



Title: A Blinded Long-term Extension Study to Evaluate the Safety and Efficacy of Pioglitazone (AD-4833 Sustained Release 0.8 mg Daily) to Slow the Progression of Cognitive Decline in Subjects Who Have Completed the AD-4833/TOMM40_301 Study With Diagnosis of Mild Cognitive Impairment Due to Alzheimer Disease

NCT Number: NCT02284906

Protocol Approve Date: 19 January 2016

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PROTOCOL AMENDMENT

A Blinded Long-term Extension Study to Evaluate the Safety and Efficacy of Pioglitazone (AD-4833 Sustained Release 0.8 mg Daily) to Slow the Progression of Cognitive Decline in Subjects Who Have Completed the AD-4833/TOMM40_301 Study With Diagnosis of Mild Cognitive Impairment Due to Alzheimer Disease

AD-4833/TOMM40_303 Extension Study of the Safety and Efficacy of Pioglitazone to Slow Cognitive Decline in Subjects With Mild Cognitive Impairment Due to Alzheimer Disease

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Study Number: AD-4833/TOMM40_303

IND Number: 112,403 **EudraCT Number:** 2013-004984-30

Compound: AD-4833

Date: 19 January 2016 **Amendment Number:** 3

Amendment History:

Date	Amendment Number	Amendment Type	Region
21 March 2014	Initial Protocol	Not Applicable	Global
31 March 2015	1	Substantial	Global
29 July 2015	2	Substantial	Global
19 January 2016	3	Substantial	Global

Document generated using Protocol Phase 2-4 Template, G-TMPL-RD-005 Version: 03

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1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

TDC sponsored investigators per country requirements 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	Europe Contact	Australia Contact
Serious adverse event and pregnancy reporting	Confidential Company Information		
Medical Monitor (medical advice on protocol, compound, and medical management of subjects)	[Redacted]		
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	Protected Personal Data		

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

Protected Personal Data



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 3 Summary of Changes

This document describes changes in reference to the Protocol incorporating Amendment 3.

The primary purpose of this amendment is to update the protocol regarding laboratory exclusion criteria and to remove the adjudication process for diagnosis of dementia. Full details on changes of text are given in [Appendix G](#). The following is a summary of the changes made in the amendment;

1. Removal of exclusion criterion #3.

Justification: HbA1c >8% as a criteria for exclusion has been removed because, while this assessment will still be collected at Baseline, it is no longer considered an important eligibility criterion for this study. Any medical concerns with a subject's baseline HbA1c result will be handled on a case by case basis. While the intent to prohibit insulin, triple oral antidiabetic therapy and PPAR- γ agonists remains, since insulin and PPAR- γ agonists are already in the Excluded Medications and Treatments Table 7.a, triple oral antidiabetic therapy will be added to the table to be consistent with the original exclusion intent.

2. Correction to exclusion criterion #8.

Justification: Criterion #8 was modified to allow the eligibility decision to be based on the laboratory results available prior to the AD-4833/TOMM40_301 EOS/303 Baseline visit to confirm/ensure eligibility for this extension study.

3. Removed the adjudication process for confirmation of the diagnosis of dementia and added CDR Global score of ≥ 1.0 as a minimum standard for consistency in diagnosis of AD dementia.

Justification: The study investigators are more familiar with the criteria for the diagnosis of Alzheimer's Disease (AD) than for Mild Cognitive Impairment due to AD and therefore, can reliably make this diagnosis without the need for the confirmation by the Adjudication Committee. Additionally, conversion from MCI due to AD to AD dementia is a secondary endpoint for this study and the AD data will be analyzed for trends, not statistical significance.

4. Removed MRI and CT scan (for subjects with contraindication to MRI) at the Unscheduled Visit to support the possible dementia diagnosis.

Justification: With the removal of the adjudication process for confirmation of the diagnosis of dementia, the MRI or CT scan for the purpose of supporting the diagnosis as an endpoint event is not required.

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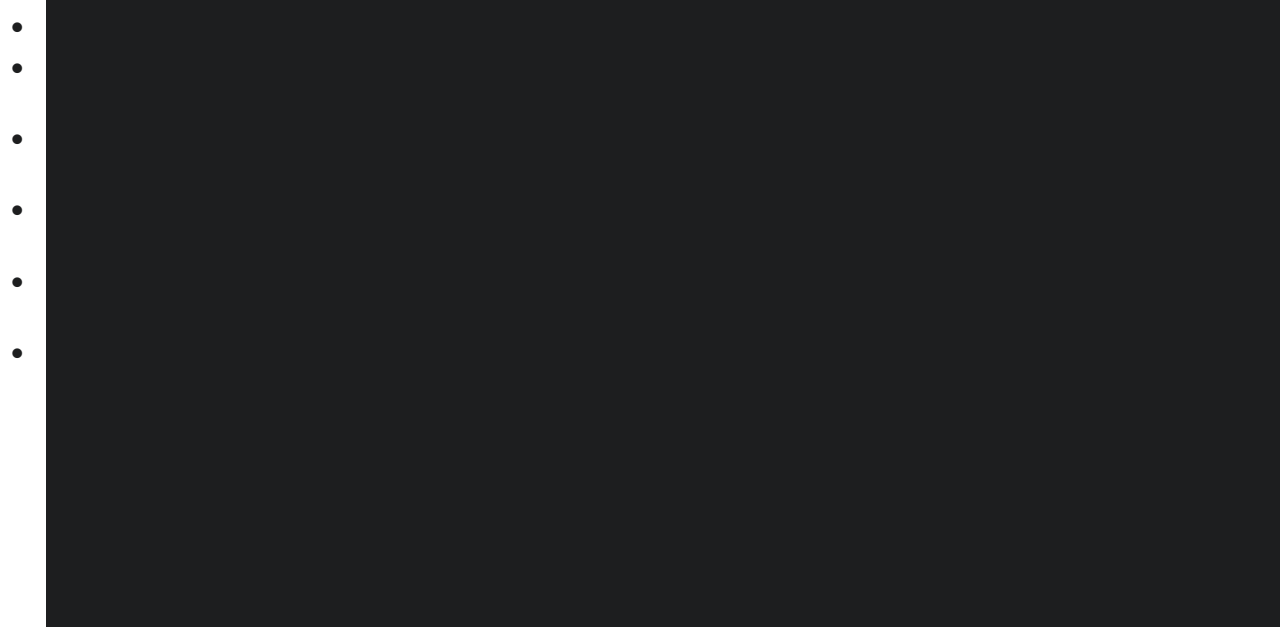
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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc.	Compound: AD-4833	
Title of Protocol: A Blinded Long-term Extension Study to Evaluate the Safety and Efficacy of Pioglitazone (AD-4833 Sustained Release 0.8 mg Daily) to Slow the Progression of Cognitive Decline in Subjects Who Have Completed the AD-4833/TOMM40_301 Study With Diagnosis of Mild Cognitive Impairment Due to Alzheimer Disease	IND No.: 112,403	EudraCT No.: 2013-004984-30
Study Number: AD-4833/TOMM40_303	Phase: 3	
Study Design: <p>This is a blinded, placebo-controlled, multicenter, parallel group long-term extension study. The study is designed to further evaluate the efficacy and safety of pioglitazone on cognitive function in subjects who have an adjudicated diagnosis of mild cognitive impairment (MCI) due to Alzheimer disease (AD) (according to the National Institute on Aging/Alzheimer’s Association definition) and have completed the pivotal AD-4833/TOMM40_301 study with a diagnosis of MCI due to AD. Subjects who have an adjudicated diagnosis of MCI due to AD in the 301 study may be eligible to participate in this extension study depending on their site’s participation in the 303 study. The treatment assignment from the pivotal study will remain unchanged, that is, subjects will continue to receive the same study medication they received during the pivotal AD-4833/TOMM40_301 study, either pioglitazone or placebo. The extension study will follow subjects from the time they complete the pivotal AD-4833/TOMM40_301 study until 2 years after the pivotal AD-4833/TOMM40_301 study is concluded, allowing the last subject enrolling into the extension study a follow up period of 2 years in the extension study. Of the 222 potential subjects from both the high- and low-risk arms of the pivotal AD-4833/TOMM40_301 study it is expected that approximately 149 subjects will enroll into this extension study.</p>		
Primary Objective: <ul style="list-style-type: none"> To evaluate the effect of pioglitazone at 24 months compared with placebo on cognitive decline in high-risk subjects who have completed the AD-4833/TOMM40_301 study with an MCI due to AD diagnosis. 		
Secondary Objective: <ul style="list-style-type: none"> To evaluate the effect of pioglitazone compared with placebo on the delay of onset of AD dementia in high-risk study subjects. 		
Additional Objectives Safety Objective: <ul style="list-style-type: none"> To evaluate long-term safety and tolerability of pioglitazone during the course of the treatment. Exploratory Objectives: <ul style="list-style-type: none"> Company Confidential Information 		

Company Confidential Information



Subject Population: Male and female subjects, at least 65 years of age at time of Baseline Visit, who have completed the pivotal AD-4833/TOMM40_301 study with an adjudicated diagnosis of MCI due to AD.

Number of Subjects: Approximately 149 subjects will be enrolled.	Number of Sites: Estimated total: up to 60 in North America, Europe, Australia.
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Dose Level(s): AD-4833 sustained release 0.8 mg tablet once daily (QD) Placebo QD	Route of Administration: Oral
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Duration of Treatment: Minimum of 2 years (24 months)	Period of Evaluation: Minimum 2-year Blinded Treatment period
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- Main Criteria for Inclusion:**
- The subject completed the pivotal AD-4833/TOMM40_301 study with an adjudicated diagnosis of MCI due to AD without ongoing serious adverse events from study AD-4833/TOMM40_301.
 - The subject must be living independently or in nonmedical residential care.
 - The subject has a project partner able to separately consent on his/her own behalf and take part in the study (with the intent to do so as long as the subject is enrolled), providing information on the cognitive, functional, and behavioral status of the subject (and self reported, if voluntarily agreed to) and assisting with observation of adverse events and monitoring of study medication, if needed. (Project partners participating in the pivotal AD-4833/TOMM40_301 study are encouraged to participate in this extension study in this capacity.)

- Main Criteria for Exclusion:**
- The subject completed the pivotal AD-4833/TOMM40_301 study with an adjudicated diagnosis of AD dementia.
 - The subject has a current diagnosis of significant psychiatric illness, per Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (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 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.

- The subject is required to take excluded medications as specified in the Excluded Medications Section.
- The subject had any of the following values at the second comprehensive medical follow-up visit in the AD-4833/TOMM40_301 study (or time of last collection in the pivotal 301 study):
 - A serum total bilirubin value $>1.5 \times$ upper limit of normal (ULN).
 - A serum alanine aminotransferase or aspartate aminotransferase value $>2 \times$ ULN.
 - Unexplained microscopic/macrosopic hematuria on one repeat examination within 2 weeks.
- The subject has a disease 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.
- The subject has any cancer that has been in remission for less than 2 years from the extension study Baseline Visit. Subjects with basal cell or stage I squamous cell carcinoma of the skin will be eligible. Subjects with current diagnosis of bladder cancer are not eligible irrespective of the remission status.
- The subject has a current diagnosis of macular edema or macular degeneration.
- The subject has a history or current diagnosis of congestive heart failure, New York Heart Association class III-IV.

Main Criteria for Evaluation and Analyses:

Efficacy:

The primary endpoint for this study:

- Change from extension study Baseline to 24 months on the composite score of the cognitive test battery.

Secondary endpoint for this study:

- Time to diagnosis of AD dementia.

Statistical Considerations:

The primary null hypothesis in this study assumes that there is no difference in the cognitive decline of MCI due to AD between the placebo-treated and active-treated subjects in the high-risk group. The alternative hypothesis is that there is a difference in cognitive decline between pioglitazone and placebo. The change in the composite cognitive test battery score from extension study Baseline to 24 months will be analyzed using mixed models repeated measures (MMRM). The other secondary endpoints will be analyzed using MMRM, 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 2-sided 0.05 level. The ability of demonstrating a difference between active and placebo may be limited by study design as the determination of number of subjects is not based on statistical consideration and the subjects are not randomized at the beginning of this study.

Sample Size Justification:

The sample size for this study was not based on statistical considerations. Subjects who have an event of MCI due to AD, without a diagnosis of AD dementia, in the pivotal AD-4833/TOMM40_301 study may be eligible to enroll into this extension study, depending on their site's participation in the 303 study. In the pivotal AD-4833/TOMM40_301 study, approximately 222 subjects (including both high and low risk, and including all races and ethnicities) are expected to have an event of MCI due to AD or AD dementia. Approximately 149 of 222 subjects (67%) are anticipated to consent to participate in the 303 extension study.

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-Related 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 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
A β	amyloid-beta
AD	Alzheimer's Disease
ADCS ADL-MCI	Alzheimer's Disease Cooperative Study Activities of Daily Living – Mild Cognitive Impairment
ADCS CGIC-MCI	Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change – Mild Cognitive Impairment
ADCS IADL	Alzheimer's Disease Cooperative Study Instrumental Activities of Daily Living
ADCS-RUI	Alzheimer's Disease Cooperative Study- Resource Use Inventory
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BVMT-R	Brief Visuospatial Memory Test – Revised
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating – Sum of Boxes
CFR	Code of Federal Regulations
CHF	congestive heart failure
C-SSRS	Columbia-Suicide Severity Rating Scale
CVLT-II	California Verbal Learning Test – 2nd Edition
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EQ-5D	Euro Quality of Life-5D includes single item measures of: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression
FDA	Food and Drug Administration
FAS	full analysis set
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
HbA1c	glycosylated hemoglobin
HDPE	high-density polyethylene
HRQoL	health-related quality of life
ICH	International Conference on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IVRS	interactive voice response system
IWRS	interactive web response system
LFT	liver function test
MCI	mild cognitive impairment
MCI-AD	mild cognitive impairment due to Alzheimer's Disease

MedDRA	Medical Dictionary for Regulatory Activities
MetS	metabolic syndrome
MINT	Multilingual Naming Test
MMRM	mixed models repeated measures
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NIA	National Institute on Aging
NPI-Q	Neuropsychiatric Inventory Questionnaire
PPAR- γ	peroxisome proliferator-activated receptor gamma
PRO	patient reported outcome
PTE	pretreatment event
QD	once daily
rCBF	regional cerebral blood flow
RU	resource utilization
SAE	serious adverse event
SAP	statistical analysis plan
SR	sustained release
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
TMT	Trail Making Test
TOMM40	translocase of the outer mitochondrial membrane 40 homolog
TZD	thiazolidinedione
ULN	upper limit of normal
vMRI	volumetric magnetic resonance imaging
WAIS	Weschler Adult Intelligence Scale
WPAI:MM-CG	Work Productivity and Activity Impairment Questionnaire: Mood and Mental State, Caregiver Version

3.4 Corporate Identification

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

4.0 INTRODUCTION

4.1 Background

Alzheimer disease (AD) is a progressive and fatal brain disorder that causes the death of brain cells and atrophy of the brain. It is the most common type of dementia: 50% to 80% of all dementia cases are diagnosed as AD [1]. The disease pathoetiology includes disturbances in synaptic function, energy, lipid metabolism, and inflammatory responses within the brain [2]. Symptoms include loss of memory, reasoning, and other brain functions. The hallmarks of the advanced stages of AD brain neuropathology are amyloid-beta ($A\beta$) plaques, composed of microscopic aggregates of $A\beta$ peptides that deposit in the brain parenchyma, and intracellular tau protein hyperphosphorylation and accumulation. These features are accompanied by impairment of neuronal metabolism and function.

AD is characterized as being either early (before 65 years of age) or late (after 65 years of age) onset, referring to the age of onset of declines in cognitive performance and physical functioning [3]. Both forms involve steady cognitive decline in the years after onset [4,5], with late-onset AD being the most common form, accounting for approximately 96% of AD cases in the United States [3].

While the exact sequence of events leading to AD manifestation remains a subject of debate, the pathophysiologic changes that underlie the clinical presentation are known to begin decades before the first symptoms appear, and to develop slowly over what is now recognized as a preclinical/presymptomatic phase. The prodromal, symptomatic phase is marked by impaired cognition, commonly described as mild cognitive impairment (MCI). This phase describes the first point at which cognitive impairment is noted, without significant effects on functional abilities. As a person's cognitive ability continues to deteriorate and activities of daily living also become impaired, the MCI phase converts to clinical AD dementia. The gradually progressing clinical symptoms of AD are characterized by cognitive deficits (eg, learning and retaining new information, difficulty handling complex tasks, impaired reasoning ability), accompanied by neuropsychiatric symptoms (eg, apathy, diminished interest, agitation, depression, and delusions), and in later phase of the disease motor systems abnormalities [6].

Although not all persons with MCI will develop AD, the conversion rate from MCI to AD in the general population is about 15% per year, or 5 to 10 times that of cognitively normal individuals. Overall, this slow, progressive trajectory of decline is now recognized as the continuum of AD [7-9].

There is great interest in finding treatments to prevent AD by intervening at an even earlier stage than diagnosed MCI [10]. By the time clinical symptoms appear, neurons may have died or undergone irreversible damage. Thus a strategy of delaying the onset of the disease, rather than waiting to treat symptoms, could have substantial medical, economic, and societal impact.

Pioglitazone is currently being investigated in the AD-4833/TOMM40_301 study as a treatment to delay the onset of MCI due to AD in cognitively normal elderly subjects at high risk of developing symptoms of cognitive decline associated with AD based on the translocase of the outer

mitochondrial membrane 40 homolog (TOMM40) rs10524523 and apolipoprotein E genotype as well as age.

Pioglitazone HCl (marketed globally under ACTOS and other trade names), is an oral antidiabetic agent indicated for the treatment of type 2 diabetes mellitus (T2DM). It belongs to the thiazolidinedione (TZD) class of drugs and exhibits a mechanism of action different from the sulfonylureas, the biguanides, or the α -glucosidase inhibitors.

The mechanism of action of pioglitazone involves primarily the decrease of insulin resistance in muscle and other tissues. Pioglitazone is a potent and highly selective agonist of peroxisome proliferator-activated receptor-gamma (PPAR- γ), which is found in tissues important for insulin action (including adipose tissue, skeletal muscle, liver, and the brain) [11]. Activation of PPAR- γ nuclear receptors modulates the transcription of a number of insulin-responsive genes involved in the control of glucose and lipid metabolism.

The mechanism of action through which PPAR- γ agonists affect AD pathophysiology is not known at this time; in vitro and in vivo animal models of AD have demonstrated effects of PPAR- γ agonists that could be relevant in AD treatment and prevention, although the mechanism of action through which this activity occurs is not known at this time. Effects of PPAR- γ agonists in AD models include potentiation of glucose-induced thermogenesis and oxygen consumption in brain homogenates; inhibitory effects on A β -stimulated proinflammatory responses and neurotoxicity; neuroprotective effects through reductions in microglial activation, inflammatory gene expression, and A β deposition in the brain; and normalization of cerebral blood flow (perfusion) and cerebral glucose uptake (metabolism).

In addition, PPAR- γ receptors have direct effects on mitochondrial function and adenosine triphosphate production. It is thought that mitochondria may play a chief role in the cerebral hypometabolism observed in AD. It is postulated that PPAR- γ agonists will improve mitochondrial function in AD [12], and this may be the source of favorable outcomes on memory and cognition in AD patients that have been observed in some recent clinical studies of PPAR- γ agonists [13-17].

The efficacy of pioglitazone on cognition, regional cerebral blood flow (rCBF), and plasma levels of A β 40 and A β 42 has been demonstrated in a 6-month, randomized, open-controlled pilot study in subjects with mild AD accompanied with T2DM. Since launch in the United States in July 1999, through 31 January 2012, the total patient-years of exposure to pioglitazone (including monotherapy and fixed-dose combination) globally is estimated to be approximately 29,542,000 [18]. 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.

Adverse events (AEs) associated with pioglitazone, listed in the Warnings and Precautions section of the Company Core Data Sheet [19], 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: edema, body weight increase, decreases in hemoglobin and hematocrit, increases (or elevations) in creatine kinase (creatin phosphokinase), congestive heart failure

(CHF) and peripheral edema due to dose-related fluid retention, cardiac failure, hepatocellular dysfunction (post-marketing event), macular edema (post-marketing event), increased incidence of fractures in female population, hypoglycemia, and bladder cancer. A detailed discussion of the safety profile of pioglitazone is provided in the Investigator's Brochure [11].

Sato et al conducted a 6-month, randomized, open-controlled pilot study of pioglitazone efficacy on cognition, rCBF, and plasma A β 40 and A β 42 [20]. 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), Wechsler Memory Scale-revised logical memory-I) and rCBF at 6 months compared with Baseline (Visit 2), while untreated subjects did not. Untreated subjects did, however, have increased plasma A β 40 /A β 42 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) [21]. 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 with controls, as evidenced by either improvement, stabilization, or lesser decline in performance on cognitive testing.

4.2 Rationale for the Proposed Study

The design of this extension study would allow the evaluation of the efficacy of pioglitazone in reducing the change in cognitive decline in subjects who have been diagnosed with MCI due to AD in the pivotal AD-4833/TOMM40_301 study. Progression from MCI due to AD to a diagnosis of AD dementia is expected in a subset of the subjects.

This extension study will provide continued treatment and follow-up for consenting participants who complete the pivotal AD-4833/TOMM40_301 study after receiving an adjudicated diagnosis of MCI due to AD. Although MCI due to AD is a condition that can carry a substantial risk of dementia, the exact magnitude of this risk is uncertain given that the MCI due to AD construct itself is relatively new and had not been operationalized until the AD-4833/TOMM40_301 study. While anticipated not to be statistically powered due to constraints of sample size and feasible follow-up duration, this extension study will be first to examine the efficacy of pioglitazone in reducing the change in cognitive decline in subjects with established diagnosis of MCI due to AD according to the criteria developed by the NIA and the Alzheimer's Association (AA) in Albert et al, 2011 [22]. As a secondary objective, the study will prospectively explore the efficacy of pioglitazone in delaying the conversion from MCI due to AD diagnosis to diagnosis of AD dementia [23]. Finally, long-term exposure data will be gathered to further assess the safety profile of once-daily (QD) low-dose pioglitazone in the elderly.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- The objective of this study is to evaluate the effect of pioglitazone at 24 months compared with placebo on cognitive decline in high-risk subjects who have completed the AD-4833/TOMM40_301 study with an adjudicated diagnosis of MCI due to AD.

5.1.2 Secondary Objectives

- To evaluate the effect of pioglitazone compared with placebo on the delay of onset of AD dementia in high-risk study subjects.

5.1.3 Additional Objectives

5.1.3.1 Safety Objective

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

5.1.3.2 Exploratory Objectives

- **Company Confidential Information**
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Company Confidential Information

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5.2 Endpoints

5.2.1 Primary Endpoint

- Change from extension study Baseline to 24 months in the composite score of the cognitive test battery.

5.2.2 Secondary Endpoint

- Time to diagnosis of AD dementia [23].

5.2.3 Additional Endpoints

5.2.3.1 Safety Endpoint

- Safety and tolerability: AEs (including AEs of special interest), vital signs, body weight, electrocardiogram (ECG), magnetic resonance imaging (MRI), clinical laboratory data, and physical examination findings.

5.2.3.2 Exploratory Endpoints

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6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a blinded, placebo-controlled, multicenter, parallel group long-term extension study. The study is designed to further evaluate the efficacy and safety of pioglitazone on cognitive function in subjects who have completed the pivotal AD-4833/TOMM40_301 study with an adjudicated diagnosis of MCI due to AD (according to the NIA/AA definition [22]). Subjects who have an adjudicated diagnosis of MCI due to AD in the 301 study and meet the entry criteria described in Section 7.0, may be eligible to participate in the 303 extension study depending on their site's participation in the 303 study. The treatment assignment from the pivotal study will remain unchanged, that is, subjects will continue to receive the same study medication they received during the pivotal AD-4833/TOMM40_301 study, either pioglitazone or placebo.

The study participants will be men or women, at least 65 years of age at the time of the extension study Baseline Visit. The extension study will follow subjects from the time they complete the pivotal AD-4833/TOMM40_301 study for a minimum of approximately 2 years and a maximum of approximately 7 years, that is, the extension study will be terminated 2 years after the pivotal AD-4833/TOMM40_301 study is concluded, allowing the last subject enrolling into the extension study a follow up period of approximately 2 years in the extension study. Although MCI due to AD is the primary endpoint event expected in the 301 study, AD dementia is a diagnostic event that also counts toward the total needed for that event-driven study; however, subjects diagnosed with AD dementia in the pivotal AD-4833/TOMM40_301 study will not be eligible to participate in this extension study.

Each subject must have a project partner able to separately consent 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 remains in the study. It is recommended that the same project partner (spouse, adult child, or other person familiar with the participant's health and daily functioning) participating in the pivotal AD-4833/TOMM40_301 study will also participate in the extension study.

The data collected in the pivotal AD-4833/TOMM40_301 study will be used in the analyses of the extension study. This includes results of all cognitive, psychiatric, and medical assessments performed at all scheduled pivotal AD-4833/TOMM40_301 study visits and any subsequent comprehensive medical follow-up evaluations as stipulated in the pivotal AD-4833/TOMM40_301 study protocol. The End of Study Visit of the pivotal AD-4833/TOMM40_301 study will serve as the Baseline Visit for the extension study once appropriate informed consent is signed, with additional assessments carried out as outlined in Section 6.2.

A 0.8 mg tablet of SR pioglitazone or placebo will be used in this extension study, the same as that used in the pivotal AD-4833/TOMM40_301 study. The tablet will be administered QD for a minimum period of 24 months, in accordance with the extension study duration. Study medication will be dispensed at the end of the extension study Baseline Visit and subjects will be instructed to

take the first dose of study medication in the morning on the day following the extension study Baseline Visit (if all eligibility criteria are confirmed).

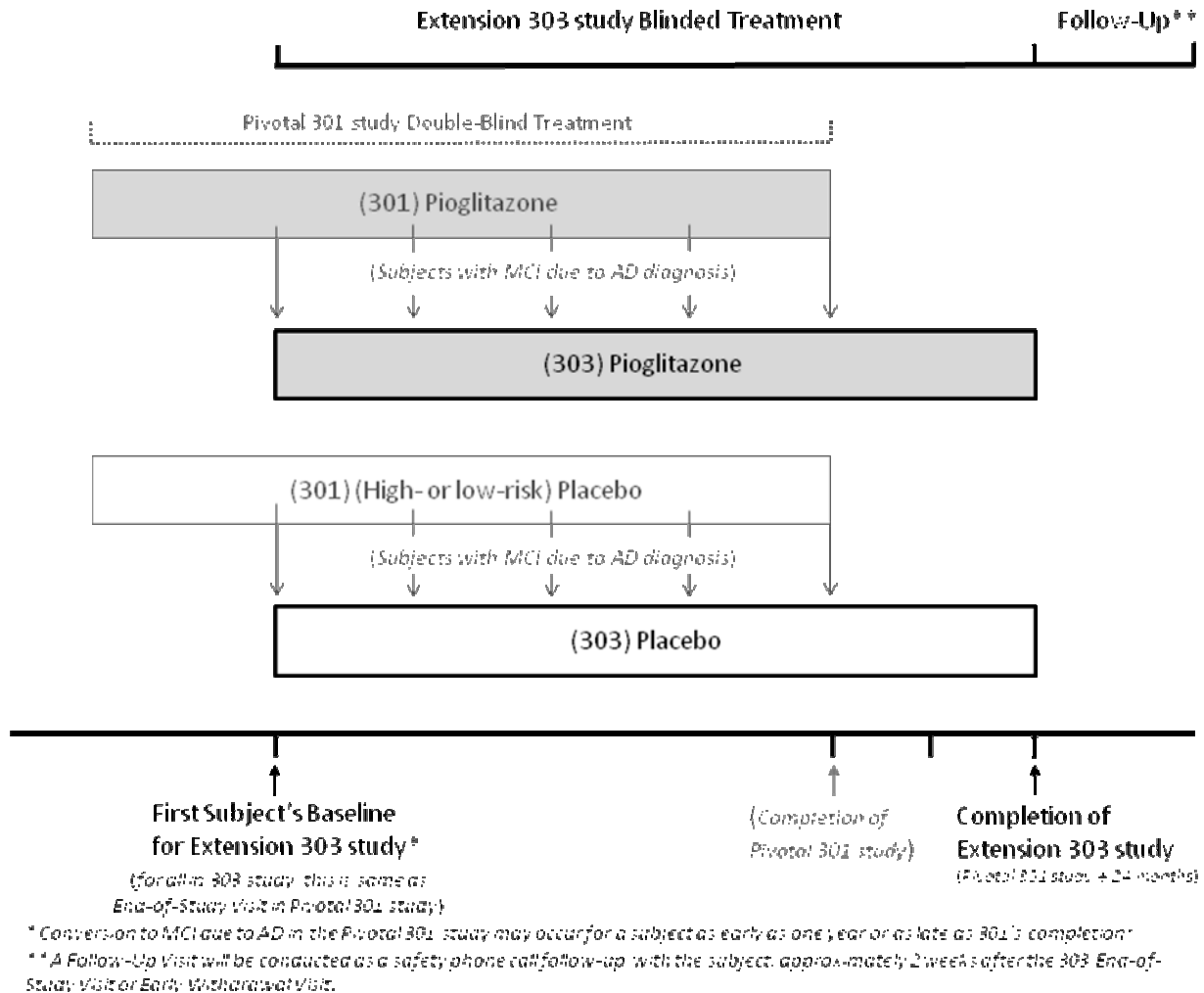
Based on the underlying assumptions, of the approximately 222 potential subjects from both the high- (approximately 213 potential subjects) and low-risk (approximately 9 potential subjects) arms of the pivotal AD-4833/TOMM40_301 study it is expected that approximately 67% will enroll into this extension study (ie, a total of approximately 149 subjects). While it is preferred that subjects and their project partners consent to the AD-4833/TOMM40_303 study while attending the AD-4833/TOMM40_301 End of Study Visit, subjects will be allowed to return to the clinic and consent for the extension study within 1 month of the AD-4833/TOMM40_301 End of Study Visit, as described in the Schedule of Study Procedures. They will complete the AD-4833/TOMM40_303 baseline evaluations (if needed) once informed consent is provided and within the 1 month window.

Subjects and their project partners are expected to attend on-site study visits every 6 months after Baseline, for regular assessments of safety, efficacy, and treatment compliance. In addition, the subject will be contacted for telephone-based safety checks between visits. While it is preferred that subject's project partners attend the on-site study visits, it is not required and they may offer their information via telephone. Project partners who voluntarily take part in completion of the 2 self reported project partner questionnaires (outline in Section 9.1.14.4), will be required to attend the study visits when the questionnaires are obtained. If between in clinic visits, worsening of cognitive impairment, potential AD dementia, or a potential safety issue is suspected, requiring further evaluation of the subject, an unscheduled clinic visit may be conducted as described in Section 6.2.3. Up to 60 sites globally may participate in this study (the same sites that participated in the AD-4833/TOMM40_301 study, although all sites may not participate in 303).

The last MRI scan or that obtained at a second consecutive comprehensive medical follow-up evaluation in the AD-4833/TOMM40_301 study will serve as the baseline vMRI time point for this study. This baseline vMRI scan will be reviewed against the vMRI measure acquired in this extension study. Subjects with contraindications for vMRI assessments will not be excluded from the extension study for this reason.

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



6.2 Subject Flow Based on Cognitive and Functional Assessments

6.2.1 Assessments at Baseline Visit (Visit 1)

The End of Study Visit of the pivotal AD-4833/TOMM40_301 study will serve as the Baseline Visit for the extension study once appropriate informed consent and partner acknowledgment, or consent (if needed) are signed (or within a 1 month window from the 301 End of Study Visit). The data collected at the End of Study Visit of the pivotal AD-4833/TOMM40_301 study, including the most recent cognitive assessments, will supplement the additional AD-4833/TOMM40_303 study baseline visit procedures and will be used as the baseline values for each subject. At this visit, after extension study informed consent for the subjects and acknowledgement, or consent (if needed) from their partners are signed, the ADCS CGIC-MCI Baseline assessment will be

completed with the subject and project partner. The ADCS ADL-MCI will also be completed by the project partner.

At the end of the extension study Baseline Visit (Visit 1), a blood sample will be collected for glycosylated hemoglobin (HbA1c) testing, and study medication will be dispensed.

6.2.2 Assessments at Scheduled Study Visits

Neuropsychological testing and functional assessments will be conducted at each scheduled visit (see [Appendix A](#) for a full listing) using a broad cognitive test battery and functional measurements (including investigator's clinical judgment) as described in Section 9.1.14 and in [Appendix A](#). The extension study's cognitive test battery is the same as that employed in the pivotal study and consists of the Brief Visuospatial Memory Test – Revised (BVMT-R), California Verbal Learning Test – 2nd Edition (CVLT-II), Semantic Fluency, Lexical/Phonemic Fluency, Digit Span (forward and backwards), Multilingual Naming Test (MiNT), Trail Making Tests (TMT) Parts A and B, and the Clock-drawing test (see Section 9.1.14). The scores from each neuropsychological instrument described above will be converted to a common metric (z-score). In addition, subjects will be administered the MMSE. Subjects will be evaluated for depression using the GDS. Activities of daily living (ADCS ADL-MCI) will be assessed with the project partner. Additional details regarding test administration will be provided in the Training Manual provided by the vendor selected by Takeda.

In addition, investigators, certified and trained accordingly, will complete the Clinical Dementia Rating (CDR). 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. Without referring to the cognitive test battery or the MMSE, the investigator will complete the CDR scale and assign a CDR global score and CDR-SB scores.

The physician, preferably an experienced neurologist or psychiatrist, will review the totality of available information once fully scored (ie, medical history, CDR ratings, and CDR-SB scores; ADCS-CGIC-MCL, ADCS ADL-MCI, GDS, and NPI-Q data; cognitive test results; and laboratory test results). At this point he/she in consultation with the site neuropsychologist, will determine whether the diagnosis of the subject has changed from MCI due to AD. If possible or probable AD dementia is diagnosed, the subject will be considered to have completed the study. If non-AD dementia is diagnosed, the subject will be withdrawn from the study. The physician can be the same individual who completed the CDR.

6.2.3 Assessments at an Unscheduled Visit for Suspected Cognitive or Functional Decline

There are 2 types of Unscheduled Visits in this study: (1) Unscheduled Visits conducted to address any emerging concerns, including safety, and; (2) Unscheduled Visits conducted to evaluate suspected cognitive or functional decline.

Unscheduled Visits conducted to address any emerging concerns, including safety, are described in Section 9.3.3.

Unscheduled Visits to evaluate suspected cognitive or functional decline may be conducted, as needed, for study subjects outside of regularly scheduled visits based on either of the following trigger criteria being met: (1) the subject or their project partner express concern of the subject's cognitive or functional decline to the principal investigator or coordinator between regularly scheduled study visits and/or (2) a non-study physician expresses concern (with or without prescription of any dementia drug treatment) between regularly scheduled visits. Based on these triggers, the principal investigator will decide whether evidence is present to suspect a diagnosis of possible or probable AD dementia [23]. If a diagnosis of possible or probable AD dementia is suspected, an Unscheduled Visit to further evaluate suspected cognitive or functional decline should take place within approximately 1 month, of this provisional diagnosis. A CDR Global score of ≥ 1.0 will be required in order to set a consistent minimum standard for AD dementia as an endpoint in the study. Visit procedures for the unscheduled visit for suspected cognitive or functional decline are noted in [Appendix A](#).

6.3 Randomization Procedure

Subjects will continue the treatment assignment they were assigned in the pivotal AD-4833/TOMM40_301 in a blinded fashion, taking either pioglitazone or placebo.

6.4 Justification for Study Design, Dose, and Endpoints

6.4.1 Study Design

The design of this extension study is one that allows evaluation of the efficacy of pioglitazone on cognitive decline in subjects who have been diagnosed with MCI due to AD from the pivotal AD-4833/TOMM40_301 study. Cognitive and functional status of study participants will be closely monitored using validated neuropsychological and functional instruments in a quantifiable construct that is sensitive to the continued brain changes that precede the diagnosis of AD dementia. Progression of cognitive decline to diagnosis of AD dementia is expected in a subset of the subjects.

The annual conversion rate from any form of MCI to the diagnosis of AD ranges from 3.3% to 41% per year, with memory deficits and older age identified as risk factors. In the Cache County study, composed of populations similar to that expected to enroll to the extension study, conversion rate was 46% over 3 years. Rates of progression to dementia are generally higher for specialized or clinic-based samples (eg, 15% per year) and for classifications in which an amnesic syndrome predominates (eg, 13% biannually). A minimum of 2 years follow up from completion of the pivotal AD-4833/TOMM40_301 study per subject (ie, 2.5 years from onset of MCI due to AD diagnosis) is therefore expected to yield a substantial number of conversions to diagnosis of AD dementia, despite the constraints of study size and expected high dropout rates consequent to multiple years of concatenated follow-up in the pivotal and extension clinical trials.

There are currently no approved therapies for subjects with any type of MCI. However, multiple clinical trials have been conducted over the past decade in MCI populations in an attempt to reduce the rate of cognitive decline and extend time to progression to AD diagnosis. The majority of studies conducted to date recruited subjects at a mean age of 70, used various criteria to define

MCI eligibility, and employed a diverse set of cognitive, functional, and clinical instruments to evaluate progression. Most of the studies defined the primary endpoint as time to, or incidence of, AD diagnosis, an approach that required large sample sizes and long follow-up durations. Another drawback of this approach is reflected in reports of lower than expected conversion rate to AD diagnosis. Other studies targeted change from baseline in global cognition (or also global function) and lasted 6 months to 1 year, with 250 to 800 subjects enrolled.

All of these previously conducted studies missed their primary endpoints. Some postulated that the measurements used were insensitive to the early AD phases of MCI and that the follow-up durations were likely too short. While anticipated to be statistically underpowered, the current extension study is therefore designed to focus on the more tangible primary endpoint, that is, overall change from Baseline in cognitive performance over 24 months, which has become the generally accepted approach by the field experts and regulators, as published by the Task Force on Designing Clinical Trials in early (predementia) AD in 2011 [24].

Experience with TZDs in MCI populations is very limited. Three relevant studies were conducted with rosiglitazone: in a pilot study (N=30), Watson et al demonstrated that 6 months of rosiglitazone treatment in elderly with normal glucose tolerance and MCI or early-AD was beneficial on cognitive measures of delayed recall and selective attention as compared with placebo [15]. In an observational study, elderly subjects with amnesic MCI and T2DM were followed up for 36 weeks, with the combination therapy metformin/rosiglitazone reported as associated with stable cognitive performance on all neuropsychological tests over time, contrary to comparator groups treated with metformin alone or a well-controlled diet without active treatment [25]. Results of The Rosiglitazone Effects on Cognition for Adults in Later Life study, completed in mid-2010 (ClinicalTrials.gov identifier: NCT00242593) in subjects with MCI over 18 months follow-up, have yet to be reported.

For pioglitazone, a pilot, 6-month follow-up study in subjects with AD and amnesic MCI with T2DM has been reported, showing significant improvement in the drug arm in global cognition and verbal memory measures. However, only 1 prior clinical study was conducted with pioglitazone in MCI cases solely: the “pioglitazone or exercise to treat mild cognitive impairment (POEM)” study (NCT00736996). In this study, treatment with high-dose pioglitazone (30-45 mg) or endurance exercise training were hypothesized to improve, stabilize, or attenuate decline in cognitive function over 6 months compared with control. This short-term study enrolled adults aged 55 years or older with both MetS and MCI at baseline. Results have not been published yet.

The battery of cognitive tests used in the extension AD-4833/TOMM40_303 study is identical to the cognitive test battery employed in the pivotal AD-4833/TOMM40_301 study (Table 6.a), and is appropriate for the target age range. It also carries a relatively low burden to study participants and their partners. This battery was specifically selected to characterize subtle early changes in cognition across 5 different domains suitable for detecting the first signs of MCI due to AD (ie, incipient MCI due to AD), and to follow-up the progression of cognitive impairment onward. Instruments capturing functional and clinical decline are also used, with outcomes analyzed as secondary endpoints, complementary to the composite cognitive decline score. Furthermore, because this extension study clearly defines MCI due to AD at eligibility, it is anticipated to yield

a high conversion rate to AD dementia, as has been noted in clinical trials of MCI [26] and longitudinal studies [27].

The composition of the cognitive test battery selected for this extension study is the same as that used in the pivotal AD-4833/TOMM40_301 study, thus allowing for continuity of measurement from the beginning of the pivotal AD_4833/TOMM40_301 study throughout to end of the extension AD-4833/TOMM40_303 study. The progression endpoints are therefore uniquely equipped to investigate changes in cognitive, functional and clinical performance not only from enrollment into the extension study, but also from enrollment into the pivotal study, using data collected throughout all semiannual assessments conducted in between.

Table 6.a Cognitive Test Battery for the Extension AD-4833/TOMM40_303 Study

Cognitive Domain	Tests
Episodic Memory	CVLT-II BVMT-R
Executive Function	TMT (Part B) WAIS-III Digit Span Test – backwards span
Language	MINT Semantic Fluency (animals) Lexical/phonemic fluency
Attention	WAIS-III Digit Span Test – forward span TMT (Part A)
Visuospatial	Clock Drawing Test Copy of BVMT figures

WAIS= Wechsler Adult Intelligence Scale.

Note: The neuropsychological test battery of the extension study is identical to that used in the pivotal AD_4833/TOMM40_301 study and includes 12 measures derived from 8 neuropsychological tests: The CVLT-II involves 2 primary measures (ie, short delay recall, and long delay recall); BVMT-R has 2 measures (ie, copy and recall); Digit Span has 2 measures (ie, forward and backward span); and TMT has 2 measures (ie, Parts A and B). There is 1 total score for each of the remaining tests: clock drawing, MINT, animal fluency, and letters F, A, and S.

In secondary prevention and early intervention clinical trials of AD, subjects enroll into the clinical trial with a pre-existing cognitive impairment that predisposes them to convert to AD dementia. However, not all cases of MCI convert to AD, with some subjects maintaining stable cognitive performance with minimal functional impairment for many years and others revert back to normal cognition. It is therefore essential that therapeutics investigated within the frameworks of early intervention targeting this stage along the AD continuum display a highly favorable safety profile. To this end, extensive pioglitazone exposure data has been gathered thus far in thousands of patients globally at doses significantly higher than the dose employed by the pivotal AD-4833/TOMM40_301 study, which is intended to be used in this extension AD-4833/TOMM40_303 study as well. 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. The meta-analysis included 35 trials covering 22,131 patients, of whom 12,213 (55%) were randomized to pioglitazone and 9918

(45%) to the comparator. Overall, across all trials for pioglitazone, the estimated major adverse cardiovascular events (defined as cardiovascular death, stroke, or myocardial infarction) risk was lower for pioglitazone compared with control (hazard ratio=0.80; 95% CI=0.70-0.93).

Brain alterations have been shown to occur early on in AD predisposed individuals, preceding clinical manifestation of cognitive decline. Furthermore, neuroimaging modalities have been proposed as potentially useful techniques for prediction of progression in subjects with MCI. The sensitivity and specificity of the different modalities or biomarkers are a subject of intense research in the early stages of the AD continuum, with incipient MCI being of particular interest. Of these, vMRI has been shown to capture gross neuronal loss causing whole brain and regional brain atrophy, typical of cognitive decline processes along the AD continuum. These atrophic changes seem to correlate well with clinical disease stage, as well as cognitive and functional decline in cognitively impaired individuals. The grey matter shrinkage affects the cortical and subcortical brain, and is particularly apparent in the medial-temporal lobe in AD brains. The general pattern of atrophy starts at the hippocampus and the entorhinal cortex, which are the regions most notably affected in the MCI stage. To this end, a report by the Alzheimer's Disease Neuroimaging Initiative has recently identified volumetric atrophy of the hippocampus as the second earliest AD biomarker to become dynamic, with the first being impairment in episodic memory (reflected through performance on a verbal learning test). Nonetheless, increased brain atrophy rates have also been reported in cognitively normal elderly with low cerebrospinal fluid amyloid depositions ($A\beta_{1-42}$). Assessments of vMRI will be collected at the extension study Baseline (last MRI completed in 301 study) and at study termination to test for correlation with disease progression within and across study arms.

6.4.2 Study Dose

Subjects will retain their original blinded treatment assignment, either a 0.8 mg SR tablet of pioglitazone or a matching placebo tablet will be used, the same as that used in the pivotal AD-4833/TOMM40_301 study. The tablet will be administered QD for a minimum period of 24 months.

6.4.3 Study Endpoints

This study is an extension to the pivotal AD-4833/TOMM40_301 study and as such may be statistically underpowered due to constraints of sample size and feasible follow-up duration. The primary objective is to examine the efficacy of pioglitazone on cognitive decline in subjects with established diagnosis of MCI due to AD according to the criteria developed by the NIA/AA [22]. As a secondary objective, the study will prospectively explore the efficacy of pioglitazone in delaying the conversion from MCI due to AD to diagnosis of AD dementia. In parallel, long-term exposure data will be gathered, so as to further characterize the safety profile of daily administration of low-dose pioglitazone in the elderly.

This study acknowledges the importance of both cognitive and functional decline as key components along the continuum of AD and includes both of these recommended outcomes. One of the core clinical criteria for the MCI due to AD diagnosis is preservation of independence in functional abilities. As participants in the extension study are followed up, however, simultaneous

decline in functional, as well as cognitive performance is expected. This course will most likely lead to AD dementia. The progression of decline in the extension study will be assessed comprehensively on 5 cognitive domains, as well as functional ratings obtained through structured interviews of participants and their project partners, compared between pioglitazone and placebo treated subjects.

6.5 Premature Termination or Suspension of Study or Investigational Site

6.5.1 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 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.
- In the instance that the pivotal AD-4833/TOMM40_301 study is prematurely terminated based on futility analysis, that is, the study is unlikely to demonstrate treatment efficacy.

6.5.2 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.

6.5.3 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 test results, need to be confirmed prior to randomization.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

1. The subject completed the pivotal AD-4833/TOMM40_301 study with an adjudicated diagnosis of MCI due to AD without ongoing serious adverse events (SAEs) from AD-4833/TOMM40_301.
2. The subject is male or female and is at least 65 years of age at the time of the Baseline Visit.
3. In the opinion of the investigator, the subject is capable of understanding and complying with the protocol requirements.
4. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form (ICF) and any required privacy authorization prior to the initiation of any study procedures.
5. The subject must be living independently or in nonmedical residential care.
6. Subject has a project partner able to separately consent on his/her own behalf and take part in the study (with the intent to do so as long as the subject is enrolled), providing information on the cognitive, functional, and behavioral status of the subject (and self reported, if voluntarily agreed to) and assisting with observation of AEs and monitoring of study medication, if needed. Project partners participating in the pivotal AD-4833/TOMM40_301 study are encouraged to participate in this extension study in this capacity.

7.2 Exclusion Criteria

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

1. The subject completed the pivotal AD-4833/TOMM40_301 study with an adjudicated diagnosis of AD dementia [23].
2. The subject has a current diagnosis of significant psychiatric illness, per Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (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 clinically significant unstable illness, for example, hepatic impairment or renal insufficiency, or cardiovascular, pulmonary, gastrointestinal (including s/p gastric bypass surgery), endocrine, neurological, rheumatologic, immunologic, infectious, skin and subcutaneous tissue disorders, or metabolic disturbance.
4. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, pivotal, child, sibling) or may consent under duress.

5. The subject is required to take excluded medications as specified in the Excluded Medications Section.
6. The subject has a history of hypersensitivity or allergies to pioglitazone or related compounds.
7. The subject had any of the following values at the second comprehensive medical follow-up visit in the AD-4833/TOMM40_301 study (or time of last collection in the pivotal 301 study):
 - a. A serum total bilirubin value $>1.5\times$ upper limit of normal (ULN).
 - b. A serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value $>2\times$ ULN.
 - c. Unexplained microscopic/macroscopic hematuria on one repeat examination within 2 weeks.
8. The subject has a disease 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.
9. The subject has received any investigational compound, with the exception of treatment during the AD-4833/TOMM40_301 study, within 30 days prior to Baseline or 5 half-lives prior to Baseline or is currently participating in another study that entails the administration of an investigational or marketed drug, supplement, or intervention including, but not limited to diet, exercise, lifestyle, or invasive procedure.
10. The subject has any cancer that has been in remission for less than 2 years from the extension study Baseline Visit. Subjects with basal cell or stage I squamous cell carcinoma of the skin will be eligible. Subjects with current diagnosis of bladder cancer are not eligible irrespective of the remission status.
11. The subject has a current diagnosis of macular edema or macular degeneration.
12. The subject has a history or current diagnosis of CHF, New York Heart Association class III-IV.

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. To date, there are no approved therapies for subjects with any type of MCI. However, if an approved drug becomes available for the indication of MCI due to AD during the conduct of this trial, it may be offered to the subject by the investigator and the subject may be able to continue their participation in this extension, based on discussions with the medical monitor. If the subject plans to take any other cognitive enhancing treatments, these also MUST be discussed with the medical monitor prior to initiation of such treatments. [Table 7.a](#) describes medications disallowed prior to enrollment and medications disallowed during the course of the study.

Table 7.a Excluded Medications and Treatments

Drug Class	Use Parameters (Subject Disposition)	
	At Extension Study 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, ie, amphetamine and dextroamphetamine [Adderall], methylphenidate [Concerta], dextroamphetamine [Dexedrine])	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 enrollment (Subject eligible if condition met) Allowed , if any prior episodic use, eg, inhaler to treat seasonal allergies. Oral medication should not be taken within 5 days of the Baseline Visit. (Subject eligible)	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]) Allowed , if episodic use, eg, inhaler to treat seasonal allergies. Oral medication should not be taken within 5 days of the study visit. (Subject continues)
Antidepressants	Conditional , if stable dose at least 3 months prior to enrollment (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 enrollment 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 for conditions other than schizophrenia or bipolar disorder (eg, use in a subject with depression) (Subject continues if condition met [a])

Footnotes are on last table page.

Table 7.a Excluded Medications and Treatments (continued)

Drug Class	Use Parameters (Subject Disposition)	
	At Extension Study Baseline Visit	During the Study
Benzodiazepines and nonbenzodiazepines sleep aides (zopiclone, eszopiclone, zolpidem)	Conditional , if stable dose at least 3 months prior to enrollment (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 enrollment (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 enrollment (Subject eligible if condition met)	Prohibited , if <u>chronic</u> use initiated (Subject must be discontinued)
Dopamine agonists [used for restless leg syndrome] (eg, ropinerole [Requip], pramipexole [Mirapex], rotigotine transdermal system [Neupro], gabapentin enacarbil [Horizant])	Conditional , if stable dose at least 3 months prior to enrollment (Subject eligible if condition met [a])	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])
L-Dopa/carbidopa or any other Parkinson's medication for the treatment of Parkinson's 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 enrollment (Subject eligible if condition met)	Prohibited , if <u>chronic</u> use initiated (Subject must be discontinued) Allowed , if <u>episodic</u> use (Subject continues)
CYP2C8 inducers (eg, rifampin)	Conditional , if prior use was stopped 30 days or 5 half-lives, whichever is longer, prior to enrollment (Subject eligible if condition met)	Prohibited , if <u>chronic</u> use initiated (Subject must be discontinued) Allowed , if <u>episodic</u> use (Subject continues)
Insulin	Prohibited , if any prior <u>chronic</u> use (Subject not eligible) Allowed , if any prior <u>episodic</u> use, eg, to treat nonketotic hyperglycemic coma (Subject eligible)	Prohibited , if <u>chronic</u> use initiated (Subject must be discontinued) Allowed , if <u>episodic</u> use (Subject continues)
PPAR-γ agonists (other than study drug)	Prohibited , if initiated	Prohibited , if initiated (Subject must be discontinued)
Triple Oral Antibiotic Therapy	Prohibited , if initiated	Prohibited , if initiated (Subject must be discontinued)
Chemotherapy drugs(b)	No use in the past 2 years before the Extension study Baseline Visit	Prohibited , if initiated (Subject must be discontinued)

Footnotes are on the following page.

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 following 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 (eCRF) using the following categories. For baseline failure subjects, refer to Section 9.1.12.

1. Pretreatment event (PTE) or 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 AEs of special interest please refer to Section 10.2.1.3.

- Liver Function Test (LFT) Abnormalities

Based on local country criteria, subjects in a clinical trial who experience ALT and/or AST $>3\times$ ULN and total bilirubin $>2\times$ ULN and satisfy the following 2 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 $>3\times$ 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 $>3\times$ 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 $>8\times$ ULN, or
 - ALT or AST $>5\times$ ULN and persists for more than 2 weeks, or
 - ALT or AST $>3\times$ ULN in conjunction with elevated total bilirubin $>2\times$ ULN or international normalized ratio (INR) >1.5 , or
 - ALT or AST $>3\times$ ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$).
2. Significant protocol deviation. The discovery post-study entry 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.
 3. Voluntary withdrawal. The subject or project partner wishes to withdraw from the study.

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).

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. Type and date of last contact should be recorded on the eCRF.
5. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
6. Other.

Note: The specific reasons should be recorded in the “specify” field of the eCRF.

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 Early Termination Visit. Discontinued or withdrawn subjects will not be replaced.

In addition to normal follow-up contact attempts, a subject’s project partner should be contacted if the subject is suspected to be lost to follow-up.

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 AD-4833 SR 0.8 mg tablets and placebo orally administered tablets.

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 high-density polyethylene (HDPE) bottle contains 100 tablets and a desiccant and has a child resistant cap. The bottles will be labeled with a blinded 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 blinded 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 SR 0.8 mg and placebo tablets.

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, blinded, parallel group study comparing AD-4833 SR 0.8 mg tablet to placebo. Subjects will keep the treatment assignment they were randomized into in the pivotal AD-4833/TOMM40_301 in a blinded fashion, taking either pioglitazone or placebo.

[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 AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0, Pretreatment Events and Adverse Events.

SAEs 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 interactive web response system (IWRS) at Baseline to obtain the subject study number. The investigator or the investigator's designee will utilize the IWRS to continue each qualified subject into the same treatment assignment from the pivotal AD-4833/TOMM40_301 study at Baseline (Visit 1). During this contact, the investigator or designee will provide the necessary subject-identifying information, to identify the subject's treatment assignment from the pivotal AD-4833/TOMM40_301 study randomization table.

The investigator or investigator's designee will access the IWRS at each dispensing visit to obtain Med ID Numbers for 2 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.

Subjects should be informed as follows that if they miss a scheduled dose:

- If it is almost time for the next dose (within 12 hours), skip the missed dose and take the next dose when it is due.

- Otherwise, take the missed dose as soon as it is remembered, and then go back to taking the investigational drug as usual.
- Do not take a double dose to make up for a missed dose.

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 Baseline 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 site will receive a confirmation email from the IWRS providing the Med IDs 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.

8.3 Randomization Code Creation and Storage

The subjects will not be re-randomized at the beginning of the extension study. Subjects will continue to receive the same medication from the pivotal AD-4833/TOMM40_301 study, either AD-4833 SR 0.8 mg or placebo.

The IWRS vendor generated the randomization schedule for the 301 study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

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 eCRF.

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 and placebo tablets.

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 and 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 and placebo, on a sponsor-approved drug accountability log or within IWRS. The following information will be recorded at a minimum (as applicable to IWRS): protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, 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.

The investigator will be notified of any expiry date or retest date extension of clinical study material during the study conduct. On expiry date notification from the sponsor or designee, the

site must complete 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.

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) may 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: Hypertext Transfer Protocol Secure, File Transfer Protocol Secure, and Secure Sockets Layer. The vendor will store the recordings on a secure, password protected server. Recordings will be deleted 1 year after the last subject visit.

9.1.1.1 *Pharmacogenomic Informed Consent Procedure*

Informed consent to participate in the pharmacogenomics component of the study and to storage of the 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 pharmacogenomic sample is independent of consent to the other aspects of the study

9.1.1.2 *Project Partner Acknowledgement Form/Informed Consent Procedure*

The subjects must have a project partner able to complete an Acknowledgement Form, or an ICF (if needed) 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 self reported, if voluntarily agreed to and to assist with monitoring of study medication, if needed, for as long as the subject is in the study. While it is preferred that the Project Partner attend study visits with the subject, they may elect to provide the subject information noted above, via telephone. Project partners who voluntarily take part in the completion of 2 self reported project partner questionnaires (outline in Section 9.1.14.4), will be required to attend the study visits when the questionnaires are obtained. The Project Partner Acknowledgement Form, or ICF (if needed) 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 9.1.14.4. Should the project partner change during the course of the study, an Acknowledgement Form, or ICF (if needed) 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 collected during the pivotal AD-4833/TOMM40_301 study will be utilized in this study. This information includes, date of birth or age, sex, Hispanic ethnicity, race as described by the subject, years of education and academic degrees, bilingualism, years lived in the country/region, socioeconomic status, drinking habits, and smoking status of the subject. In countries that do not allow collection of date of birth, a subject's age will be collected.

For this extension study, medical history refers to any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent for the extension study, and may include resolved AEs from the pivotal AD-4833/TOMM40_301 study. AEs that resolved during the pivotal study but were significant, that is, represented a new diagnosis (eg, myocardial infarction) and/or resulted in unplanned surgery or procedure (eg, coronary artery bypass graft surgery) or met any of the seriousness criteria should be recorded into the medical history. Non-serious adverse events such as headache or nausea which resolved during the pivotal study do not need to be recorded into the medical history of this extension study.

Ongoing conditions are considered concurrent medical conditions (see Section 9.1.7). Medical history will be collected at Baseline, coinciding with the pivotal AD-4833/TOMM40_301 End of Study Visit.

Medication history will be obtained during the pivotal AD-4833/TOMM40_301 study, and will not be collected during this study. Concomitant medications will be collected (see Section 9.1.6).

9.1.3 Physical Examination Procedure

A baseline physical and neurological examination having been conducted as part of the End of Study Visit for the pivotal AD-4833/TOMM40_301 study, will serve as baseline data for the extension AD-4833/TOMM40_303 study. The examinations 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 each yearly visit (eg, Month 12, 24) of blinded treatment, Unscheduled Visit, and End of Study Visit/Early Withdrawal Visit. Neurological examination will be performed at every 6 month visit and yearly visit, during blinded treatment, Unscheduled Visit, and End of Study Visit/Early Withdrawal Visit.

9.1.4 Weight and Height

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

Weight and height, measured as part of the End of Study Visit for the pivotal AD-4833/TOMM40_301 study, will serve as baseline data for the extension AD-4833/TOMM40_303 study. Within the extension study, weight will be measured at every 6 month visit and yearly visit during blinded treatment, and End of Study Visit/Early Withdrawal 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, measured as part of the End of Study Visit for the pivotal AD-4833/TOMM40_301 study, will serve as baseline data for the extension AD-4833/TOMM40_303 study. Within the extension study, vital signs will be measured at each 6-month, and yearly in-clinic visit of blinded treatment, Unscheduled Visit and at the End of Study Visit/Early Withdrawal 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, 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 eCRF.

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 21 mL, and the approximate total volume of blood for the study is 129 mL. The approximate total volume of blood will vary based on timing of subject's enrollment into the study, and the extent of their duration of treatment. Details of these procedures and required safety monitoring will be given in the laboratory manual. 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 (c)
Red blood cells	ALT	pH
White blood cells count with differentials (Neutrophils, eosinophils, basophils, lymphocytes, monocytes)	Alkaline phosphatase AST Total bilirubin Direct bilirubin (a)	Specific gravity Protein Glucose Blood Nitrite
Hemoglobin	Total protein	
Hematocrit	Albumin	
Platelets	Creatinine	
HbA1c (b)	Blood urea nitrogen γ -Glutamyl transferase Potassium Sodium Glucose Calcium, Parathyroid hormone Thyrotropin, free T4 Vitamin B12, folate (d) Rapid plasma reagin (e)	

(a) Assess only if total bilirubin ≥ 2.0 mg/dL.

(b) To be done at Baseline and at the End of Study Visit.

(c) Microscopic examination (leucocytes, erythrocytes, and casts) should be performed only if any of the urine evaluations are abnormal.

(d) As part of the Unscheduled Visit to rule out other causes of dementia.

(e) At End of Study only.

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.

If subjects experience ALT or AST $>3 \times \text{ULN}$, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, γ -glutamyl transferase, and INR) should be performed within a maximum of 7 days and preferably within 48 to 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 LFTs in relation to ALT or AST $>3 \times \text{ULN}$ in conjunction with total bilirubin $>2 \times \text{ULN}$.)

If the ALT or AST remains elevated $>3 \times \text{ULN}$ 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 LFTs for reporting requirements).

The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

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 eCRF from the subject's ECG trace: heart rate, QT interval, QRS interval, and QT (corrected). The ECG conducted at the End of Study visit for the pivotal AD-4833/TOMM40_301 study will serve as the baseline measurement. ECG will be recorded at each yearly visit (eg, Month 12, 24) of blinded treatment, and End of Study Visit/Early Withdrawal Visit.

9.1.11 Pharmacogenomic Sample Collection

DNA and RNA form the basis for the genes that make the body produce proteins such as enzymes, drug transporters or drug targets, and may be evaluated for the genetic contribution of how the drug is broken down, or how the drug affects the body. This is called a "Pharmacogenomics research study." Specific purposes of this study include:

- Identifying genetic reasons why certain people respond differently to pioglitazone
- Finding out more information about how pioglitazone works.
- Generating information needed for research, development, and regulatory approval of tests to predict response to pioglitazone.
- Identifying variations in genes related to the biological target of pioglitazone.

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.

Prior to sampling of whole blood for pharmacogenomic analysis, every subject must sign informed consent/be consented in order to participate in the study. As the pharmacogenomics study is subject-optional, if a subject declines participation in the pharmacogenomics study, it will not have any bearing on the subject's ability to participate in the main study.

Two whole blood samples (2.5 mL per sample) will be collected at each time point at the Month 12 Visit for the duration of the study, an Unscheduled Visit, and at the End of Study Visit for RNA pharmacogenomic analysis from each subject in the study, into a PAXGene tube. Note: if samples are collected at an Unscheduled Visit, they will not be required to be collected at the End of Study Visit.

See [Appendix E](#) for directions on collecting, handling, and storing pharmacogenomic samples. These samples are optional and should be collected from those subjects who provide independent consent to do so.

Samples for RNA analysis will be stored and analyses may be performed to examine whether variation in gene expression plays a role in the mode of action of pioglitazone, the development of AD, mitochondrial function/dysfunction, and neurodegeneration.

In the event of an unexpected AE or the observation of unusual response, 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, genome-wide association studies 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 absorption, 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 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. Pharmacogenomic data from this sample will not be provided back to the investigator or the subject.

9.1.12 Documentation of Baseline Failure

Investigators must account for all subjects who sign informed consent.

If the subject is found to not be eligible at the Baseline Visit, the investigator should complete the appropriate eCRF. The IWRS/IWRS should be contacted as a notification of baseline failure.

The primary reason for baseline failure is recorded in the eCRF 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, specify reason.
- Study termination.
- Other, specify reason.

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

9.1.13 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for continuation in the extension of the pivotal AD-4833/TOMM40_301 treatment phase. The IWRS should be contacted as a notification for the Baseline Visit. The IWRS will automatically continue the treatment assignment, AD-4833 0.8 mg SR tablets or AD-4833 placebo, for each subject from the pivotal AD-4833/TOMM40_301 study.

If the subject is found to be not eligible for the treatment phase, the investigator should record the primary reason for failure on the appropriate eCRF. The IWRS should be contacted as a notification of baseline failure.

9.1.14 Assessments

9.1.14.1 Cognitive Test at Baseline Visit (Visit 1)

The End of Study Visit of the pivotal AD-4833/TOMM40_301 study will serve as the Baseline Visit for the extension study once appropriate informed consent is signed (or within a 1-month window). At this visit, after extension study informed consent is given by both subjects and their partners, the project partners will also complete the ADCS ADL-MCI and ADCS-CGIC-MCI. The data collected at End of Study Visit of the pivotal AD-4833/TOMM40_301 study, the extension AD-4833/TOMM40_303 study Baseline Visit and results of the most recent cognitive test battery assessment in the pivotal AD-4833/TOMM40_301 study are intended to provide the baseline (ie, before extension study medication) values for each subject on the cognitive assessments.

9.1.14.2 Efficacy Assessments

Cognitive testing will be conducted at each Month 12 Visit and at the End of Study Visit using a broad cognitive test battery. The instruments used in the battery are those commonly used to evaluate AD in the clinical setting. They are commercially available tests with well-documented validation in US and European populations and are in common use globally. The cognitive test battery is identical to the cognitive test battery employed semiannually towards the primary endpoint of the pivotal AD-4833/TOMM40_301 study.

- Brief Visuospatial Memory Test - Revised (BVMT-R [28]): The original, as well as 1 of the 5 equivalent alternate forms of the BVMT-R will be used to assess immediate and delayed nonverbal memory. The subject is presented with a card depicting 6 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. Between 15-30 minutes after the initial presentation, the subject is asked to draw the designs again. Immediately thereafter, a yes/no recognition trial is administered. Form 4 is the BVMT-R alternate form that will also be used along with Form 1 in this study based on published validation data suggesting these 2 forms (1 and 4) have optimal psychometric characteristics over the other alternative versions (highest alternative form reliability). The forms will be alternated between visits according to a predetermined counterbalance schedule.
- California Verbal Learning Test – 2nd Edition (CVLT-II [29]): (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 4 words from each of 4 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 1 trial. This second list contains words drawn from 2 semantic categories of List A (animals, vegetables) and 2 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 between 15-30 minutes later. Indices of learning include total number of words correctly recalled across Trials 1 to 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 predetermined counterbalance schedule.

- Digit Span [30]: The Wechsler Adult Intelligence Scale (WAIS) –Third Edition Digit Span subtest is used to assess auditory attention and working memory. Both forward and backward span is assessed. Both tests consist several number sequences that the psychometrist reads aloud 1 at a time. After each sequence is read, the subject must repeat the digits back in the same (forward) or reverse (backward) order.
- Multilingual Naming Test (MINT [31]): The MINT is a test of confrontation naming ability that was designed to measure this aspect of language 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. Preliminary studies support its sensitivity to detecting mild naming deficits [31]. The test is comprised of 32 items, which are presented to the participant in increasing order of difficulty. The maximum score is 32.
- Trail Making Test (TMT [32]) A and B: 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 2 categories in sequential order (1-A, 2-B, 3-C, and so on) and time to completion is recorded.
- Semantic Fluency [33]: Semantic fluency measures verbal production, semantic memory, and language. Subjects are asked to name as many examples of animals as possible in 1 minute.
- Lexical/Phonemic Fluency [33]: For lexical fluency, the subject is asked to produce as many words as possible that begin with a specified letter. Subjects will have one minute to produce exemplars for each letter (eg, F, A, and S for English). The number of words from each letter will be combined for a total score.
- BVMT-R Constructional Praxis: Brief Visuospatial Memory Test - Revised (BVMT-R [28]): Two-dimensional constructional praxis will be assessed using Form 1 of the 2 equivalent alternate forms of the BVMT-R. The subject is presented with a card depicting 6 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 accuracy of reproduction of the 6 figures.
- Clock drawing test [34] is an easily administered test that taps elements of visuospatial analysis, planning, organization, and semantic knowledge. The scoring method evaluates the subject's ability to reproduce 3 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 3 error subtypes, with higher scores indicating better performance.

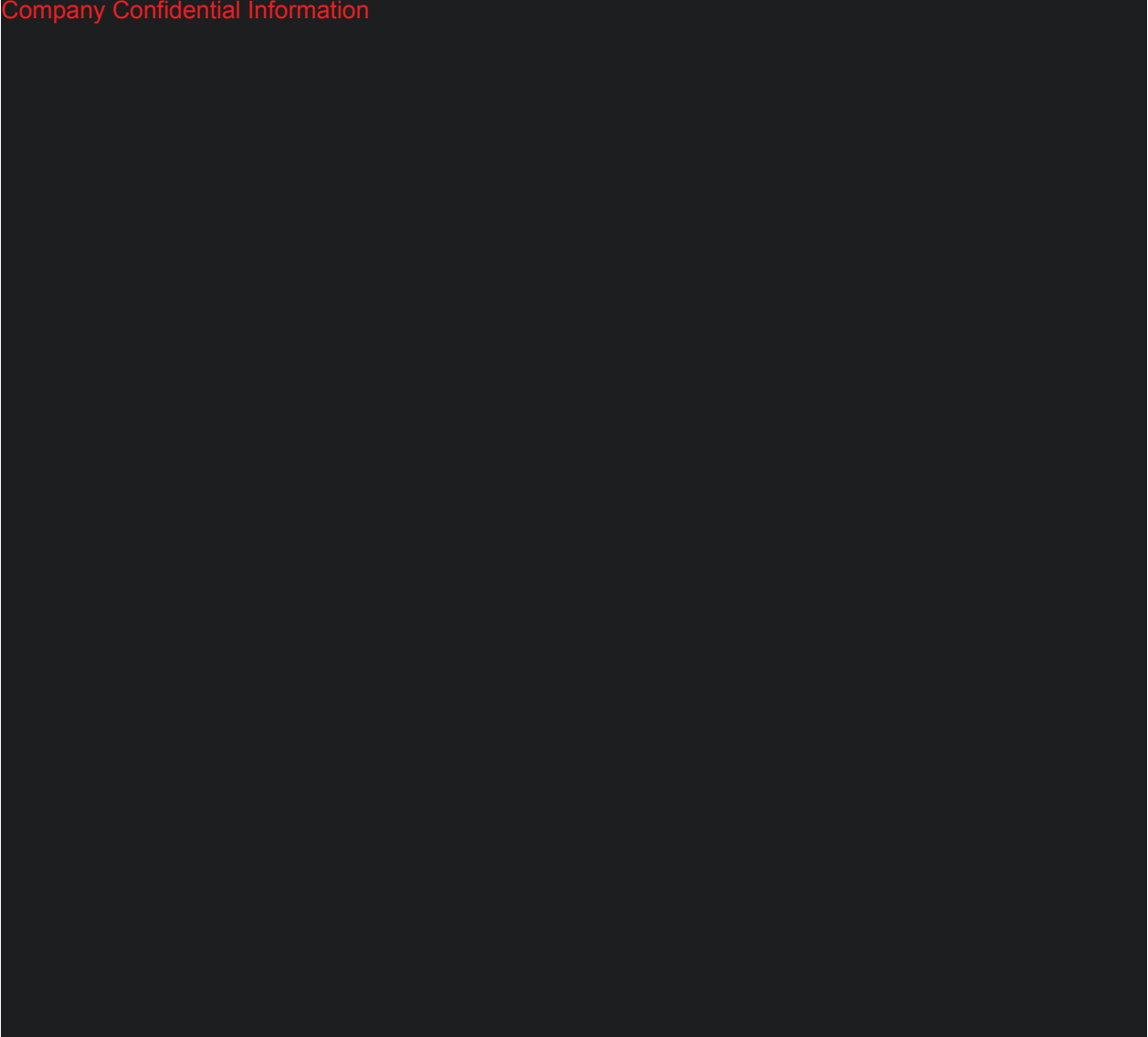
9.1.14.3 Subject-Reported Outcome Questionnaires

In addition to occurring yearly with the cognitive test battery, the following assessment will also be conducted at each 6 month study visit and End of Study Visit to monitor for psychiatric symptoms that might confound the diagnosis or require treatment:

- Geriatric Depression Scale (GDS [35]): This is a 15-item self-administered yes/no question test constructed for brief screening of depression in elderly persons.

9.1.14.4 Project Partner Reported Questionnaires

In addition to occurring yearly with the cognitive test battery, the following assessments will also be conducted with the subject's project partner at each 6-month study visit and the End of Study Visit:

- Company Confidential Information

-
-
-
-
-

Company Confidential Information

9.1.14.5 Other Assessments

In addition to occurring yearly with the cognitive test battery, the following assessments will also be conducted according to the Schedule of Study Procedures (the CDR and ADCS CGIC-MCI, exclusively, will also be conducted at an Unscheduled Visit) to monitor for psychiatric symptoms that might confound the diagnosis or require treatment:

- Mini-Mental State Examination (MMSE [40]): This measurement of global cognitive function includes 11 items that tap orientation to time and place, language, verbal registration, memory, and praxis. Scores on this instrument range from 0 to 30, prior to adjustment, with lower scores indicating greater cognitive impairment. Scores below 24 are generally considered impaired and suggestive of dementia. However, scores are influenced by education, age, and premorbid function. Individuals with high premorbid function can have an early dementia and scores above the commonly accepted cut point; individuals with low education or older age can have low scores and yet be cognitively normal. The MMSE will be administered by a certified tester.
- Clinical Dementia Rating (CDR [41]): The CDR is a clinician-completed structured interview with participant and informant designed to assess an individual's cognitive and functional performance in 6 areas for purposes of determining the severity of dementia symptoms. The 6 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. A CDR global score of 0 indicates normal function. Whereas, a CDR global score of 0.5 indicate 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 6 individual domain scores, resulting in a "sum of boxes" (CDR-SB) score. Clinicians will complete the global rating, as well as determine individual box ratings.
- Assessment of HRQoL will be done using the EQ-5D measure from the EuroQOL Group. These assessments will be completed by all subjects enrolled in the study.
- Healthcare RU during the study period will be measured by the 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. 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.
- Alzheimer 's disease Cooperative Study Clinical Global Impression of Change – Mild Cognitive Impairment (ADCS CGIC-MCI [42]): This measure captures change in the

participant's condition between the Baseline Visit, coinciding with the pivotal AD-4833/TOMM40_301 End of Study Visit, and each 6-month follow-up time point, Unscheduled Visit and End of Study Visit. It is intended to determine whether any treatment effects are detectable by an experienced clinician during a comprehensive interview. The clinician rates the subject on a 7 point scale (1: marked improvement ranging to 7: marked deterioration). At Baseline, each of the subsequent 6 month visits, Unscheduled Visit and End of Study Visit, the clinician collects information from the subject and informant in an interview fashion. At the Baseline Visit, all available information is used by the physician to develop a comprehensive assessment of how the individual is doing. At follow-up the clinician focuses on observations of the subject's cognitive, functional, and behavioral performance at the time of the evaluation and in the prior 6 months to make an assessment of whether the individual appears to be changing from the study Baseline. The global impression of the subject will be completed by the investigator at the end of each follow-up study visit.

9.1.14.6 Assessment of Suicidal Ideation and Behavior

In addition to occurring yearly with the cognitive test battery, the following assessment will also be conducted at each 6-month study visit, End of Study Visit and Follow-up Visit, to monitor for psychiatric symptoms that might confound the diagnosis or require treatment:

- The Columbia–Suicide Severity Rating Scale (C-SSRS; [43]) 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 sub questions assessing the severity. The tool is administered via interview with the subject.

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-serious AEs in accordance with the standard AE reporting requirements (eg, if a pre-existing suicidal ideation recorded on the baseline 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 eCRF 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, that is, self-imposed cigarette burns, will be collected as nonserious AEs.

9.1.14.7 MRI Assessment

Subjects enrolled in the extension study will be required (unless medically contraindicated) to participate in a vMRI scan where volumetric measurements will be taken, for the purpose of assessing atrophy of the brain. vMRI scans will take place at the following time points, as noted in the Schedule of Study Procedures ([Appendix A](#)): extension study Baseline (last MRI collected at

End of Study Visit or second comprehensive medical follow-up visit for the pivotal AD-4833/TOMM40_301 study) and at extension study End of Study/Early Withdrawal Visit.

9.1.14.8 Health Economics and Outcomes Research Assessments

Both the HRQoL and RU assessments will be completed by all subjects enrolled in the study. The HRQoL instruments will not be used as a primary means to collect AEs. However, should the investigator become aware of potential AEs through the information collected with this instrument, proper follow-up with the patient for medical evaluation should be undertaken. If it is determined through this follow-up that an AE not previously reported has been identified, normal reporting requirements should be applied.

9.1.14.9 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 [44]. 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% [45]. Weight-bearing exercise can be as simple as brisk walking. Diet and exercise evaluation will be performed at every 6 and 12 month visit during the treatment phase, and End of Study Visit/Early Withdrawal Visit.

9.1.15 Order of Assessments

Sites should make every attempt to adhere to the assessment schedule in [Table 9.b](#). Should an interruption occur during the visit, the subject may return to the site within 2 weeks to complete the assessments. 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 tests.

Table 9.b Order of Assessments

Cognitive Test/Questionnaire	Visit	Assessor
MMSE	Every 6 and 12 month visit during the Treatment Period, End of Study/Early Withdrawal 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. Clock Drawing Test	Every yearly visit during the treatment period, End of Study/Early Withdrawal Visit	Certified tester
GDS	Every 6 and 12 month visits during the Treatment Period, End of Study/Early Withdrawal Visit	Study subject
EQ-5D	Month 24 visit during the Treatment Period, End of Study/Early Withdrawal Visit	Study subject
ADCS ADL-MCI	At 303 study Baseline Visit (ADCS ADL- MCI), then every 6 and 12 month visits during the Treatment Period, End of Study/Early Withdrawal Visit (ADCS ADL-MCI)	Trained tester

Table 9.b Order of Assessments (continued)

Cognitive Test/Questionnaire	Visit	Assessor
NPI-Q	Every 6 and 12 month visits during the Treatment Period, End of Study/Early Withdrawal Visit	Project partner
ADCS RUI	Every 6 and 12 month visits during the Treatment Period, End of Study/Early Withdrawal Visit	Trained tester
CDR	Every 6 and 12 month visits during the Treatment Period, Unscheduled Visit, and End of Study/Early Withdrawal Visit	Investigator/subinvestigator
ADCS CGIC-MCI	At 303 study Baseline Visit, then every 6 and 12 month visits during the Treatment Period, End of Study/Early Withdrawal Visit and Unscheduled Visit	Trained tester
AE assessment	Every 3, 6, 9, and 12 month visit, Unscheduled Visit, End of Study/Early Withdrawal Visit and Follow-up Visit	Investigator/subinvestigator
C-SSRS	Every 6 and 12 month visits during the Treatment Period, End of Study/Early Withdrawal Visit and Follow-up Visit	Certified tester

9.1.15.1 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 validated translations provided by Takeda (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 eCRF.

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.

9.1.16 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.

9.1.17 Imaging

Prior to the start of the study, each site should identify a study MRI machine. Each MRI machine will be qualified by the imaging vendor before starting the study, if not already qualified as part of participation in the pivotal AD-4833/TOMM40_301 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 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 eCRF. Detailed instructions for the processing and shipping of images will be provided separately.

Subjects who have contraindications for MRI procedure (such as unremovable ferromagnetic dental work, cardiac pacemakers, etc) will not be excluded from the study.

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 eCRF. The project partner will also be asked to assess the subject's compliance.

Compliance will be reviewed during each 3, 6, 9, and 12 month visit and at the End of Study/Early Withdrawal Visit. During telephone visits that will occur yearly on the 3 month and 9 month interval, treatment compliance should be evaluated during the conversation.

If a subject is persistently noncompliant with the study medication, defined as missing >20% of dosing for the required visit period (eg, 6 months), it may be appropriate to withdraw the subject from the study. 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.

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 Study Entrance (Baseline)

Study entrance (Baseline) will take place on Day 0, and will coincide with the End of Study Visit of the pivotal AD-4833/TOMM40_301 study, which will serve as the Baseline Visit for the

extension study once appropriate informed consent is signed. See [Appendix A](#) for a list of procedures that will be performed. Subjects will be entered into IWRS after informed consent is provided. It is anticipated that this visit will take about 4 hours in length.

While it is preferred that subjects and their project partners consent to the AD-4833/TOMM40_303 study while attending the AD-4833/TOMM40_301 study End of Study Visit, subjects will be allowed to return to the clinic and consent for the extension study within 1 month of the AD-4833/TOMM40_301 End of Study Visit. They will complete the AD-4833/TOMM40_303 baseline evaluations (that were not completed at the AD-4833/TOMM40_301 End of Study Visit or last Comprehensive Medical Follow-up Visit) once informed consent is provided and within the 1 month window.

9.3.2 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.

9.3.3 Unscheduled Visit

There are 2 types of Unscheduled Visits in this study: 1) Unscheduled Visits conducted to address any emerging concerns, including safety, and 2) Unscheduled Visits conducted to evaluate suspected cognitive or functional decline after meeting a trigger relating to cognitive status (see Section [6.2.3](#)).

9.3.3.1 *Unscheduled Visits for Emerging 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 (noncognitive) concerns, the investigator is expected to conduct whatever assessments are necessary to manage the needs of the subject appropriately.

9.3.3.2 *Unscheduled Visit for Suspected Cognitive or Functional Decline*

An unscheduled visit may be conducted if worsening of cognitive impairment or potential AD dementia is suspected in between regularly scheduled visits when 1 of the triggers described in Section [6.2.3](#) has been met. A CDR Global score of ≥ 1.0 will be required in order to set a consistent minimum standard for AD dementia as an endpoint in the study. This type of Unscheduled Visit will include the assessments noted in [Appendix A](#). It is anticipated this visit will be about 3 to 4 hours in length, if an MRI is completed during the visit.

9.3.4 Final Visit or Early Termination

The End of Study/Early Withdrawal Visit is an ad hoc visit that, for study completion, will take place as soon as possible after a regularly scheduled or unscheduled study visit, either at study end, at extension study termination, after a subject has withdrawn prematurely from the study, or after

the subject has been diagnosed with AD or non-AD dementia. The efficacy assessments will not need to be captured at this visit in cases where the secondary endpoint of AD dementia diagnosis has been reached or if it is less than 3 months from the last administration of the assessment.

For all subjects receiving study medication, the investigator must complete the End of Study eCRF page.

9.3.5 Follow-up

Follow-up will begin the first day after the End of Study/Early Withdrawal Visit and will continue until 2 weeks later.

Subjects will be contacted for a Safety Follow-up call approximately 2 weeks after the End of Study/Early Termination Visit. See [Appendix A](#) for list of procedures that will be performed and documented. Subjects who withdraw their consent should still be contacted for a Safety Follow-up call, but the contact should only be recorded in the subjects records (and not the eCRF), according to data protection regulations.

9.3.6 Poststudy Care

The study medication will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

9.4 Biological Sample Retention and Destruction

9.4.1 Pharmacogenomics

In this study, specimens for analysis will be collected as described in [Appendix E](#). The samples will be retained at a central storage vendor 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.

The sponsor and researchers working with the sponsor will have access to the samples collected and any test results. All samples collected during the study will be stored securely with limited access and the sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

Subjects who consented and provided a pharmacogenomic sample for RNA analysis can withdraw their consent and request disposal of a stored sample at any time. Notify sponsor of consent withdrawal.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Events

A pretreatment event (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 eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.

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 Special Interest AEs

A special interest AE (serious or nonserious) 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. AEs of special interest are listed in Section 10.2.1.3.

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.

10.1.6 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.

10.1.7 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 (Baseline Visit) or until 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 (Baseline Visit [Day 0]). Collection of AEs will commence from the time that the subject is first administered study medication (Baseline Visit). Routine collection of AEs will continue until the 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. Nonserious 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 eCRF, 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 Special Interest AE Reporting

Special Interest Adverse Event (serious or nonserious) 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.

This extension study will be conducted in elderly subjects diagnosed with MCI due to AD. Pioglitazone appears to be safe and well tolerated in the elderly population, based on the available information from healthy volunteers and subjects with T2DM in Takeda-sponsored trials or from patients with AD in Takeda-supported studies [13,14]. Based on the available safety information in the diabetic population, the following safety procedures will be implemented when specific AEs of special interest 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 class III-IV will be excluded from the study. If a subject develops CHF 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.
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 undergo a fundoscopic examination. 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 current 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 $>3 \times \text{ULN}$, 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 $>3 \times \text{ULN}$ 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 [44]. Among women aged 75 years and older, muscle strengthening and balance exercises have been shown to reduce the risk of falls and fall-related injuries by 75% [45]. 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 tested 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 the subjects with the following AEs will be closely monitored using the following event categories:
 - 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 this special interest AE, which occurs during the Treatment Period or the Follow-up Period, is considered to be clinically significant based on the criteria below, it should be recorded in a Special Interest Form or an SAE Form. The form should be completed and reported to Takeda Pharmacovigilance or appropriate safety vendor within 24 hours.

Special interest AE criteria include:

- Laboratory value threshold if applicable.
- Premature termination for the special interest AE, if applicable.
- Any other specific criteria.

The special interest AEs have to be recorded as AEs in the eCRF. An evaluation form along with all other required documentation must be submitted to the sponsor.

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 form must be completed, in English and 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.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.1.

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

If a subject is noted to have ALT or AST elevated $>3\times$ ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases eCRF 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 $>3\times$ ULN and total bilirubin $>2\times$ 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 eCRF 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 form or provide other written documentation and fax it immediately 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, 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 investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products 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 Independent Data and 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 AEs of special interest. This group will include individuals with expertise in, endocrinology, neuro-radiology, cardiology, AD specialist, and statistics.

Details of the Independent DSMB will be captured in a charter prior to the start of the trial.

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 Drug Dictionary.

12.1 CRFs (Electronic and Paper)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are entered directly onto eCRFs.

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 to eCRFs 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 eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs 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 eCRFs. The completed eCRFs 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 eCRFs, 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 study database lock or 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 data review will be conducted prior to clinical database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods. Analogous to the pivotal AD-4833/TOMM40_301 study, the primary efficacy analysis population will be for high-risk non-Hispanic/Latino Caucasian subjects. An additional analysis will be done for all high-risk subjects (including subjects of all races and ethnicities).

13.1.1 Analysis Sets

All efficacy variables will be analyzed using the full analysis set (FAS). The FAS will consist of all participating subjects. The FAS will be analyzed according to the treatment to which each subject was randomized in the pivotal 301 study. All safety variables will be analyzed using the safety population, which will consist of all subjects who receive at least 1 dose of blinded study medication. The safety population will be analyzed according the actual treatment each subject received.

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

The primary null hypothesis in this study assumes that there is no difference in the cognitive decline of MCI due to AD between the placebo-treated and active-treated subjects in the high risk group. The alternative hypothesis is that there is a difference in cognitive decline between pioglitazone and placebo in the high-risk group. The ability of demonstrating a difference between active and placebo may be limited by study design as the determination of number of subjects is not based on statistical considerations and the subjects are not randomized at the beginning of this study.

In order to test the primary null hypothesis, the change in the composite cognitive test battery score from extension study baseline to 24 months will be analyzed using mixed models repeated measures (MMRM), controlling for age group, educational level, study site, and sex. If this test is significant at the 5% level, it can be concluded that pioglitazone was effective in reducing the change in cognitive decline in subjects with a diagnosis of MCI due to AD at Baseline.

Composite scores will be derived from the test battery consistent with practices used in the pivotal AD-4833/TOMM40_301 study. Each test in the battery falls into 1 of the following cognitive

domains: Episodic Memory (CVLT-II, BVMT-R), Executive Function (Trail Making Part B, Digit Span Backwards), Language (Animals, Lexical/Phonemic Fluency), Attention (Digit Span Forward, Trail Making Part A), and Visuospatial (Clock Drawing, BVMT-Copy). Only the domains of episodic memory, executive function, language, and attention will be used for the calculation of composite score (ie, Clock Drawing, 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 2 tests for each domain, the composite can still be calculated if 1 test is missing. In the case of memory, however, both tests are required to calculate the composite.

All data collected in the study will be listed and summarized either by mean, SD, median, minimum, and maximum for continuous data or by frequency tables for categorical data.

Similar to the primary efficacy endpoint, the secondary endpoints of change from Baseline will be analyzed using available data and MMRM for each of the following 2 choices for Baseline:

- Baseline of the AD-4833/TOMM40_303 study.
- Baseline of the AD-4833/TOMM40_301 study.

And 2 choices for evaluation end period, as appropriate:

- Two-year postenrolment into the AD-4833/TOMM40_303 study.
- End of the AD-4833/TOMM40_303 study.

Other secondary endpoints will examine change from Baseline by visit (ie, Months 6, 12, 18, 30, 36, and up to the last visit, depending on the schedule of visits for any given endpoint) and will be analyzed using MMRM. For the time to onset of AD dementia secondary endpoint, time-to-event data will be analyzed to compare the placebo and active groups using a Cox proportional hazards model, including an investigation of the effects of covariates (including age, educational level, study site, and sex). As for the primary analysis, the secondary endpoints will be tested at the 2-sided 0.05 level. Note that the population for this study consists of subjects who had an event of MCI due to AD in the pivotal AD-4833/TOMM40_301 study and consented to participate in the AD-4833/TOMM40_303 study. This study is not powered to show a difference with respect to time-to-event of AD dementia, and the time-to-event analysis will be provided for informational purposes.

The primary endpoint of cognitive decline at 24 months is a continuous variable and will include all available data. Subjects who discontinue from the extension study prior to its conclusion will be censored for the analysis of time to AD dementia diagnosis. For completeness, follow-up information will be collected on as many subjects as possible, including the reason for discontinuation. For other continuous variables such as test scores, MMRM using all available data will be used to evaluate changes by visit.

The rules for handling missing items from each of the scales are designed so that as much reliable data as possible can be used in the analyses 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.

There may still be missing values for the continuous variables and the analyses for continuous variables are based on a Missing at Random 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.

The following variables will also be analyzed in a manner similar to the primary efficacy endpoint and secondary efficacy endpoints and using MMRM: CDR-SB, ADCS CGIC-MCI, ADCS ADL-MCI and NPI-Q, and GDS.

13.1.4 Other Analyses

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

13.1.5 Safety Analysis

Adverse Events

AEs will be reported throughout the study by the subject and/or project partner.

Treatment-emergent AEs are any new or worsened events that occurred within 30 days following discontinuation of study medication from the subject's completion of the AD-4833/TOMM40_303 extension study. 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 extension study 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 Determination of Sample Size

The sample size for this study was not based on statistical considerations. Subjects who have an adjudicated diagnosis of MCI due to AD (without a diagnosis of AD dementia) in the pivotal AS-4833/TOMM40_301 study may be eligible to enroll into this extension study depending on their site's participation in the 303 study. In the pivotal AD-4833/TOMM40_301 study, approximately 222 subjects (approximately 213 high-risk and approximately 9 low-risk subjects) are expected to have an event of MCI due to AD or AD dementia. It is expected that approximately 149 subjects (ie, 67% of the 222 subjects) will consent to participate in this 303 extension study.

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 eCRFs. 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 (contract research organization) 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 eCRFs 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) 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 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 form, 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 the 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 drug/notification no protocol activities, 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. 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 eCRF).

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.

16.0 REFERENCE3S

1. Alzheimer Association Research Center. Science and progress: What we know today about Alzheimer's disease and dementia. Accessed October 2013. Available at: http://www.alz.org/research/science/alzheimers_research.asp.
2. Landreth G, Jiang Q, Mandrekar S, Heneka M. PPARgamma agonists as therapeutics for the treatment of Alzheimer's disease. *Neurotherapeutics* 2008;5(3):481-9.
3. Alzheimer's Association. 2013 Alzheimer's Disease Facts and Figures. Published 2013. Accessed October 2013. Available at: http://www.alz.org/downloads/facts_figures_2013.pdf.
4. van Duijin C. Epidemiology of the dementias: recent developments and new approaches. *J Neurol Neurosurg Psychiatry* 1996;60(5):478-88.
5. Alzheimer's Disease International. World Alzheimer Report 2013: Journey of Caring: An analysis of long-term care for dementia. 2013:1-92.
6. Cummings JL, Cole G. Alzheimer disease. *JAMA* 2002;287(18):2335-8.
7. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7(3):280-92.
8. Wilson RS, Leurgans SE, Boyle PA, Bennett DA. Cognitive decline in prodromal Alzheimer disease and mild cognitive impairment. *Arch Neurol* 2011;68(3):351-6.
9. Dubois B, Feldman HH, Jacova C, Cummings JL, Dekosky ST, Barberger-Gateau P, et al. Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol* 2010;9(11):1118-27.
10. Petersen RC. Early diagnosis of Alzheimer's disease: is MCI too late? *Curr Alzheimer Res* 2009;6(4):324-30.
11. AD-4833-TOMM40 Global Investigator's Brochure 12th Edition. Takeda Global Research & Development Center, Inc, 22 November 2013.
12. Roses AD, Saunders AM, Huang Y, Strum J, Weisgraber KH, Mahley RW. Complex disease-associated pharmacogenetics: drug efficacy, drug safety, and confirmation of a pathogenetic hypothesis (Alzheimer's disease). *Pharmacogenomics J* 2007;7(1):10-28.
13. Geldmacher DS, Fritsch T, McClendon MJ, Landreth G. A randomized pilot clinical trial of the safety of pioglitazone in treatment of patients with Alzheimer disease. *Arch Neurol* 2011;68(1):45-50.
14. Sato T, Hanyu H, Hirao K, Kanetaka H, Sakurai H, Iwamoto T. Efficacy of PPAR-gamma agonist pioglitazone in mild Alzheimer disease. *Neurobiol Aging* 2009.

15. Watson GS, Cholerton BA, Reger MA, Baker LD, Plymate SR, Asthana S, et al. Preserved cognition in patients with early Alzheimer disease and amnesic mild cognitive impairment during treatment with rosiglitazone: a preliminary study. *Am J Geriatr Psychiatry* 2005;13(11):950-8.
16. Risner ME, Saunders AM, Altman JF, Ormandy GC, Craft S, Foley IM, et al. Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. *Pharmacogenomics J* 2006;6(4):246-54.
17. Gold M, Alderton C, Zvartau-Hind M, Egginton S, Saunders AM, Irizarry M, et al. Rosiglitazone monotherapy in mild-to-moderate Alzheimer's disease: results from a randomized, double-blind, placebo-controlled phase III study. *Dement Geriatr Cogn Disord* 2010;30(2):131-46.
18. Periodic Safety Update Report for Pioglitazone HCl. 28th Report for the Period 01 February 2013 to 31 July 2013. Takeda Pharmaceutical Co., Ltd., 23 September 2013.
19. Company Core Data Sheet for Pioglitazone Hydrochloride. Takeda Pharmaceutical Co., Ltd., 24 July 2013.
20. Sato T, Hanyu H, Hirao K, Kanetaka H, Sakurai H, Iwamoto T. Efficacy of PPAR-gamma agonist pioglitazone in mild Alzheimer disease. *Neurobiol Aging* 2011;32(9):1626-33.
21. National Institute on Aging. Pioglitazone or exercise to treat mild cognitive impairment (MCI) (POEM). *Clinical Trials.gov*. Updated 30 June 2009. Accessed 23 April 2012. Available at:
<http://www.clinicaltrials.gov/ct2/show/NCT00736996?term=nct00736996&rank=1>.
22. Albert MS, Dekosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7(3):270-9.
23. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Jr., Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7(3):263-9.
24. Aisen PS, Andrieu S, Sampaio C, Carrillo M, Khachaturian ZS, Dubois B, et al. Report of the task force on designing clinical trials in early (predementia) AD. *Neurology* 2011;76(3):280-6.
25. Abbatecola AM, Lattanzio F, Molinari AM, Cioffi M, Mansi L, Rambaldi P, et al. Rosiglitazone and cognitive stability in older individuals with type 2 diabetes and mild cognitive impairment. *Diabetes Care* 2010;33(8):1706-11.
26. Visser PJ, Scheltens P, Verhey FR. Do MCI criteria in drug trials accurately identify subjects with predementia Alzheimer's disease? *J Neurol Neurosurg Psychiatry* 2005;76(10):1348-54.

27. Mayeux R, Reitz C, Brickman AM, Haan MN, Manly JJ, Glymour MM, et al. Operationalizing diagnostic criteria for Alzheimer's disease and other age-related cognitive impairment-Part 1. *Alzheimers Dement* 2011;7(1):15-34.
28. Benedict R. Brief Visuospatial Memory Test - Revised (BVMT-R). Odessa, Florida: Psychological Assessment Resources, Inc; 1997.
29. Delis D, Kramer J, Kaplan E, Ober B. California Verbal Learning Test – Second Edition (CVLT –II). 2nd ed. Washington, DC: Pearson Education Inc; 2000.
30. Wechsler D. Adult Intelligence Scale. 3rd ed. San Antonio, TX: Psychological Corporation; 1997.
31. Gollan TH, Weissberger G, Runnqvist E, Montoya RI, Cera CM. Self-ratings of spoken language dominance: A multi-lingual naming test (MINT) and preliminary norms for young and aging Spanish-English bilinguals. *Bilingualism: Language and Cognition* 2012;15:594-615.
32. Reitan RM, Wolfson D. The Halstead-Reitan neuropsychological test battery for adults: theoretical, methodological, and validation bases. In: Goldstein G, Beers S, editors. *Comprehensive Handbook of Psychological Assessment. Intellectual and Neuropsychological Assessment*. Hoboken, NJ: John Wiley and Sons; 2004:Vol. 1.
33. Strauss E, Sherman EMS, Spreen O. A compendium of neuropsychological tests: Administration, norms, and commentary. 3rd ed. New York: Oxford University Press; 2006.
34. Cahn DA, Salmon DP, Monsch AU, Butters N, Wiederholt WC, Corey-Bloom J, et al. Screening for dementia of the alzheimer type in the community: the utility of the Clock Drawing Test. *Arch Clin Neuropsychol* 1996;11(6):529-39.
35. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* 1982;17(1):37-49.
36. Galasko D, Bennett DA, Sano M, Marson D, Kaye J, Edland SD. ADCS Prevention Instrument Project: assessment of instrumental activities of daily living for community-dwelling elderly individuals in dementia prevention clinical trials. *Alzheimer Dis Assoc Disord* 2006;20(4 Suppl 3):S152-69.
37. Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillan A, Shelley T, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. *J Neuropsychiatry Clin Neurosci* 2000;12(2):233-9.
38. Cummings JL. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology* 1997;48(5 Suppl 6):S10-6.
39. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993;4(5):353-65.

40. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12(3):189-98.
41. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* 1993;43(11):2412-4.
42. Schneider LS, Raman R, Schmitt FA, Doody RS, Insel P, Clark CM, et al. Characteristics and performance of a modified version of the ADCS-CGIC CIBIC+ for mild cognitive impairment clinical trials. *Alzheimer Dis Assoc Disord* 2009;23(3):260-7.
43. Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry* 2011;168(12):1266-77.
44. The North American Menopause Society. Management of osteoporosis in postmenopausal women: 2010 position statement of The North American Menopause Society. *Menopause* 2010;17(1):25-54; quiz 5-6.
45. Robertson MC, Campbell AJ, Gardner MM, Devlin N. Preventing injuries in older people by preventing falls: a meta-analysis of individual-level data. *J Am Geriatr Soc* 2002;50(5):905-11.

Appendix A Schedule of Study Procedures

Month	Baseline (Coincides With 301 End of Study Visit (a))	<i>Repeated Yearly</i>				Unscheduled Visit (b)	End of Study Visit/Early Withdrawal (c)	Follow-up Visit EoS/EW+0.5 (e)
		3 (d)	6	9 (d)	12			
Visit Window	+30 days	±2 wks	±2 wks	±2 wks	±2 wks			
Informed consent (subject)	X							
Informed consent (pharmacogenomic)	X							
Informed consent (project partner)	X							
Incl/excl criteria	X							
Medical history	X							
Concurrent conditions	X							
Body weight and height(g)	X (f)		X		X		X	
Review of concurrent medications	X	X	X	X	X	X	X	X
Contact IWRS	X		X		X		X	
Dispense study drug	X		X		X			
Collect study drug			X		X		X	
Compliance review		X	X	X	X		X	
AEs (including AEs of Special Interest)	X (f)	X	X	X	X	X	X	X
Physical examination	X (f)				X	X	X	
Vital signs	X (f)		X		X	X	X	
Neurological examination	X (f)		X		X	X	X	
12-lead ECG	X (f)				X		X	
vMRI (h)	X (f)						X	
Clinical chemistry, hematology and urinalysis labs	X (f)				X	X (i)	X	
HbA1c test (j)	X						X	
Pharmacogenomic RNA samples					X	X (k)	X (l)	
C-SSRS	X (f)		X		X		X	X
Diet and exercise evaluation	X (f)		X		X		X	
MMSE (d)	X (f)		X		X		X	
CVLT-II	X (f)				X		X	
BVMT-R	X (f)				X		X	
Lexical fluency	X (f)				X		X	
Semantic fluency	X (f)				X		X	
MINT	X (f)				X		X	
Digit Span	X (f)				X		X	
Trail Making Tests	X (f)				X		X	
Clock Drawing	X (f)				X		X	

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

Month	Baseline (Coincides With 301 End of Study Visit (a)	<i>Repeated Yearly</i>				Unscheduled Visit (b)	End of Study Visit/Early Withdrawal (c)	Follow-up Visit EoS/EW+0.5 (e)
		3 (d)	6	9 (d)	12			
GDS	X (f)		X		X		X	
CDR	X (f)		X		X	X	X	
ADCS ADL- MCI	X		X		X		X	
NPI-Q	X (f)		X		X		X	
ADCS CGIC-MCI	X		X		X	X(m)	X	
ADCS RUI	X (f)		X		X		X	
EQ-5D (subject) (o)	X (f)						X	
EQ-5D (project partner) n)	X						X	
WPAI(n)	X						X	

EoS=End of Study, EW=Early Withdrawal.

- (a) Subjects who are unable to consent for the extension study or to complete all extension study baseline visit evaluations at the same time as their End of Study Visit for the pivotal AD-4833/TOMM40_301 study will be allowed to return to the clinic and to complete these evaluations within a 1 month window.
- (b) Procedures listed should be conducted in the event of an Unscheduled Visit for suspected cognitive or functional decline. Procedures related to Unscheduled Visits for any other emerging concern, such as safety, are at the discretion of the investigator.
- (c) End of Study/Early Withdrawal Visit is an ad hoc visit that, for study completion, would take place as soon as possible after a regularly scheduled or unscheduled study visit, either at study end, at extension study termination, after a subject has withdrawn prematurely from the study or after the subject has been diagnosed with AD or non-AD dementia. The efficacy assessments will not need to be captured at this visit in cases where the secondary endpoint of AD dementia diagnosis has been reached or if it is less than 3 months from the last administration of the assessment.
- (d) Telephone contact with the subject (should be every 3 months between the semiannual clinic visits for the duration of the study)
- (e) Telephone call approximately 2 weeks after the End of Study or Early Withdrawal Visit.
- (f) These assessments, conducted as part of the end of study visit for the pivotal AD-4833/TOMM40_301 study or at most recent comprehensive medical Follow-up Visit, will serve as baseline data for the extension AD-4833/TOMM40_303 study.
- (g) Height will only be collected at the end of study visit for the pivotal AD-4833/TOMM40_301 study or at most recent comprehensive medical Follow-up Visit, and will serve as baseline data for the extension AD-4833/TOMM40_303 study
- (h) vMRI assessments will take place at extension study Baseline (ie, coinciding with the End of Study Visit for the pivotal AD-4833/TOMM40_301 study or most recent MRI or that obtained at the second consecutive comprehensive medical follow-up Visit) and at extension study end.
- (i) Standard blood chemistry and tests used in evaluating cognitively impaired and dementia patients (eg, thyroid profile, vitamin B12).
- (j) A blood sample will be collected at the extension Baseline Visit and End of Study/Early Withdrawal Visit for HbA1c testing.
- (k) If an Unscheduled Visit is conducted, RNA samples will be collected during this visit. In this instance, RNA samples will not need to be collected at the End of Study/Early Withdrawal Visit.
- (l) RNA samples will only be collected at the End of Study/Early Withdrawal Visit if samples were not collected at an Unscheduled Visit.
- (m) ADCS CGIC-MCI will only need to be administered if it occurs greater than 3 months from the last administration of this assessment.
- (n) EQ-5D will be completed by subject at Month 24 and at End of Study in the extension study and the EQ-5D and WPAI will be completed by project partner at Baseline, Month 24 and End of Study.

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 (nonroutine/nonstandard 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 eCRFs, 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

Two 2.5 mL whole blood samples for RNA extraction will be collected from each subject who agreed to pharmacogenomic participating in the informed consent form. A sample will be collected at each Month 12 visit, Unscheduled Visit, or End of Study Visit (if not collected at an Unscheduled Visit) for the duration of the study into PAXgene tubes.

Instructions for Processing and Shipping of Whole Blood Samples for RNA Analysis

- Ensure that the PAXGene Blood RNA tubes are at room temperature prior to collection.
- Collect the venous blood into 2 plastic PAXgene tubes (2.5 mL) for each time point.
- Mix immediately by gently inverting the tube several times (at least 8-10 times) to mix the additive with the collected blood.
- Set PAXgene tubes at room temperature for 2 to 3 hours and then store frozen at -20°C until shipment.
- Ship RNA samples frozen on dry ice per the instructions in the laboratory manual.

Sample Shipment

RNA pharmacogenomic samples will be shipped frozen after collection.

Ship samples only on Monday, Tuesday, or Wednesday, and at least 2 days prior to a national holiday, to minimize the possibility of samples in transit over a weekend or holiday. The laboratory must confirm arrival of the shipped samples.

For instructions on shipping 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 central storage vendor per shipping instructions in the laboratory manual.

Sample Storage

Covance will store the 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 Operational Criteria for AD [23]

Dementia:

- A. Cognitive problems observed interfere with the individual's ability to function at work or at usual activities.
- 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 (eg, ADCS ADL-MCI; CDR scale with informant; CGIC; Informant Questionnaire on Cognitive Decline).
- 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 (eg, MMSE) or neuropsychological testing.
- E. The cognitive or behavioral impairment involves a minimum of 2 of the following domains, established by the testing battery or from interval history and clinical interview:
 - i. Memory: CVLT-II; BVMC-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: Trail Making; 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 BVMC figures; Clock Drawing Test
 - 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 (eg, tools or utensils), or trouble with spatial awareness, dressing etc.
 - iv. Language: Verbal fluency (F, A, and S test), animal fluency, MINT naming
 - a. Defined as newly acquired problems with 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 [23] 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. A CDR Global score of ≥ 1.0 will be required in order to set a consistent minimum standard for AD dementia as an endpoint in the study.
3. Insidious onset (over months or years, not sudden over hours or days).
4. Clear worsening of cognition across visits—by report or by documented worsening upon repeated cognitive test scores or MMSE.
5. Initial and most prominent impairment¹ is documented on 1 of the following domains:
 - a. Amnestic: Impaired new learning and memory, as evidenced in the clinician examination, history, or by impairment on at least 1 of the following subtests:
 - i. BVMT-R Delayed recall.
 - ii. CVLT-II, short-delay, free recall.
 - iii. CVLT-II, long-delay, free recall.
 - b. Nonamnestic: Impairment on performance on at least 1 test of visuospatial ability, language, or executive function: Trails A, Trails B, Digit Span Total, MINT, Semantic fluency, Lexical fluency, or Clock Drawing Test; or based on observation, or clinical history.
6. Evidence of cognitive dysfunction in at least 1 other domain noted in criteria #4.
7. 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 1 of the following domains: amnesic or nonamnesic, as defined for probable AD *and*
 - b. Evidence of cognitive dysfunction in 1 other domain from amnesic or nonamnesic 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 (eg, sudden onset; pronounced aphasia), or insufficient historical detail or objective cognitive documentation of progressive decline.

If probable or possible AD is confirmed the visit at which the AD dementia diagnosis was made will be considered the onset time for the secondary endpoint. Subjects will be referred to standard of care and will be considered study completers.

If probable or possible AD or non-AD dementia is not confirmed, subject will remain in the study, unless there is a medical reason to withdraw the subject from the study.

Non-AD dementia: for example, vascular dementia, dementia due to Parkinson disease, frontal temporal dementia, or dementia due to other less common causes will be withdrawn from the study.

Appendix G Detailed Description of Amendments to Text

This appendix describes changes in reference to Protocol incorporating Amendment 3.

Page 2, Section 1.1, Contacts

Existing Text

Issue	North America Contact	Europe Contact	Australia Contact
Serious adverse event and pregnancy reporting	Confidential Company Information		
Medical Monitor (medical advice on protocol, compound, and medical management of subjects)			
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	Protected Personal Data		

Revised Text

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

Rationale for Amendment

To update with current Medical personnel.

Page 3, Section 1.2, Approval

Takeda signatories have been updated to reflect current roles and titles.

Rationale for Amendment

Update to reflect change in personnel and titles for Takeda signatories.

Page 11, Section 2.0, Primary Objective

Existing Text

To evaluate the effect of pioglitazone at 24 months compared with placebo on cognitive decline in subjects who have completed the AD-4833/TOMM40_301 study with an MCI due to AD diagnosis.

Revised Text

To evaluate the effect of pioglitazone at 24 months compared with placebo on cognitive decline in **high-risk** subjects who have completed the AD-4833/TOMM40_301 study with an MCI due to AD diagnosis.

Rationale for Amendment

To be consistent with objective as stated in Section 5.1.1 of protocol.

Page 12-13, Section 2.0, Main Criteria for Inclusion and Exclusion

Existing Text

Main Criteria for Inclusion:

- The subject completed the pivotal AD-4833/TOMM40_301 study with an adjudicated diagnosis of MCI due to AD without ongoing serious adverse events from study AD-4833/TOMM40_301.
- The subject must be living independently or in nonmedical residential care.
- The subject has a project partner able to separately consent on his/her own behalf and take part in the study (with the intent to do so as long as the subject is enrolled), providing information on the cognitive, functional, and behavioral status of the subject and assisting with observation of adverse events and monitoring of study medication, if needed. (Project partners participating in the pivotal AD-4833/TOMM40_301 study are encouraged to participate in this extension study in this capacity.)

Main Criteria for Exclusion:

- The subject completed the pivotal AD-4833/TOMM40_301 study with a diagnosis of AD dementia.
- The subject has a current diagnosis of significant psychiatric illness, per Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (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 a glycosylated hemoglobin >8% at the extension study Baseline Visit or requires treatment with insulin, triple oral antidiabetic therapy, or a peroxisome proliferator-activated receptor-gamma agonist.*

- 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.
- The subject is required to take excluded medications as specified in the Excluded Medications Section.
- The subject had any of the following values at the extension study Baseline Visit:
 - A serum total bilirubin value $>1.5\times$ upper limit of normal (ULN).
 - A serum alanine aminotransferase or aspartate aminotransferase value $>2\times$ ULN.
 - Unexplained microscopic/macrosopic hematuria on one repeat examination within 2 weeks.
- The subject has a disease 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.
- The subject has any cancer that has been in remission for less than 2 years from the extension study Baseline Visit. Subjects with basal cell or stage I squamous cell carcinoma of the skin will be eligible. Subjects with current diagnosis of bladder cancer are not eligible irrespective of the remission status.
- The subject has a current diagnosis of macular edema or macular degeneration.
- The subject has a history or current diagnosis of congestive heart failure, New York Heart Association class III-IV.

Revised Text

Main Criteria for Inclusion:

- The subject completed the pivotal AD-4833/TOMM40_301 study with an adjudicated diagnosis of MCI due to AD without ongoing serious adverse events from study AD-4833/TOMM40_301.
- The subject must be living independently or in nonmedical residential care.
- The subject has a project partner able to separately consent on his/her own behalf and take part in the study (with the intent to do so as long as the subject is enrolled), providing information on the cognitive, functional, and behavioral status of the subject (**and self reported, if voluntarily agreed to**) and assisting with observation of adverse events and monitoring of study medication, if needed. (Project partners participating in the pivotal AD-4833/TOMM40_301 study are encouraged to participate in this extension study in this capacity.)

Main Criteria for Exclusion:

- The subject completed the pivotal AD-4833/TOMM40_301 study with an **adjudicated** diagnosis of AD dementia.

- The subject has a current diagnosis of significant psychiatric illness, per Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (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 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.
- The subject is required to take excluded medications as specified in the Excluded Medications Section.
- The subject had any of the following values at the **second comprehensive medical follow-up visit in the AD-4933/TOMM40_301 study (or time of last collection in the pivotal 301 study)**:
 - A serum total bilirubin value $>1.5 \times$ upper limit of normal (ULN).
 - A serum alanine aminotransferase or aspartate aminotransferase value $>2 \times$ ULN.
 - Unexplained microscopic/macrosopic hematuria on one repeat examination within 2 weeks.
- The subject has a disease 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.
- The subject has any cancer that has been in remission for less than 2 years from the extension study Baseline Visit. Subjects with basal cell or stage I squamous cell carcinoma of the skin will be eligible. Subjects with current diagnosis of bladder cancer are not eligible irrespective of the remission status.
- The subject has a current diagnosis of macular edema or macular degeneration.
- The subject has a history or current diagnosis of congestive heart failure, New York Heart Association class III-IV.

Rationale for Amendment

To reflect the language as stated in Section 7.0 of the protocol. HbA1c $>8\%$ as a criteria for exclusion has been removed because, while this assessment will still be collected at Baseline, it is no longer considered an important eligibility criterion for this study. Any medical concerns with a subject's baseline HbA1c result will be handled on a case by case basis. Criterion regarding liver function tests was modified to allow the eligibility decision to be based on the laboratory results available prior to the AD-4833/TOMM40_301 EOS/303 Baseline visit to confirm/ensure eligibility for this extension study.

Page 24, Section 6.1, Study Design, fifth and seventh paragraph,

Existing Text

A 0.8 mg tablet of SR pioglitazone or placebo will be used in this extension study, the same as that used in the pivotal AD-4833/TOMM40_301 study. The tablet will be administered QD for a

minimum period of 24 months, in accordance with the extension study duration. Study medication will be dispensed at the end of the extension study Baseline Visit and subjects will be instructed to take the first dose of study medication in the morning on the day following the extension study Baseline Visit.

Subjects and their project partners are expected to attend on-site study visits every 6 months after Baseline, for regular assessments of safety, efficacy, and treatment compliance. In addition, the subject will be contacted for telephone-based safety checks between visits. While it is preferred that subject's project partners attend the on-site study visits, it is not required and they may offer their information via telephone. Project partners who voluntarily take part in completion of the 2 self reported project partner questionnaires (outline in Section 9.1.14.4), will be required to attend the study visits when the questionnaires are obtained. If between in clinic visits, worsening of cognitive impairment, potential AD dementia, or a potential safety issue is suspected, requiring further evaluation of the subject, an unscheduled clinic visit may be conducted as described in Section 6.2.3. *Suspected dementia cases will be forwarded for evaluation by an independent Cognitive Impairment Adjudication Committee (CIAC) as described in Section 6.2.4.* Up to 60 sites globally may participate in this study (the same sites that participated in the AD-4833/TOMM40_301 study, although all sites may not participate in 303).

Revised Text

A 0.8 mg tablet of SR pioglitazone or placebo will be used in this extension study, the same as that used in the pivotal AD-4833/TOMM40_301 study. The tablet will be administered QD for a minimum period of 24 months, in accordance with the extension study duration. Study medication will be dispensed at the end of the extension study Baseline Visit and subjects will be instructed to take the first dose of study medication in the morning on the day following the extension study Baseline Visit **(if all eligibility criteria are confirmed)**.

Subjects and their project partners are expected to attend on-site study visits every 6 months after Baseline, for regular assessments of safety, efficacy, and treatment compliance. In addition, the subject will be contacted for telephone-based safety checks between visits. While it is preferred that subject's project partners attend the on-site study visits, it is not required and they may offer their information via telephone. Project partners who voluntarily take part in completion of the 2 self reported project partner questionnaires (outline in Section 9.1.14.4), will be required to attend the study visits when the questionnaires are obtained. If between in clinic visits, worsening of cognitive impairment, potential AD dementia, or a potential safety issue is suspected, requiring further evaluation of the subject, an unscheduled clinic visit may be conducted as described in Section 6.2.3. Up to 60 sites globally may participate in this study (the same sites that participated in the AD-4833/TOMM40_301 study, although all sites may not participate in 303).

Rationale for Amendment

To clarify when study drug for this extension study should begin.

To remove the adjudication process from the study.

Page 27, Section 6.2.2, Assessments at Scheduled Study Visits, third paragraph

Existing Text

The physician, preferably an experienced neurologist or psychiatrist, will review the totality of available information once fully scored (ie, medical history, CDR ratings, and CDR-SB scores; ADCS-CGIC-MCL, ADCS ADL-MCI, GDS, and NPI-Q data; cognitive test results; and laboratory test results). At this point he/she in consultation with the site neuropsychologist, will determine whether the diagnosis of the subject has changed from MCI due to AD. *If a diagnosis of AD dementia is suspected, the investigator will determine whether to send the subject's case to adjudication, described in Section 6.2.4.* The physician can be the same individual who completed the CDR.

Revised Text

The physician, preferably an experienced neurologist or psychiatrist, will review the totality of available information once fully scored (ie, medical history, CDR ratings, and CDR-SB scores; ADCS-CGIC-MCL, ADCS ADL-MCI, GDS, and NPI-Q data; cognitive test results; and laboratory test results). At this point he/she in consultation with the site neuropsychologist, will determine whether the diagnosis of the subject has changed from MCI due to AD. **If possible or probable AD dementia is diagnosed, the subject will be considered a have completed the study. If non-AD dementia is diagnosed, the subject will be withdrawn from the study.** The physician can be the same individual who completed the CDR.

Rationale for Amendment

To remove the adjudication process for confirmation of the diagnosis of dementia.

Page 28, Section 6.2.3, Assessments at an Unscheduled Visit for Suspected Cognitive or Functional Decline, third paragraph

Existing Text

Unscheduled Visits to evaluate suspected cognitive or functional decline may be conducted, as needed, for study subjects outside of regularly scheduled visits based on either of the following trigger criteria being met: (1) the subject or their project partner express concern of the subject's cognitive or functional decline to the principal investigator or coordinator between regularly scheduled study visits and/or (2) a non-study physician expresses concern (with or without prescription of any dementia drug treatment) between regularly scheduled visits. Based on these triggers, the principal investigator will decide whether evidence is present to suspect a diagnosis of possible or probable AD dementia [23]. If a diagnosis of possible or probable AD dementia is suspected, an Unscheduled Visit to further evaluate suspected cognitive or functional decline should take place *within 1 month* of this provisional diagnosis. Visit procedures for the unscheduled visit for suspected cognitive or functional decline are noted in [Appendix A](#).

Revised Text

Unscheduled Visits to evaluate suspected cognitive or functional decline may be conducted, as needed, for study subjects outside of regularly scheduled visits based on either of the following

trigger criteria being met: (1) the subject or their project partner express concern of the subject's cognitive or functional decline to the principal investigator or coordinator between regularly scheduled study visits and/or (2) a non-study physician expresses concern (with or without prescription of any dementia drug treatment) between regularly scheduled visits. Based on these triggers, the principal investigator will decide whether evidence is present to suspect a diagnosis of possible or probable AD dementia [23]. If a diagnosis of possible or probable AD dementia is suspected, an **Unscheduled Visit** to further evaluate suspected cognitive or functional decline should take place **within approximately 1 month** of this provisional diagnosis. **A CDR Global score of ≥ 1.0 will be required in order to set a consistent minimum standard for AD dementia as an endpoint for the study.** Visit procedures for the unscheduled visit for suspected cognitive or functional decline are noted in [Appendix A](#).

Rationale for Amendment

To allow greater flexibility in when the **Unscheduled Visit** occurs and to ensure consistency in the diagnosis of AD dementia as an endpoint for the study.

Page 29-31, Section 6.2.4, Adjudication

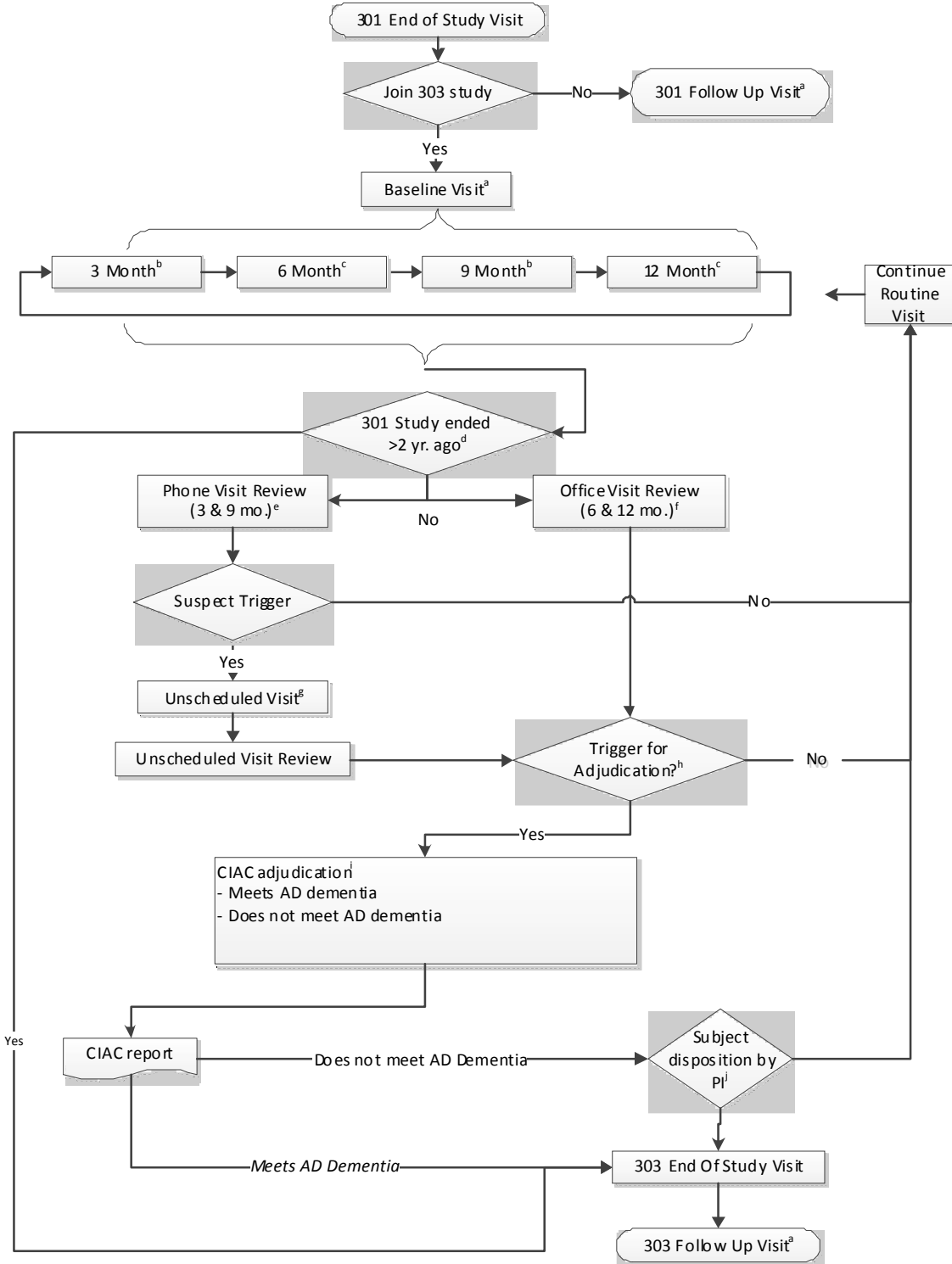
Existing Text

*After each regularly scheduled visit, or an **Unscheduled Visit** relating to cognitive status, the investigator in consultation with the site neuropsychologist, will consider the totality of information collected for the subject and decide subject flow within the study (ie, send or not to adjudication). Suspected cases of dementia will be sent to the CIAC. If a subject is assigned a dementia diagnosis as judged by the investigator [22], then he/she will complete a diagnostic worksheet and send the case to adjudication. When adjudication is required, data from all previous visits may be shared with the adjudication committee, who will be blinded to the subject's treatment-assignment. The adjudication process will result in 1 of 2 possible outcomes of clinical assessment: (1) AD dementia (possible or probable); (2) does not meet criteria for AD dementia.*

Operational criteria for adjudicated diagnoses are noted in [Appendix F](#).

The adjudication flow of subjects through the study, as described above, is illustrated in [Figure 6.b](#).

Figure 6.b Subject Flow Chart



Footnotes are on following page.

- (a) AD-4833/TOMM40_301 Follow-up phone call.*
- (b) The Baseline Visit will coincide with the End of Study Visit for the pivotal AD-4833/TOMM40_301 study. The randomization scheme to pioglitazone or placebo from the pivotal AD-4833/TOMM40_301 study will remain unchanged. After the Baseline Visit, subjects and their project partners will enter a repetitive yearly regularly scheduled Visit Cycle, ending at (1) subject diagnosed to an endpoint, (2) subject withdrawal, or (3) study end.*
- (c) Subjects will be assessed by the site staff after every regularly scheduled visit (3, 6, 9, 12 months).*
- (d) Once the pivotal AD-4833/TOMM40_301 study has been completed for 2 years, subjects in the AD-4833/TOMM40_303 study will have an End of Study Visit and Follow-up Visit scheduled.*
- (e) If (1), the subject or their project partner express concern of the subject's cognitive or functional decline to the principal investigator or coordinator between regularly scheduled study visits (including but not limited to phone visits at 3 and 9 months) and/or (2) a non-study physician expresses concern (with or without prescription of any dementia drug treatment) between regularly scheduled visits.*
- (f) At each regularly scheduled visit review, the subject will be reviewed for cognitive functional and clinical performance, and conversion to AD dementia. If possible or probable diagnosis of AD is suspected, the principal investigator will decide subject flow within the study (ie, send or not to adjudication).*
- (g) If the principal investigator suspects the subject may possibly meet possible or probable AD dementia based on concerns raised as noted in Section 6.2.3, the principal investigator will conduct the procedures listed in the Unscheduled Visit in Appendix A. If, after evaluation, the principal investigator does not suspect the subject needs to be sent to adjudication, they will return to the regularly scheduled Visit Schedule. The triggers warranting evaluation are described in Section 6.2.*
- (h) At the Unscheduled Visit Review or after regularly scheduled visits, the investigator will consider the totality of information collected for the subject and decide subject flow within the study (ie, send or not to adjudication) based on the criteria in Section 6.2.4. Those subjects not sent for adjudication will return to the regularly scheduled Visit Schedule. The investigator will send to adjudication subjects whom they judged has reached one of the study outcomes.*
- (i) All data from any subject visit may be shared with the CIAC. The adjudication process possible outcomes are described in Section 6.2.4.*
- (j) If the CIAC determines that the subject does not meet AD dementia, the principal investigator will determine at this time, based on clinical judgment, the subject's ability to continue in study.*

In addition to regular sponsor surveillance, the ethical and safety interests of subjects will be evaluated by an independent Data and Safety Monitoring Board (DSMB) in a manner that will protect, as far as possible, the scientific integrity of the study.

Revised Text

The entire section has been deleted.

Rationale for Amendment

To remove the adjudication process for confirmation of the diagnosis of dementia.

Page 31, Section 6.4.1, Study Design, tenth paragraph, last sentence

Existing Text

Assessments of vMRI will be collected at the extension study Baseline (last MRI completed in 301 study) *as part of the scan collected to support a diagnosis sent for adjudication or* at study termination to test for correlation with disease progression within and across study arms.

Revised Text

Assessments of vMRI will be collected at the extension study Baseline (last MRI completed in 301 study) and at study termination to test for correlation with disease progression within and across study arms.

Rationale for Amendment

As a result of adjudication being removed, the MRI to rule out other causes of dementia has also been removed.

Page 33-34, Section 7.2, Exclusion Criteria, #3 and 8

Existing Text

3. The subject has an HbA1c >8% at the extension study Baseline Visit or requires treatment with insulin, triple oral antidiabetic therapy or a PPAR- γ agonist.
8. The subject had any of the following values at the extension study Baseline Visit:
 - a) A serum total bilirubin value >1.5 \times upper limit of normal (ULN).
 - b) A serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >2 \times ULN.
 - c) Unexplained microscopic/macroscopic hematuria on one repeat examination within 2 weeks.

Revised Text

7. The subject had any of the following values **at the second comprehensive medical follow-up visit in the AD-4833/TOMM40_301 study (or time of last collection in the pivotal 301 study)**:
 - a) A serum total bilirubin value >1.5 \times upper limit of normal (ULN).
 - b) A serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >2 \times ULN.
 - c) Unexplained microscopic/macroscopic hematuria on one repeat examination within 2 weeks.

Rationale for Amendment

HbA1c >8% as a criteria for exclusion has been removed because, while this assessment will still be collected at Baseline, it is no longer considered an important eligibility criterion for this study. Any medical concerns with a subject's baseline HbA1c result will be handled on a case by case basis.

Criterion #8 was modified to allow the laboratory results to be available prior to the AD-4833/TOMM40_301 EOS/303 Baseline visit to confirm/ensure eligibility for this extension study.

Page 36, Table 7.a, Excluded Medications and Treatments

Added to existing Table

Triple Oral Antibiotic Therapy	Prohibited , if initiated	Prohibited , if initiated (Subject must be discontinued)
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Rationale for Amendment

The exclusion of triple oral antidiabetic therapy has been removed in exclusion criterion #3 and added to the Excluded Medications and Treatments Table 7.a (insulin and PPAR- γ agonist where already included in Table 7.a).

Page 54, Section 9.1.14.7, MRI Assessment

Existing Text

The MRI collected in this extension study may be used for both structural and volumetric analyses, to support the possible dementia diagnosis and to support the imaging endpoint, respectively.

Subjects enrolled in the extension study will be required (unless medically contraindicated) to participate in a vMRI scan where volumetric measurements will be taken, for the purpose of assessing atrophy of the brain. vMRI scans will take place at the following time points, as noted in the Schedule of Study Procedures ([Appendix A](#)): extension study Baseline (last MRI collected at End of Study Visit or second Comprehensive Medical Follow-up Visit for the pivotal AD-4833/TOMM40_301 study) and in extension study *as part of the scan collected to support a diagnosis sent for adjudication or* at End of Study/Early Withdrawal Visit.

MRI will be collected when cognitive or functional decline is suspected, to rule out other causes of dementia and provide supplemental information for the CIAC review of suspected dementia cases. 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.

Revised Text

Subjects enrolled in the extension study will be required (unless medically contraindicated) to participate in a vMRI scan where volumetric measurements will be taken, for the purpose of assessing atrophy of the brain. vMRI scans will take place at the following time points, as noted in the Schedule of Study Procedures ([Appendix A](#)): extension study Baseline (last MRI collected at End of Study Visit or second Comprehensive Medical Follow-up Visit for the pivotal AD-4833/TOMM40_301 study) and at extension study End of Study/Early Withdrawal Visit.

Rationale for Amendment

As a result of adjudication being removed, the MRI to rule out other causes of dementia has also been removed.

Page 58, Section 9.1.17, Imaging

Existing Text

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 starting the study, if not already qualified as part of participation in the pivotal AD-4833/TOMM40_301 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 eCRF. 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.*

Revised Text

Prior to the start of the study, each site should identify a study MRI machine. Each MRI machine will be qualified by the imaging vendor before starting the study, if not already qualified as part of participation in the pivotal AD-4833/TOMM40_301 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 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 eCRF. Detailed instructions for the processing and shipping of images will be provided separately.

Subjects who have contraindications for MRI procedure (such as unremovable ferromagnetic dental work, cardiac pacemakers, etc) **will not be excluded from the study.**

Rationale for Amendment

As a result of adjudication being removed, the MRI to rule out other causes of dementia has also been removed.

Page 59, Section 9.3.3.2, Unscheduled Visit for suspected Cognitive or Functional Decline

Existing Text

An unscheduled visit may be conducted if worsening of cognitive impairment or potential AD dementia is suspected in between regularly scheduled visits when 1 of the triggers described in Section 6.2.3 has been met. This type of Unscheduled Visit will include the assessments noted in Appendix A. It is anticipated this visit will be about 3 to 4 hours in length, if an MRI is completed during the visit.

Revised Text

An unscheduled visit may be conducted if worsening of cognitive impairment or potential AD dementia is suspected in between regularly scheduled visits when 1 of the triggers described in Section 6.2.3 has been met. **A CDR Global score of ≥ 1.0 will be required in order to set a**

consistent minimum standard for AD dementia as an endpoint for the study. This type of Unscheduled Visit will include the assessments noted in [Appendix A](#). It is anticipated this visit will be about 3 to 4 hours in length, if an MRI is completed during the visit.

Rationale for Amendment

To ensure consistency in the diagnosis of AD dementia as an endpoint for the study.

Page 59, Section 9.3.4, Final Visit or Early Termination

Existing Text

The End of Study/Early Withdrawal Visit is an ad hoc visit that, for study completion, will take place as soon as possible after a regularly scheduled study visit, either at study end, or at extension study termination, or after a subject has withdrawn prematurely from the study. In cases where the secondary endpoint of AD dementia diagnosis has been reached, the efficacy assessments will not need to be captured at this visit.

For all subjects receiving study medication, the investigator must complete the End of Study eCRF page.

Revised Text

The End of Study/Early Withdrawal Visit is an ad hoc visit that, for study completion, will take place as soon as possible after a regularly scheduled or **unscheduled study visit**, either at study end, at extension study termination, after a subject has withdrawn prematurely from the study, or after the subject has been diagnosed with AD or non-AD dementia. The efficacy assessments will not need to be captured at this visit in cases where the secondary endpoint of AD dementia diagnosis has been reached or if it is less than 3 months from the last administration of the assessment.

For all subjects receiving study medication, the investigator must complete the End of Study eCRF page.

Rationale for Amendment

To clarify when the End of Study/Early Withdrawal Visit should occur and what procedures will need to be completed at the visit.

Page 60, Section 9.3.5, Follow-up

Existing Text

Follow-up will begin the first day after the End of Study/Early Withdrawal Visit and will continue until 2 weeks later.

Subjects will be contacted for a Safety Follow-up call approximately 2 weeks after the End of Study/Early Termination Visit. See [Appendix A](#) for list of procedures that will be performed and documented. 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 eCRF), according to data protection regulations.

Revised Text

Follow-up will begin the first day after the End of Study/Early Withdrawal Visit and will continue until 2 weeks later.

Subjects will be contacted for a Safety Follow-up call approximately 2 weeks after the End of Study/Early Termination Visit. See [Appendix A](#) for list of procedures that will be performed and documented. Subjects who withdraw their consent should still be contacted for a Safety Follow-up call, but the contact should only be recorded in the **subjects** records (and not the eCRF), according to data protection regulations.

Rationale for Amendment

To provide clarity on where the Follow-up call will be documented for subjects that do not have medical records.

Page 70, Section 11.2, Adjudication Committee

Existing Text

The Cognitive Impairment Adjudication Committee that adjudicated primary endpoint events in the pivotal AD-4833/TOMM40_301 study will adjudicate clinical diagnoses of AD in this study. The Adjudication Committee will meet periodically, review data on suspected cases of dementia, and perform final adjudication of the diagnosis of AD dementia. Materials to be reviewed will include the complete dossier for the 303 study subject, whose case is forwarded for adjudication, and may include all appropriate records from the pivotal AD-4833/TOMM40_301 study, including assessment results conducted during the subject's participation in AD-4833/TOMM40_301

Revised Text

Removed the entire section.

Rationale for Amendment

To remove the adjudication process for confirmation for the diagnosis of dementia.

Page 86, Appendix A, Schedule of Study Procedures

Existing Text

Appendix A Schedule of Study Procedures

Month	Baseline (Coincides With 301 End of Study Visit (a))	<i>Repeated Yearly</i>				Unscheduled Visit (b)	End of Study Visit/Early Withdrawal (c)	Follow-up Visit
		3 (d)	6	9 (d)	12			
Visit Window	+30 days	±2 wks	±2 wks	±2 wks	±2 wks			EoS/EW+0.5 (e)
Informed consent (subject)	X							
Informed consent (pharmacogenomic)	X							
Informed consent (project partner)	X							
Incl/excl criteria	X							
Medical history	X							
Concurrent conditions	X							
Body weight and height(g)	X (f)		X		X		X	
Review of concurrent medications	X	X	X	X	X	X	X	X
Contact IWRS	X		X		X		X	
Dispense study drug	X		X		X			
Collect study drug			X		X		X	
Compliance review		X	X	X	X		X	
AEs (including AEs of Special Interest)	X (f)	X	X	X	X	X	X	X
Physical examination	X (f)				X	X	X	
Vital signs	X (f)		X		X	X	X	
Neurological examination	X (f)		X		X	X	X	
12-lead ECG	X (f)				X		X	
<i>vMRI (h)(i)</i>	<i>X (f)</i>					<i>X (i)</i>	<i>X</i>	
<i>Clinical chemistry and hematology labs</i>	X (f)				X	X (j)	X	
HbA1c test (k)	X						X	
Pharmacogenomic RNA samples					X	X (l)	X (m)	
C-SSRS	X (f)		X		X		X	X
Diet and exercise evaluation	X (f)		X		X		X	
MMSE (d)	X (f)		X		X		X	
CVLT-II	X (f)				X		X	
BVMT-R	X (f)				X		X	
Lexical fluency	X (f)				X		X	
Semantic fluency	X (f)				X		X	
MINT	X (f)				X		X	
Digit Span	X (f)				X		X	

	Baseline (Coincides With 301 End of Study Visit (a))	<i>Repeated Yearly</i>				Unscheduled Visit (b)	End of Study Visit/Early Withdrawal (c)	Follow-up Visit
Month	0 (Day 0)	3 (d)	6	9 (d)	12			EoS/EW+0.5 (e)
Trail Making Tests	X (f)				X		X	
Clock Drawing	X (f)				X		X	

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

	Baseline (Coincides With 301 End of Study Visit (a))	<i>Repeated Yearly</i>				Unscheduled Visit (b)	End of Study Visit/Early Withdrawal (c)	Follow-up Visit
Month	0 (Day 0)	3 (d)	6	9 (d)	12			EoS/EW+0.5 (e)
GDS	X (f)		X		X		X	
CDR	X (f)		X		X	X	X	
ADCS ADL- MCI	X		X		X		X	
NPI-Q	X (f)		X		X		X	
ADCS CGIC-MCI	X		X		X	X(n)	X	
ADCS RUI	X (f)		X		X		X	
EQ-5D (subject) (o)	X (f)						X	
EQ-5D (project partner) (o)	X						X	
WPAI(o)	X						X	

EoS=End of Study, EW=Early Withdrawal.

- (a) Subjects who are unable to consent for the extension study or to complete all extension study baseline visit evaluations at the same time as their End of Study Visit for the pivotal AD-4833/TOMM40_301 study will be allowed to return to the clinic and to complete these evaluations within a 1 month window.
- (b) Procedures listed should be conducted in the event of an Unscheduled Visit for suspected cognitive or functional decline. Procedures related to Unscheduled Visits for any other emerging concern, such as safety, are at the discretion of the investigator.
- (c) End of Study/Early Withdrawal Visit is an ad hoc visit that, for study completion, would take place as soon as possible after a regularly scheduled study visit, either at study end, occurring concurrently with completion of the pivotal AD-4833/TOMM40_301 study or at extension study termination, or after a subject has withdrawn prematurely from the study. In cases where the secondary endpoint of AD dementia diagnosis has been reached, the efficacy assessments will not need to be captured at this visit.
- (d) Telephone contact with the subject (should be every 3 months between the semiannual clinic visits for the duration of the study)
- (e) Telephone call approximately 2 weeks after the End of Study or Early Withdrawal Visit.
- (f) These assessments, conducted as part of the end of study visit for the pivotal AD-4833/TOMM40_301 study or at most recent comprehensive medical Follow-up Visit, will serve as baseline data for the extension AD-4833/TOMM40_303 study.
- (g) Height will only be collected at the end of study visit for the pivotal AD-4833/TOMM40_301 study or at most recent comprehensive medical Follow-up Visit, and will serve as baseline data for the extension AD-4833/TOMM40_303 study
- (h) vMRI assessments will take place at extension study Baseline (ie, coinciding with the End of Study Visit for the pivotal AD-4833/TOMM40_301 study or most recent MRI or that obtained at the second consecutive comprehensive medical Follow-up Visit) and for adjudication or at extension study end.
- (i) MRI will be collected for suspected cognitive or functional decline to rule out other causes of dementia and provide supplemental information for the CIAC review of suspected dementia cases. The MRI collected in this extension study may be used for both structural and volumetric analyses, to support the possible dementia diagnosis and to support the imaging endpoint, respectively.
- (j) Standard blood chemistry and tests used in evaluating cognitively impaired and dementia patients (eg, thyroid profile, vitamin B12).
- (k) A blood sample will be collected at the extension Baseline Visit and End of Study/Early Withdrawal Visit for HbA1c testing.

- (l) If an Unscheduled Visit is conducted, RNA samples will be collected during this visit. In this instance, RNA samples will not need to be collected at the End of Study/Early Withdrawal Visit.
- (m) RNA samples will only be collected at the End of Study/Early Withdrawal Visit if samples were not collected at an Unscheduled Visit.
- (n) *This assessment will only need to be administered at the unscheduled visit if it occurs greater than 3 months from the last administration of this assessment.*
- (o) EQ-5D will be completed by subject at Month 24 and at End of Study in the extension study and the EQ-5D and WPAI will be completed by project partner at Baseline, Month 24 and End of Study.

Revised Text

Appendix A Schedule of Study Procedures

Month	Baseline (Coincides With 301 End of Study Visit (a))	Repeated Yearly				Unscheduled Visit (b)	End of Study Visit/Early Withdrawal (c)	Follow-up Visit
		3 (d)	6	9 (d)	12			
Visit Window	0 (Day 0) +30 days	±2 wks	±2 wks	±2 wks	±2 wks			EoS/EW+0.5 (e)
Informed consent (subject)	X							
Informed consent (pharmacogenomic)	X							
Informed consent (project partner)	X							
Incl/excl criteria	X							
Medical history	X							
Concurrent conditions	X							
Body weight and height(g)	X (f)		X		X		X	
Review of concurrent medications	X	X	X	X	X	X	X	X
Contact IWRS	X		X		X		X	
Dispense study drug	X		X		X			
Collect study drug			X		X		X	
Compliance review		X	X	X	X		X	
AEs (including AEs of Special Interest)	X (f)	X	X	X	X	X	X	X
Physical examination	X (f)				X	X	X	
Vital signs	X (f)		X		X	X	X	
Neurological examination	X (f)		X		X	X	X	
12-lead ECG	X (f)				X		X	
vMRI (h)	X (f)						X	
Clinical chemistry, hematology and urinalysis labs	X (f)				X	X (i)	X	
HbA1c test (j)	X						X	
Pharmacogenomic RNA samples					X	X (k)	X (l)	
C-SSRS	X (f)		X		X		X	X
Diet and exercise evaluation	X (f)		X		X		X	

Month	Baseline (Coincides With 301 End of Study Visit (a)	Repeated Yearly				Unscheduled Visit (b)	End of Study Visit/Early Withdrawal (c)	Follow-up Visit EoS/EW+0.5 (e)	
		0 (Day 0)	3 (d)	6	9 (d)				12
		MMSE (d)	X (f)		X				
CVLT-II	X (f)				X		X		
BVMT-R	X (f)				X		X		
Lexical fluency	X (f)				X		X		
Semantic fluency	X (f)				X		X		
MINT	X (f)				X		X		
Digit Span	X (f)				X		X		
Trail Making Tests	X (f)				X		X		
Clock Drawing	X (f)				X		X		

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

Month	Baseline (Coincides With 301 End of Study Visit (a)	Repeated Yearly				Unscheduled Visit (b)	End of Study Visit/Early Withdrawal (c)	Follow-up Visit EoS/EW+0.5 (e)	
		0 (Day 0)	3 (d)	6	9 (d)				12
		GDS	X (f)		X				
CDR	X (f)		X		X	X	X		
ADCS ADL- MCI	X		X		X		X		
NPI-Q	X (f)		X		X		X		
ADCS CGIC-MCI	X		X		X	X(m)	X		
ADCS RUI	X (f)		X		X		X		
EQ-5D (subject) (n)	X (f)						X		
EQ-5D (project partner) (n)	X						X		
WPAI(n)	X						X		

EoS=End of Study, EW=Early Withdrawal.

(a) Subjects who are unable to consent for the extension study or to complete all extension study baseline visit evaluations at the same time as their End of Study Visit for the pivotal AD-4833/TOMM40_301 study will be allowed to return to the clinic and to complete these evaluations within a 1 month window.

(b) Procedures listed should be conducted in the event of an Unscheduled Visit for suspected cognitive or functional decline. Procedures related to Unscheduled Visits for any other emerging concern, such as safety, are at the discretion of the investigator.

(c) End of Study/Early Withdrawal Visit is an ad hoc visit that, for study completion, would take place as soon as possible after a regularly scheduled or **unscheduled study visit**, either at study end, at extension study termination, after a subject has withdrawn prematurely from the study **or after the subject has been diagnosed with AD or non-AD dementia. The efficacy assessments will not need to be captured at this visit in cases where the secondary endpoint of AD dementia diagnosis has been reached or if it is less than 3 months from the last administration of the assessment.**

(d) Telephone contact with the subject (should be every 3 months between the semiannual clinic visits for the duration of the study)

(e) Telephone call approximately 2 weeks after the End of Study or Early Withdrawal Visit.

(f) These assessments, conducted as part of the end of study visit for the pivotal AD-4833/TOMM40_301 study or at most recent comprehensive medical Follow-up Visit, will serve as baseline data for the extension AD-4833/TOMM40_303 study.

(g) Height will only be collected at the end of study visit for the pivotal AD-4833/TOMM40_301 study or at most recent comprehensive medical Follow-up Visit, and will serve as baseline data for the extension AD-4833/TOMM40_303 study

(h) vMRI assessments will take place at extension study Baseline (ie, coinciding with the End of Study Visit for the pivotal

AD-4833/TOMM40_301 study or most recent MRI or that obtained at the second consecutive Comprehensive Medical Follow-up Visit) and at extension study end.

- (i) Standard blood chemistry and tests used in evaluating cognitively impaired and dementia patients (eg, thyroid profile, vitamin B12).
- (j) A blood sample will be collected at the extension Baseline Visit and End of Study/Early Withdrawal Visit for HbA1c testing.
- (k) If an Unscheduled Visit is conducted, RNA samples will be collected during this visit. In this instance, RNA samples will not need to be collected at the End of Study/Early Withdrawal Visit.
- (l) RNA samples will only be collected at the End of Study/Early Withdrawal Visit if samples were not collected at an Unscheduled Visit.
- (m) The ADCSCGIC-MCI assessment will only need to be administered if it occurs greater than 3 months from the last administration of this assessment.
- (n) EQ-5D will be completed by subject at Month 24 and at End of Study in the extension study and the EQ-5D and WPAI will be completed by project partner at Baseline, Month 24 and End of Study.

Rationale for Amendment

To update Appendix A to reflect all protocol changes.

Page 95, Appendix F, Operational Criteria for AD

Existing Text

Dementia:

- A. Cognitive problems observed interfere with the individual's ability to function at work or at usual activities.
- 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 (eg, ADCS ADL-MCI; CDR scale with informant; CGIC; Informant Questionnaire on Cognitive Decline).
- 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 (eg, MMSE) or neuropsychological testing.
- E. The cognitive or behavioral impairment involves a minimum of 2 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: Trail Making; 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; Clock Drawing Test
 - a. Defined as problems in visuo-perceptual analysis. Could be manifest by difficulty in recognition of faces, objects despite good acuity. Trouble with operating simple implements (eg, tools or utensils), or trouble with spatial awareness, dressing etc.
 - iv. Language: Verbal fluency (F, A, and S test), animal fluency, MINT naming
 - a. Defined as newly acquired problems with 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 [23] 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 impairment¹ is documented on 1 of the following domains:
 - a. Amnesic: Impaired new learning and memory, as evidenced in the clinician examination, history, or by impairment on at least 1 of the following subtests:
 - i. BVMT-R Delayed recall.
 - ii. CVLT-II, short-delay, free recall.
 - iii. CVLT-II, long-delay, free recall.

- b. Nonamnesic: Impairment on performance on at least 1 test of visuospatial ability, language, or executive function: Trails A, Trails B, Digit Span Total, MINT, Semantic fluency, Lexical fluency, or Clock Drawing Test; or based on observation, or clinical history.
5. Evidence of cognitive dysfunction in at least 1 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 1 of the following domains: amnesic or nonamnesic, as defined for probable AD *and*
 - b. Evidence of cognitive dysfunction in 1 other domain from amnesic or nonamnesic 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 (eg, sudden onset; pronounced aphasia), or insufficient historical detail or objective cognitive documentation of progressive decline.

If probable or possible AD is confirmed, *subject will count toward the total number of events needed for the secondary efficacy analysis*; the visit at which the AD dementia diagnosis was made will be considered the onset time for the secondary endpoint. Subjects will be referred to standard of care and will be considered study completers.

If probable or possible AD or non-AD dementia is not confirmed, subject will remain in the study, unless there is a medical reason to withdraw the subject from the study.

Non-AD dementia: for example, vascular dementia, dementia due to Parkinson disease, frontal temporal dementia, or dementia due to other less common causes will be withdrawn from the study.

Revised Text

Dementia:

- A. Cognitive problems observed interfere with the individual's ability to function at work or at usual activities.
- 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 (eg, ADCS ADL-MCI; CDR scale with informant; CGIC; Informant Questionnaire on Cognitive Decline).

- 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 (eg, MMSE) or neuropsychological testing.
- E. The cognitive or behavioral impairment involves a minimum of 2 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: Trail Making; 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; Clock Drawing Test
 - a. Defined as problems in visuo-perceptual analysis. Could be manifest by difficulty in recognition of faces, objects despite good acuity. Trouble with operating simple implements (eg, tools or utensils), or trouble with spatial awareness, dressing etc.
 - iv. Language: Verbal fluency (F, A, and S test), animal fluency, MINT naming
 - a. Defined as newly acquired problems with 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 [23] 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. **A CDR Global score of ≥ 1.0 will be required in order to set a consistent minimum standard for AD dementia as an endpoint in the study.**
3. Insidious onset (over months or years, not sudden over hours or days).
4. Clear worsening of cognition across visits—by report or by documented worsening upon repeated cognitive test scores or MMSE.
5. Initial and most prominent impairment¹ is documented on 1 of the following domains:
 - a. Amnestic: Impaired new learning and memory, as evidenced in the clinician examination, history, or by impairment on at least 1 of the following subtests:
 - i. BVMT-R Delayed recall.
 - ii. CVLT-II, short-delay, free recall.
 - iii. CVLT-II, long-delay, free recall.
 - b. Nonamnestic: Impairment on performance on at least 1 test of visuospatial ability, language, or executive function: Trails A, Trails B, Digit Span Total, MINT, Semantic fluency, Lexical fluency, or Clock Drawing Test; or based on observation, or clinical history.
6. Evidence of cognitive dysfunction in at least 1 other domain noted in criteria #4.
7. 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 1 of the following domains: amnestic or nonamnestic, as defined for probable AD *and*
 - b. Evidence of cognitive dysfunction in 1 other domain from amnestic or nonamnestic 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 (eg, sudden onset; pronounced aphasia), or insufficient historical detail or objective cognitive documentation of progressive decline.

If probable or possible AD is confirmed the visit at which the AD dementia diagnosis was made will be considered the onset time for the secondary endpoint. Subjects will be referred to standard of care and will be considered study completers.

If probable or possible AD or non-AD dementia is not confirmed, subject will remain in the study, unless there is a medical reason to withdraw the subject from the study.

Non-AD dementia: for example, vascular dementia, dementia due to Parkinson disease, frontal temporal dementia, or dementia due to other less common causes will be withdrawn from the study.

Rationale for Amendment

The amendment adds the requirement of a CDR Global score of ≥ 1.0 for AD dementia.

Amendment 3 – A Blinded Long-term Extension Study to Evaluate the Safety and Efficacy of Pioglitazone (AD-4833 Sustained Release 0.8 mg Daily) to Slow the Progression of Cognitive Decline in Subjects Who Have Completed the AD-4833/TOMM40_301 Study With Diagnosis of Mild Cognitive Impairment Due to Alzheimer Disease

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date <small>(dd-MMM-yyyy HH:mm)</small>
Protected Personal Data	Biostatistics Approval	25-Jan-2016 20:57
	Clinical Science Approval	26-Jan-2016 14:24
	Clinical VP Approval	28-Jan-2016 12:10