ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

# Pharmacogenomics and Translational Medicine in Delay of Onset of Mild Cognitive Impairment due to Alzheimer's Disease

Stephen Brannan, MD, Pharmaceutical Development Division,

Takeda Pharmaceuticals International, Inc., for the Zinfandel-Takeda Alliance Investigators

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

# Introduction

- The field is moving toward earlier treatment of Alzheimer's disease (AD).
  - Particularly for treatments that may delay the onset of the disease.
- Such studies need a mechanism to enrich the study population with participants at elevated risk for AD.
  - Subjects entering the trial will be cognitively normal.
  - Because subjects are cognitively normal, outcome measures with sufficient sensitivity are needed.
- Therapeutics utilized should have a well established tolerability/safety profile.
- In this particular trial:
  - It will be more similar to an epidemiology study.
    - Large numbers of healthy subjects
    - Followed for several years
  - The therapeutics' MOA is not directly related to amyloid (bioenergetics).

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

# Draft FDA Guidance Overview

- Intent is to provide guidance for clinical research prior to onset of frank dementia.
  - Provides guidance on patient selection.
    - Early AD
    - "At risk" for AD
  - Supports subject enrichment strategies.
- Provides guidance on endpoint selection.
  - A single composite (i.e., cognition and function) score may be acceptable for registration, e.g., CDR-SB.
    - Component of primary endpoint in our study.
- Recognizes that AD is a long-term process.
  - Emphasizes the need to develop, validate and use "sensitive" neuropsychological tests in the earliest AD stages.

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

# General Issues

- How does one accomplish typical P2 goals?
  - Trial duration and sample size prohibit dose finding studies etc
  - Can TM be used to guide dose selection?
- If treating “healthy normals”, what are the appropriate safety/tolerability standards?
- How are BMs to be used?
  - Enriching the patient population
  - Supportive of the outcome measures?
  - Done in all, or is a subset sufficient?
- How can we assure the generalisability of results?
  - Validation (cultural, linguistic) of Cognitive tests

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

# Program Rationale – Unmet Need

Full clinical picture of dementia as a first step of diagnosis for AD may be too late for effective intervention

Late diagnosis of AD may be the reason for failure in effectively addressing the underlying pathophysiology

New diagnostic criteria and intervention in earlier stages of the AD continuum (before clinical dementia onset) may be the answer

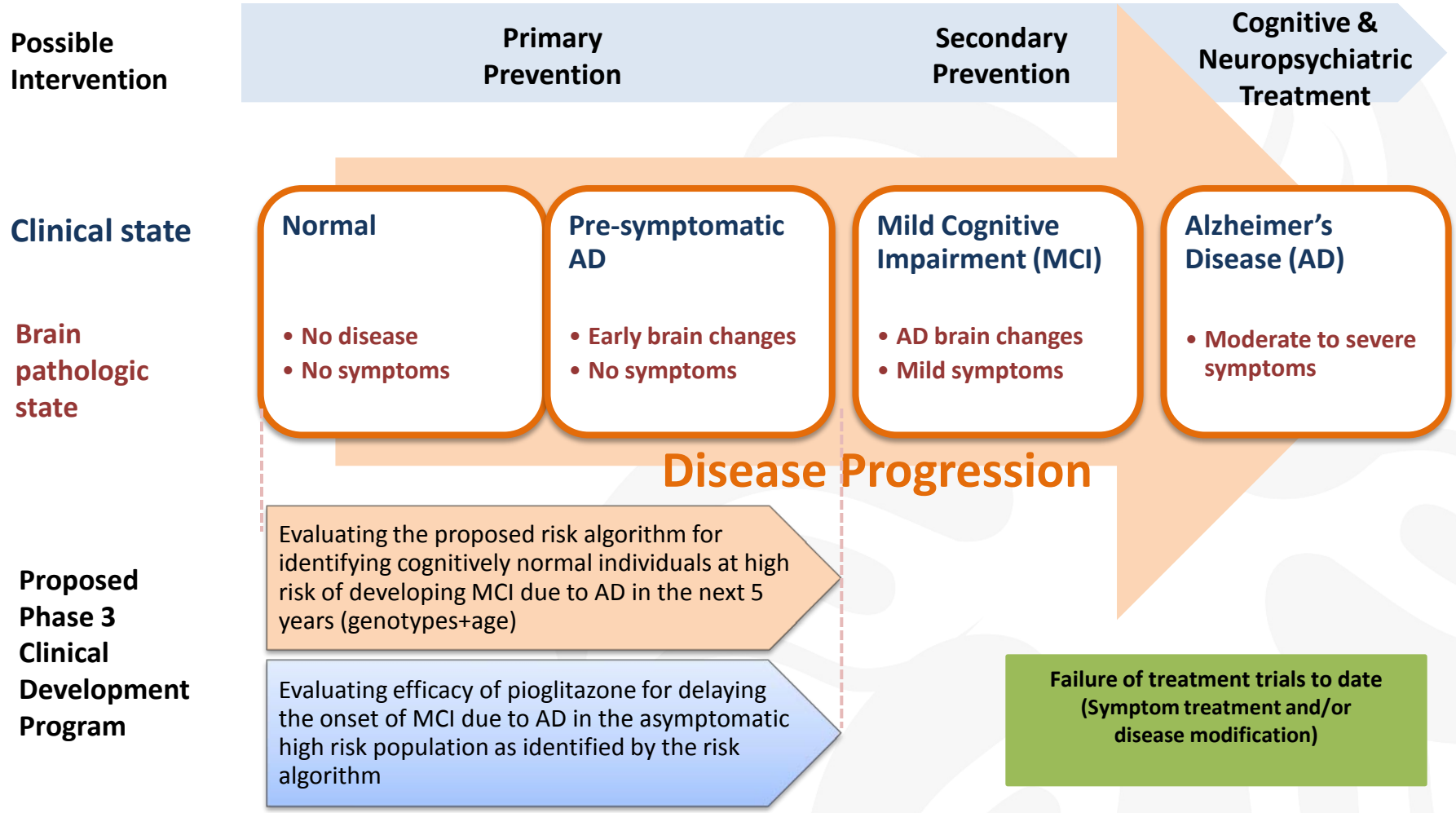
## New research dimensions

**(focus on 'pre-symptomatic' & early symptom stages of AD)**

- Drug development for prevention, early intervention and disease modification in pre-symptomatic/ early symptomatic stages of AD
- Search for new 'early diagnostic criteria' and its validation
- Development of new validated clinical assessment tools sensitive to change in different dimensions in early AD
- Search for new biomarkers to facilitate early diagnosis and evaluate efficacy in different stages of drug development

*In line with Concept paper on no need for revision of the guideline on medicinal products for the treatment of Alzheimer's disease and other dementias - EMA/CHMP/60715/2012

# The AD Continuum and Our Proposed Study



# Enriching the Study by Using a Biomarker Risk Algorithm

## Purpose

- The algorithm yields a determination of risk of developing mild cognitive impairment (MCI) due to Alzheimer's disease (AD) in cognitively normal adults ages 65-83 years over the next 5 years.

## Components to determine the risk

- APOE genotype – ε2, ε3, or ε4
- TOMM40-*523* genotype – Short (S), Long (L), or Very Long (VL)
- Age at enrollment

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

# Phase 3 Study Overview

Single, multicenter, double-blind, randomized, placebo-controlled study

- 5,800 cognitively normal subjects (male and female)
  - 4,622 subjects in the high-risk group (Caucasian)
  - 600 subjects in the low-risk group (Caucasian)
  - 578 non-Caucasian subjects (includes 60 subjects who are low-risk)
- Age at enrollment: 65-83 years
- This is an event based trial so the duration of study will be the amount of time to achieve 410 events in the high-risk Caucasian group, estimated to take approximately 4 years.

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

# Phase 3 Trial: Sites Around the World

# Phase 3 Study Objectives

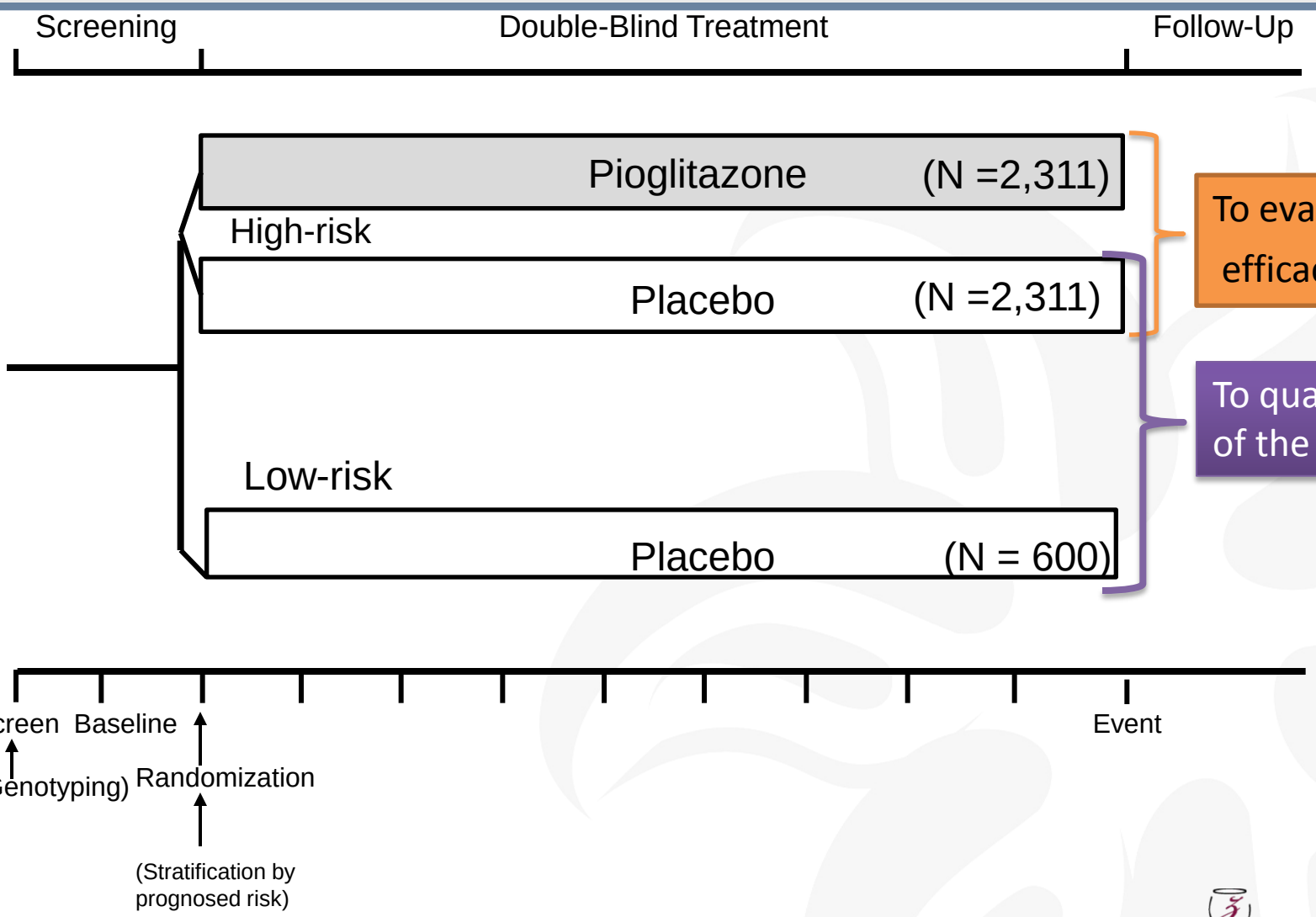
**Primary Objective**

- For biomarker qualification:
  - To qualify the use of the biomarker risk algorithm composed of TOMM40 rs10524523 genotype, APOE genotype, and age for prognosis of the risk of developing MCI due to AD within 5 years.
- For efficacy evaluation of a low dose of pioglitazone:
  - To evaluate the efficacy of pioglitazone to delay the onset of MCI due to AD, in cognitively normal subjects who are at high risk for developing MCI due to AD within 5 years, as identified by the biomarker risk algorithm at enrollment.

**Primary Endpoints**

- For biomarker qualification:
  - Time to diagnosis of MCI due to AD for placebo-treated high-risk subjects versus placebo-treated.
- For efficacy evaluation of a low dose of pioglitazone:
  - Time to diagnosis of MCI due to AD for pioglitazone-treated subjects versus placebo-treated subjects in the high-risk stratum.

# Phase 3 Study Schematic



# Phase 3 Study
# Clinical Criteria for End Points

| Core Clinical Criteria (Albert 2011) | Core Clinical Criteria (Operationalized) |
|---|---|
| **Establish clinical and cognitive criteria** | |
| • Cognitive concern reflecting a change in cognition reported by subject or informant or clinician (*i.e*., historical or observed evidence of decline over time).<br><br>• Objective evidence of impairment in one or more cognitive domains, typically including memory (*i.e*., formal or bedside testing to establish level of cognitive function in multiple domains).<br><br>• Preservation of independence in functional abilities.<br><br>• Not demented. | • Clinical dementia rating scale score of 0.5, AND one of the following:<br>• Fails at least one of the two memory tests in the cognitive test battery.<br>• Fails 2 or more of the 12 measures in the cognitive test battery, representing separate cognitive domains. |

Albert et al. *Alzheimers Dement.* 2011;7(3):270-9.

# Phase 3 Study
# Clinical Criteria for End Points

| Core Clinical Criteria (Albert 2011) | Core Clinical Criteria (Operationalized) |
|---|---|
| **Examine etiology of MCI consistent with AD pathophysiological process** | |
| • Rule out vascular, traumatic, medical causes of cognitive decline, where possible. | • Rule out vascular, traumatic, and other proximal medical causes of cognitive decline. |
| • Provide evidence of longitudinal decline in cognition, when feasible. | • Continued evidence of cognitive impairment or continued decline on 6 month follow-up (*i.e.*, 2 consecutive study visits showing impairment). |

# Phase 3 Study – Cognitive Test Battery

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

# Phase 3 Study
# Additional Study Objectives

## Secondary Objectives

- Effect of a low dose of pioglitazone on:
  - progression of cognitive decline
  - functional decline and activities of daily living

## Safety Objectives

- Long-term safety and tolerability of pioglitazone versus placebo
- Incidence of treatment-emergent ARIA in cognitively normal elderly patients who received pioglitazone for 6 months (in a subset of subjects)

## Exploratory Objectives

- Effects of pioglitazone on safety/efficacy pharmacogenetics to identify genetic loci associated with drug response and/or conversion to MCI due to AD
- Effects of pioglitazone on vMRI over time (in the same subset of subjects enrolled in the ARIA substudy)
- Retrospective evaluation and optimization of the prognostic characteristics of the biomarker risk algorithm for age of onset for MCI due to AD in non-white subjects

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

# Summary of Efficacy Assessments

| | Screening | Baseline | Randomization | Double-Blind Treatment *Repeated yearly* | | | | Unscheduled Visit | End of Study Visit/Early Withdrawal | Follow-Up Visit |
|---|---|---|---|---|---|---|---|---|---|---|
| Study Month: | -1 | -0.5 | 0 (Day1) | 3 | 6 | 9 | 12 | | | EoS/EW+1 |
| Efficacy | | | | | | | | | | |
| MMSE | X | X | | | X | | X | | X | |
| IQCODE | | X | | | X | | X | | X | |
| CVLT-II | | X | | | X | | X | | X | |
| BVMT-R | | X | | | X | | X | | X | |
| Semantic Fluency | | X | | | X | | X | | X | |
| Lexical/Phonemic Fluency | | X | | | X | | X | | X | |
| MINT (32 items) | | X | | | X | | X | | X | |
| Digit Span | | X | | | X | | X | | X | |
| Trail Making Tests | | X | | | X | | X | | X | |
| Clock Drawing | | X | | | X | | X | | X | |
| GDS | | X | | | X | | X | | X | |
| Self-Rating of Memory Functions: ADCS | | X | | | X | | X | | X | |
| CDR | | X | | | | | | X | X | |
| ADCS ADL-PI | | X | | | X | | X | | X | |
| NPI-Q | | X | | | | | | X | X | |
| ADCS-CGIC | | | | | X | | X | X | X | |
| EQ-5D | | X | | | X | | X | X | X | |
| SF-36 | | X | | | X | | X | X | X | |
| Health care RU | | X | | | X | | X | X | X | |

# Clinical Laboratory Tests

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

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

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

# Phase 3 Extension Study : Supportive Study for the Program

Based on feedback from FDA and EMA, this study could provide important supportive evidence for the novel endpoint of MCI due to AD in the marketing applications.

Population: converters from cognitively normal to MCI due to AD during the main phase 3 study.

Design: double-blind extension to the main phase 3 study; subjects will continue on the same treatment (pioglitazone or placebo).

Objective: evaluate the safety and efficacy of pioglitazone in slowing the progression of cognitive decline in subjects with MCI due to AD.

Sample size: N max=472.*

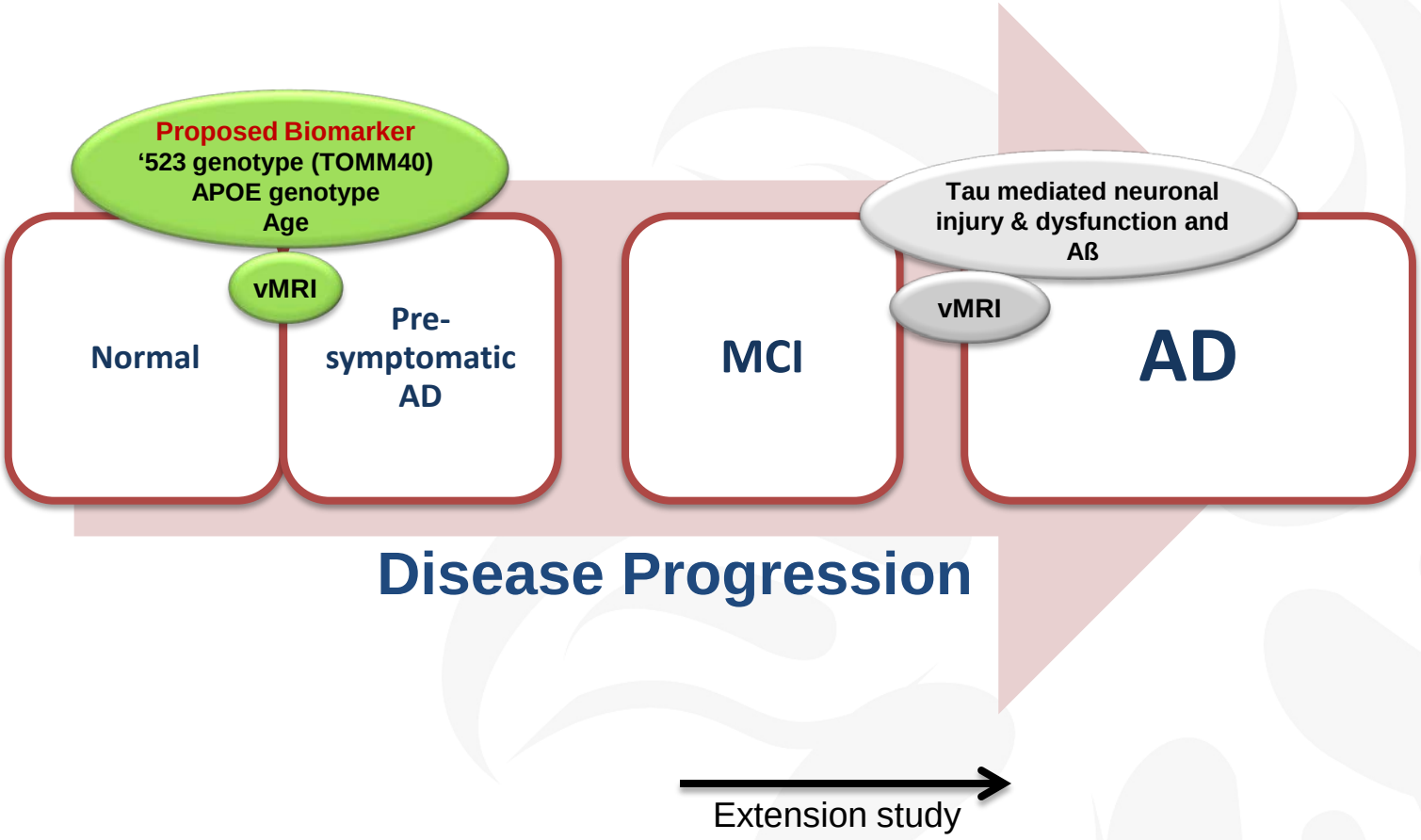
N expected~316 (~67%)

Primary endpoint: Change of cognitive impairment from extension study baseline to at least 2 years post study completion (composite cognitive test battery score).

–Important secondary endpoint in this study is the number of convertors from MCI to AD.

** All converters from high-risk (410 Caucasian + 41 non-Caucasian =451) and low-risk (21) groups*

# Proposed Biomarker vs Qualified Biomarkers

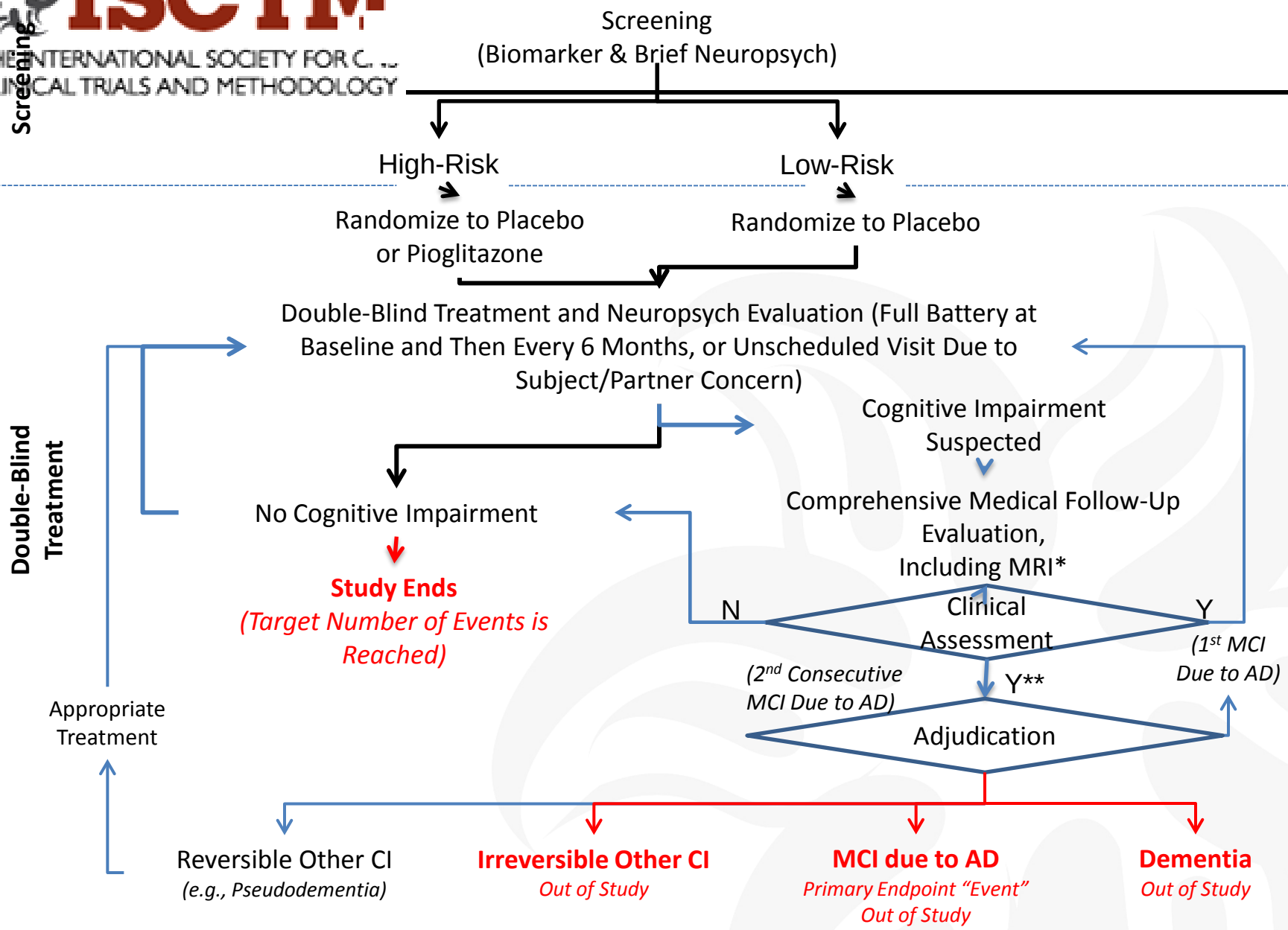


ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

# Rationale for the Use of Pioglitazone

- Peroxisome proliferator-activated receptor gamma (PPARγ) agonists, including pioglitazone, modulate a number of pathways implicated in the pathogenesis of AD: energy metabolism, insulin sensitivity, lipid metabolism, amyloid β homeostasis, and inflammation [Landreth G et al. 2008].
- PPARγ agonists also play critical roles in energy metabolism due to their direct effects on mitochondrial function, biogenesis and, ultimately, ATP production and neuronal glucose utilization.
- Pioglitazone has salutary effects in mouse models of AD and in small sample-size human studies [Sato et al. 2011; Nicolakakis, et al. 2010].
- Any pharmaceutical agent used in cognitively normal people must be supported by extensive patient exposure data and be well tolerated.
- There is substantial patient experience and exposure with pioglitazone (22 million patient-years).

# Subject Flow in the Study



ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

# Adjudication Process

- When adjudication is required, all pertinent data will be shared with an adjudication committee, comprised of at least three expert clinicians, who are blinded to the subject's risk and treatment assignments. The process will result in one of four possible clinical assessments and subsequent outcomes:
  1. Mild cognitive impairment due to Alzheimer's disease (MCI due to AD, primary study endpoint)
     - If confirmed, subject will be a study completer and will count toward the total number of events needed for the primary efficacy analysis; the initial visit at which the MCI due to AD diagnosis was made will be considered the onset time for the primary endpoint.
     - If not confirmed, subject will remain in the study unless there is a medical reason for withdrawal.
  2. Alzheimer's disease dementia
     - If confirmed, subject will be a study completer and will count toward the total number of events needed for the primary efficacy analysis.

# Adjudication Process (continued)

3. Other cognitive impairment (i.e., not MCI due to AD), including etiologies of vascular dementia, Creutzfeldt-Jakob Disease, and others that may be reversible or irreversible. This event will not count toward the total number of events recorded for the primary efficacy analysis.
   - If considered irreversible, a subject will be discontinued from the study and referred for appropriate care and follow-up.
   - If considered reversible (e.g., pseudodementia), the subject will be given appropriate medical care and remain in the study.
4. Dementia other than AD dementia. This event will not count toward the study endpoint.
   - Subject will stop study treatment and be referred for appropriate care.

ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

# Summary

- Alzheimer's disease is increasing due to the aging population worldwide.
- The field is moving toward treating earlier in the continuum of AD for several reasons.
- Takeda and Zinfandel are collaborating in a clinical development program that will qualify a biomarker risk algorithm to prognose cognitively normal individuals who are at high risk for developing MCI due to AD, and will also provide a useful enrichment strategy for disease events within a 5-year treatment window.
- This program will also assess the effects of pioglitazone in delaying the onset of MCI due to AD in individuals at high risk as determined by the biomarker risk algorithm.
- This program will have a novel endpoint of time to onset of MCI due to AD, which a group of experts operationalized for this study.
- This groundbreaking program will likely bring significant insight into the Alzheimer's disease scientific field. If successful, it will also have the potential to significantly impact the life of individuals at risk for MCI due to AD, their families, and society as a whole.