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

SAP Approve Date: 14 September 2018

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

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

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

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: AD-4833/TOMM40_303

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

PHASE 3

Version**:** Final

Date**:** 14 September 2018

Prepared by:

Protected Personal Data

Based on:

Protocol Version: Amendment 3

Protocol Date: 19 January 2016

1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

2.0 TABLE OF CONTENTS

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3.0 LIST OF ABBREVIATIONS

AA	Alzheimer's Association
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-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-SB	Clinical Dementia Rating – Sum of Boxes
CDT	Clock Drawing Test
CVLT-II	California Verbal Learning Test – 2nd Edition
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
GDS	Geriatric Depression Scale
HbA1c	glycosylated hemoglobin
HRQoL	health-related quality of life
MCI	mild cognitive impairment
MCI-AD	mild cognitive impairment due to Alzheimer's Disease
MedDRA	Medical Dictionary for Regulatory Activities
MINT	Multilingual Naming Test
MRI	magnetic resonance imaging
NIA	National Institute on Aging
NPI-Q	Neuropsychiatric Inventory Questionnaire
PTE	pretreatment event
QD	once daily
RU	resource utilization
SAE	serious adverse event
SAP	statistical analysis plan
SR	sustained release
TOMM40	translocase of the outer mitochondrial membrane 40 homolog
vMRI	volumetric magnetic resonance imaging
WPAI:MM-CG	Work Productivity and Activity Impairment Questionnaire: Mood and Mental State, Caregiver Version

4.0 INTRODUCTION

This document describes the statistical analyses to be performed and data presentations to be produced for this double-blind, placebo-controlled, multicenter, parallel group long-term extension study 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 [1]).

This study was an extension of Study AD-4833/TOMM40_301 (TOMORROW). The interim futility assessment in AD-4833/TOMM40_301 conducted in January 2018 showed that the available efficacy data for pioglitazone didn't meet pre-specified sponsor criteria for continuation of AD-4833/TOMM40_301. Therefore, Study AD-4833/TOMM40_301 was terminated; and consequently, this study was terminated.

The purpose of this statistical analysis plan (SAP) is to ensure the credibility of the study findings by specifying the statistical approaches to the analysis of the double-blind data prior to database lock. It also reflects the impact of the early termination of the study on the analysis planned in the protocol. This SAP was developed based on the International Conference on Harmonisation (ICH) E3 and E9 Guidelines and in reference to the following document:

- ProtAmend-2016-01-19-APP-3---000001.pdf (AD-4833/TOMM40_303 Protocol Amendment #3 (Final Version), dated 19 January 2016.)

Any deviations during the analysis and reporting process from the current statistical analysis plan will be described and justified in the final report. Analysis issues that suggest changes to the principal features stated in the protocol will be documented in a protocol amendment. Otherwise, the statistical analysis plan will be updated through an amendment with the changes in the analyses documented in the amendment.

5.0 OBJECTIVES

5.1 Primary Objectives

- 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.

5.2 Secondary Objectives

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

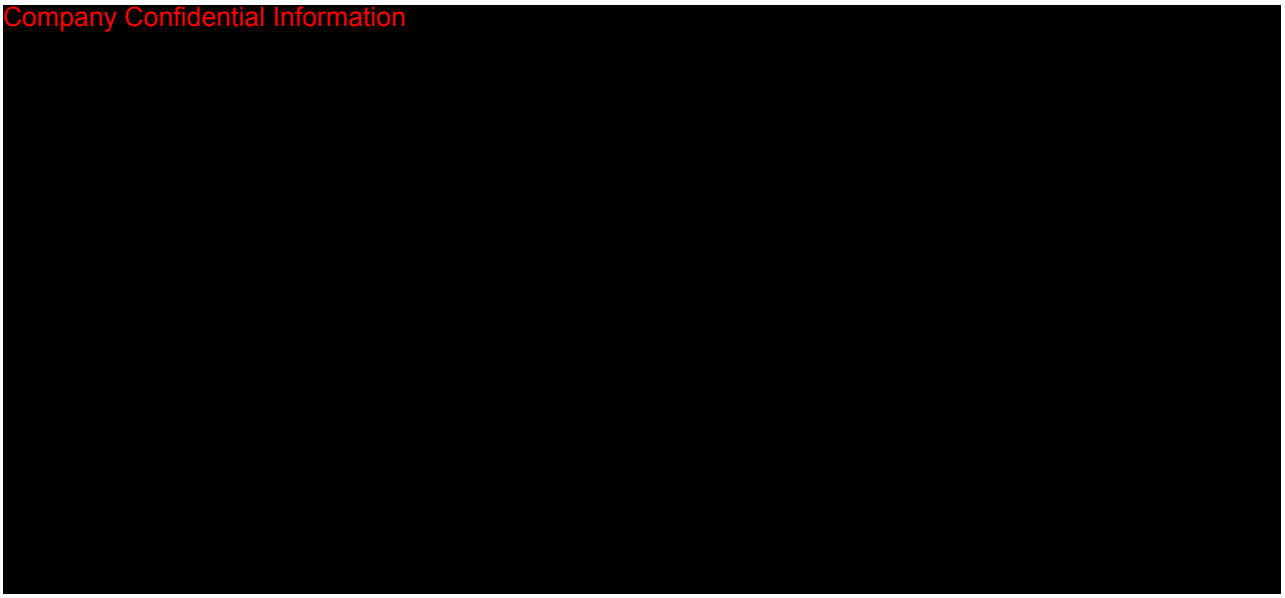
5.3 Additional Objectives

5.3.1 Safety Objective

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

5.3.2 Exploratory Objectives

- Company Confidential Information

- Company Confidential Information 

5.4 Study Design

This is a double-blind, 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. Subjects who have an adjudicated diagnosis of MCI due to AD in the 301 study and meet the entry criteria described in Protocol [2] 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 Protocol 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.

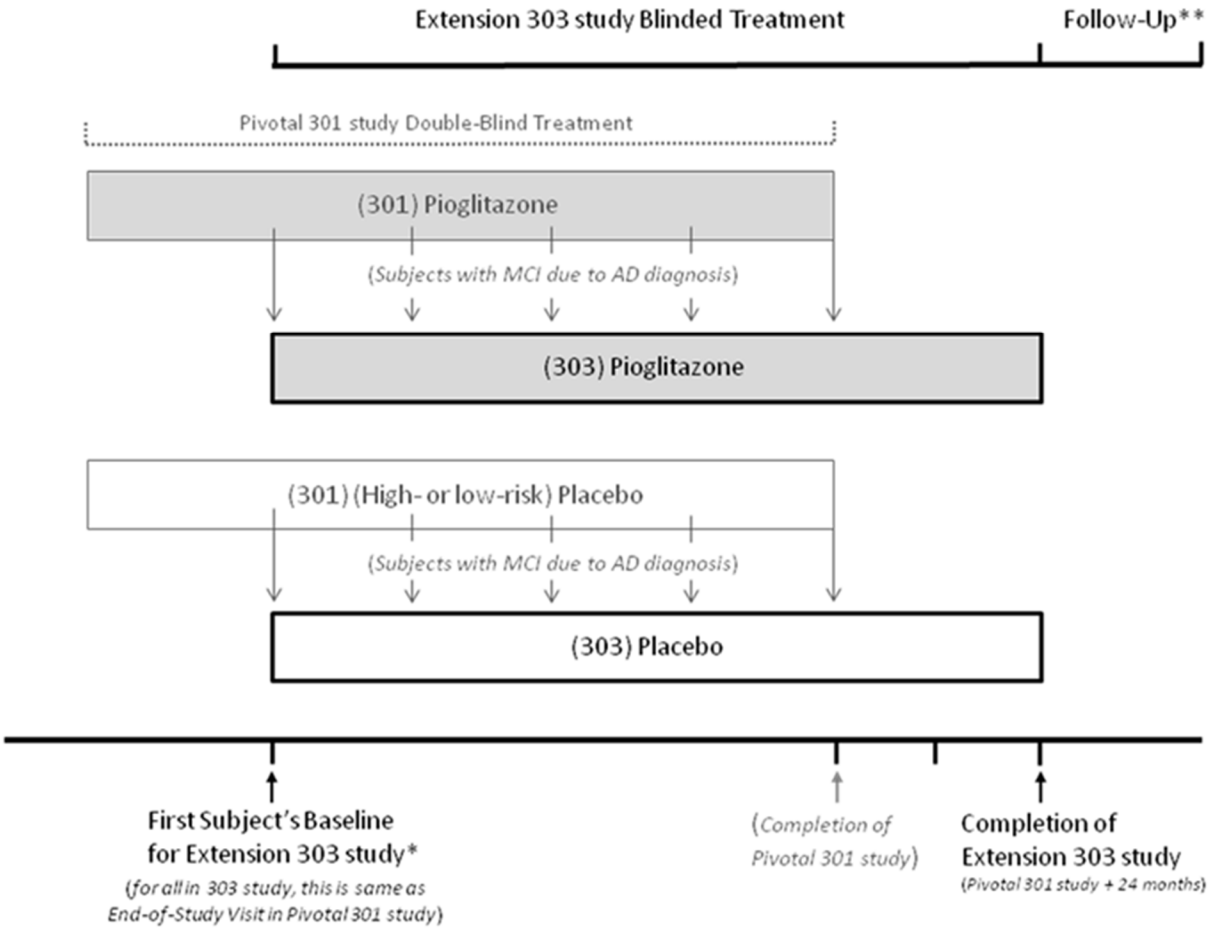
Subjects and their project partners are expected to attend on-site study visits every 6 months after Baseline, for regular assessments of safety, efficacy, and treatment compliance. In addition, the subject will be contacted for telephone-based safety checks between visits. While it is preferred that 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 Protocol 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 Protocol 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 5.a Schematic of Study Design. A schedule of assessments is listed in Appendix A.

Figure 5.a Schematic of Study Design



** Conversion to MCI due to AD in the Pivotal 301 study may occur for a subject as early as one year or as late as 301's completion;*
*** A Follow-Up Visit will be conducted as a safety phone call follow-up with the subject, approximately 2 weeks after the 303 End-of-Study Visit or Early Withdrawal Visit.*

6.0 ANALYSIS ENDPOINTS

6.1 Primary Endpoint

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

6.2 Secondary Endpoint

- Time to diagnosis of AD dementia.

6.3 Additional Endpoints

6.3.1 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.

6.3.2 Exploratory Endpoints

- Company Confidential Information [redacted]

- Company Confidential Information
- [redacted]

7.0 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.

8.0 METHODS OF ANALYSIS AND PRESENTATION

8.1 General Principles

The enrollment to this study has been terminated at the time of the SAP development. Due to limited number of enrolled subjects and insufficient treatment duration, all efficacy data will be listed without summarization nor analysis.

8.1.1 Summary Statistics and Precision

All study-related raw data for enrolled subjects, including derived data, will be presented in data listings. All tabulations of results will include summaries for all three treatment groups: high-risk placebo, high-risk pioglitazone, and low-risk placebo.

Disposition, demographic and baseline characteristics, study drug exposure, and safety data will be summarized descriptively by treatment groups.

For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation (SD) or standard error (SE) as appropriate, minimum, median, and maximum. The number of decimal places displayed for each statistic will be determined as follows:

- Mean and median: 1 more than the number of reported decimal places. (For electronic case report form (eCRF) data, the number of reported decimal places will be equal to the number of decimal places allotted in the eCRF.)
- SD and SE: 2 more than the number of reported decimal places allotted in the eCRF.
- Minimum and maximum: equal to the number of reported decimal places allotted in the eCRF.

For categorical data, frequency counts and percentages will be presented. Percentages will be reported to 1 decimal place. In summary tables for categorical data for which categories are defined on the eCRF, all categories will be presented as specified, even if the subject count within that category is zero. For other categorical data (eg, adverse events), only categories with at least 1 subject will be presented.

8.1.2 Definition of Study Day and Study Visit Windows

A windowing convention will be used to determine the analysis value for a given study visit that applies to observed data.

Study Day 1 is defined to be the date of the first dose of study medication, which is the day following the extension study Baseline Visit (Day -1). Other study days are relative to Study Day 1. Relative day is calculated as (date of interest – date of first dose +1) for study days on or after the date of first dose and as (date of interest – date of first dose) for study days prior to the first dose date.

The assessments performed at the End of Study Visit of the pivotal AD-4833/TOMM40_301 study are expected to serve as the Baseline for the extension study once appropriate informed

consent is signed. However, not all subjects are able 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. Therefore, the baseline value for a variable is defined as the most recent non-missing observation before the first dose of extension study medication.

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. For each visit, a window will be defined such that the lower and upper bounds of each window is generally the midpoint between 2 consecutive study visits. The visit windows and applicable study day ranges are presented below in Table 8.a.

Table 8.a Visit Windows

Nominal Visit Month	Nominal Visit Day	vMRI, HbA1c, EQ-5D, WPAI	Height, ECG, Chemistry, Hematology and Urinalysis, PE, etc.(b)	All Other Variables
Baseline	-1 (a)	≤1	≤1	≤1
6	183			2—273
12	365		2—547	274—456
18	548			457—638
24	731		548—912	639—821
30	913			822—1003
36	1096		913—1277	1004—1186
42	1278			1187—1369
48	1461		1278—1643	1370—1551
54	1644			1552—1734
60	1826		1644—1917	1735—1917
66/Final (c)	2009	>1	≥1918	≥1918

(a) Consistent with SDTM dataset standards, date of first dose of double-blind study drug is defined as Day 1, and the day before is defined as Day –1. Per the protocol, the first dose of double-blind study drug is to be taken the morning after the Baseline Visit.
(b) These procedures are performed in a 12 months interval: Height, ECG, Chemistry, Hematology and Urinalysis, PE, Pharmacogenomic RNA samples, CVLT-II, BVMT-R, Lexical fluency, Semantic fluency, MINT, Digit span, Trail making tests, and Clock drawing. No baseline assessment for Pharmacogenomic RNA samples.
(c) The extension study will be terminated 2 years after the pivotal 301 study is concluded.

For safety variables, visit windows are exhaustive and the lower and upper bounds of each window are the midpoints between the scheduled visit days for the current visit and the adjacent visits.

More than 1 result for a parameter may be obtained in a visit window. In such an event, the result with the date closest to the scheduled visit day will be used. In the event of 2 observations equidistant to the scheduled visit day, the later of the observations will be used.

Adverse events that start more than 30 days after the last dose of double-blind study medication (start date – last dose date >30) will be listed, but excluded from the summaries and analyses. For other safety data, data that are obtained more than 7 days after the last dose of double-blind study medication (visit date – last dose date > 7) will be listed, but excluded from summaries and analyses.

If the date of first dose of double-blind study drug collected in the eCRF is missing, then for summary purposes the day after the first dispense date-will be used as an estimate for the date of first dose. However, if all dispensed study drug is returned, then the subject is assumed to have not taken any study drug, and the first dose date will not be imputed.

If the date of last double-blind study drug dose collected in the eCRF is missing, then the earliest of the following dates will be used for the last dose date for analysis and summary purposes: date of death, date of last visit (recorded in the eCRF), last double-blind study drug return date, and the last double-blind study drug dispense date (following the last drug return date) + 200 days (ie, the double-blind study drug dispensing interval corresponding to the number of study drug tablets dispensed).

The study window convention will not be applied to the eCRF data listings. The data listings for eCRF data will display the raw data as collected and entered in the eCRF.

8.1.3 Imputation of partial/missing AE dates

8.1.3.1 Imputation of missing or partial dates of AE start dates

The following methods will be used to impute missing or partial dates of AE start dates.

- Month/year available and day missing:
  - If the month and year are the same as those in the first dose date and the event is not indicated as a pre-treatment event, the first dose date is to be used to impute the AE start date.
  - If the month and year are the same as those in the first dose date and the event is indicated as a pre-treatment event, the date prior to the first dose date is to be used to impute the AE start date. If the date prior to the first dose date is in previous month/year, set the start month/year to the previous month/year.
  - If the month and year are different from those in the first dose date, the first day of the month will be used for the start date.
- Year available and month/day missing:
  - If the year is the same as the year of the first dose and the event is not indicated as a pre-treatment event, the first dose date is to be used to impute the AE start date.
  - If the year is the same as the year of the first dose date and the event is indicated as a pre-treatment event, the date prior to the first dose date is to be used to impute the AE

start date. If the date prior to the first dose date is in previous month/year, set the start month/year to the previous month/year.

  - If the year is not the same as the year of the first dose date, set the start date as January 1.

- Year/month/day all missing:
  - If the event is not indicated as a pre-treatment event, the first dose date is to be used to impute the AE start date.
  - If the event is indicated as a pre-treatment event, the date prior to the first dose date is to be used to impute the AE start date.

8.1.3.2 Imputation of missing or partial dates of AE end dates

The following methods will be used to impute missing or partial dates of AE end dates.

If the event is indicated as ongoing at the end of the study, no imputation is needed.

If the event is not indicated as ongoing:

- Month/year available and day missing:
  - Use the last day of the month to impute the AE end date. If the imputed end date is before the AE start date, keep the end date same as the start date. If the subject died, use the date of death to impute the end date.
- Year available and month/day missing:
  - If the year is the same as or before the year of the last dose, set the end date as December 31.
  - If the year is after the year of the last dose, set the end date as January 1.
- Year/month/day all missing:
  - Impute the end date as December 31 of the last dose year. If the imputed end date is before the AE start date, keep the end date same as the start date. If the subject died, use the date of death to impute the end date.

8.1.4 Statistical Software

All statistical analyses will be performed using the SAS System® Version 9.2 or higher.

8.2 Analysis Sets

The Safety Analysis Set will include all subjects who were enrolled and received at least 1 dose of double-blind study medication in 303. All demographic and safety variables will be analyzed using the Safety Analysis Set. In safety summaries, subjects will be analyzed according to the actual treatment each subject received. In the event that a subject receives more than one treatment, the actual treatment will be defined as the one which is used most frequently. If the

two most common treatments are used with equal frequency, then the randomized treatment during the pivotal 301 study will be used as the actual treatment.

8.3 Disposition of Subjects

Disposition for all enrolled subjects will be summarized by treatment group and overall.

Disposition categories include:

- Number of enrolled / enrolled but not treated subjects.
- Number of subjects completing the study drug/visits.
- Number of subjects who prematurely discontinued the study drug/visits.
- The primary reason for premature discontinuation of the study drug/visits.

The reasons for premature discontinuation of the study drug and study visits include: pretreatment event/adverse event, major protocol deviation, lost to follow-up, voluntary withdrawal, study termination, and other.

A summary of baseline failures and listing of inclusion/exclusion criteria responses for subjects who failed at least one entrance criterion will be provided.

Significant protocol deviations captured on the electronic Case Report Form (eCRF) will be listed and summarized.

8.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics including date of birth or age, gender, Hispanic/Latino ethnicity, race as identified by the subject, non-Hispanic/Latino Caucasian determination, years of education, primary language, ability to communicate in primary language, bilingualism, years lived in the country/region, smoking status, drinking habit, height, weight, body mass index (BMI), diabetic status, and baseline statin use will be listed and summarized for each treatment group and overall. The demographic and baseline characteristics summary will be based on the safety analysis set in the extension AD-4833/TOMM40_303 study. All demographic information utilized in this study was collected during the start of the pivotal AD-4833/TOMM40_301 study except height and weight, which will be collected at the baseline visit of the extension study.

In countries that do not allow collection of date of birth, a subject's age will be collected at each post-Baseline Study Visit, Unscheduled Visit (as needed), and at the End of Study / Early Withdrawal Visit.

Height and weight values will be presented in metric units (cm and kg respectively). BMI is calculated as [weight (kg)/height (m) ^{2}], using the weight and height collected at Baseline.

Race is classified into White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander. In addition, ethnicity (Hispanic or Latino) is also captured.

For continuous variables, the number of non-missing values and the mean, median, SD, minimum and maximum will be tabulated by treatment group and overall. For the categorical variables, the count and percentages of each possible value will be tabulated by treatment group and overall.

All individual demographic and baseline data will be listed by treatment, study center and subject number.

8.5 Medical History and Concurrent Medical Conditions

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.

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.

Medical history and concurrent medical conditions data will be listed.

8.6 Medication History and Concomitant Medications

Medication history will be obtained during the pivotal AD-4833/TOMM40_301 study, and will not be collected during this study.

Concomitant medication is any drug given in addition to the study medication that the subjects continued taking or took from time of Informed Consent through end of study. 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.

The concomitant medications data will be listed.

8.7 Study Drug Exposure and Compliance

The summary of study drug exposure and compliance will be based on the safety analysis set.

Duration of exposure to double-blind study medication is defined as (date of last dose – date of first dose + 1).

Treatment duration will be summarized by duration category in months and the number of subjects in each duration category by treatment group.

- <6 months (1 to 161 days).
- 6 to <12 months (162 to 344 days).
- 12 to <18 months (345 to 526 days).
- 18 to <24 months (527 to 709 days).
- 24 to <30 months (710 to 892 days).
- 30 to <36 months (893 to 1074 days).
- 36 to <42 months (1075 to 1257 days).
- >=42 months (>=1258 days).

Treatment duration (months) will also be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum).

Percent of study drug compliance is defined as {(number of tablets dispensed - number of tablets returned)/(date of last dose - date of first dose +1)}x100%. If a value for the number of returned tablets is missing or the return date is missing, then 100% compliance will be assigned for each day up to the number of tablets dispensed, up to the date of return, or up to the date of the last visit, whichever is earliest.

For each treatment group, study medication compliance will be summarized by compliance category (<80%, 80 to 120%, and >120%) and the number of subjects in each compliance category. Study medication compliance will also be summarized as a continuous variable using descriptive statistics (n, mean, SD, median, minimum, and maximum) for each treatment group.

All study drug administration and accountability data will be listed by treatment, study site, and subject number. The following variables will be listed: subject identifier, visit, first and last dose dates, medication identification number, drug dispensed and drug returned dates, number of tablets dispensed and returned, and percent compliance.

8.8 Efficacy Analysis

Since the enrollment of the extension study was terminated when there were 40 subjects enrolled, and very few subjects achieved their 24 months visits (the primary endpoint visit) or greater, the efficacy data will only be listed but not summarized due to the lack of enrollment and observed data at the time of study termination.

8.8.1 Primary Efficacy Endpoint

The composite score of the cognitive test battery through 24 months will be listed.

The cognitive test battery by domain is described in Appendix E. Composite scores will be derived from the test battery consistent with practices used in the pivotal AD-833/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). As listed below, 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).

Episodic Memory domain	CVLT-II Short-delay free recall correct CVLT-II Long-delay free recall correct BVMT-R Delayed Recall
Executive Function domain	Trail Making (Part B) – Total Seconds WAIS-III Digit Span – Backward
Language domain	Semantic fluency (animals) Lexical/phonemic fluency (letters "F-A-S")
Attention	WAIS-III Digit Span – Forward Trail Making Test (Part A) – Total Seconds

To form the composite score, z-scores will be calculated for each test. The z-scores for measures in each domain will be averaged to create the four domain scores, and all four domain scores will be averaged to form the cognitive battery composite score. Because there are two tests for each domain, the domain score can still be calculated if one test is missing. One exception is the case of memory domain, where at least one subtest from each of the episodic memory tests (CVLT-II and BMVT-R) is required to calculate the composite (ie, BVMT-R Delayed Recall must be non-missing; and CVLT-II Short-delay free recall correct and/or CVLT-II Long-delay free recall correct must be non-missing). For the calculation of the memory domain score, the following 3 measures are used (and given equal weight): CVLT-II Short-delay free recall correct, CVLT-II Long-delay free recall correct, and BVMT-R Delayed Recall. If any of the domain scores is missing, then the composite score is set to missing.

For any visit, the z-score for a measure is calculated by taking the value for the measure at that visit, subtracting off the baseline mean for that measure, and then dividing by the baseline standard deviation for that measure. The baseline mean and baseline standard deviation for a measure will be calculated using all of the non-missing baseline values for subjects in the primary efficacy analysis population of high-risk, non-Hispanic/Latino Caucasian subjects.

8.8.2 Secondary Efficacy Endpoint

Time from Day 1 to the visit date that the subject meets the diagnostic criteria for AD dementia will be listed.

8.8.3 Additional Efficacy Endpoint

Not applicable.

8.9 Pharmacokinetic/Pharmacodynamic Analysis

Not applicable.

8.10 Pharmacogenomic Analysis

Pharmacogenomic data will be listed.

8.11 Other Outcomes

Not applicable.

8.12 Safety Analysis

All summaries of safety data are based on subjects in the Safety Analysis Set. Safety endpoints: AEs, vital signs, body weight, electrocardiogram (ECG), magnetic resonance imaging (MRI), clinical laboratory data, and physical examination findings will be collected and summarized. Unless otherwise specified, the safety data will be summarized by treatment group and overall.

8.12.1 Adverse Events

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

8.12.1.1 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.

Pretreatment events/ serious events will be summarized by system organ class and preferred term.

8.12.1.2 Adverse Events

An adverse event (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.

Treatment-emergent AEs (TEAEs) are any new or worsened events that occurred after the first dose of study medication and within 30 days following discontinuation of study medication from the subject's completion of the AD-4833/TOMM40_303 extension study.

Serious adverse events (SAEs) with onset that occurs after receiving study drug and within 30 days after receiving the last dose of study drug will be summarized.

All adverse events will be included in the data listings but only treatment-emergent adverse events will be included in the summary tables. 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. AEs with missing severity will be classified as having the highest severity. AEs with missing relationship will be classified as being related to study drug.

The following summaries will be presented:

- Overview of TEAEs during the study.
- TEAEs by SOC and preferred term.
- TEAEs by SOC and preferred term by gender (male and female).
- TEAEs by SOC and preferred term by age group (<75, >=75).
- Relationship of TEAEs to study drug by SOC, and preferred term.
- Intensity of TEAEs by SOC and preferred term.
- Drug-related TEAEs by SOC and preferred term.
- Intensity of drug-related TEAEs by SOC and preferred term.
- TEAEs leading to study discontinuation by SOC and preferred term.
- Treatment-emergent SAEs by SOC and preferred term.
- Most frequent TEAEs and non-serious TEAEs (>=5% based on total number of safety set subjects in any treatment group) by SOC and preferred term.
- Standardized MedDRA quaries (SMQs) and Takeda MedDRA quaries (TMQs) were used to determine the following adverse events of special interest (AESIs):
  - Congestive Heart Failure.
  - Macular Edema.
  - Hepatic Effects.
  - Bone Fractures.
  - Bladder Cancer.
  - Hypoglycemic Events.

The following listings of information from the liver function test eCRF pages will also be presented: Study drug interruption, signs and symptoms, event history, test results and reports, and additional comments.

8.12.2 Clinical Laboratory Evaluations

Table 8.b is a list of all protocol-specified clinical laboratory tests. The central laboratory will perform laboratory tests for serum chemistries, hematology, and urinalysis. All laboratory test parameters will be displayed in individual subject data listings in SI units.

For each laboratory parameter, the following will be displayed for each scheduled time point (each visit and end of study):

- Summary statistics by treatment group and overall for the actual values and change-from-Baseline values.
- Shift tables for the change from Baseline to each post-baseline time point will be presented.
- Markedly abnormal values for laboratory parameters, as defined in Appendix B, will be summarized by treatment group and overall.

Listings of all laboratory data will be provided. Laboratory data outside of the normal reference range will be flagged on the listings along with values meeting MAV criteria. The listings will also include the age (at consent) and gender of the subject. Listings of MAV laboratory values will also be presented. Direct bilirubin and rapid plasma reagin (RPR) will not be summarized but will be listed.

Table 8.b Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis (c)
Red blood cells White blood cells count with differentials (Neutrophils, eosinophils, basophils, lymphocytes, monocytes) Hemoglobin Hematocrit Platelets HbA1c (b)	ALT Alkaline phosphatase AST Total bilirubin Direct bilirubin (a) Total protein Albumin Creatinine Blood urea nitrogen γ-Glutamyl transferase Potassium Sodium Glucose Calcium, Parathyroid hormone Thyrotropin, free T4 Vitamin B12, folate (d) Rapid plasma reagin (e)	pH Specific gravity Protein Glucose Blood Nitrite

(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.

If a lab test with quantitative results has a value that is reported using a non-numeric qualifier (eg, less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier. However, these values will be displayed as is when the individual subject data listings are presented.

8.12.3 Vital Signs

Within the extension study, vital signs will be measured at each 6-month, and yearly in-clinic visit of double-blind treatment, Unscheduled Visit and at the End of Study Visit/Early Withdrawal Visit.

Vital signs include body temperature, sitting blood pressure, and pulse. Vital signs and weight at scheduled visits and their changes from Baseline will be summarized for each treatment group and overall using descriptive statistics by visit and end of study. The number and percentage of subjects with at least one post-Baseline MAV vital sign value during the double-blind treatment period will be presented for each variable over all visits. A listing of MAV vital signs values will also be presented. The criteria for identification of MAV vital signs values are provided in Appendix C.

8.12.4 12-Lead ECGs

ECG will be recorded at each yearly visit (eg, Month 12, 24) of double-blind treatment, and End of Study Visit/Early Withdrawal Visit.

ECG variables at scheduled visits and their changes from Baseline will be summarized for each treatment group and overall using descriptive statistics by study visit and end of study. A shift table for the investigator's ECG interpretation will provide the number of subjects in each of the appropriate categories (Normal, Abnormal but not clinically significant, or Abnormal and clinically significant) at the scheduled visit relative to the Baseline status. The number and percentage of subjects with at least one post-Baseline MAV ECG value during the blind treatment period will be presented for each variable over all visits. A listing of MAV ECG values will also be presented. The criteria for identification of MAV ECG values are provided in Appendix D.

8.12.5 Magnetic Resonance Imaging (MRI)

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 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.

The following volumetric measurements will be determined on MRI scans obtained at Baseline and End of Study/Early Withdrawal Visits of all subjects:

- Left and Right Hippocampus Volume (baseline/Visit 1 only).
- Ventricle Volume (baseline/Visit 1 only).
- Whole Brain Volume (baseline/Visit 1 only).
- Hippocampal Atrophy (End of Study/Early Withdrawal Visit).
- Ventricular Enlargement (End of Study/Early Withdrawal Visit).

- Whole Brain Atrophy (End of Study/Early Withdrawal Visit).

The possible categories for the MRI interpretation results recorded in the CRF are: Within Normal Limits; Abnormal, Not Clinical Significant; and Abnormal, Clinical Significant. All MRI scan interpretation results will be presented in the listings.

8.12.6 Physical and Neurological Examination

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. Physical examination will be performed at each yearly visit (eg, Month 12, 24) of double-blind 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 double-blind treatment, Unscheduled Visit, and End of Study Visit/Early Withdrawal Visit. All physical and neurological examination findings will be listed by treatment, study center and subject number.

8.13 Interim Analysis

Not applicable.

8.14 Changes in the Statistical Analysis Plan

For the efficacy analysis, the primary null hypothesis in the study protocol 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. 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. 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). The other efficacy endpoints will be analyzed in a manner similar to the primary efficacy endpoint and using MMRM. However, due to limited number of enrolled subjects and insufficient treatment duration, all the efficacy analysis will not be performed as planned.

9.0 REFERENCES

1. 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.
2. 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. Takeda Development Center Americas, Inc., Protocol No. AD-4833/TOMM40_303, Amendment #3, dated 19 January, 2016.

Appendix A Schedule of Study Procedures

	Baseline (Coincides With 301 End of Study Visit (a)					**Unscheduled Visit (b)**	**End of Study Visit/Early Withdrawal (c)**	**Follow-up Visit**
		Repeated Yearly						
Month	0 (Day -1)	3 (d)	6	9 (d)	12			EoS/EW+0.5 (e)
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	

	Baseline (Coincides With 301 End of Study Visit (a)					**Unscheduled Visit (b)**	**End of Study Visit/Early Withdrawal (c)**	**Follow-up Visit**
		Repeated Yearly						
Month	0 (Day -1)	3 (d)	6	9 (d)	12			EoS/EW+0.5 (e)
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	
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) (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) ADCS CGIG-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 Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

Parameter	Low Abnormal	High Abnormal
Red blood cells	<0.8 x LLN	>1.2 x ULN
White blood cells	<0.5 x LLN	>1.5 x ULN
Neutrophils	<0.5 x LLN	>1.5 x ULN
Eosinophils	--	>2 x ULN
Basophils	--	>3 x ULN
Lymphocytes	<0.5 x LLN	>1.5 x ULN
Monocytes	--	>2 x ULN
Hemoglobin	<0.8 x LLN	>1.2 x ULN
Hematocrit	<0.8 x LLN	>1.2 x ULN
Platelets (conventional)	$<75 \times 10^3/\mu L$	$>600 \times 10^3/\mu L$
Platelets (SI)	$<75 \times 10^9/L$	$>600 \times 10^9/L$
HbA1c (conventional)	--	>7%
HbA1c (SI)	--	>0.07

Chemistry—Criteria for Markedly Abnormal Values

Parameter	Low Abnormal	High Abnormal
ALT	--	>3 x ULN
Alkaline phosphatase	--	>3 x ULN
AST	--	>3 x ULN
Total bilirubin (conventional)	--	>2.0 mg/dL
Total bilirubin (SI)	--	>34.2 μmol/L
Direct bilirubin	--	>2 x ULN
GGT	--	>3 x ULN
Total protein	<0.8 x LLN	>1.2 x ULN
Albumin (conventional)	<2.5 g/dL	--
Albumin (SI)	<25 g/L	--
Creatinine (conventional)	--	>2 mg/dL
Creatinine (SI)	--	>177 μmol/L
Blood urea nitrogen (conventional)	--	>30 mg/dL
Blood urea nitrogen (SI)	--	>10.7 mmol/L
Potassium (conventional)	<3.0 mEq/L	>6.0 mEq/L
Potassium (SI)	<3.0 mmol/L	>6.0 mmol/L
Sodium (conventional)	<130 mEq/L	>150 mEq/L
Sodium (SI)	<130 mmol/L	>150 mmol/L
Glucose (conventional)	<50 mg/dL	>350 mg/dL
Glucose (SI)	<2.8 mmol/L	>19.4 mmol/L
Calcium (conventional)	<7.0 mg/dL	>11.5 mg/dL
Calcium (SI)	<1.75 mmol/L	>2.88 mmol/L
Thyroid Stimulating Hormone (TSH)	<0.8 x LLN	>2.0 x ULN
Vitamin B12 (conventional)	<125 pg/mL	--
Vitamin B12 (SI)	<92 pmol/L	--
Folate (conventional)	<2.2 pg/dL	>17.5 pg/dL
Folate (SI)	<5.0 nmol/L	>39.7 nmol/L
Parathyroid hormone (PTH)	<0.8 x LLN	>2.0 x ULN
Free thyroxine (Free T4)	<0.8 x LLN	>2.0 x ULN
Rapid plasma reagin (RPR)	positive	positive

ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=γ-glutamyl transferase, LLN=lower limit of normal, N/A=not applicable, ULN=upper limit of normal.

Urinalysis—Criteria for Markedly Abnormal Values

Parameter	Low Abnormal	High Abnormal
pH	N/A	N/A
Specific Gravity	N/A	N/A
Protein	N/A	N/A
Glucose	N/A	N/A
Blood	N/A	N/A
Nitrite	N/A	N/A

Appendix C Criteria for Abnormal Changes from Baseline of Vital Signs

Vital Sign	Criterion Value	Change Relative to Baseline
Systolic arterial blood pressure	>180 mm Hg	Increase of ≥20 mm Hg
	<85 mm Hg	Decrease of ≥20 mm Hg
Diastolic arterial blood pressure	>110 mm Hg	Increase of ≥15 mm Hg
	<50 mm Hg	Decrease of ≥15 mm Hg
Pulse	>120 bpm	
	<50 bpm	
Body Temperature	>37.7 degrees Celsius	
	<35.6 degrees Celsius	
Weight		Change of greater than 7% body weight

Both the criterion value and the change from Baseline must be met.

Appendix D Criteria for Out-of-Range Values for the 12-Lead ECG Parameters

	Criteria	
ECG Parameter	**Lower Criteria**	**Upper Criteria**
Heart Rate	<50 bpm	>120 bpm
QT Interval	<280 msec	≥460 msec
QTc Interval	<340 msec	≥500 msec OR ≥450 msec and ≥30 msec change from baseline

Appendix E Cognitive Test Battery

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

* Note: There are 12 measures derived from 8 neuropsychological tests in the battery: The CVLT-II test 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 Trails has 2 measures (ie, Parts A and B). There is one total score for each of the remaining tests: clock drawing, MINT, animal fluency and lexical fluency.
**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.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
Protected Personal Data	Biostatistics Approval	17-Sep-2018 13:02 UTC
	Biostatistics Approval	17-Sep-2018 13:56 UTC
	Clinical Approval	17-Sep-2018 17:29 UTC
	Pharmacovigilance Approval	17-Sep-2018 22:27 UTC