria (3 or more red blood cells per high power field on microscopic urine test), confirmed by a repeat test (within 14 days of the initial assessment), subject will be referred to a urologist for additional follow-up testing according to local standard diagnostic approach. If the diagnosis of the bladder cancer cannot be excluded the subject will be withdrawn from the study.

6. Subjects with T2DM who are on a stable antidiabetic regimen for at least 3 months prior to enrollment that does not require the use of insulin, oral triple therapy and/or PPAR-γ agonists will be allowed in the study. Subjects who develop a new onset T2DM during the study will be referred to an endocrinologist. If the use of prohibited medications (such as insulin or PPAR-γ agonists) is considered necessary, the subject will be withdrawn from the study. Pioglitazone alone especially at a low dose is not likely to cause hypoglycemia in elderly subjects without T2DM. However, subjects with T2DM taking pioglitazone with an insulin secretagogue (eg, sulfonylurea or glitinide) may be at increased risk for developing hypoglycemia. Therefore all subjects with the following AEs will be closely monitored using the following event categories [70].

   - **Severe hypoglycemia:** an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Blood glucose may not be available.
   - **Documented symptomatic hypoglycemia:** typical symptoms of hypoglycemia accompanied by blood glucose ≤70 mg/dL (3.9 mmol/L).
   - **Asymptomatic hypoglycemia:** Blood glucose ≤70 mg/dL (3.9 mmol/L), but with no typical symptoms.
   - **Probable symptomatic hypoglycemia:** Symptoms of hypoglycemia that are not accompanied by blood glucose determination ≤70 mg/dL (3.9 mmol/L).
   - **Relative hypoglycemia:** Symptoms of hypoglycemia, but with a measured blood glucose >70 mg/dL (3.9 mmol/L).

   If any subject is noted to have a hypoglycemic event, the hypoglycemia (e)CRF should be completed within 24 hours of the investigator's awareness of the event.

All special interest AEs also have to be recorded as AEs in the (e)CRF.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

A Takeda SAE eCRF must be completed, in English, and electronically signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.2.3 Reporting of Abnormal Liver Function Tests

When reviewing liver function tests (LFTs), if a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases (e)CRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease. Follow-up laboratory tests as described in Section 9.1.8 must also be performed. In addition, an LFT Increases (e)CRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE eCRF within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency (EMA), investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be

submitted within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an IMP or that would be sufficient to consider changes in the IMPs administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 Neuropsychology Advisory Board

The selection of the neuropsychology instruments for the cognitive test battery, the relevant domains for testing, establishment of thresholds, and composite scores was defined by a neuropsychology advisory board that has been formed by Takeda/Zinfandel alliance.

11.2 Data Safety Monitoring Board

In addition to regular sponsor surveillance, the safety of subjects will be evaluated by an independent DSMB. The DSMB will meet periodically to review all safety data from the study, including adverse events of special interest. This group will include individuals with expertise in endocrinology, neuro-radiology, AD specialist, Cardiology and statistics.

Details of the independent DSMB are captured in a charter.

11.3 Cognitive Impairment Adjudication Committee

Adjudication to determine if a subject has reached the study endpoint event of MCI due to AD diagnosis will be carried out by independent experts who will review and adjudicate each event in a blinded fashion. Because AD dementia will also be considered a diagnostic event that will count toward the total number of events in AD-4833/TOMM40_301, the CIAC will also adjudicate potential occurrences of possible or probable AD dementia, as defined by the criteria described by McKhann et al., 2011 [41]. The adjudication of these events will be performed based on criteria outlined in the adjudication charter. The experts will adjudicate each event independently of each other. If the experts' initial adjudications are not identical, they will review these cases together and come to a conclusion by unanimous consensus. Details of the adjudication procedure will be captured in an Adjudication Charter.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 (e)CRFs

Completed (e)CRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to (e)CRFs. The sponsor will make arrangements to train appropriate site staff in the use of the (e)CRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. (e)CRFs must be completed in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The principal investigator must review the (e)CRFs for completeness and accuracy and must sign and date the appropriate (e)CRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the (e)CRFs.

(e)CRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the (e)CRFs. The completed (e)CRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper should be copied and certified, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of (e)CRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section

8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted prior to unblinding of the subjects' treatment assignments. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

All efficacy and safety variables will be analyzed using the full analysis set (FAS). The FAS will consist of all randomized subjects. The per-protocol population will be described in the SAP.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized using the FAS with descriptive statistics or frequency counts as appropriate.

13.1.3 Efficacy Analysis

There are 2 independent null hypotheses in this protocol: (1) assumes that there is no difference in conversion rate between the placebo-treated high-risk and low-risk groups as defined by the prognostic biomarker test and (2) assumes that there is no difference in conversion rate between the high-risk active- and placebo-treated subjects. The alternate hypotheses are: (1) there is a difference between the high- and low-risk groups treated with placebo, and (2) there is a difference between placebo and active treatment in the high-risk group.

In order to test the first hypothesis, a test from a Cox proportional hazards survival model will be used to compare data from non-Hispanic/Latino Caucasians in the (placebo-treated) low-risk group (ie, the combined placebo groups) with data from non-Hispanic/Latino Caucasians in the placebo-treated subjects in the high-risk group. The event in this analysis will be the diagnosis of cognitive impairment. If this test is significant at the 0.01 level, it can be concluded that the diagnostic prognostic test has differentiated between subjects at low and high risk of being diagnosed with cognitive impairment within 5 years of taking the test.

A similar analysis will be used to compare the placebo- and active-treated non-Hispanic/Latino Caucasian subjects within the high-risk group. If this test is significant at the 0.01 level, it can be concluded that active treatment has delayed the development of cognitive impairment within the 5-year period.

A secondary all-comers analysis will be done to compare the placebo and active-treated subjects within the high-risk group.

All data collected in the study will be listed and summarized either by mean, SD, median, and range or by frequency tables, as appropriate to the data.

Time-to-event data will be analyzed using a Cox proportional hazard model, including an investigation of the effects of covariates (testing center, age, sex, etc). The incidence of MCI due to AD will also be compared using a chi-squared test and the difference in incidence will be reported along with 95% confidence intervals.

Following a significant finding for the primary efficacy endpoint, a sequential testing hierarchy will test the rate of cognitive decline endpoint first and then, if significant, proceed to testing the impairment of functional abilities using the functional impairment assessment ADCS ADL-PI As for the primary analysis, these key secondary endpoints will be tested at the alpha = 0.01 level. The analyses for these endpoints will be analysis of covariance (ANCOVA) for change from baseline using mixed models repeated measures (MMRM).

The other secondary endpoints will be analyzed using ANCOVA, logistic regression, survival analyses, or chi-squared tests as appropriate to the data. As for the primary analysis, the secondary endpoints will be tested at the alpha = 0.01 level.

The primary endpoint in this study is event-based and subjects who discontinue from the study prior to having the event will be censored in the primary analysis. However, for completeness, follow-up information will be collected on as many subjects as possible, including the reason for discontinuation. For the continuous variables such as the composite scores, mixed models repeated measures using all available data will be used to evaluate changes over time.

The rules for handling missing items from each of the scales are designed so that as much data as possible can be used in the analyses, yet with reliable information, when calculating total scores.

Missing data may occur in the course of the study or may be due to drop-out. With regard to neuropsychological data collection within the study, missing data can occur under several scenarios. In an interview setting administration of some portions of the test battery may be precluded by tester error or factors attributable to the patient (illness, refusal, or other problems). Neuropsychological technicians will be trained to avoid missing data whenever possible. In the event that an item or a test is missing, technicians will be trained to record the reason for missing data. When tests are scored, the reason for missing data will be coded in a uniform, standardized manner across sites. Test scores will be prorated wherever possible.

Composite scores will be derived from the test battery. Each test in the battery falls into one of the following cognitive domains: Episodic Memory (CVLT-II, BVMT-R), Executive Function (TMT Part B, Digit Span Backwards), Language (Animals, Lexical/Phonemic Fluency), Attention (Digit Span Forward, TMT Part A), and Visuospatial (CDT, BVMT-Copy). Only the domains of episodic memory, executive function, language, and attention will be used for the composite score (ie, CDT, BVMT-Copy and the MINT, which do not allow generation of standard z scores, will only be used for diagnostic purposes and will be excluded from the calculation of the composite score). To form the composite, z-scores will be calculated for each

test, each z-score for the domain will be averaged, and then all relevant domains will be averaged to form the composite. Because there are two tests for each domain, the composite can still be calculated if one test is missing. In the case of memory however, both tests are required to calculate the composite.

There may still be missing values for the continuous variables and the analyses for continuous variables are based on a Missing at Random (MAR) assumption. As a sensible sensitivity analysis, the pattern mixture models using standard SAS STAT procedures will be performed. This method uses sequential regression and multiple imputation methodology to impute missing values after subjects' discontinuation from the study. The missing values from both control and experimental treatment arms are imputed based on the available data from control subjects and through using PROC MI's methodology for imputation of monotone missing data patterns to impute the outcome variables at consecutive visits in a sequential (chain) manner.

Additional analyses may be done to assess the contribution of age, APOE genotype, and TOMM40 rs10524523 genotype to the risk assignment algorithm.

It is anticipated that approximately 20% of the subjects will be diabetic. Subgroup analyses for non-diabetic subjects and for diabetic subjects will be done to support the results of the primary analysis.

In addition to the primary analysis population, it is anticipated that approximately 5% as many subjects will be Hispanic/Latino and/or non-Caucasian. Additional analyses for Hispanic/Latino and/or non-Caucasian subjects and for all subjects will be done to support the results of the primary analysis. These analyses will be the same as those conducted for the primary subgroup of the Caucasian subjects in order to evaluate the biomarker effectiveness within this extra subpopulation and the efficacy for pioglitazone within high-risk non-Caucasian subjects.

13.1.4 Pharmacokinetic Analysis

Sparse plasma samples from approximately 30% per region of the study subjects will be collected to estimate population PK/PD of pioglitazone, random inter/intra-subject variability, random residual variability associated with PK and PD model parameters, and to identify sources of variability (continuous or categorical covariates) that may influence pioglitazone PK and PD profiles in study subjects.

13.1.5 Other Analysis

Any sensitivity or other analyses (eg, using additional covariates) will be described in the SAP.

13.1.6 Safety Analysis

AEs

AEs will be reported throughout the study.

Treatment-emergent AEs are any new or worsened events that occurred after the first dose of study medication and within 30 days following discontinuation of study medication. AEs will be coded using MedDRA and will be summarized by system organ class and preferred term.

AEs that were reported more than once by a subject during the same period will be counted only once for that subject and period at the maximum severity.

Clinical Evaluations

Observed values and changes from screening/baseline in clinical safety laboratory tests, vital signs, ECG parameters, and body weight will be summarized for each treatment group using descriptive techniques. Values outside normal ranges and potentially clinically significant values will be flagged and tabulated. Physical examination findings will also be summarized for each treatment group.

13.2 Futility Analysis and Criteria for Early Termination

Tracking of confirmed events of MCI due to AD, as adjudicated by the CIAC, will be done on an ongoing basis, in a blinded fashion. There will be two types of analyses conducted during the study to assess futility: an 'operational futility analysis' and an 'efficacy futility analysis'. The study will be declared to be 'operationally futile' if the accrual of confirmed events is too slow to allow completion of the study in a feasible time frame. The timeframe for assessing operational futility is described in the SAP.

If operational futility is not declared, an analysis for futility for efficacy will be conducted once approximately 33% (66 out of 202) of the anticipated events (ie, conversions from cognitively normal status to adjudicated diagnosis of MCI due to AD, or to AD dementia) have occurred in the high-risk, Caucasian, non-Hispanic/Latino group. However, since the biomarker risk stratum information is blinded, the time of the futility analysis will be estimated using all subjects (both high-risk and low-risk) in the Caucasian, non-Hispanic/Latino group. Therefore, the efficacy futility analysis will occur when approximately 69 events have been confirmed through adjudication in the Caucasian, non-Hispanic/Latino group (including both high-risk and low-risk subjects). Note that no adjustment of the alpha level is required for an analysis for futility, and that for this study the results of the futility analysis will be considered to be non-binding with respect to efficacy for purposes of decision making around study continuation.

If operational futility is declared, an early efficacy futility analysis (ie, prior to reaching 33% of anticipated events as described above) will be done as soon as practicable (ie, after all pertinent data for the futility analyses has been cleaned as per the specifications outlined in the Interim Database Lock Plan) and will be provided to the DSMB. This will not replace the efficacy futility analysis that is planned following the accrual of 33% of the anticipated events.

Further details of the operational and efficacy futility analyses are given in the SAP.

Because a review of unblinded data is involved, the DSMB will oversee this process. Once the total number of target events has been reached, the DSMB will be unblinded for a review of

actual treatment groups with respect to the primary efficacy endpoint (and potentially other analyses as described in the SAP, as applicable); this review would take place at the next regularly-scheduled DSMB meeting or at an ad hoc DSMB meeting.

The primary futility analysis for efficacy will be conducted by the DSMB Statistician, based on the treatment effect within the high-risk, Caucasian, non-Hispanic/Latino group. The calculation is a test from a Cox proportional hazards survival model to evaluate a difference between the treatment groups (pioglitazone versus placebo) for the high-risk comparison at the time of the interim futility analysis. Additionally, Kaplan-Meier curves by treatment group (including low-risk placebo) will be provided for the primary analysis population of non-Hispanic/Latino Caucasian subjects. If the primary futility analysis indicates futility, then the CCI Unblinded DSMB Statistician will provide an additional set of secondary futility analyses (described in the SAP). The DSMB could then recommend study continuation to completion for the targeted number of events or recommend (based on pre-specified criteria documented in the SAP) that the study be considered futile with respect to the primary efficacy endpoint, high-risk comparison.

Immediately after the efficacy futility analysis data review meeting takes place (ie, either after an efficacy futility analysis following operational futility or the efficacy futility analysis following accrual of 33% of events), the DSMB recommendation regarding the continuation of the study will be promptly communicated to the DSMB Liaison. If the data indicate that study termination should be considered, the DSMB Liaison will promptly convene an ad-hoc meeting within the Takeda/Zinfandel alliance senior management (ie, the Executive Committee) to further discuss the results of the futility analyses and make the final decision as to whether or not to terminate the study. In a similar manner to the DSMB, the Executive Committee will be unblinded to the results of the futility analyses, will keep all futility analysis results and discussions strictly confidential, and will have no involvement with the daily project activities of the study or study team.

If the alliance Executive Committee decides to terminate the study as a result of the futility analyses, this decision will be promptly communicated to all the stakeholders including the AD-4833/TOMM40 project team, investigators, ethics committees, and regulatory agencies. Details of the stopping rules and analyses will be given in the DSMB Charter and in the SAP.

13.3 Determination of Sample Size.

Background Information for Determining Sample Sizes

Using 73 years as the age at entry (+5 years = age 78), a conversion rate of around 18% over 5 years can be expected (see Table 13.a). This is based on:

- The TOMM40 rs10524523 allele frequencies from the Duke Alzheimer's Disease Research Center (ADRC), Cache County, and Wisconsin cohorts.
- The assessment of peer-reviewed published incident MCI in normal individuals.
- The effect of APOE on the incidence of AD.

Table 13.a Conversion Rate Estimates Based on Analysis of 3 Cohorts, Cognitive Impairment Incidence, and Observed TOMM40 rs10524523 Allele Frequencies

TOMM40 rs10524523 Genotype	Duke Bryan ADRC Frequency	Wisconsin Frequency	Cache Frequency	Cohort Total Count	Age 78 (Proportion Converted)	
					Proportion	Number of Converted Subjects
L/L	0.05	0.04	0.02	189	0.53	100
VL/L	0.14	0.15	0.13	543	0.34	185
S/L	0.17	0.20	0.14	669	0.22	147
S/S	0.23	0.16	0.17	929	0.14	130
S/VL	0.31	0.31	0.36	1236	0.10	124
VL/VL	0.11	0.14	0.18	433	0.05	22
			Total count = 3999		Total converted	708
					Overall conversion rate	0.177

Taking into account the age ranges that will be enrolled in the phase 3 study, a 5-year conversion rate of 15% will be assumed for non-Hispanic/Latino Caucasian placebo subjects within the high-risk stratum identified by the enrichment process. Based on the expected 5-year conversion rate of 15%, the time-to-event was modeled using an exponential mathematical model for planning the study sample size.

Similarly, a 5-year conversion rate of 4% will be assumed for non-Hispanic/Latino Caucasian placebo subjects within the low-risk stratum. Thus, it is important to recognize that this summary of the data demonstrates nearly a four-fold enrichment of events over the population rate using the risk algorithm.

Determination of Sample Size for the Phase 3 Study Based on the High-Risk Stratum

The sample size for this study is based on the event-driven analysis that is planned for comparing treatment groups within the high-risk stratum. For the purposes of this study, it is assumed that the placebo-treated non-Hispanic/Latino Caucasian subjects in the high-risk stratum will have an event rate of 15% over a 5-year period. This is more conservative than the 18% cited in the table, to assure adequate sample size. With an expected improvement of a reduction in event rate of 40%, the target event rate for the active treatment group will be 9% over 5 years. Furthermore, the following specifications are used: alpha=0.01, a 2-sided statistical test based on survival analysis, power=90%, annual dropout rate of 12% (or cumulative dropout rate of 47% over 5 years). In order to detect a difference of the specified magnitude (≥40% reduction in conversion rates over 5 years), at least 202 events must be observed during the course of the study in non-

Hispanic/Latino Caucasian subjects (primary analysis). Based on these assumptions and the fact that only non-Hispanic/Latino Caucasian subjects will be used for the primary analyses, a total of 2,346 non-Hispanic/Latino Caucasian subjects (1,173 on pioglitazone/1,173 on placebo) are required from the high-risk stratum for randomization.

Sample Size for the Phase 3 Study Based On Qualifying the Test Used to Stratify Subjects

While using data from the results of risk stratification and not a comparison between randomized groups, the same analysis as specified for comparing the treatment groups within the high-risk stratum will also be used to compare the two placebo groups (high-risk placebo and low-risk placebo). Thus, assuming that the placebo-treated subjects in the low-risk stratum will have a conversion rate of 4% over a 5-year follow-up period, then approximately 314 non-Hispanic/ Latino Caucasian subjects identified as low-risk for the event are required in that stratum. While this number of subjects enrolled in the low-risk stratum will provide very high power (99% with alpha=0.01) to validate the enrichment algorithm with the assumed 5-year conversion rates (ie, 15% vs. 4%).

13.4 Biomarker Qualification

At the end of this study, data from the analyses comparing high and low risk placebo groups will provide the data necessary to qualify the biomarker risk algorithm as a prognostic test and an important new tool for therapeutic decision making. Specifically, the high risk placebo group and low risk placebo group will provide the data needed to estimate the positive predictive value (PPV) and negative predictive value (NPV) of the biomarker risk algorithm. Kaplan Meier curves will be generated for TOMM40 rs10524523 and APOE genotypes and compared to previous results.

Receiver operating characteristic curves, hazard ratios and positive and negative predictive values will be reported for the performance of the biomarker risk algorithm. Specifically, calculations will be made of the time dependent positive (PPV[t]) and negative predictive values (NPV[t]), where PPV(t) is the proportion of subjects who are predicted to develop MCI due to AD during the 5 years who do develop MCI due to AD in the high risk group, and NPV(t) is the proportion of subjects predicted to be free of MCI due to AD at 5 years who are free of MCI due to AD at 5 years in the low risk group.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the (e)CRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of (e)CRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the medical monitor (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospective approved deviation) from the inclusion or exclusion criteria.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects, project partners) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those United States (US) sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent forms, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject and project partner. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's [e]CRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable law, regulation and guidance, Takeda will, at a minimum register all clinical trials conducted in patients that it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before trial initiation. Takeda contact information, along with investigator's city, state (for US investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of this clinical trial, regardless of outcome, on ClinicalTrials.gov or other publicly accessible websites, as required by applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Study Procedures

	Screen-ing Visit 1	**Base-line Visit 2**	**Random-ization Visit 3**	**Double-Blind Treatment** ***Repeated yearly***				**Unscheduled - CMFV (q) (v)**	**EoS / EW Visit (b) (j)**	**Follow-up Visit (c)**
Study Month:	-4	-1	0 (Day 0)	3 (a)	6	9 (a)	12			EoS/EW+0.5
Visit Window (t):	Max Day -125	Max Day -35		±2 weeks	±2 weeks	±2 weeks	±2 weeks	Within approx. 30 days of trigger		
Screening informed consent or Full study Informed consent (Subject)(r)	X									
Study entry informed consent (Subject)(r)		X								
Informed consent (PGx)			X							
Acknowledgement Form (Project partner)		X								
Incl/Excl Criteria	X	X	X							
Medical history	X									
Demographic Information	X				X(p)		X(p)	X(i,p)	X(p)	
Medication History	X									
Family History					X (l)				X	
Concurrent Conditions		X								
Height		X					X		X	
Body weight		X			X		X		X	
Review of concurrent medications		X	X	X	X	X	X	X	X	X
Dispense study drug			X		X		X			
Collect study drug					X		X		X	
Compliance review				X	X	X	X		X	
Contact IWRS	X	X	X		X		X		X	
Genetics (blood samples)										
TOMM40 rs10524523, APOE (Risk stratification)	X									
Safety/efficacy PGx (DNA and RNA samples) – subject-optional			X(g, n)				X(n)		X(n)	

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

	Screen-ing Visit 1	Base-line Visit 2	Random-ization Visit 3	Double-Blind Treatment *Repeated yearly*				Unscheduled - CMFV (q) (v)	EoS / EW Visit (b) (j)	Follow-up Visit (c)
Study Month:	-4	-1	0 (Day 0)	3 (a)	6	9 (a)	12			EoS/EW+0.5
Visit Window (t):	Max Day -125	Max Day -35		±2 weeks	±2 weeks	±2 weeks	±2 weeks	Within approx. 30 days of trigger		
Safety										
PTEs		X	X							
AEs (including AESIs) (e)			X	X	X	X	X	X	X	X
Physical exam		X					X	X	X	
Vital Signs		X			X		X	X	X	
Neurological exam		X			X		X	X	X	
12-lead Electrocardiogram		X					X		X	
MRI (vMRI sub-study)	(Please refer to Appendix H)									
MRI (ad hoc) (f)								X		
Clinical chemistry, hematology and urinalysis labs (m)		X					X	X	X	
PK samples (o)							X	X	X	
C-SSRS			X		X		X		X	X
Diet and Exercise Evaluation (k)		X			X		X		X	
Efficacy										
MMSE	X	X			X		X		X	
Cognitive Test Battery (h)		X			X		X	X(i)	X(i)	

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

	Screen-ing Visit 1	**Base-line Visit 2**	**Random-ization Visit 3**	**Double-Blind Treatment** ***Repeated yearly***				**Unscheduled - CMFV (q) (v)**	**EoS / EW Visit (b) (j)**	**Follow-up Visit (c)**
Study Month:	-4	-1	0 (Day 0)	3 (a)	6	9 (a)	12			EoS/EW+0.5
Visit Window (t):	Max Day -125	Max Day -35		±2 weeks	±2 weeks	±2 weeks	±2 weeks	Within approx. 30 days of trigger		
Efficacy (continued)										
GDS		X			X		X		X(u)	
ADCS-MCFSI		X			X		X		X(u)	
EQ-5D		X						X	X(u)	
SF-36		X						X	X(u)	
IQCODE		X			X		X		X(u)	
ADCS ADL-PI		X			X		X		X(u)	
NPI-Q		X						X	X(u)	
ADCS-RUI		X			X		X	X	X(u)	
CDR		X						X	X(u)	
ADCS-CGIC- MCI		X			X		X	X (u)	X(u)	

Footnotes are on the following page.

Excl=exclusion, Incl=inclusion.
(a) Telephone contact (should be every 3 months between the semi-annual clinic visits for the life of the study).
(b) EoS/EW Visit is an ad hoc visit that, for study completion, would take place as soon as possible after a regularly scheduled Study Visit, either after the CIAC has confirmed that the subject has reached the MCI due to AD primary endpoint event (or any other irreversible cognitive impairment or dementia) or after a subject has withdrawn prematurely from the study. In cases where the endpoint has been reached, the efficacy assessments will not need to be captured at this Visit.
(c) Subjects will have a safety follow-up call 2 weeks after completion or withdrawal. Subjects who withdraw their consent should still be contacted for a safety follow-up call, but the contact should only be recorded in the medical records (and not in the [e]CRF), according to data protection regulations.
(d) footnote deleted
(e) Please refer to Section 10.2.1.3.
(f) As part of the comprehensive medical follow-up evaluation to rule out other causes of dementia and confirm the clinical diagnosis of MCI due to AD (See section 6.2.4). An MRI scan is not required to be performed if a study related MRI scan was collected within 6 months of the CMFV. For subjects who have contraindications for the MRI procedure (such as unremovable ferromagnetic dental work, cardiac pacemakers, etc) a CT scan can be done instead.
(g) DNA sample expected to be collected at this visit, but if necessary, may be collected at any visit after randomization.
(h) Sites should make every attempt complete the cognitive test battery in the order of outlined in Section 9.1.17.
(i) Cognitive Battery is completed at an Unscheduled Visit or EoS/EW Visit if the visit occurs greater than 3 months after the previous regularly scheduled visit.
(j) Subjects who discontinue study medication prematurely should be contacted by the study site every 6 months until the conclusion of the study via telephone to assess the general well being of the subject as well as to obtain any changes in medications related to cognitive health. In the event the subject is not able to be reached, the subject's project partner or primary care physician can be contacted to obtain this information.
(k) female subjects only.
(l) Family history is captured at the first 6 month visit during year 1 of the study.
(m) Please refer to Table 9.a and lab manual for detailed test schedule.
(n) RNA sample to be collected at Day 0, Month 12 of Year 1, Year 2, Year 3, Year 4 and EoS.
(o) Greater detail is given below. Note: If subject has been off drug for 3 or more days prior to Unscheduled CMFV, or EoS/EW Visit, the PK samples should not be collected.
(p) A subject's age will be collected at these post-Baseline study Visits only in countries that do not allow collection of a subject's date of birth.
(q) Procedures for Unscheduled visits for CMFV includes the assessments marked, and should only be conducted after appropriate criteria are met as described in Section 6.2.4. Unscheduled visits for other concerns, including safety, the investigator is expected to conduct whatever assessments are necessary.
(r) If sites prefer to split the ICF process at Visit 1 and Visit 2 into a screening informed consent and study entry informed consent and have IEC/RIB approval to do so, this is permitted.
(s) ADCS-RUI should be administered every 6 months.
(t) Visit Window also applies to Project Partner assessments.
(u) These assessments only need to be administered at the applicable visit if it occurs greater than 3 months from the last administration of the particular assessment.
(v) At the Investigator's discretion, CMFV assessments may be conducted at the routine Month 6 or Month 12 Visit in situations where the CMFV conducted as an outcome of the previous scheduled office visit resulted in an MCI due to AD diagnosis. Refer to Section 6.2.4 for further detail.

Schedule for Pharmacokinetic Sample Collection

Group	Dosing Time (approximate)	Sample Collection(a)			
			Sample Collection Time Post-Dose		
		Pre-Dose	1-1.5 hr	Start of visit	End of visit
1(b)	8:00 AM	X	X		
2 (c)	8:00 AM			X	X
3 (d)	8:00 AM			X	X
4 (e)	8:00 AM			X	X

(a) Samples will be collected at each yearly visit, starting with the 12 month visit for all subjects who consent to have PK samples collected (approximately 30% within each region), Unscheduled Visit, and EoS/EW Visit.
(b) Subjects will arrive at the clinic prior to study drug administration.
(c) Subjects will arrive between 9 am and noon, one PK sample will be taken at the beginning of the visit and one at the end of the visit.
(d) Subjects will arrive between noon and 3 PM, one PK sample will be taken at the beginning of the visit and one at the end of the visit.
(e) Subjects will arrive after 3 PM, one PK sample will be taken at the beginning of the visit and one at the end of the visit.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (non routine/non standard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including (e)CRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.

19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that

the restricted use or disclosure of such information may impact the scientific integrity of the research; and

e) that the subject's identity will remain confidential in the event that study results are published.

25. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix E Collection, Shipment, and Storage of Pharmacogenomic Samples (Separate from the risk stratification sample)

CCI [redacted]

For instructions on shipping, both ambient and refrigerated, and packing follow the laboratory manual and shipping instructions provided by the central laboratory.

Before shipping, ensure the sample tubes are tightly sealed. Ship samples to CCI [redacted]. Shipping information can be found in the pharmacogenomic lab manual.

Sample Storage

CCI [redacted] will store the DNA and RNA samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on AD-4833/TOMM40 continues for up to but not longer than 15 years or as required by applicable law.

The storage provider has validated procedures in place for transport, delivery, retention, retrieval, and destruction of the specimens, and will appropriately retain the specimens.

Appendix F Collection, Storage, and Shipment of Bioanalytical Samples

Instructions for Processing of Plasma Samples for Pharmacokinetic Analysis of Pioglitazone

CCI

[redacted]

Shipping of Plasma Samples

The following instructions are recommended unless they differ from the site's Standard Operation Procedures (SOPs) for labeling, packaging, or shipping of pharmacokinetic samples.

1. Biological samples (ie, plasma or urine) should be shipped on dry ice to prevent thawing during transit. Samples should be shipped only on Monday, Tuesday, or Wednesday, and at least 2 days prior to a national holiday, in order to minimize the possibility of samples in transit over a weekend or holiday. If duplicate samples are to be shipped, send SET 1 samples and await confirmation of arrival before shipping the duplicate SET 2 samples.
2. Before shipping, make sure the sample tubes are tightly sealed. Separate each subject's samples as follows:
3. Separate the duplicate SET 2 samples from the SET 1 samples.
   a) Place SET 1 samples for each subject into self-sealing bag (eg, Ziploc) containing additional absorbent material.

b) Using a permanent marker, write the 4-digit randomization sequence number, sample matrix (ie, plasma), number of samples, and "SET 1" on each self-sealing bag.

c) Place the bags of individual subject's samples into a larger plastic bag so that samples are double bagged. Duplicate SET 2 samples should be returned to the freezer for storage. Repeat steps 3 through 6 above when preparing duplicate samples for shipment, except self-sealing bags should be marked "SET 2."

4. An inventory of individual samples should accompany each shipment and should include the Sponsor's name (Takeda), study medication (pioglitazone), protocol number (AD-4833/TOMM40_301), investigator's name, sample type (ie, plasma), subject randomization sequence number, collection day and time, and intended sample storage conditions. When duplicate SET 2 samples are being shipped, make a copy of the original SET 1 sample inventory and mark as "SET 2." Place the inventory paperwork into a large self-sealing bag. SET 1 samples will be shipped first on dry ice, followed by shipment of duplicate SET 2 samples after SET 1 samples have been received by the analytical laboratory.
5. For sample packing, utilize dry ice generously (eg, 20-25 pounds per day of transit) to safeguard against longer than expected shipping times and delays. Use newspaper or other material to insulate the double-bagged samples from direct contact with the dry ice. Place the sample bundles into a styrofoam container (or other suitable container) and fill the excess space with dry ice slabs or ice pellets (preferably the latter). Make a note of the estimated weight of the dry ice used per shipping container.
6. Place the inventory paperwork (in a large self-sealing bag) on top of the dry ice in the styrofoam container. Place the lid on the styrofoam container and seal completely with strapping tape. Place the styrofoam container in a cardboard shipping carton and seal securely with strapping tape.
7. Mark the outside of shipping carton(s) with a tally number (eg, 1 of 5, 2 of 5).
8. Affix an address label to each shipping carton. Complete the address label as per the instructions in the laboratory manual.
9. Affix a carbon dioxide label on each carton, specifically:

   Carbon Dioxide Solid UN-1845
   Class 9 PKG GR III
   Quantity _____
   (fill in weight to nearest lb/kg and specify unit of measure used)
10. Affix 2 dry ice symbol labels on opposite sides of the carton. Mark KEEP FROZEN on each carton. Specify a return address and contact person on the carton.
11. Obtain the airway bill number and a receipt of shipment from the carrier.

Appendix G Corrections to the MMSE based on Education and Age

At the Screening Visit, the MMSE should be adjusted at the site by the following:

- Low Education Strata: +1

Country	Low Education (in years)
Australia	0-9
Germany	0-11
Switzerland	0-11
U.K.	0-10
U.S.	0-11

- Old Age (76-83): +1

Appendix H A Sub Study To Evaluate the Effects of Pioglitazone on Whole and Regional Brain Volume over Time

Study Title

Assessment of pioglitazone effects on whole and regional brain volume in a sub-population of cognitively normal elderly subjects enrolled in a double blind, randomized, placebo controlled, parallel group study to simultaneously qualify a biomarker algorithm for prognosis of risk of developing mild cognitive impairment due to Alzheimer's disease (MCI due to AD) and to test the safety and efficacy of pioglitazone (AD-4833 SR 0.8 mg QD) to delay the onset of MCI due to AD in cognitively normal subjects.

Study Design

In addition to their participation in the main phase 3 study, approximately 300 cognitively normal elderly subjects will participate in a sub study at selected sites. Subjects will sign a separate informed consent form (ICF) in order to participate in this sub-study. Subjects who fulfill all inclusion criterion and none of the exclusion criteria for the sub-study will be selected in a double-blind fashion to represent a 5:4 randomization ratio between pioglitazone and placebo assignment. Subjects in this sub-study will be scanned to assess brain volume (vMRI). Serial brain MRI scans will be performed at baseline, 2 years, and EoS/EW (3 timepoints in total). If an MRI scan has been performed for the main study or the sub study within 6 months of a required timepoint, a separate MRI scan does not need to be performed.

Schedule of Additional Study Procedures for the Sub-Study

	Screening Visit 1	Baseline Visit 2	Randomization Visit 3	Double-Blind Treatment	EoS/EW Visit
Study Month:	-4	-1	0 (Day 0)	24	
Visit Window:	Max Day -125	Max Day -35		±2 weeks	
Informed consent (a)	X	X			
Incl/Excl Criteria	X	X	X		
vMRI scan (Brain Volume)		X		X (b)	X (b)

(a) All subjects should sign a separate informed consent to participate in the sub-study at either visit 1 or visit 2, must occur prior to any sub-study procedures taking place.
(b) This assessment only needs to be administered at this visit if it occurs greater than 6 months from the last administration for either the main study or the sub study.

Duration of Treatment

The total duration of the vMRI sub study will be the same duration as the main study.

Primary Objective

1. To evaluate changes in brain volume in subjects receiving pioglitazone versus subjects receiving placebo.

Primary Endpoint

1. Changes from baseline in vMRI in whole brain and specific brain regions of interest at 2 years and EoS/EW (in subjects enrolled in the sub study).

Inclusion / Exclusion Criterion

All inclusion/exclusion criteria specified in the main study will also apply to the sub-study. An additional exclusion criterion to the main study for the sub study is as follows:

1. Subject has a contraindication to having MRI, for example because of ferromagnetic foreign bodies (eg, unremovable ferromagnetic dental work), medical devices such as aneurysm clips or cardiac pacemakers, or lead-based tattoos.

Sample Size

This substudy is not designed or powered to assess any quantitative changes in the brain. Based on clinical judgment, a sample size of 300 subjects is believed to be sufficient to evaluate possible qualitative changes in the brain via vMRI.

IVRS/IWRS will be utilized to randomize subjects into this sub study in order to provide balance between high risk placebo and high risk pioglitazone.

MRI protocol minimum standards

All MRI scans will be reviewed centrally at a designated imaging lab. All MRI scans will also be reviewed at the local labs for safety.

Brain volumetric measurements will be done using T1-weighted MRI. Specific MRI parameters to be used in this study along with further instructions about the imaging will be detailed in the imaging procedure manual.

Appendix I Operationalized Criteria for AD Dementia

The endpoint of AD dementia requires that the criteria for dementia are fulfilled.

Dementia:

A. Cognitive problems observed interfere with the individual's ability to function at work or at usual activities; and

B. This functional change represents a decline from previous levels of functioning and performing as captured in this trial by clinician impression of change since baseline or by clear impairments on scales of daily functional ability (e.g. ADCS ADL-PI/-MCI; Clinical Dementia Rating Scale with informant; CGIC; IQCODE),

C. The disorder is not explained by delirium or major psychiatric disorder;

D. Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment, either a "bedside" mental status examination (e.g. MMSE) or neuropsychological testing

E. The cognitive or behavioral impairment involves a minimum of two of the following domains, established by the testing battery or from interval history and clinical interview:

   i. Memory: CVLT-II; BVMT-R
      a. Defined as an impaired ability to acquire and retain new information. Clinical symptoms could include repetitive questions, getting lost in familiar areas, forgetting appointments or important events, misplacing personal objects.
   ii. Executive/ Reasoning: TMT; Digit Span
      a. Defined as impaired reasoning and ability to handle complex tasks. Can be manifest as poor judgment, poor understanding of safety risks; impaired money management; poor decision making; trouble in planning or executing sequential activities.
   iii. Visuospatial: Copy of BVMT figures; CDT
      a. Defined as problems in visuoperceptual analysis. Could be manifest by difficulty in recognition of faces, objects despite good acuity. Trouble with operating simple implements (e.g. tools or utensils), or trouble with spatial awareness, dressing etc.
   iv. Language: Verbal fluency (FAS test), animal fluency, MiNT naming

a. Defined as newly acquired problems with either speaking, reading or writing. Symptoms may include word search, speech hesitation, speech errors, writing and spelling difficulty.

v. Personality or comportment: informant interview and NPI

a. Defined as changes in personality, behavior or comportment. Symptoms may include mood fluctuations, agitation, impaired motivation, apathy, loss of empathy, social withdrawal, compulsive or obsessive behaviors, social inappropriateness.

The differentiation between dementia and MCI rests on the determination of whether or not there is significant interference in the ability to function at work or in usual daily activities. This is a clinical judgment which relies on a skilled clinician assessing current function based on knowledge of the individual participant's circumstance and information from a knowledgeable informant.

The endpoint of AD dementia will be specified if the participant (after fulfilling dementia criteria above) fulfills criteria for possible or probable AD dementia. Possible or probable AD dementia, are defined by the NIA-AA criteria [McKhann et al., 2011] and operationalized in this study as follows:

Probable AD:

1. Meets criteria A through E for dementia as noted above AND the following characteristics (2-6):
2. Insidious onset (over months or years, not sudden over hours or days)
3. Clear worsening of cognition across visits – by report or by documented worsening upon repeated cognitive test scores or MMSE
4. Initial and most prominent impairment[1] is documented on one of the following domains:
    a. Amnestic: Impaired new learning & memory, as evidenced in the clinician examination, history, or by impairment on at least one of the following subtests:
        i. BVMT-R Delayed recall
        ii. CVLT-II, short-delay, free recall
        iii. CVLT-II, long-delay, free recall
    b. Non-amnestic: Impairment on performance on at least one test of visuospatial ability, language, or executive function: TMT A, TMT B, Digit Span Total, MiNT, Semantic fluency, Lexical fluency, or CDT; or based on observation, or clinical history.

5. Evidence of cognitive dysfunction in at least one other domain noted in criteria #4
6. Absence of clinical history or laboratory tests that suggest another condition can explain the cognitive decline in its entirety.

Possible AD:

1. Meets criteria for dementia, as defined above and criteria a and b are met:
    a. Initial and most prominent impairment is documented on one of the following domains: Amnestic or Non-amnestic, as defined for Probable AD *and*
    b. Evidence of cognitive dysfunction in one other domain from Amnestic or Non-amnestic domains, as defined for Probable AD.

HOWEVER, possible AD is distinguished from probable AD by either of the following 2 characteristics:

1) Etiology is mixed or complex: presence of medical condition, a neurological disease, or medication use that can partially explain the deficits, *or*
2) Atypical course as determined by the investigator (e.g. sudden onset; pronounced aphasia etc), or insufficient historical detail or objective cognitive documentation of progressive decline.

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[1]Impairment is guided by quantitative or qualitative aspects of an individual's function, defined as either: 1) scores falling at least 1.5sd below demographically adjusted normative mean, OR 2) based on the clinical judgment of the site Neuropsychologist / Investigator that significant cognitive impairment has occurred and represents a significant overall change from the individual's established premorbid level of function as measured at baseline of 301.

Appendix J Detailed Description of Amendments to Text

This document describes changes in reference to Protocol Incorporating Amendment No. 5.

Page 3, Section 1.1, Contacts

Existing Text

Issue	North America Contact	European Contact	Australia Contact
Serious adverse event and pregnancy reporting	PPD		
Medical Monitor (medical advice on protocol, compound, and medical management of subjects)			
Responsible Medical Officer (carries overall responsibility for the conduct of the study)			

Revised Text

Issue	North America Contact	European Contact	Australia Contact
Serious adverse event and pregnancy reporting	PPD		
Medical Monitor (medical advice on protocol, compound, an medical management o subjects)			
Responsible Medical Officer (carries overall responsibility for the conduct of the study)			

Rationale for Amendment

Study contacts have been updated in accordance with personnel changes.

Page 4, Section 1.2, Approval

Existing Text

SIGNATURES

PPD

Revised text

SIGNATURES

PPD

Rationale for Amendment

Protocol signatories updated in accordance with personnel changes.

Page 34, Section 5.2.3.2, Additional Endpoints

Existing Text

- Changes from baseline in vMRI in whole brain and specific brain regions of interest at 2 years, and *4 years or study termination*.

Revised Text

- Changes from baseline in **volumetric magnetic resonance imaging (**vMRI**)** in whole brain and specific brain regions of interest at 2 years and **End of Study (EoS)/Early Withdrawal (EW)**.

Rational for Amendment

This endpoint has been updated to correctly reflect the planned timepoints for analysis.

Page 36-37, Section 6.1, Study Design

Existing Text

A project partner will be required to participate with the subject in the study visits, including eligibility at Baseline (Visit 2) and follow-up. The project partner is a spouse, adult child, or other person familiar with the participant's health and daily functioning for a minimum of two years prior to the Baseline Visit. Subjects and their project partners are expected to attend study visits every 6 months after randomization, for assessments of safety, efficacy, and treatment compliance. In addition, the subject will be contacted for telephone-based safety checks between visits. In-person participation of the project partner is *mandatory* at Baseline (Visit 2), *c*omprehensive *m*edical *f*ollow-up, and *End-of-Study* Visits; while in-person participation is also strongly encouraged at all other study visits, telephone assessments for project partners will be acceptable in cases when in-person participation is not possible. If a comprehensive medical follow-up evaluation is needed (see Section 9.1.15) or if a safety issue is suspected, further evaluation of the subject may be required, which may include an unscheduled clinic visit. The project partner should attend unscheduled visits, whenever possible. If the original project partner is not able to continue participation in the study for any reason, he/she may be replaced by a different individual who also meets the criteria described above. The new project partner must sign the acknowledgement form prior to any of the project partner protocol directed procedures being performed.

Revised Text

A project partner will be required to participate with the subject in the study visits, including eligibility at Baseline (Visit 2) and follow-up. The project partner is a spouse, adult child, or other person familiar with the participant's health and daily functioning for a minimum of two years prior to the Baseline Visit. Subjects and their project partners are expected to attend study visits every 6 months after randomization, for assessments of safety, efficacy, and treatment compliance. In addition, the subject will be contacted for telephone-based safety checks between

visits. In-person participation of the project partner is **required** at Baseline (Visit 2), **C**omprehensive **M**edical **F**ollow-up **Visits (CMFV)**, and **EoS** Visits. **In exceptional cases and with prior approval of the Sponsor, when in-person participation of the project partner is not possible for a CMFV or the EoS/EW Visit, assessments may be performed during Home Visits or by telephone (see Section 6.2.4).** While in-person participation is also strongly encouraged at all other study visits, telephone assessments for project partners will be acceptable in cases when in-person participation is not possible. If a comprehensive medical follow-up evaluation is needed (see Section 9.1.15) or if a safety issue is suspected, further evaluation of the subject may be required, which may include an unscheduled clinic visit. The project partner should attend unscheduled visits, whenever possible. If the original project partner is not able to continue participation in the study for any reason, he/she may be replaced by a different individual who also meets the criteria described above. The new project partner must sign the acknowledgement form prior to any of the project partner protocol directed procedures being performed.

Rationale for Amendment

Revisions have been made to this section in accordance with changes made in section 6.2.4 of the Protocol to provide greater flexibility to sites in scheduling and conducting CMFVs and EoS/EW Visits, in order to ensure that critical data can be collected in circumstances when on-site attendance of the project partner is not possible.

Page 42, Section 6.2.4, Assessments after Randomization, Figure 6.b, Subject Flow Chart

Existing Text

Legend

…

F: *Comprehensive Medical Follow up Visit (*CMFV*)*. *A* CMFV *should not* be conducted on the same day as a regularly scheduled in-clinic visit (ie, Month 6 or Month 12 of any year).

Revised Text

Legend

…

F: CMFV. **At the discretion of the investigator, the** CMFV **may** be conducted on the same day as a regularly scheduled in-clinic visit (ie, Month 6 or Month 12 of any year) **in situations when the CMFV conducted as an outcome of the previous scheduled office visit resulted in a MCI due to AD diagnosis and therefore the next scheduled visit will automatically result in the requirement to perform a CMFV, irrespective of a CMFV trigger being met**.

Rationale for Amendment

This change gives sites the ability to help ease subject burden by preventing the need for an additional visit in situations where it is known in advance that a CMFV will be required following a routine visit.

Page 43-44, Section 6.2.4, Assessments after Randomization

Existing Text

Additional comprehensive medical follow-up assessments will be carried out for any subject who has any of the outcomes above; these assessments will require an Unscheduled Visit, which should take place within *one month* of the routine study Visit when one of these triggers was met. A *comprehensive medical follow-up visit (*CMFV*)* should not be conducted on the same day as a regularly scheduled in-clinic visit (ie, Month 6 or Month 12 of any year).

A comprehensive medical follow-up evaluation (which the subject's project partner *must* attend), triggered by any of the above, will include:

c) Neurological examination (includes information from project partner).

4. CDR assessment.

5. NPI-Q completed by the project partner.

6. Standard blood chemistry and tests used in evaluating cognitively impaired and dementia subjects (eg, thyroid profile, Vitamin B12).

7. Cognitive Test Battery (only if beyond 3 months from last study visit; otherwise the neuropsychological outcome battery from the last visit would be used in the evaluation).

8. Magnetic resonance imaging (MRI) will be required at a subject's second consecutive comprehensive medical evaluation when other evaluation results corroborate a diagnosis of MCI due to AD. This requirement does not preclude the conduct of an MRI on a for-cause basis or to support a potential diagnosis other than MCI due to AD, after discussion with the medical monitor. For subjects who have contraindications for MRI procedure (such as unremovable ferromagnetic dental work, cardiac pacemakers, etc) a computerized axial tomography (CT) scan may be performed instead.

After the comprehensive medical follow-up evaluation, the Investigator will consider the totality of information collected for the subject and make a clinical assessment which will determine subject flow within the study. The timing of sending a subject's data to the adjudication committee after a first (of any potential two consecutive) *comprehensive medical follow-up Visits* will depend on the Investigator's clinical assessment.

- If an Investigator's clinical assessment is that the subject is cognitively normal (ie, the comprehensive medical follow-up test results did not support the original trigger concern) or that the subject has a reversible cognitive impairment (eg, depression, hypothyroidism,

vitamin B12 deficiency), the subject will continue with routine study Visits, and the subject's data **will not be** forwarded to the adjudication committee at this time.

- *Since an outcome of MCI due to AD will require two consecutive diagnoses by the investigator,* if an Investigator's clinical assessment is that the subject meets criteria for an MCI due to AD diagnosis for the first time, the subject will also continue with routine study Visits, and the subject's data **will not be** forwarded to the adjudication committee at this time.
- If an Investigator's clinical assessment is dementia of any type or an irreversible cognitive impairment not associated with AD, the subject's data **will be** forwarded to the adjudication committee immediately.

Revised Text

Additional comprehensive medical follow-up assessments will be carried out for any subject who has any of the outcomes above; these assessments will require an Unscheduled Visit, which should take place within **approximately 30 days** of the routine study Visit when one of these triggers was met. A CMFV should not be conducted on the same day as a regularly scheduled in-clinic visit (ie, Month 6 or Month 12 of any year)**, except in situations where the CMFV conducted as an outcome of the previous scheduled office visit resulted in an MCI due to AD diagnosis and therefore the next scheduled visit will automatically result in the requirement to perform a CMFV, irrespective of a CMFV trigger being met. In these cases, at the Investigator's discretion, the CMFV assessments may be collected at the routine Month 6 or Month 12 Visit**. **Any assessments that are scheduled to be performed at both the routine visit and the CMFV do not need to be performed twice when combining visits in this way.**

A comprehensive medical follow-up evaluation (which the subject's project partner **should make every effort to** attend**, if possible**), triggered by any of the above, **at minimum** will include **the following assessments (refer to Appendix A for a full list of assessments required to be performed at a CMFV)**:

- Neurological examination (includes information from project partner).
- CDR assessment.
- NPI-Q completed by the project partner.
- Standard blood chemistry and tests used in evaluating cognitively impaired and dementia subjects (eg, thyroid profile, Vitamin B12).
- Cognitive Test Battery (only if beyond 3 months from last study visit; otherwise the neuropsychological outcome battery from the last visit would be used in the evaluation).
- Magnetic resonance imaging (MRI) will be required at a subject's second consecutive comprehensive medical evaluation when other evaluation results corroborate a diagnosis of

MCI due to AD **in the opinion of the investigator. (Note that this does not need to be the second consecutive investigator diagnosis of MCI due to AD, only the second consecutive CFMV.)** This requirement does not preclude the conduct of an MRI on a for-cause basis or to support a potential diagnosis other than MCI due to AD, after discussion with the medical monitor. **If an MRI scan has been performed for the study within 6 months of the CMFV, an additional MRI scan will not be required and the existing scan may be used.** For subjects who have contraindications for MRI procedure (such as unremovable ferromagnetic dental work, cardiac pacemakers, etc) a computerized axial tomography (CT) scan may be performed instead.

If a site determines that a subject and/or project partner are unable to return to the clinic for the CMFV within approximately 30 days of the routine study visit, or for the EoS/EW Visit, the following options will be permitted in order to collect the required assessments within that timeframe:

- **Home Visit: with prior approval from Sponsor on a case-by-case basis, qualified site personnel may arrange a visit to the subject or project partner's home in order to perform CMFV or EoS/EW assessments. If necessary (ie, confirmatory rule-out for MCI diagnosis at second of two consecutive CMFVs), the MRI scan will be performed on the subject in-clinic at the earliest opportunity.**
- **Assessment via telephone: If the project partner is not able to return to the site for the CMFV or the EoS/EW Visit, the site may, with prior approval of the Sponsor on a case-by-case basis, conduct the required assessments with the project partner via telephone call. The assessments must be carried out by appropriately qualified personnel in advance of the subject assessments and within a maximum of one day of the subject's visit. Visit assessments of the subject will still be required in clinic.**

After the comprehensive medical follow-up evaluation, the Investigator will consider the totality of information collected for the subject and make a clinical assessment which will determine subject flow within the study. The timing of sending a subject's data to the adjudication committee after a first (of any potential two consecutive) **CMFVs** will depend on the Investigator's clinical assessment.

- If an Investigator's clinical assessment is that the subject is cognitively normal (ie, the comprehensive medical follow-up test results did not support the original trigger concern) or that the subject has a reversible cognitive impairment (eg, depression, hypothyroidism, vitamin B12 deficiency), the subject will continue with routine study visits, and the subject's data **will not be** forwarded to the adjudication committee at this time.
- If an Investigator's clinical assessment is that the subject meets criteria for an MCI due to AD diagnosis for the first time, the subject will also continue with routine study visits, and the subject's data **will not be** forwarded to the adjudication committee at this time.

- If an Investigator's clinical assessment is dementia of any type or an irreversible cognitive impairment not associated with AD, the subject's data **will be** forwarded to the adjudication committee immediately.

Rationale for Amendment

The timing of CMFVs has been softened from a hard window of 30 days to "approximately 30 days" in recognition of the fact that it is sometimes challenging for sites and subjects to return to the site for the CMFV within this timeframe. The language has been revised to be consistent with other studies on the AD-4833/TOMM40 program.

The ability to combine the CMFV with the routine Month 6 or Month 12 visit in cases where it is known in advance that a CMFV must be performed has been introduced to help ease subject burden and prevent the need for an additional visit where possible.

Providing sites with the ability to perform selected assessments at a subject's home or by telephone in exceptional circumstances has been included to help mitigate the risk of not collecting critical study data due to the challenges associated with conducting the study in an elderly population where subjects approaching endpoint are repeatedly triggering, requiring multiple additional visits that increases subject burden and may result in withdrawal due to study fatigue.

Clarity has been provided to the assessments conducted during CMFVs. The required timing of MRI scans performed at CMFVs has been clarified and the requirement to perform multiple MRI scans within a short period of time, which adds to subject burden, has been removed.

Erroneous text stating that two consecutive diagnoses by the investigator are required to reach an outcome of MCI due to AD has been removed. Two consecutive diagnoses of MCI due to AD by the CIAC are required for the subject to meet endpoint and it is possible that these diagnoses differ from the investigator's.

Page 56, Section 7.5, Procedures for Discontinuation or Withdrawal of a Subject

Existing Text

Subjects who discontinue study medication prematurely should be contacted by the study site every 6 months until the conclusion of the study via telephone to assess the general well-being of the subject as well as to obtain any changes in medications. In the event the subject is not able to be reached, the subject's caregiver or primary care physician can be contacted to obtain this information.

Revised Text

Subjects who discontinue study medication prematurely should be contacted by the study site every 6 months until the conclusion of the study via telephone to assess the general well-being of the subject as well as to obtain any changes in medications **related to cognitive health**. In the

event the subject is not able to be reached, the subject's caregiver or primary care physician can be contacted to obtain this information.

Rationale for Amendment

This revision more accurately describes the limited information that will be collected during 6 monthly telephone follow-up calls for subjects who have discontinued study drug

Page 66, Section 9.1.8, Procedures for Clinical Laboratory Samples

Existing Text

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis *(c)*
Red blood cells White blood cells count with differentials (Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes) Hemoglobin Hematocrit Platelets HbA1c (b)	Alanine aminotransferase Alkaline phosphatase Aspartate aminotransferase Total bilirubin Direct bilirubin (a) γ-Glutamyl transferase Total protein Albumin Creatinine Blood urea nitrogen Potassium Sodium Glucose Calcium, PTH TSH, free T4 Vitamin B12, folate (*d*) Rapid plasma reagin (RPR) (*d*)	pH Specific gravity Protein Glucose Blood Nitrite
Blood		
Hepatitis panel, including HBsAg and anti-HCV (b)		

(a) Assess only if total bilirubin ≥2.0 mg/dL.
(b) To be done at Baseline only.
(c) *Microscopic examination (leucocytes, erythrocytes and casts) should be performed only if any of the urine evaluations are abnormal.*
(d) At Baseline and as part of the comprehensive medical follow-up evaluation to rule out other causes of dementia.

Revised Text

Table 9.a Clinical Laboratory Tests

Hematology	**Serum Chemistry**	**Urinalysis**
Red blood cells White blood cells count with differentials (Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes) Hemoglobin Hematocrit Platelets HbA1c (b)	Alanine aminotransferase Alkaline phosphatase Aspartate aminotransferase Total bilirubin Direct bilirubin (a) γ-Glutamyl transferase Total protein Albumin Creatinine Blood urea nitrogen Potassium Sodium Glucose Calcium, **parathyroid hormone (**PTH**)** **Thyroid-stimulating hormone (**TSH**)**, free **thyroxine (**T4**)** Vitamin B12, folate (**c**)** Rapid plasma reagin (RPR) (**c**)	pH Specific gravity Protein Glucose Blood Nitrite **Microscopic examination (Leucocytes, Erythrocytes, Casts)**
Blood		
Hepatitis panel, including HBsAg and anti-HCV (b)		

(a) Assess only if total bilirubin ≥2.0 mg/dL.
(b) To be done at Baseline only.
(c) At Baseline and as part of the comprehensive medical follow-up evaluation to rule out other causes of dementia.

Rationale for Amendment

Microscopic examinations will be performed on all samples at the initial assessment, rather than in response to findings on macroscopic examinations, in order to reduce burden to the subject by preventing the need for them to return to the site to provide another urine sample.

Page 75, Section 9.1.15.2, Efficacy Assessments

Existing Text

Project Partner-Reported Questionnaires

- Neuropsychiatric Inventory Questionnaire (NPI-Q) [62]: The NPI-Q is a brief validated version of the standard NPI [63]. It is designed to assess NPS common in AD and related dementias. The NPI-Q is designed to be a self-administered and queries the presence of symptoms in each of 12 specific domains and is queried over the past 30 days: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, disturbances of sleep, and disturbances of appetite/eating. The scale is constructed such that a screening

question is asked for each symptom domain. If this item is endorsed, then specific follow up questions are asked to clarify the nature of the symptoms, their frequency, severity, degree of change from premorbid, and treatment. The NPS outcome variable is defined as either the presence or absence of a given NPS domain. The NPI can also be analyzed by dividing into absence of any NPS versus >1 NPS (NPI Total). NPI severity can also be calculated. The physician reviews the form and clarifies the nature and the presence of symptoms endorsed. This questionnaire will be completed at Visit 2 (Baseline), Unscheduled Visit, and *End of Study Visit*/*Early Withdrawal* Visit.

Revised Text

Project Partner-Reported Questionnaires

- Neuropsychiatric Inventory Questionnaire (NPI-Q) [62]: The NPI-Q is a brief validated version of the standard NPI [63]. It is designed to assess NPS common in AD and related dementias. The NPI-Q is designed to be a self-administered and queries the presence of symptoms in each of 12 specific domains and is queried over the past 30 days: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, disturbances of sleep, and disturbances of appetite/eating. **In special cases when Sponsor permission is given for the project partners to have the CMFV or EoS/EW Visit conducted by telephone, the questionnaire will no longer be self administered but will be conducted aurally over the telephone, more in keeping with the standard NPI, which was designed to be clinician administered with a query question (the items on the NPI-Q) followed by more detailed interviewing.** The scale is constructed such that a screening question is asked for each symptom domain. If this item is endorsed, then specific follow up questions are asked to clarify the nature of the symptoms, their frequency, severity, degree of change from premorbid, and treatment. The NPS outcome variable is defined as either the presence or absence of a given NPS domain. The NPI can also be analyzed by dividing into absence of any NPS versus >1 NPS (NPI Total). NPI severity can also be calculated. The physician reviews the form and clarifies the nature and the presence of symptoms endorsed. This questionnaire will be completed at Visit 2 (Baseline), Unscheduled Visit, and **EoS/EW** Visit.

Rationale for Amendment

This revision explains how completion of the NPI-Q will differ in exceptional cases where the site is performing the CMFV or EoS/EW Visit assessments for the project partner via telephone.

Page 80, Section 9.2, Monitoring Treatment Compliance

Existing Text

Subjects will be required to bring study medication containers to each dispensing site visit. The number of pills returned will be captured in the subject's source documentation and (e)CRF. The project partner will also be asked to assess the subject's compliance.

All subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

Revised Text

Subjects will be required to bring study medication containers to each dispensing site visit. The number of pills returned will be captured in the subject's source documentation and (e)CRF. The project partner will also be asked to assess the subject's compliance.

Subjects will be considered to be non-compliant with study medication if they miss >20% of doses required for the visit period, or take more than 100% of the doses for the required visit period. Non-compliance with study medication must be reported in the (e)CRF and subjects should be reminded of the importance of being compliant with dosing instructions. Any detected overdose must be reported on an Overdose page of the (e)CRF.

All subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

Rationale for Amendment

Formal limits on study drug treatment compliance have been added to ensure that all Investigators are consistently identifying and reporting cases of non-compliance with study medication.

Page 82, Section 9.3.5.2, Comprehensive Medical Follow-Up

Existing Text

A Comprehensive Medical Follow-Up evaluation (which the subject's project partner *must* attend), should be conducted within *one month* of the trigger when one of the triggers described in Section 6.2.4 has been met. This type of Unscheduled Visit will include the assessments noted in Appendix A and Section 6.2.4. It is anticipated this visit will be about 5 to 6 hours in length, if an MRI is completed during the visit.

Revised Text

A Comprehensive Medical Follow-Up evaluation (which the subject's project partner **should make every effort to** attend**, if possible, or otherwise complete during a Home Visit or via telephone if appropriate**), should be conducted within approximately 30 days of the trigger when one of the triggers described in Section 6.2.4 has been met. This type of Unscheduled Visit will include the assessments noted in Appendix A and Section 6.2.4. **If appropriate, the CMFV assessments may be performed during the routine visit if the specific criteria specified in Section 6.2.4 are met.** It is anticipated this visit will be about 5 to 6 hours in length, if an MRI is completed during the visit.

Rationale for Amendment

Additional options for performing CMFVs, as presented in Section 6.2.4, have been introduced in order to provide sites and subjects with flexibility in scheduling these visits to ensure that the procedures and assessments that are required are collected.

Page 82, Section 9.3.6, Final Visit or Early Termination

Existing Text

The Final visit will be performed once the total number of endpoints are reached, which is expected to occur four years after enrollment ends, or at the *Early Termination* Visit. See Appendix A for a list of procedures that will be performed and documented.

For all subjects receiving study medication, the investigator must complete the *End of Study* (e)CRF page.

Revised Text

The Final visit will be performed once the total number of endpoints are reached, which is expected to occur four years after enrollment ends, or at the **EoS/EW** Visit **for subjects who complete the study or withdraw before the total number of endpoints are reached**. See Appendix A for a list of procedures that will be performed and documented.

For all subjects receiving study medication, the investigator must complete the **EoS** (e)CRF page.

Rationale for Amendment

This section has been revised to clarify when the Final Visit will occur for all subjects, using nomenclature that is consistent with the rest of the protocol.

Page 90-91, Section 10.2.1.3, AESI Reporting

Existing Text

2. Macular edema: All subjects and their project partners will be asked to promptly report symptoms potentially associated with macular edema (eg, blurred vision, distortion of images, missing areas, dimming or "graying-out" of vision from loss of contrast sensitivity, and changes in the way color is perceived). If symptoms are reported, the subject will be evaluated by an ophthalmologist. Any subject who develops macular edema will stop taking study medication, be withdrawn from the study, and be managed by his or her regular physician using the local standard of care.

2. …

6. Subjects with T2DM who are on a stable antidiabetic regimen for at least 3 months prior to enrollment that does not require the use of insulin, oral triple therapy and/or PPAR-γ agonists will be allowed in the study. Subjects who develop a new onset T2DM during the study will

be referred to an endocrinologist. If the use of prohibited medications (such as insulin or PPAR-γ agonists) is considered necessary, the subject will be withdrawn from the study. Pioglitazone alone especially at a low dose is not likely to cause hypoglycemia in elderly subjects without T2DM. However, subjects with T2DM taking pioglitazone with an insulin secretagogue (eg, sulfonylurea or glitinide) may be at increased risk for developing hypoglycemia. Therefore *the* subjects with the following AEs will be closely monitored using the following event categories [70].

- **Severe hypoglycemia:** an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Blood glucose may not be available.
- **Documented symptomatic hypoglycemia:** typical symptoms of hypoglycemia accompanied by blood glucose ≤70 mg/dL (3.9 mmol/L).
- **Asymptomatic hypoglycemia:** Blood glucose ≤70 mg/dL (3.9 mmol/L), but with no typical symptoms.
- **Probable symptomatic hypoglycemia:** Symptoms of hypoglycemia that are not accompanied by blood glucose determination ≤70 mg/dL (3.9 mmol/L).
- **Relative hypoglycemia:** Symptoms of hypoglycemia, but with a measured blood glucose >70 mg/dL (3.9 mmol/L).

If *a* subject is noted to have a hypoglycemic event, the hypoglycemia eCRF should be completed within 24 hours of the investigator's awareness of the event.

Revised Text

2. Macular edema: All subjects and their project partners will be asked to promptly report symptoms potentially associated with macular edema (eg, blurred vision, distortion of images, missing areas, dimming or "graying-out" of vision from loss of contrast sensitivity, and changes in the way color is perceived). If symptoms are reported, the subject will be evaluated by an ophthalmologist. **Subjects diagnosed with macular degeneration during the study will be followed up by an ophthalmologist and have retinal imaging (eg, Optic Coherence Tomography or Heidelberg Confocal Laser Doppler Imaging) performed at least every six months until study completion or early withdrawal to confirm that the condition is stable.** Any subject who develops macular edema will stop taking study medication, be withdrawn from the study, and be managed by his or her regular physician using the local standard of care.
3. …
6. Subjects with T2DM who are on a stable antidiabetic regimen for at least 3 months prior to enrollment that does not require the use of insulin, oral triple therapy and/or PPAR-γ agonists will be allowed in the study. Subjects who develop a new onset T2DM during the study will be referred to an endocrinologist. If the use of prohibited medications (such as insulin or

PPAR-γ agonists) is considered necessary, the subject will be withdrawn from the study. Pioglitazone alone especially at a low dose is not likely to cause hypoglycemia in elderly subjects without T2DM. However, subjects with T2DM taking pioglitazone with an insulin secretagogue (eg, sulfonylurea or glitinide) may be at increased risk for developing hypoglycemia. Therefore **all** subjects with the following AEs will be closely monitored using the following event categories [70].

- **Severe hypoglycemia:** an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Blood glucose may not be available.
- **Documented symptomatic hypoglycemia:** typical symptoms of hypoglycemia accompanied by blood glucose ≤70 mg/dL (3.9 mmol/L).
- **Asymptomatic hypoglycemia:** Blood glucose ≤70 mg/dL (3.9 mmol/L), but with no typical symptoms.
- **Probable symptomatic hypoglycemia:** Symptoms of hypoglycemia that are not accompanied by blood glucose determination ≤70 mg/dL (3.9 mmol/L).
- **Relative hypoglycemia:** Symptoms of hypoglycemia, but with a measured blood glucose >70 mg/dL (3.9 mmol/L).

If **any** subject is noted to have a hypoglycemic event, the hypoglycemia **(**e**)**CRF should be completed within 24 hours of the investigator's awareness of the event.

Rationale for Amendment

Revisions have been made to clarify that specific, ongoing follow-up is required for subjects diagnosed with macular degeneration during the study to ensure that there is no impact on their performance of the cognitive test battery due to worsening eyesight.

Clarification also provided that hypoglycemic events must be reported as per the AESI guidance for any subjects participating in the study, not just those with T2DM or those taking insulin secretagogues in addition to study medication.

Page 100-101, Section 13.2, Futility Analysis and Criteria for Early Termination

Existing Text

An analysis for futility will be conducted once approximately *50% (101 out of 202)* of the anticipated events (ie, conversions from cognitively normal status to adjudicated diagnosis of MCI due to AD, or to AD dementia) have occurred in the high-risk, Caucasian, non-Hispanic/Latino group. However, since the biomarker risk stratum information is blinded, the time of the futility analysis will be estimated using all subjects (both high-risk and low-risk) in the Caucasian, non-Hispanic/Latino group. *This* will occur when approximately *106* events have been confirmed through adjudication in the Caucasian, non-Hispanic/Latino group (including both high-risk and low-risk subjects). *This analysis will have two parts, performed*

hierarchically: first, an analysis to determine futility based on lack of pioglitazone efficacy, and second, an analysis to determine futility based on the biomarker risk algorithm not having performed as expected to enrich the sample population. The second analysis is only conducted if futility is identified for the primary comparison within the high-risk, Caucasian, non-Hispanic/Latino group. Because a review of unblinded data is involved, the DSMB will oversee this process. Note that no adjustment of the alpha level is required for an analysis for futility, and that for this study the results of the futility analysis will be considered to be non-binding with respect to efficacy for purposes of decision making around study continuation.

Once the total number of target events has been reached, the DSMB will be unblinded for a review of actual treatment groups with respect to the primary efficacy endpoint *only*; this review would take place at the next regularly-scheduled DSMB meeting.

The futility analysis will be conducted by the DSMB Statistician, based on the treatment effect within the high-risk, Caucasian, non-Hispanic/Latino group. The calculation is a test from a Cox proportional hazards survival model to evaluate a difference between the treatment groups (pioglitazone versus placebo) for the high-risk comparison at the time of the interim futility analysis. The DSMB could then recommend study continuation to completion for the targeted number of events or recommend (based on pre-specified criteria documented in the SAP) that the study be considered futile with respect to the primary efficacy endpoint, high-risk comparison. *If futility is indicated for the high-risk primary efficacy endpoint comparison, then a futility analysis will be conducted for the biomarker comparison.*

Immediately after the futility analysis data review meeting takes place, the DSMB recommendation regarding the continuation of the study will be promptly communicated to the DSMB Liaison. If the data indicate that study termination should be considered, the DSMB Liaison will promptly convene an ad-hoc meeting within the Takeda/Zinfandel alliance senior management to further discuss the results of the *analysis with the DSMB* and *to* make the final decision as to whether or not to terminate the study. If the alliance *c*ommittee decides to terminate *or modify* the study as a result of the futility analys*is*, this decision will be promptly communicated to all the stakeholders including the AD-4833/TOMM40 project team, investigators, ethics committees, and regulatory agencies. Details of the stopping rules and analyses will be given in the DSMB Charter and in the SAP.

Revised Text

Tracking of confirmed events of MCI due to AD, as adjudicated by the CIAC, will be done on an ongoing basis, in a blinded fashion. There will be two types of analyses conducted during the study to assess futility: an 'operational futility analysis' and an 'efficacy futility analysis'. The study will be declared to be 'operationally futile' if the accrual of confirmed events is too slow to allow completion of the study in a feasible time frame. The timeframe for assessing operational futility is described in the SAP.

If operational futility is not declared, an analysis for futility **for efficacy** will be conducted once approximately **33% (66 out of 202)** of the anticipated events (ie, conversions from cognitively normal status to adjudicated diagnosis of MCI due to AD, or to AD dementia) have occurred in the high-risk, Caucasian, non-Hispanic/Latino group. However, since the biomarker risk stratum information is blinded, the time of the futility analysis will be estimated using all subjects (both high-risk and low-risk) in the Caucasian, non-Hispanic/Latino group. **Therefore, the efficacy futility analysis** will occur when approximately **69** events have been confirmed through adjudication in the Caucasian, non-Hispanic/Latino group (including both high-risk and low-risk subjects). Note that no adjustment of the alpha level is required for an analysis for futility, and that for this study the results of the futility analysis will be considered to be non-binding with respect to efficacy for purposes of decision making around study continuation.

If operational futility is declared, an early efficacy futility analysis (ie, prior to reaching 33% of anticipated events as described above) will be done as soon as practicable (ie, after all pertinent data for the futility analyses has been cleaned as per the specifications outlined in the Interim Database Lock Plan) and will be provided to the DSMB. This will not replace the planned efficacy futility analysis that will occur following the accrual of 33% of the anticipated events.

Further details of the operational and efficacy futility analyses are given in the SAP.

Because a review of unblinded data is involved, the DSMB will oversee this process. Once the total number of target events has been reached, the DSMB will be unblinded for a review of actual treatment groups with respect to the primary efficacy endpoint **(and potentially other analyses as described in the SAP, as applicable)**; this review would take place at the next regularly-scheduled DSMB meeting **or at an ad hoc DSMB meeting.**

The **primary** futility analysis **for efficacy** will be conducted by the DSMB Statistician, based on the treatment effect within the high-risk, Caucasian, non-Hispanic/Latino group. The calculation is a test from a Cox proportional hazards survival model to evaluate a difference between the treatment groups (pioglitazone versus placebo) for the high-risk comparison at the time of the interim futility analysis. **Additionally, Kaplan-Meier curves by treatment group (including low-risk placebo) will be provided for the primary analysis population of non-Hispanic/Latino Caucasian subjects. If the primary futility analysis indicates futility, then the** CCI **Unblinded DSMB Statistician will provide an additional set of secondary futility analyses (described in the SAP).** The DSMB could then recommend study continuation to completion for the targeted number of events or recommend (based on pre-specified criteria documented in the SAP) that the study be considered futile with respect to the primary efficacy endpoint, high-risk comparison.

Immediately after the **efficacy** futility analysis data review meeting takes place **(ie, either after an efficacy futility analysis following operational futility or the efficacy futility analysis following accrual of 33% of events)**, the DSMB recommendation regarding the continuation of the study will be promptly communicated to the DSMB Liaison. If the data indicate that study

termination should be considered, the DSMB Liaison will promptly convene an ad-hoc meeting within the Takeda/Zinfandel alliance senior management **(ie, the Executive Committee)** to further discuss the results of the **futility analyses** and make the final decision as to whether or not to terminate the study. **In a similar manner to the DSMB, the Executive Committee will be unblinded to the results of the futility analyses, will keep all futility analysis results and discussions strictly confidential, and will have no involvement with the daily project activities of the study or study team.**

If the alliance **Executive C**ommittee decides to terminate the study as a result of the futility analys**es**, this decision will be promptly communicated to all the stakeholders including the AD-4833/TOMM40 project team, investigators, ethics committees, and regulatory agencies. Details of the stopping rules and analyses will be given in the DSMB Charter and in the SAP.

Rationale for Amendment

Section updated following revisions to the planned futility analysis, including plans for a formal test of 'operational futility'. The revisions will enable an earlier assessment of 'efficacy futility', protecting study subjects and the Sponsor from continuation of an ultimately futile study, whilst keeping the risk of a futility 'false negative' finding at an acceptably low probability. The inclusion of an assessment of operational futility will enable an assessment of whether the study can feasibly be completed within an acceptable timeframe, based on the accrual rate of adjudicated cases meeting the endpoint definition.

Page 115-118, Appendix A, Schedule of Study Procedures

Existing Text

	Screen-ing Visit 1	Base-line Visit 2	Random-ization Visit 3	Double-Blind Treatment *Repeated yearly*				Unschedu led - *Comprehe nsive Medical Follow-up* (q)	*End of Study* (EoS)/*Early Withdrawal* (EW) Visit (b) (j)	Follow-up Visit (c)
Study Month:	-4	-1	0 (Day 0)	3 (a)	6	9 (a)	12			EoS/EW+0.5
Visit Window (t):	Max Day -125	Max Day -35		±2 weeks	±2 weeks	±2 weeks	±2 weeks	Within 30 days of trigger		
Genetics (blood samples)										
TOMM40 rs10524523, APOE (Risk stratification)	X									
Safety/efficacy PGx (DNA and RNA samples) – subject-optional			X(g, n)				X(n)			

(f) As part of the comprehensive medical follow-up evaluation to rule out other causes of dementia and confirm the clinical diagnosis of MCI due to AD (See section 6.2.4). For subjects who have contraindications for the MRI procedure (such as unremovable ferromagnetic dental work, cardiac pacemakers, etc) a CT scan can be done instead.
(j) Subjects who discontinue study medication prematurely should be contacted by the study site every 6 months until the conclusion of the study via telephone to assess the general well being of the subject as well as to obtain any changes in medications. In the event the subject is not able to be reached, the subject's project partner or primary care physician can be contacted to obtain this information.
(n) RNA sample to be collected at Day 0, Month 12 of Year 1, Year 2, Year 3, Year 4, and *Year 5*.
(o) Greater detail is given below. Note: If subject has been off drug for 3 or more days prior to Unscheduled CMF*U Visit*, *End of Study Visit,* or *Early Withdrawal*, the PK samples should not be collected.
(q) Procedures for Unscheduled visits for CMF*V* includes the assessments marked, and should only be conducted after appropriate *trigger is* met as described in Section 6.2.4. Unscheduled visits for other concerns, including safety, the investigator is expected to conduct whatever assessments are necessary.

Revised Text

	Screen-ing Visit 1	**Base-line Visit 2**	**Random-ization Visit 3**	**Double-Blind Treatment** ***Repeated yearly***				**Unscheduled – CMFV (q) (v)**	**EoS/ EW Visit (b) (j)**	**Follow-up Visit (c)**
Study Month:	-4	-1	0 (Day 0)	3 (a)	6	9 (a)	12			EoS/EW+0.5
Visit Window (t):	Max Day -125	Max Day -35		±2 weeks	±2 weeks	±2 weeks	±2 weeks	Within **approx.** 30 days of trigger		
Genetics (blood samples)										
TOMM40 rs10524523, APOE (Risk stratification)	X									
Safety/efficacy PGx (DNA and RNA samples) – subject-optional			X(g, n)				X(n)		**X(n)**	

(f) As part of the comprehensive medical follow-up evaluation to rule out other causes of dementia and confirm the clinical diagnosis of MCI due to AD (See section 6.2.4). **An MRI scan is not required to be performed if a study related MRI scan was collected within 6 months of the CMFV.** For subjects who have contraindications for the MRI procedure (such as unremovable ferromagnetic dental work, cardiac pacemakers, etc) a CT scan can be done instead.
(j) Subjects who discontinue study medication prematurely should be contacted by the study site every 6 months until the conclusion of the study via telephone to assess the general well being of the subject as well as to obtain any changes in medications **related to cognitive health**. In the event the subject is not able to be reached, the subject's project partner or primary care physician can be contacted to obtain this information.
(n) RNA sample to be collected at Day 0, Month 12 of Year 1, Year 2, Year 3, Year 4 and **EoS**.
(o) Greater detail is given below. Note: If subject has been off drug for 3 or more days prior to Unscheduled CMF**V**, or **EOS/EW Visit**, the PK samples should not be collected.
(q) Procedures for Unscheduled visits for CMF**V** includes the assessments marked, and should only be conducted after appropriate **criteria are** met as described in Section 6.2.4. Unscheduled visits for other concerns, including safety, the investigator is expected to conduct whatever assessments are necessary.
(v) At the Investigator's discretion, CMFV assessments may be conducted at the routine Month 6 or Month 12 Visit in situations where the CMFV conducted as an outcome of the previous scheduled office visit resulted in an MCI due to AD diagnosis. Refer to Section 6.2.4 for further detail.

Rationale for Amendment

Footnotes for Appendix A have been updated in line with revisions made elsewhere in the protocol. In addition, the acronym used for the Comprehensive Medical Follow-up Visit has been corrected in line with nomenclature used throughout the protocol.

Page 126, Appendix E, Collection, Shipment, and Storage of Pharmacogenomic Samples (Separate from the risk stratification sample)

Existing Text

RNA Sample Collection

One 2.5 mL whole blood sample for RNA extraction will be collected from each subject who consented to pharmacogenomic research. A sample will be collected at Day 0, Month 12 of Year 1, Year 2, Year 3, Year 4 and *Year 5* into a PAXgene tube.

Revised Text

RNA Sample Collection

One 2.5 mL whole blood sample for RNA extraction will be collected from each subject who consented to pharmacogenomic research. A sample will be collected at Day 0, Month 12 of Year 1, Year 2, Year 3, Year 4 and **EoS** into a PAXgene tube.

Rationale for Amendment

Section 9.1.11.2 has always stated that RNA sample collection should occur at EoS since yearly RNA collection was introduced into the protocol in Amendment 2, however the visits at which collection should occur was incorrectly listed in Appendix E. Appendix E has been updated to ensure consistency within the protocol in the timing of RNA sample collection and to ensure that RNA samples are collected at EoS.

Page 136, Appendix H, A Sub Study To Evaluate the Effects of Pioglitazone on Whole and Regional Brain Volume over Time

Existing Text

Study Design

In addition to their participation in the main phase 3 study, approximately 300 cognitively normal elderly subjects will participate in a sub study at selected sites. Subjects will sign a separate informed consent form (ICF) in order to participate in this sub-study. Subjects who fulfill all inclusion criterion and none of the exclusion criteria for the sub-study will be selected in a double-blind fashion to represent a 5:4 randomization ratio between pioglitazone and placebo assignment. Subjects in this sub-study will be scanned to assess brain volume (vMRI). Serial brain MRI scans will be performed at baseline, 2 years, and *end of study*/*early termination* (3 timepoints in total).

Schedule of Additional Study Procedures for the Sub-Study

	Screening Visit 1	**Baseline Visit 2**	**Randomization Visit 3**	**Double-Blind Treatment**	***End of Study* (EoS)/*Early Withdrawal* (EW) Visit**
Study Month:	-4	-1	0 (Day 0)	24	
Visit Window:	Max Day -125	Max Day -35		±2 weeks	
Informed consent (a)	X	X			
Incl/Excl Criteria	X	X	X		
vMRI scan (Brain Volume)		X		X	X (b)

(a) All subjects should sign a separate informed consent to participate in the sub-study at either visit 1 or visit 2, must occur prior to any sub-study procedures taking place.
(b) This assessment only needs to be administered at this visit if it occurs greater than 6 months from the last administration.

Duration of Treatment

The total duration of the vMRI sub study will be the same duration as the main study.

Primary Objective

1. To evaluate changes in brain volume in subjects receiving pioglitazone versus subjects receiving placebo.

Primary Endpoint

1. Changes from baseline in vMRI in whole brain and specific brain regions of interest at 2 years, and *4 years or study termination* (in subjects enrolled in the sub study).

Revised Text

Study Design

In addition to their participation in the main phase 3 study, approximately 300 cognitively normal elderly subjects will participate in a sub study at selected sites. Subjects will sign a separate informed consent form (ICF) in order to participate in this sub-study. Subjects who fulfill all inclusion criterion and none of the exclusion criteria for the sub-study will be selected in a double-blind fashion to represent a 5:4 randomization ratio between pioglitazone and placebo assignment. Subjects in this sub-study will be scanned to assess brain volume (vMRI). Serial brain MRI scans will be performed at baseline, 2 years, and **EoS**/**EW** (3 timepoints in total).

Schedule of Additional Study Procedures for the Sub-Study

	Screening Visit 1	Baseline Visit 2	Randomization Visit 3	Double-Blind Treatment	EoS/EW Visit
Study Month:	-4	-1	0 (Day 0)	24	
Visit Window:	Max Day -125	Max Day -35		±2 weeks	
Informed consent (a)	X	X			
Incl/Excl Criteria	X	X	X		
vMRI scan (Brain Volume)		X		X **(b)**	X (b)

(a) All subjects should sign a separate informed consent to participate in the sub-study at either visit 1 or visit 2, must occur prior to any sub-study procedures taking place.
(b) This assessment only needs to be administered at this visit if it occurs greater than 6 months from the last administration **for either the main study or the sub study**.

Duration of Treatment

The total duration of the vMRI sub study will be the same duration as the main study.

Primary Objective

1. To evaluate changes in brain volume in subjects receiving pioglitazone versus subjects receiving placebo.

Primary Endpoint

1. Changes from baseline in vMRI in whole brain and specific brain regions of interest at 2 years and **EoS/EW** (in subjects enrolled in the sub study). **If an MRI scan has been performed for the main study or the sub study within 6 months of a required timepoint, a separate MRI scan does not need to be performed.**

Rationale for Amendment

The text in this section has been revised to accurately reflect the timepoints at which analysis for this endpoint will occur using nomenclature that is consistent throughout the protocol. It has also been updated to clarify that MRI scans do not need to be performed if a scan has been collected for the study within 6 months or the required timepoint, to reduce subject burden in collecting additional MRI scans which are considered unnecessary.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical VP Approval	16-Oct-2016 07:16 UTC
	Biostatistics Approval	17-Oct-2016 14:36 UTC
	Clinical Approval	17-Oct-2016 19:15 UTC