Protocol I8D-MC-AZES (Version 7.1)

A 24-month, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Efficacy, Safety, Tolerability, Biomarker, and Pharmacokinetic Study of AZD3293 in Early Alzheimer's Disease (The AMARANTH Study)

NCT02245737

Approval Date: 17-Jul-2017

Revised Clinical Study Protocol	
Drug Substance	AZD3293 [LY3314814; lanabecestat]
Study Code	D5010C00009 [I8D-MC-AZES]
Edition Number	7.1
Date	See approval date below

A 24-Month, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy, Safety, Tolerability, Biomarker, and Pharmacokinetic Study of AZD3293 in Early Alzheimer's Disease (The AMARANTH Study)

Sponsor: Eli Lilly and Company, Indianapolis, IN 46285

IND number: 116,692

EudraCT number: 2014-002601-38

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
01	24 November 2014	01 (Korea)	24 February 2015
02	12 March 2015		
03	12 June 2015		
04	30 June 2016		
5.1	See approved date below		

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change
01	02 September 2014		

Approval Date: 17-Jul-2017 GMT

PROTOCOL SYNOPSIS

A 24-Month, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy, Safety, Tolerability, Biomarker, and Pharmacokinetic Study of AZD3293 in Early Alzheimer's Disease (The AMARANTH Study)

International Co-ordinating Investigator

Study centers and number of patients planned

The study is expected to enroll a total of approximately 2202 patients from across the globe.

Study period		Phase of development
Estimated date of first patient enrolled	Q4 2014	Phase 2/3
Estimated date of last patient completed	Q3 2019	

Objectives

Primary objective: to test the hypothesis that AZD3293, administered orally at doses of 20 and 50 mg daily for 104 weeks, will slow the decline of Alzheimer's disease (AD) as compared with placebo in patients with early AD dementia as measured by the 13-item Alzheimer's Disease Assessment Scale – Cognitive subscale ($ADAS\text{-}Cog_{13}$). Early AD is defined as the continuum of patients with mild cognitive impairment (MCI) due to AD (ie, prodromal AD) and patients diagnosed with mild dementia of the Alzheimer's type.

Double-Blind Treatment Period	
Secondary Objectives	**Endpoints**
Clinical efficacy objectives: • To evaluate the efficacy of AZD3293 on functional, clinical, and cognitive outcomes in patients with early AD dementia at the end of the Double-Blind Treatment period (Week 104).	• Functional Outcome Measures o The Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory instrumental items (ADCS-iADL) score o Functional Activities Questionnaire (FAQ) score • Cognitive/Functional Outcome Measures o Integrated Alzheimer's Disease Rating Scale (iADRS) score o Clinical Dementia Rating – Sum of Boxes (CDR-SB) score • Clinical Outcome Measures o CDR-Global Score o Neuropsychiatric Inventory (NPI) score • Cognitive Outcome Measures o Mini-Mental State Examination (MMSE)
• To evaluate the relationship between treatment effect of AZD3293 and time (at points other than the end of the Double-Blind Treatment period [Week 104], such as Week 26, Week 52 and Week 78). Specific time points will vary by instrument.	• ADAS-Cog$_{13}$, ADCS-iADL, FAQ, CDR-SB, and iADRS
• To test the hypothesis that AZD3293 will slow the rate of cognitive and functional decline associated with AD, compared with placebo	• ADAS-Cog$_{13}$, ADCS-iADL, and FAQ using a slope analysis from a repeated-measures model
• To evaluate the efficacy of AZD3293 to prolong time in the current disease state	• CDR global score
• To evaluate the clinical worsening and need for symptomatic treatments	• AD symptomatic treatments time of initiation
Biomarker objectives: • To evaluate the effect of AZD3293 on cerebrospinal fluid (CSF) amyloid beta peptide (Aβ) pharmacodynamics (PD) markers	• CSF $A\beta_{1-42}$ and $A\beta_{1-40}$ concentrations
• To evaluate the effect of AZD3293 on CSF markers of neurodegeneration	• CSF total tau and phosphorylated tau concentrations
• To evaluate the effect of AZD3293 on brain amyloid burden	• Florbetapir amyloid scan
• To evaluate the effect of AZD3293 on brain aggregated tau levels	• ^{18}F-AV-1451 Tau PET [separate addendum]
• To evaluate the effect of AZD3293 on brain metabolism	• Fluorodeoxyglucose (FDG) positron emission tomography (PET) [separate addendum]
• To evaluate the effect AZD3293 on brain atrophy	• Brain volumes measured by magnetic resonance imaging (MRI)

Pharmacokinetic objective: • To assess the population PK of AZD3293 and metabolite AZ13569724 in patients with early AD dementia	• Apparent Oral Clearance of AZD3293 • Central Volume of Distribution of AZD3293
Safety Objective • To evaluate the safety and tolerability of AZD3293 in patients with early AD dementia	• Standard safety assessments: o spontaneously reported adverse events (AEs) o clinical laboratory tests o vital sign and body weight measurements o 12-lead electrocardiograms (ECGs) o physical examinations including neurological examinations • Additional safety assessments: o Eye examinations o Skin examinations o Serial MRI o Columbia-Suicide Severity Rating Scale (C-SSRS)
Exploratory Objectives*	**Endpoints***
• To evaluate the efficacy of AZD3293 on executive function	• Changes from baseline in the Letter Fluency, Category Fluency, and Digit Symbol-Coding test scores
• To evaluate the efficacy of AZD3293 on neuropsychological status	• Change from screening in the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score
• To explore the effects of AZD3293 on resource utilization and health status	• Change from baseline in the Resource Utilization in Dementia (RUD)-Lite and EQ-5D-5L score
• To explore the effects of AZD3293 on caregiver distress	• Change from baseline in the NPI-D score
• To evaluate the dose-exposure effect relationships for selected efficacy, safety, and biomarker endpoints	• Changes in scales, adverse events and blood, CSF and imaging biomarkers in relation to exposure
• To explore the genetic effects of APOE4 allele status (carrier or non-carrier)	• Change from baseline on selected efficacy, safety, and biomarker endpoints
• To explore the effect of AZD3293 on gene expression.	• Change in levels of whole blood messenger ribonucleic acid (mRNA) and on plasma and CSF micro-ribonucleic acid (miRNA) levels and the relation to selected efficacy, safety and biomarker endpoints
• To explore the effect of AZD3293 on peripheral and central nervous system protein expression.	• Change in CSF or peripheral protein biomarkers, including CSF or plasma $A\beta_{1-42}$ and $A_{\beta 1-40}$, neurodegenerative inflammatory markers, and proteomic assessments and the relation to selected efficacy, safety, and other biomarker endpoints
• To examine AZD3293 population PK/PD	• Exposure and selected measures of efficacy and/or tolerability
• To optionally collect and store	• Association of genetic variation with selected

deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence response (that is, distribution, safety, tolerability, and efficacy) to AZD3293. Genes that will be tested for heritable genetic (DNA) or expression (mRNA, miRNA) effects will be limited to those for which a hypothesis for involvement in the pharmacology of AZD3293 or in the pathogenesis of AD can be formulated, as currently understood and as directed by future scientific progress in the field.	endpoints (optional pharmacogenomics sampling)

***Note**: the results of analyses that address some exploratory objectives may not form part of the Clinical Study Report, but may be described in supplementary reports as appropriate.

Study design

This is a multicenter, randomized, parallel-group, double-blind, placebo-controlled, international study of 2 fixed dose levels of AZD3293 in patients with early AD. Patients who meet other study entry requirements will be required to be amyloid positive. They may undergo a florbetapir F 18 amyloid PET scan or a lumbar puncture for CSF sampling (but not both) at screening to document the presence of abnormal levels of amyloid for study inclusion.

The study includes 2 longitudinal biomarker sub-studies: a longitudinal florbetapir F 18 amyloid PET sub-study and a longitudinal CSF sub-study. Patients who undergo a florbetapir F 18 PET scan at screening to document the presence of amyloid will be included in the florbetapir F 18 PET sub-study, and patients who undergo a lumbar puncture for CSF sampling at screening will be included in the CSF sub-study. However, all enrolled patients will be required to demonstrate amyloid positivity by PET or CSF collection at screening or by a historical amyloid PET scan. In addition, there are two longitudinal sub-studies of FDG and ^{18}F-AV-1451 PET at applicable sites (see addenda for details).

Target patient population

Men and women, aged 55 to 85 years, with early AD (defined as the continuum of patients with MCI due to AD and patients diagnosed with mild dementia of the Alzheimer's type). All enrolled patients must have an MMSE score of 20 to 30 inclusive. For a diagnosis of mild AD, the patient must (1) meet the National Institute on Aging (NIA) and the Alzheimer's Association (AA) (NIA-AA) criteria for probable AD and (2) have a CDR global score of 0.5 or 1, with the memory box score $\geq$0.5. For a diagnosis of MCI due to AD, the patient must (1) meet NIA-AA criteria for MCI due to AD and (2) have a CDR global score of 0.5, with the memory box score $\geq$0.5.

Investigational product, dosage and mode of administration

AZD3293 20 mg or 50 mg, administered as tablets orally once daily (in the morning).

Comparator, dosage and mode of administration

Placebo matching AZD3293, administered as tablets orally once daily (in the morning).

Duration of treatment

The overall study duration will be approximately 118 weeks, including a screening period of approximately 8 weeks, a baseline assessment period of approximately 1 week, a double-blind treatment period of 104 weeks, and a follow-up period of 4 to 6 weeks. Of note, those patients who complete 104 weeks of treatment in Study I8D-MC-AZES (AZES) and wish to continue treatment may enter a separate double-blind extension trial, Study I8D-MC-AZFD (AZFD).

Statistical methods

General principles

A comprehensive Statistical Analysis Plan (SAP) will be prepared and finalized before the study data are unblinded. An interim analysis SAP will be prepared and finalized before each interim analysis.

A graphical multiplicity strategy will be used for testing key secondary hypotheses to protect against Type I error of falsely rejecting a null hypothesis. The use of a prespecified analysis plan that employs Bretz' graphical approach will provide strong control of the study-wise Type I error rate for the primary and key secondary hypotheses at level α=0.05. The order of testing of hypotheses and control of Type 1 error will be prespecified in the graphical analysis as stated in the SAP.

A separate family of biomarkers will be tested at α=0.05. The family will include the biochemical biomarkers (CSF $A\beta_{1-42}$, total tau, and phosphorylated tau), as well as imaging biomarkers (florbetapir F 18 amyloid PET and volumetric MRI).

Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established to monitor data on an ongoing basis to ensure the continuing safety of patients enrolled in this study, to ensure the integrity of the blinded nature of the study, and to oversee the 4 planned interim analyses. The IDMC will be composed of individuals external to the sponsor. An IDMC charter will be developed which will specify the Committee's responsibilities, authorities, and procedures along with details of the interim analysis planning, decision-making guidance, and dissemination of the results as well as the recommendations and decisions after the interim analyses. Formal implementation and communication of IDMC recommendations will be managed by the sponsor Executive Committee, which will be unrelated to the AZD3293 project team. A firewall will be established to ensure the maintenance of the study blind for the sponsor, the investigational site staff, and study patients and their study partners.

Interim analyses

Four interim analyses may be conducted during this study, overseen by the IDMC and an Independent Statistical Center.

Interim analysis 1

The first interim analysis (IA1) will be performed when approximately 70 patients per group have 13 weeks' worth of data. It is expected that, at IA1, approximately 500 patients will have

been randomized globally. The objective of IA1 is to assess the viability of continuing with AZD3293 with regard to safety.

One of the following IDMC recommendations will result from IA1:

- Continue the study unmodified
- Discontinue enrollment in 1 or both AZD3293 treatment groups for reasons of an unacceptable safety profile.
  - If 1 AZD3293 treatment group is discontinued for enrollment at IA1, the randomization ratio for newly enrolled patients will remain 2:1 (active:placebo). Patients in the discontinued AZD3293 treatment group will be switched to the other AZD3293 treatment group; for analysis purposes, these patients will be included in their originally assigned AZD3293 treatment group.
  - Stop the study if enrollment in both AZD3293 treatment groups is discontinued

Interim analysis 2

The second interim analysis (IA2) will be performed when approximately 80% of patients have been randomized. IA2 will assess the viability of continuing AZD3293 treatment groups with regard to safety and will re-assess the total sample size based on the Bayesian predictive probability of the ADAS-Cog_{13}, ADCS-iADL, and/or FAQ.

One or more of the following IDMC recommendations will result from IA2:

- Continue the study unmodified
- If neither AZD3293 treatment group was discontinued at IA1 and, therefore, both AZD3293 treatment groups remain in the study at IA2:
  - Discontinue enrollment in 1 or both AZD3293 treatment groups for reasons of an unacceptable safety profile. If 1 dose is discontinued for enrollment at IA2, the randomization ratio for newly enrolled patients will remain 2:1 (active:placebo). Patients in the discontinued AZD3293 treatment group will be switched to the other AZD3293 treatment group; for analysis purposes, these patients will be included in their originally assigned AZD3293 treatment group.
  - Stop the study if both AZD3293 treatment groups are discontinued
- If 1 AZD3293 treatment group was discontinued at IA1 and, therefore, 1 AZD3293 treatment group remains in the study at IA2:
  - Discontinue enrollment in the remaining AZD3293 treatment group for reasons of an unacceptable safety profile
  - Stop the study if the remaining AZD3293 treatment group is discontinued

- Increase the sample size

Interim analysis 3

A third interim analysis (IA3) may be performed to calculate the futility of either dose. The parameters of this futility analysis will be described in the interim analysis and the end-of-study analysis SAPs.

Interim analysis 4

A fourth interim analysis (IA4) may be performed to assess for futility and for early stopping of the study for efficacy. This interim analysis will be described in the interim analysis and end-of-study analysis SAPs.

Efficacy analyses

All analyses will be performed in a manner that is consistent with the intent-to-treat (ITT) principle. When change from baseline is assessed, patients will be included in the analysis only if both a baseline and a post-baseline measure are available.

Primary analysis

The primary efficacy endpoint, change from baseline at Week 104 in ADAS-Cog_{13} score, will be analyzed using a mixed-effect repeated-measures (MMRM) model that includes the fixed effects of treatment, visit (categorical covariate), treatment-by-visit interaction, disease status at baseline (MCI due to AD or mild AD), APOE4 status (carrier versus non-carrier), baseline ADAS-Cog_{13} score (continuous covariate), concomitant acetylcholinesterase inhibitors (AChEI) use at baseline (yes/no), age at baseline, country, and baseline ADAS-Cog_{13} score-by-visit interaction. Differences between treatment groups will be assessed using appropriate linear contrasts of the parameters in the MMRM model.

Secondary analyses

When a comparison between an AZD3293 dose group and the placebo group is statistically significant on the primary efficacy endpoint, the secondary efficacy endpoints for the AZD3293 dose group will be tested through a graphical approach which includes the primary efficacy endpoint. The order of testing and control of Type 1 error will be prespecified in the graphical analysis as stated in the SAP.

Exploratory efficacy variables will be analyzed using the MMRM models described above as well as with descriptive statistical analyses. These variables are listed above and in the SAP.

Biomarkers

Changes from screening in CSF biomarkers (eg, $A\beta_{1-42}$, total tau, and phosphorylated tau) will be analyzed using an MMRM analysis that includes the fixed effects of treatment, visit (categorical covariate), treatment-by-visit interaction, disease status at baseline (MCI due to AD versus mild AD), APOE4 status (carrier versus non-carrier), and predose biomarker value (continuous covariate).

Estimates of global cortical load from florbetapir F 18 amyloid PET and volumetric brain measures from MRI will be analyzed using the same methodology as described above for the CSF biomarker data.

Pharmacokinetics

Plasma and CSF AZD3293 and metabolite AZ13569724 concentrations will be summarized by treatment and time point using descriptive statistics.

A population PK analysis of plasma AZD3293 and AZ13569724 concentration data will be performed using a nonlinear mixed effects modelling approach. The results of the population PK analysis will be summarized in a separate report.

Pharmacokinetics-pharmacodynamics

A population PK/PD analysis implementing appropriate structural models will be conducted following completion of the study to examine the relationships between AZD3293 and/or AZ13569724 and selected measures of efficacy (eg, the primary efficacy endpoint) or tolerability (eg, AE incidence) using nonlinear mixed effects modelling. The results of the population PK/PD analysis will be provided in a separate report.

Pharmacogenomics

The analysis of pharmacogenomics (DNA) outcomes will consist of an analysis of the association of baseline variation with chosen outcome parameters, including efficacy and biomarker outcomes. The analysis of messenger ribonucleic acid (mRNA) and micro-ribonucleic acid (miRNA) outcomes will consist of descriptive statistics regarding change from baseline, including stratification by endpoints. Pharmacogenomics outcomes will be tested in a prioritized list of genes for which a scientific hypothesis for interaction with the pharmacology of AZD3293 and/or the pathophysiology of AD can be formulated, based on knowledge in the field.

Safety

The incidence and severity of treatment-emergent AEs will be summarized by treatment group. The results of clinical laboratory tests; 12-lead ECGs; physical, eye, skin, and neurological examinations; safety MRIs; suicidality evaluations (C-SSRS); body weight and body mass index; and vital sign measurements will be summarized with descriptive statistics, by treatment group, for all time points at which these variables are collected. In addition, visual displays of the time course of AEs will be generated, and analyses that account for time on study will be conducted.

Individual patient data for vital signs, ECG results, and laboratory test results will be assessed for potentially clinically significant (PCS) values according to predetermined criteria, and any PCS values identified will be summarized by treatment group.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Clinical Study Protocol.

Abbreviation or special term	Explanation
AA	Alzheimer's Association
AChEI	Acetylcholinesterase inhibitors
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive subscale
ADAS-Cog$_{13}$	13-item ADAS-Cog
ADCS-ADL	The Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory
ADCS-iADL	instrumental activities of the ADCS-ADL
ADNI	The Alzheimer´s Disease Neuroimaging Initiative
AE	Adverse event (see definition in Section 6.4.1)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APOE	Apolipoprotein E
APP	Amyloid precursor protein
ARIA	Amyloid Related Imaging Abnormalities
AST	Aspartate aminotransferase
AUC	Area under plasma drug concentration-time curve from zero to infinity
AV	atrioventricular
AZ13569724	Metabolite of AZD3293
Aβ	Amyloid beta peptide
Aβ$_{1-40}$, Aβ$_{1-42}$	Aβ protein fragments
BACE1	Beta-site amyloid precursor protein cleaving enzyme 1
BCRP	Breast cancer resistance protein
BUN	Blood urea nitrogen

Abbreviation or special term	Explanation
CDR	Clinical Dementia Rating scale
CDR-SB	Clinical Dementia Rating – Sum of Boxes
CIOMS	Council for International Organizations of Medical Sciences
CNS	Central nervous system
CRF	Case Report Form
CSA	Clinical Study Agreement
CSF	Cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Cardiovascular
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DVR	Distribution volume ratio
EC	Ethics Committee, synonymous to Institutional Review Board (IRB)
ECG	Electrocardiogram
eCRF	Electronic CRF
Enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment (synonymous with "randomized").
Enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
EQ-5D-5L™	A standardized instrument for use as a measure of health outcome (EuroQol Group; Rotterdam, The Netherlands)
ERB	Ethical Review Board
FAQ	Functional Activities Questionnaire
FSH	Follicle-stimulating hormone
FWER	Family-wise error rate
GCP	Good Clinical Practice

Abbreviation or special term	Explanation
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL	High-density lipoproteins; HDL cholesterol
HIV	human immunodeficiency virus
IA	Interim analysis
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
INR	International Normalized Ratio
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IRB	Institutional Review Board
ISHNE	International Society for Holter and Noninvasive Electrocardiology
ITT	Intention to treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KO	Knockout
LDL	Low-density lipoproteins
MACE	Major adverse cardiovascular event
MAD	Multiple ascending dose
MCI	Mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	Micro-ribonucleic acid
mITT	Modified intention to treat
MMRM	Mixed-effect repeated-measures

Abbreviation or special term	Explanation
MMSE	Mini-mental State Examination
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NIA	National Institute on Aging
NPI	Neuropsychiatric Inventory
NPI-D	Neuropsychiatric Inventory Caregiver Distress Scale
OAE	Other Significant Adverse Event (see definition in Section 11.2.1)
PCR	Polymerase chain reaction
PCS	Potentially Clinically Significant
PD	Pharmacodynamic
PET	Positron emission tomography
Pgp	P-glycoprotein
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/pharmacodynamic
QRS	ECG interval measured from the onset of the QRS complex to the J point
QT	ECG interval measured from the onset of the QRS complex to the offset of the T wave
QTcF interval	QT interval adjusted for heart rate using the Fridericia formula
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RPR	Rapid Plasma Reagin
RR	The time between corresponding points on 2 consecutive R waves on the ECG
RT-PCR	Reverse transcription polymerase chain reaction
RUD	Resource Utilization in Dementia
SAD	Single ascending dose
SAE	Serious adverse event (see definition in Section 6.4.2).
SAP	statistical analysis plan

Abbreviation or special term	Explanation
sAPPα	Soluble amyloid precursor protein - alpha
sAPPβ	Soluble amyloid precursor protein - beta
SD	standard deviation
SUSAR	Suspected Unexpected Serious Adverse Reactions
SUVR	Standardized uptake value ratio
VAS	visual analog scale
WBDC	Web Based Data Capture
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

AZD3293 (lanabecestat) is a brain-permeable inhibitor of human Beta-site amyloid precursor protein-cleaving enzyme 1 (BACE1/β-secretase). It is being developed for the modification of the clinical course of Alzheimer's disease (AD) by slowing disease progression in patients diagnosed with early AD, defined as the continuum of patients with mild cognitive impairment (MCI) due to AD (ie, prodromal AD) and patients diagnosed with mild dementia of the Alzheimer's type.

AD is a progressive and fatal neurodegenerative disorder manifested by cognitive and memory deterioration in addition to progressive impairment of activities of daily living. Current treatments are seen as minimally effective, with only minor symptomatic improvements for a limited duration, and they do not slow the progression of the disease.

AD pathology is characterized by the formation of amyloid plaques and neurofibrillary tangles. These pathologies are associated with an inflammatory response, together with loss of neurons and synapses in the neocortex, hippocampus, and other subcortical regions of the brain. AD is clinically expressed as a progressive loss of cognitive functions. Cleavage of amyloid precursor protein (APP) by proteases known as secretases (β and γ) gives rise to the group of peptide fragments known as amyloid beta peptides (Aβ). They are the main component of the amyloid plaques. Further, mutations or duplications of the APP gene constitute a genetic link to Familial AD. BACE1 is a novel type I transmembrane aspartic acid protease related to the pepsin and retroviral aspartic protease families. BACE1 cleaves APP at the β-secretase site, and APP is then cleaved by γ-secretase generating Aβ peptides.

Based on its key role in the amyloid cascade, BACE1 is considered to be a promising therapeutic target for slowing disease progression in AD. BACE1 inhibitors would be expected to prevent the generation of Aβ peptides and, consequently, reduce the detrimental effects of Aβ toxicity and the formation of amyloid plaques in the brain.

As a potent inhibitor of BACE1, AZD3293 is a potential disease-modifying therapy for the treatment of AD. AZD3293 has been shown to reduce $A\beta_{1-40}$ and $A\beta_{1-42}$ in mice, rats, guinea pigs, dogs, and humans. At sufficient exposures, AZD3293 reduces Aβ levels in the brain and cerebrospinal fluid (CSF).

Detailed information on the results of non-clinical studies with AZD3293 may be found in the Investigator's Brochure.

Protocol D5010C00009 has been amended (edition 7.1). The changes and rationales for changes are described in an amendment summary (amendment 5.1).

1.2. Research hypothesis

This study will test the hypothesis that AZD3293 will slow the decline of AD in patients with early AD, defined as the continuum of patients with MCI due to AD and patients diagnosed with mild dementia of the Alzheimer's type, as measured by change from baseline in the 13-item

Alzheimer's Disease Assessment Scale-Cognition ($ADAS\text{-}Cog_{13}$) score at Week 104 in each of the 2 AZD3293 treatment groups compared with placebo. Please see Section 12.2.4 and 12.3.1 for further details.

1.3. Rationale for conducting this study

The rationale for this study is based on the critical, unmet medical need for disease-modifying AD treatments and the potential for AZD3293 to slow the decline of cognition and function in patients with early AD by reducing Aβ production via BACE1 inhibition.

Alzheimer's disease is an insidious, progressive disorder, and accumulation of brain pathology and cognitive decline occur gradually over many years (Jack et al 2010, Villemagne et al 2013). Deficits in cognitive functioning may start to appear up to 10 years before a clinical diagnosis of AD is made (Amieva et al 2008). A review of recent Phase 3 clinical studies with anti-Aβ monoclonal antibodies suggests that intervention with anti-amyloid therapies at the moderate dementia stage of AD may be too late to be effective, but that reducing Aβ in mild AD dementia or in earlier-stage AD patients may be beneficial (Vellas et al 2013).

It is estimated that approximately 39 million people in the world currently have AD, based on 2006 prevalence estimates; this number is likely to grow by an average of 1.8 million a year and reach 70 million by the year 2030. Current AD treatments have only transient benefits on patients' symptoms, and afflicted patients face an inexorable progressive disease that robs them of their identity and ultimately leads to death. Thus, it is imperative that disease-modifying treatments be rapidly discovered, tested, and made available to patients.

This study will evaluate the potential of AZD3293 to be a disease-modifying treatment for early AD by providing evidence of the compound's impact on cognitive decline and on biomarkers relevant to AD in patients with early AD.

1.4. Preliminary human experience

Details can be found in the Investigator Brochure.

1.4.1. Safety and adverse events

No safety or tolerability concerns were identified in the Phase 1 program up to the highest AZD3293 dose given (750 mg single dose; 150 mg multiple dose) to date. Interim Analysis 1 was reviewed by the IDMC on 06 April 2016 and the committee recommended continuing the trial without changes. This action officially moves the study into Phase 3.

1.4.2. Pharmacokinetics in humans

Plasma AZD3293 reaches peak concentration in humans approximately 2 hours after administration. The plasma drug concentration-time profile of the demethylated metabolite AZ13569724 (present at >10% of plasma AZD3293 concentrations) essentially parallels that of AZD3293. Comparison of AZD3293 pharmacokinetic (PK) parameters under fed and fasted conditions showed a modest effect of food on maximum plasma drug concentration (C_{max};

reduced with food relative to fasted) but not on the area under the plasma drug concentration-time curve from zero to infinity (AUC). AZD3293 is predominantly metabolized by CYP3A4.

1.4.3. Pharmacodynamic effects in humans

Following a single oral dose of 75 mg AZD3293 in the thorough QT study, which yields an exposure equal to the steady-state exposure observed after AZD3293 50 mg daily, the mean change from baseline in QTcF interval at a concentration equal to the geometric mean C_{max} was 1.245 msec. Following a single oral dose of 450 mg AZD3293, the estimated mean change from baseline in QTcF interval at a concentration equal to the geometric mean C_{max} was 9.858 msec. The exposure following the 450 mg supra-therapeutic dose (approximately 3400 ng/mL) is approximately >3.5-fold higher than the highest C_{max} value projected for patients receiving multiple once-daily 50-mg doses of AZD3293, even if they were taking a strong CYP3A4 inhibitor. Therefore, clinically significant increases in QTcF interval are not expected in this study.

Under the 15-mg and 50-mg once-daily dosing regimens in the multiple ascending dose (MAD) study, plasma $A\beta_{1-40}$ and $A\beta_{1-42}$ concentrations were reduced rapidly, remained depressed by >75% during dosing, and recovered to 60% by 72 hours following the last dose. Cerebrospinal fluid $A\beta_{1-40}$ and $A\beta_{1-42}$ concentrations were reduced to approximately 50% or 80% for the 15-mg or 50-mg dose groups, respectively, and did not appreciably recover within 24 hours following the last dose. Similar results were obtained in both healthy elderly subjects and patients with AD.

For further information regarding preliminary human experience with AZD3293, please refer to the Investigator's Brochure.

1.5. Benefit/risk and ethical assessment

1.5.1. Benefits

There is a large unmet medical need for disease-modifying treatments for AD. Based on the key involvement of BACE1 in APP processing, inhibition of BACE1 is therefore considered a promising therapeutic approach for AD. BACE1 inhibitors would be expected to prevent the generation of Aβ peptides and consequently reduce the detrimental effects of Aβ toxicity and the formation of amyloid plaques in the brain. BACE1 inhibitors in clinical development have been reported to reduce Aβ in human CSF and/or in plasma by up to 80% to 90% (May et al 2011, Forman et al 2012, Hitt et al 2010, Hu et al 2006, Hu et al 2008, Hu et al 2010, Kim et al 2011, Koike et al 2012, Kuhn et al 2012, Lai et al 2012). Taking the demonstrated lowering of Aβ in humans into consideration, treatment with BACE1 inhibitors has the potential to be of benefit to AD patients. However, it remains to be proven that BACE1 inhibitors are able to delay the onset or slow the progression of AD.

This study will evaluate whether patients with early AD treated with AZD3293 will show evidence of disease modification. The study will also test whether patients with MCI due to AD

and patients with mild AD will show evidence of delayed development of underlying pathophysiology relative to placebo treatment.

1.5.2. Risks

A number of findings related to BACE biological function recently described in the literature point toward the non-redundant physiological significance of BACE enzyme. The list of possible functions and processes that could be affected includes normal memory function, cognition and emotional processing (Ohno et al 2004, Laird et al 2005, Wang et al 2008, Savonenko et al 2008), myelination and re-myelination upon neuronal trauma (Hu et al 2006, Hu et al 2008), sodium channel expression in the brain and threshold for epileptiform activity and neurodegeneration (Kim et al 2011, Hu et al 2010, Hitt et al 2010), axonal guidance in the olfactory bulb in development and perhaps also in adult organism (Rajapaksha et al 2011), processes of neuronal connectivity (Zhou et al 2012), adaptation to acute neuronal ischemia (Koike et al 2012), vascular development in the retina and protein processing in the retina in general (Cai et al 2012), and, finally, a number of yet-unidentified biological functions that could be deduced from identifying the unique BACE1-cleaved substrates (Kuhn et al 2012). There is a recent publication on muscle spindle changes and related locomotor effects in BACE1 knockout (KO) mice (Cheret et al 2013).

Although findings in BACE1 KO animals suggest a potential for target-related adverse events (AEs), the risk of reproducing such effects by pharmacological inhibition of BACE1 is unknown. In studies of BACE1 or BACE2 KO mice, the aforementioned physiological systems appear to have only been affected in BACE1 -/-homozygotes. In papers describing heterozygote data (ie, 50% BACE inhibition), there are no differences reported between wild-type mice and +/- heterozygotes (Laird et al 2005, Savonenko et al 2008, Kim et al 2011). Moreover, while there are currently no data available showing any detrimental effects in a conditional BACE1 KO, some of the observed KO effects may be attributed to developmental changes. These KO phenotypes were only apparent when the BACE1 gene was completely deleted from gestation onwards, and their clinical safety relevance for AD patients, in which only a degree of BACE1 inhibition will be achieved in the central nervous system (CNS), is unknown.

Potential risks include, but are not limited to, hepatic effects, QT prolongation with overdose, skin or hair hypopigmentation, rash, retinal changes, and potential interactions with other drugs. The current study will include standard safety assessments, ie, reported AEs, clinical laboratory tests, vital sign and body weight measurements, 12-lead electrocardiograms (ECGs), and physical examinations.

Additional safety assessments will include neurological examinations (as part of each physical examination), comprehensive eye examinations supervised by an ophthalmologist or optometrist, skin examinations supervised by a dermatologist, magnetic resonance imaging (MRI) examinations, and suicidality evaluations using the Columbia-Suicide Severity Rating Scale (C-SSRS). The current study will use an Independent Data Monitoring Committee (IDMC) to monitor data on an ongoing basis to ensure the continuing safety of patients enrolled in this study.

AZD3293 is a substrate of CYP3A4, and plasma AZD3293 concentrations may be increased up to 3-fold in the presence of strong CYP3A4 inhibitors like itraconazole. Co-administration with strong CYP3A4 inhibitors/inducers is, therefore, restricted in the current study. AZD3293 has been characterized as a P-glycoprotein (Pgp) substrate. Co-medication with a Pgp inhibitor could increase AZD3293 exposure, thereby possibly increasing the risk for AEs. AZD3293 has been shown to be a weak inhibitor of Pgp at the intestinal wall. AZD3293 is a breast cancer resistance protein (BCRP) substrate; coadministration of BCRP inhibitors could increase systemic AZD3293 exposure. Use of strong inhibitors/inducers of Pgp or inhibitors of BCRP will be restricted in the current study.

In a radiolabeled human mass balance study, the only quantifiable circulating metabolite observed following a single oral dose of [14C]-LY3314814 was the O-desmethyl metabolite AZ13569724 (metabolite 1).

In the 14-day MAD safety study (Study I8A-MC-AZEV/D5010C00002), daily doses of 50 mg LY3314814 resulted in steady-state plasma AUC of metabolite AZ13569724 that was approximately 30% the plasma AUC of parent. This metabolite's lower circulating concentration and 10-fold lower affinity for BACE1 indicate that it is unlikely to contribute significantly to the therapeutic effect of AZD3293. AZ13569724 is a Pgp substrate, but it did not demonstrate the potential to inhibit major CYPs (IC_{50}>20 μM) or transporters (IC_{50}>100 μM) in in vitro assays. Plasma AZ13569724 concentrations will be monitored throughout the clinical program, along with those of AZD3293.

The current study includes placebo as a comparator, and approximately one-third of the patients will be randomized to this treatment. There are currently no disease-modifying treatments for AD. Moreover, all patients during the study will have a designated study partner who will have regular face-to-face and/or telephone contact with the patient, accompany the patient to all study visits, and liaise with the study staff between visits if any issues arise (see Section 3.4 for additional information about the role of the study partner).

In conclusion, the available non-clinical and clinical data support the oral administration of AZD3293 to the intended study population according to the proposed clinical investigation plan and also provide a sufficient margin of safety for the proposed design and doses. The potential benefits of AZD3293 showing disease-modifying properties in AD are considered to outweigh the potential risks. Specific details of the non-clinical and clinical findings to date and the complete risk benefit assessment for AZD3293 can be found in the Investigator's Brochure.

2. STUDY OBJECTIVES

2.1. Primary objective

The primary objective of this study is to test the hypothesis that AZD3293, administered orally at doses of 20 and 50 mg daily for 104 weeks, will slow the decline of AD as compared with placebo in patients with early AD dementia as measured by ADAS-Cog$_{13}$. Early AD is defined as the continuum of patients with MCI due to AD (ie, prodromal AD) and patients diagnosed with mild dementia of the Alzheimer's type.

2.2. Secondary and exploratory objectives

Table 1. Objectives and Endpoints

Double-Blind Treatment Period	
Secondary Objectives	**Endpoints**
Clinical efficacy objectives: • To evaluate the efficacy of AZD3293 on functional, clinical, and cognitive outcomes in patients with early AD dementia at the end of the Double-Blind Treatment period (Week 104).	• Functional Outcome Measures o The Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory instrumental items (ADCS-iADL) score o Functional Activities Questionnaire (FAQ) score • Cognitive/Functional Outcome Measures o Integrated Alzheimer's Disease Rating Scale (iADRS) score o Clinical Dementia Rating – Sum of Boxes (CDR-SB) score • Clinical Outcome Measures o CDR-Global Score o Neuropsychiatric Inventory (NPI) score • Cognitive Outcome Measures o Mini-Mental State Examination (MMSE)
• To evaluate the relationship between treatment effect of AZD3293 and time (at points other than the end of the Double-Blind Treatment period [Week 104], such as Week 26, Week 52 and Week 78). Specific time points will vary by instrument.	• ADAS-Cog$_{13}$, ADCS-iADL, FAQ, CDR-SB, and iADRS
• To test the hypothesis that AZD3293 will slow the rate of cognitive and functional decline associated with AD, compared with placebo	• ADAS-Cog$_{13}$, ADCS-iADL, and FAQ using a slope analysis from a repeated-measures model
• To evaluate the efficacy of AZD3293 to prolong time in the current disease state	• CDR global score
• To evaluate the clinical worsening and need for symptomatic treatments	• AD symptomatic treatments time of initiation

Biomarker objectives: • To evaluate the effect of AZD3293 on cerebrospinal fluid (CSF) amyloid beta peptide (Aβ) pharmacodynamics (PD) markers	• CSF $A\beta_{1-42}$ and $A\beta_{1-40}$ concentrations
• To evaluate the effect of AZD3293 on CSF markers of neurodegeneration	• CSF total tau and phosphorylated tau concentrations
• To evaluate the effect of AZD3293 on brain amyloid burden	• Florbetapir amyloid scan
• To evaluate the effect of AZD3293 on brain aggregated tau levels	• ^{18}F-AV-1451 Tau PET [separate addendum]
• To evaluate the effect of AZD3293 on brain metabolism	• Fluorodeoxyglucose (FDG) positron emission tomography (PET) [separate addendum]
• To evaluate the effect AZD3293 on brain atrophy	• Brain volumes measured by magnetic resonance imaging (MRI)
Pharmacokinetic objective: • To assess the population PK of AZD3293 and metabolite AZ13569724 in patients with early AD dementia	• Apparent Oral Clearance of AZD3293 • Central Volume of Distribution of AZD3293
Safety Objective • To evaluate the safety and tolerability of AZD3293 in patients with early AD dementia	• Standard safety assessments: o spontaneously reported adverse events (AEs) o clinical laboratory tests o vital sign and body weight measurements o 12-lead electrocardiograms (ECGs) o physical examinations including neurological examinations • Additional safety assessments: o Eye examinations o Skin examinations o Serial MRI o Columbia-Suicide Severity Rating Scale (C-SSRS)
Exploratory Objectives*	**Endpoints***
• To evaluate the efficacy of AZD3293 on executive function	• Changes from baseline in the Letter Fluency, Category Fluency, and Digit Symbol-Coding test scores
• To evaluate the efficacy of AZD3293 on neuropsychological status	• Change from screening in the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score
• To explore the effects of AZD3293 on resource utilization and health status	• Change from baseline in the Resource Utilization in Dementia (RUD)-Lite and EQ-5D-5L score
• To explore the effects of AZD3293 on caregiver distress	• Change from baseline in the NPI-D score
• To evaluate the dose-exposure effect relationships for selected efficacy, safety, and biomarker endpoints	• Changes in scales, adverse events and blood, CSF and imaging biomarkers in relation to exposure
• To explore the genetic effects of APOE4 allele status (carrier or non-carrier)	• Change from baseline on selected efficacy, safety, and biomarker endpoints

• To explore the effect of AZD3293 on gene expression.	• Change in levels of whole blood messenger ribonucleic acid (mRNA) and on plasma and CSF micro-ribonucleic acid (miRNA) levels and the relation to selected efficacy, safety and biomarker endpoints
• To explore the effect of AZD3293 on peripheral and central nervous system protein expression.	• Change in CSF or peripheral protein biomarkers, including CSF or plasma $A\beta_{1-42}$ and $A_{\beta 1-40}$, neurodegenerative inflammatory markers, and proteomic assessments and the relation to selected efficacy, safety, and other biomarker endpoints
• To examine AZD3293 population PK/PD	• Exposure and selected measures of efficacy and/or tolerability
• To optionally collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence response (that is, distribution, safety, tolerability, and efficacy) to AZD3293. Genes that will be tested for heritable genetic (DNA) or expression (mRNA, miRNA) effects will be limited to those for which a hypothesis for involvement in the pharmacology of AZD3293 or in the pathogenesis of AD can be formulated, as currently understood and as directed by future scientific progress in the field.	• Association of genetic variation with selected endpoints (optional pharmacogenomics sampling)

***Note**: the results of analyses that address some exploratory objectives may not form part of the Clinical Study Report, but may be described in supplementary reports as appropriate.

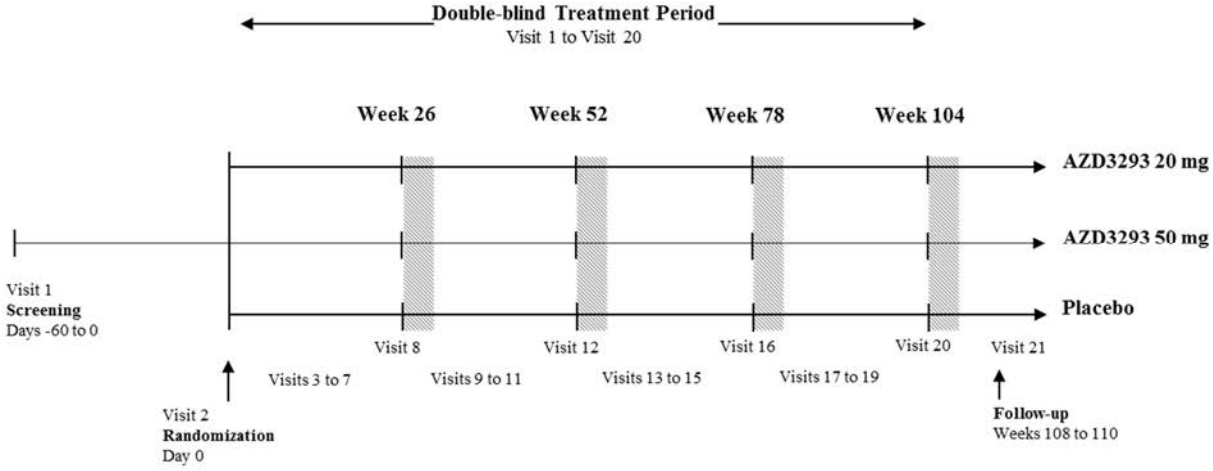
3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to sponsor standard procedures

3.1. Overall study design and flowchart

Study D5010C00009 is a multicenter, randomized, parallel-group, 104-week, double-blind, placebo-controlled, international study of 2 fixed dose levels of AZD3293 (20 mg or 50 mg) in patients with early AD (ie, the continuum of patients with MCI due to AD and patients diagnosed with mild dementia of the Alzheimer's type) and abnormal levels of amyloid. Figure 1 illustrates the study design.

The study is expected to enroll a total of approximately 2202 patients from across the globe. The total sample size may be increased, depending on the results of the second planned interim analysis (see Section 12.2.2).



Note: grey boxes after Visits 8, 12, 16, and 20 indicate the 4-week symptomatic treatment initiation window for subjects with progression of symptoms (Section 5.6.1).

Figure 1. Study flow chart for Study D5010C00009.

Male and female patients, aged 55 to 85 years, who meet all inclusion criteria and no exclusion criteria, will be randomly assigned on Day 0 to 1 of 3 treatment groups in a 1:1:1 ratio: 20 mg AZD3293, 50 mg AZD3293, or placebo (approximately 734 patients per treatment group). Study treatment will be administered once daily, in the morning, beginning on Day 1.

Every effort should be made for visits to occur on the designated study schedule. The overall treatment period in the protocol should be maintained (that is, visits should be scheduled based on the randomization date (the day prior to the first administration of study drug) rather than the previous visit). A visit may be split over multiple days as needed.

For details regarding initiation of symptomatic AD treatments see Section 5.6.1.

Randomized treatment allocation will be centrally controlled and stratified by disease status at baseline (MCI due to AD or mild AD). Randomization into either the MCI due to AD or mild AD groups may be stopped before the completion of the study to ensure an adequate distribution of both strata. In addition, all patients will undergo procedures and assessments at designated visits as per the Study Plan (Table 2).

Each patient will have a study partner who has sufficient interaction with the patient to provide meaningful input regarding the patient (see Section 3.4).

Patients who meet other study entry requirements will be required to undergo either a florbetapir F18 amyloid PET scan or a lumbar puncture for CSF sampling (but not both) at screening to document the presence of abnormal levels of brain or CSF amyloid for study inclusion (Landau et al 2013, Weigand et al 2011). Historical amyloid PET scans may be allowed for study eligibility with central reader confirmation of amyloid positivity.

3.1.1. Longitudinal Biomarker Sub-studies

The main study protocol also includes 2 mandatory longitudinal biomarker sub-studies: a florbetapir F 18 amyloid PET sub-study and a CSF sub-study. For clarification, patients who undergo a florbetapir F 18 PET scan at screening are included in the florbetapir F 18 PET substudy and will have a Visit 20 florbetapir F 18 PET scan. Patients who undergo a lumbar puncture at screening are included in the CSF substudy and will have a Visit 12 and Visit 19 lumbar puncture. At least 900 individuals will participate in the florbetapir F 18 amyloid PET sub-study and at least 175 patients will participate in the CSF sub-study. After the required number of subjects is enrolled in these 2 sub-studies, subsequent enrollment is optional and it may be discontinued at any time at the discretion of the sponsor (Figure 2).

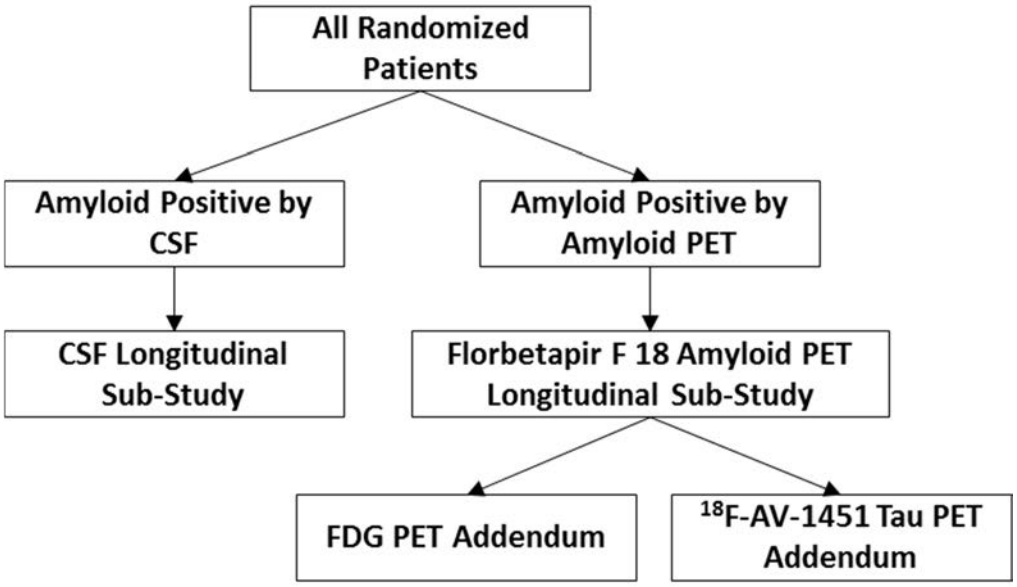
3.1.2. PET Imaging Addenda

Within the florbetapir F 18 PET sub-study, there are 2 imaging addenda:

- At least 400 individuals will participate in the FDG PET [Addendum 1]
- At least 500 individuals will participate in the ^{18}F-AV-1451 PET [Addendum 2]

Note: individuals cannot participate in both the FDG PET and ^{18}F-AV-1451 PET addenda.

After the required number of subjects is enrolled in these addenda, subsequent enrollment is optional and it may be discontinued at any time at the discretion of the sponsor.



Abbreviations: CSF cerebrospinal fluid; FDG fluorodeoxyglucose; PET positron emission tomography.

Figure 2. Schematic of flow for patients participating in the longitudinal CSF and amyloid PET sub-studies and PET imaging addenda.

An IDMC (see Section 12.4) will be established to monitor data on an ongoing basis to ensure the continuing safety of patients enrolled in this study, to ensure the integrity of the blinded nature of the study, and to oversee the 3 planned interim analyses (see Section 12.2.2). The IDMC will include individuals external to the sponsor and will consist of a Chair plus at least 1 medical expert in the relevant therapeutic area and at least 1 statistician. An IDMC charter will be developed which will specify the roles and responsibilities of the members and decision rules. Formal implementation and communication of IDMC recommendations will be managed by the sponsor Executive Committee and unrelated to the AZD3293 project team. A firewall will be established to maintain the study blind for the sponsor, the investigational site staff, and study patients and their study partners.

3.2. Summary of study visits and assessments

The procedures and assessments to be performed at designated visits are listed in this section. Selected visits may be conducted by telephone to reduce the burden on the patient. The timing of the procedures and assessments is provided in the Study Plan (Table 2). Details regarding the specific assessments are provided in Section 6.

3.2.1. Screening period (Visits 1&2) and Informed Consent

It is strongly encouraged that the duration of the screening period be as short as possible. However, for logistical purposes, approximately 8 weeks will be allowed for the screening period to confirm that patients meet all selection criteria for the study and to conduct all measurements required prior to randomization.

The investigator (or an appropriate delegate at the investigational site) will obtain signed informed consent for study participation from each patient, the patient's study partner, and, where appropriate, legally authorized representative. Patients will consent to the use of their screening data for future research purposes in the event that they do not meet the criteria for enrollment in the study.

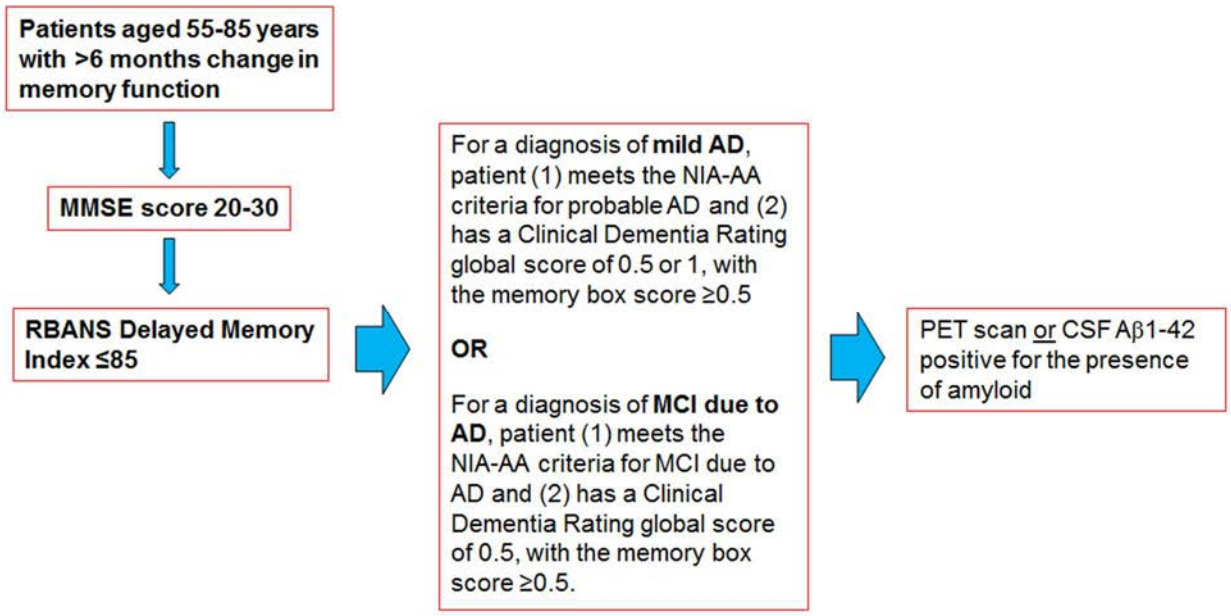
APOE testing is required and included in the main consent. Separate signed consent will be obtained for participation in the optional pharmacogenetic and pharmacogenomics sampling.

Separate signed consent will also be obtained for patients who are required to participate in either the FDG-PET or ^{18}F-AV-1451 (tau) PET addenda (addenda 1 and 2, respectively).

Each patient who provides consent to participate in the study will be assigned a unique enrollment number. The patient's study partner will also be assigned an identification code.

Those patients who have an MMSE score of 20 to 30, inclusive, a score of ≤85 on the Delayed Memory Index of the RBANS, assessed in that order, and who meet diagnostic criteria for MCI due to AD or mild AD, amyloid positivity criteria, and other selection criteria detailed in Section 4 will undergo study-specific enrollment procedures.

The hierarchical screening process for study entry is illustrated in Figure 3. If the patient fails to meet specified inclusion criteria on any measure shown, testing procedures should be discontinued.



Abbreviations: AD Alzheimer's disease; Aβ A-beta amyloid; CDR Clinical Dementia Rating; CSF Cerebrospinal fluid; MCI Mild cognitive impairment; MMSE Mini-Mental State Examination; PET Positron emission tomography; RBANS Repeatable Battery for the Assessment of Neuropsychological Status.

Figure 3. Schematic of patient screening process and entry criteria.

3.2.2. Screening - Imaging and Biomarkers

A site may use either or both methods of amyloid detection during the study, but the choice of which amyloid detection method is used for a particular patient will be at the discretion of the patient and the investigator. Patients will not be allowed to be retested with the alternate method if the results from the first method do not meet the criteria for study enrollment.

Patients previously screened for amyloid positivity for another reason may participate in this study, provided that they meet the patient selection criteria. Historical amyloid PET scans may be accepted for study eligibility with central reader confirmation of amyloid positivity. Patients who enter the study via historical amyloid PET and wish to participate in the longitudinal florbetapir F 18 amyloid PET substudy must also have a baseline florbetapir F 18 PET scan performed under this study protocol, and acquired before randomized treatment is administered.

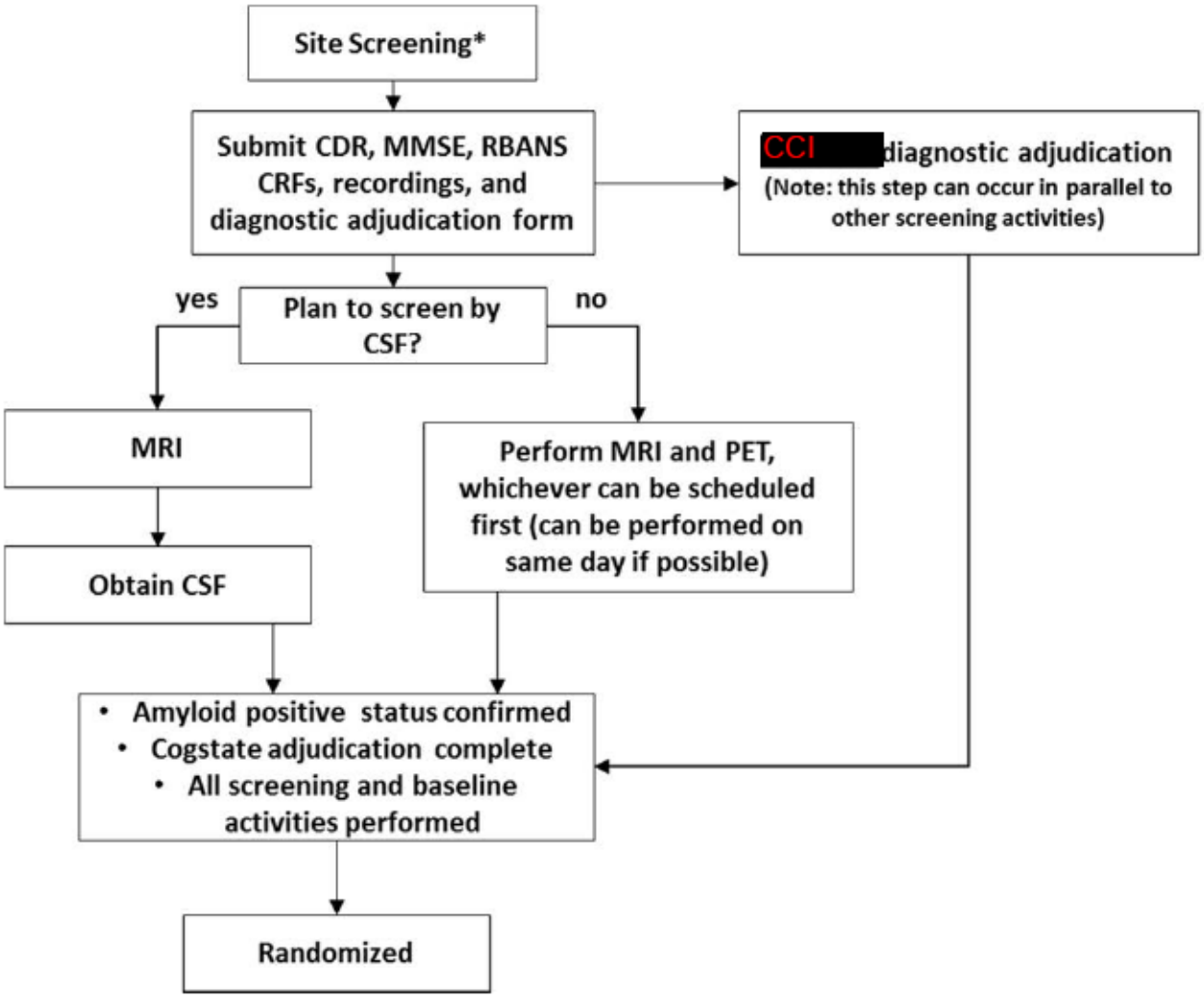
For patients who undergo florbetapir F 18 PET for amyloid screening, the MRI and florbetapir F 18 PET can occur in any order and can be obtained on the same day. For patients who undergo CSF sampling for amyloid screening, the MRI should be performed prior to the lumbar puncture (Note: MRI central read results are not required prior to CSF sampling).

Completed information relevant to the diagnosis of MCI and AD, CDR rating and results of other assessment scales, and associated documents/recordings (if applicable) will be provided to

the adjudication vendor (CCI, who will review the information and provide diagnostic adjudication prior to randomization. CCI review and other screening procedures may occur in parallel to ensure completion of all procedures in a timely fashion.

Patients who fail to meet study entry criteria at screening can be invited to return to the clinic for an informational meeting with clinic staff.

The patient-screening workflow should be as shown in Figure 4.



*If at any time patient fails to meet an inclusion criterion or meets an exclusion criterion, stop and do not proceed further with screening.
Note: Visit 1 neurocognitive testing must be performed prior to the CSF or PET screening. If LP and MRI are performed, the MRI must be done first. The order of the cognitive testing is described in Table 4 in Section 6.3.4.1.
Abbreviations: CDR Clinical Dementia Rating; CRF Case report form; CSF Cerebrospinal fluid; FAQ Functional Activities Questionnaire; MMSE Mini-Mental State Examination; MRI Magnetic resonance imaging; PET Positron emission tomography; RBANS Repeatable Battery for the Assessment of Neuropsychological Status.

Figure 4. Patient-screening workflow.

3.2.3. Re-screening of a potential study patient

Patients may rescreen a maximum of two times. Patients may be re-screened if they meet any of the following criteria:

- Patients who were ineligible to participate in the study due to the entry criteria in prior protocols, but became likely to qualify based on revised criteria from current edition may be re-screened.
- Patients who fail to make the RBANS cutoff and have had progression in their cognitive decline may be re-screened once more for this criterion, no sooner than 6 months from their initial date of RBANS screen.
- Patients who required treatment for an acute illness that resolved (for example, a urinary tract infection) or had stabilization of a chronic medical problem (for example, uncontrolled hypertension) may be re-screened.
- Patients who have vitamin B12 levels suspected to confound cognitive testing at initial screening and who have subsequently taken vitamin B12 for at least 4 weeks after the initial screening failure may be re-screened.
- Patients who are not on stable medications, including acetylcholinesterase inhibitors, (AChEI) during screening (see Section 5.6) may be re-screened once the stable dose criteria have been met.
- Patients who require more time to identify an appropriate study partner may be re-screened.
- Patients who are unable to complete screening procedures within a reasonable timeframe.

Other circumstances may also warrant rescreening. Please contact your medical monitor for specific patient questions if they are not outlined here. When re-screening is performed in the above circumstances, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number and all inclusion and exclusion criteria must be met.

3.2.4. Study Plan

The Study Plan is described in Table 2 below.

Table 2. Study Plan (D5010C00009)

Study procedure[a]	**Screening Period**[b]		**Double-blind treatment period**																	**ED**[d]	**F/U**
Visit number	**V1**	**V2**[c]	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**		**V21**
Study week			1	4	7	13	19	26	32[f]	39	45	52	58[f]	65	71[f]	78	84[f]	91	97	104		108-110[g]
Tolerance interval for Visit (days)			±3	±3	±7	±7	±7	±7	±7	±7	±7	±10	±7	±7	±7	±7	±7	±7	±7	±10		
Informed consent	X																					
Demographics	X																					
Medical /psychiatric History	X																					
Prior/concomitant treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X	X																				
NIA-AA criteria review	X										X								X		X	
FAQ		X						X				X				X				X	X	
ADCS-ADL		X						X				X				X				X	X	
CDR[h]	X							X				X				X				X	X	
MMSE	X					X		X				X				X				X	X	
RBANS	X										X								X		X	
ADAS-Cog_{13}		X				X		X				X				X				X	X	
NPI		X						X				X				X				X	X	
Letter & Category Fluency, Digit Symbol-Coding tests		X						X				X				X				X	X	
EQ-5D-5L (patient)		X					X				X					X				X	X	
RUD-Lite		X					X				X					X				X	X	
MRI[i]	X											X								X	X	
Florbetapir F 18 Amyloid PET	X																			X	X	
Lumbar puncture[j]	X											X							X		X	
Blood sample for plasma AZD3293 and AZ13569724 PK[k]				X[l]			X[m]			X[l]	X[l]			X[m]				X[n]			X	
Blood sample for plasma biomarkers[o]		X										X							X		X	

Study procedure[a]	Screening Period[b]		Double-blind treatment period																	ED[d]	F/U
Visit number	**V1**	**V2[c]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**		**V21**
Study week			1	4	7	13	19	26	32[f]	39	45	52	58[f]	65	71[f]	78	84[f]	91	97	104		108-110[g]
Tolerance interval for Visit (days)			±3	±3	±7	±7	±7	±7	±7	±7	±7	±10	±7	±7	±7	±7	±7	±7	±7	±10		
Blood sample for APOE genotyping[p]	X																					
Blood sample for pharmacogenetics[q]	X																					
Blood samples for pharmacogenomics[q]		X										X							X		X	
Laboratory tests[r]	X	X		X	X	X		X		X		X		X		X		X		X	X	
Urine drug screen	X																					
Physical, neurological examinations	X	X		X[s]		X		X[s]		X[s]		X		X[s]		X[s]		X[s]		X	X	
Comprehensive eye examination[t]		X										X								X	X	
Skin examination[u]		X				X						X				X				X	X	
Vital signs[v]	X	X	X	X	X	X	X	X		X	X	X		X		X		X	X	X	X	X
Height	X																					
Body weight	X	X				X		X				X				X				X	X	
12-Lead ECG	X	X[w]	X	X		X		X		X		X		X		X			X	X	X	X
C-SSRS[1]		X	X	X		X	X	X		X	X	X		X		X		X	X	X	X	
Dispense drug		X	X	X	X	X	X	X		X	X	X		X		X		X	X			
Assess drug compliance[x]			X	X	X	X	X	X	X[x]	X	X	X	X[x]	X	X[x]	X	X[x]	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Addenda (site specific)																						
FDG PET		X																		X	X	
or																						
^{18}F-AV-1451 PET		X										X								X	X	
US Medicare Claims[2]		X																				

a Every effort should be made for visits to occur on the designated study days. The overall treatment period in the protocol should be maintained (ie, visits should be scheduled based on the randomization date rather than the previous visit).

b The screening process will take place over more than 1 day. After consent is obtained, most screening procedures will be performed at a single visit, however additional screening visits will be necessary for some procedures, eg, MRI, lumbar puncture, etc. In addition, it may sometimes be necessary for patients to return for repeat assessments (eg, if MRI does not pass the quality control process). Therefore, the duration of the screening period may be increased with the permission of the CCI medical monitor and is not necessarily considered a screen failure. See Section 3.2.2 for order of MRI and LP testing and Section 6.3.4.1 for order of cognitive testing.

c First dose to be administered the day after Visit 2 (randomization), preferably in the morning.

d All patients who discontinue study treatment before Week 104 should have Early Discontinuation (ED) procedures and assessments performed as soon as possible. ADCS-ADL, FAQ, CDR, MMSE, RBANS, ADAS-Cog_{13}, NPI, and Letter & Category Fluency, Digit Symbol-Coding tests should be conducted at the early discontinuation visit if it has been more than 12 weeks since they were last administered. MRI, and for longitudinal sub-study participants, florbetapir F 18 amyloid PET and lumbar puncture, should only be performed if it has been at least 24 weeks since the previous assessment.
Note: Patients should be encouraged to remain in the study after their ED Visit until Week 104 (Visit 20), even if study treatment has been discontinued. Patients who discontinue treatment, but remain in the study should continue to participate in all scheduled visits and assessments, as appropriate, with the exception of PK measurements and PET scans.

e Footnote e has been deleted

f Visits at Weeks 32, 58, 71, and 84 will be conducted by telephone and may include either the patient or the study partner, or both, as appropriate. The patient or study partner may be required to visit the clinic within ±1 week of Week 32 (Visit 9), Week 58 (Visit 13), Week 71 (Visit 15), or Week 84 (Visit 17) for drug dispensing.

g Patients who complete study treatment at Week 104 or who discontinue study treatment and withdraw early should participate in a follow-up visit (Visit 21), 4 to 6 weeks after the last dose of study treatment. The follow-up visit (Visit 21) is required for patients who discontinue study treatment but remain in the study and continue to participate in scheduled visits. Patients who have completed 104 weeks of study treatment and consent to continue into the extension study, Study AZFD, are not required to complete the follow-up visit (Visit 21).

h The CDR should always be administered to the study partner first and then to the patient; the study partner and patient must be interviewed separately. The assessments should be performed at the same time of day at each visit, if possible.

i The MRI should be performed during screening and done prior to lumbar puncture in those individuals enrolled via CSF.

j Post-baseline CSF samples for patients in the longitudinal sub-study should be collected 2 to 3 hours post-dose. Lumbar punctures should be scheduled at approximately the same time of day at all visits to avoid the known circadian variation in CSF amyloid levels. If a post-baseline lumbar puncture cannot be obtained because of procedural complications or patient issues, it will not be considered a protocol violation.

k Two blood samples for AZD3293 and AZ13569724 PK analysis will be collected just after arrival at and just prior to departure from the clinic at Week 4 (Visit 4), Week 45 (Visit 11), and Week 91 (Visit 18). One blood sample for PK analysis will be collected at Week 19 (Visit 7), Week 39 (Visit 10), and Week 65 (Visit 14) or as soon as possible after treatment discontinuation (if it occurs before Week 91).

l A phone call will be made approximately 1 business day before the clinic visit to remind patients to hold the morning dose of study treatment on the day of the visit and to bring the dose to the clinic.

[m] A phone call will be made approximately 2 business days before the clinic visit to remind patients to 1) hold the morning dose of study treatment on the day prior to the visit and then take that dose late in the afternoon (at least 14 hours prior to the clinic visit) and 2) hold the morning dose of study treatment on the day of the visit and bring that dose to the clinic.

[n] A phone call will be made approximately 1 business day before the clinic visit to remind patients to take the morning dose of study treatment on the day of the visit, before arriving at the clinic.

[o] Blood samples for determination of plasma biomarkers ($A\beta_{1-40}$, $A\beta_{1-42}$) will be collected from all patients at the Visit 2 and 2-3 hours post-dose at indicated visits.

[p] APOE genotyping results are not required to be available before randomization. The APOE results are not disclosed.

[q] Patients who participate in optional pharmacogenetic and pharmacogenomics samplings will be provided a separate informed consent for the samplings. Failure to participate in optional sampling will have no influence on the eligibility of the patient for the main study.

[r] Hematology, clinical chemistry, electrolyte testing, and urinalysis are included in every laboratory determination. Coagulation tests, cholesterol (total, HDL, LDL), triglycerides, creatinine clearance, vitamin B12, folic acid, RPR, follicle-stimulating hormone (women only, with less than 12 months but more than 6 months of amenorrhea), serologic tests for hepatitis B and hepatitis C, and urine testing for drugs of abuse will be included in screening tests only. Thyroid-stimulating hormone, total thyroxine and hemoglobin A1c will be measured at screening, Week 52 (Visit 12) and Week 104 (Visit 20) or ED.

[s] Brief physical and full neurological examinations will be performed at these visits. For additional physical exam details, see Section 6.4.6

[t] Comprehensive eye examination includes corrected visual acuity, intraocular pressure, a slit lamp examination, and a dilated fundus examination. Examinations must be supervised by an ophthalmologist or optometrist. The eye examination can be performed at any point during the screening period.

[u] Complete skin examination must be supervised by a dermatologist. The skin examination can be performed at any point during the screening period.

[v] Vital signs include resting supine and standing blood pressures and pulse rates, and temperature (see Section 6.4.8).

[w] Single safety ECGs are required at all time points (see Section 6.4.7).

[x] The patient should be instructed to retain all empty drug kits after using up the medication in the kit and to bring the empty kits and any unused medication to the clinic at each visit. During visits conducted by telephone, the patient or study partner will be questioned about compliance with study treatment.

[1] The Baseline/Screen version of the C-SSRS will be administered at Visit 2 (baseline/randomization). All visits post-baseline will use the C-SSRS Since Last Visit version.

[2] Enrollment into the US Medicare Claims addendum (4) can be done at beginning of trial, but can be done at later time points as needed

Abbreviations: ADAS-Cog Alzheimer's Disease Assessment Scale-Cognition; ADCS-ADL The Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory; Aβ A-beta amyloid; BL baseline; CDR Clinical Dementia Rating; CSF Cerebrospinal fluid; C-SSRS Columbia Suicide Severity Rating Scale; DSM-V Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; ECG Electrocardiogram; ED early discontinuation; FAQ Functional Activities Questionnaire; F/U follow-up; HDL High-density lipoproteins; LDL Low-density lipoproteins; MMSE Mini-Mental State Examination; MRI Magnetic resonance imaging; NIA-AA National Institute of Aging-Alzheimer's Association; NPI Neuropsychiatric Inventory; PET Positron emission tomography; PK Pharmacokinetic; RBANS Repeatable Battery for the Assessment of Neuropsychological Status; RUD-Lite Resource Utilization in Dementia-Lite; RPR Rapid Plasma Reagin; W Week.

3.3. Rationale for study design, doses and control groups

Overall rationale and study population

The overall purpose of this study is to evaluate the potential of AZD3293 to be a disease-modifying treatment for early AD by providing evidence of the compound's safety, tolerability, and impact on cognitive decline and on biomarkers relevant to AD in patients with early AD.

The study will enroll patients with early AD, defined as the continuum of patients with MCI due to AD and patients diagnosed with mild dementia of the Alzheimer's type. In terms of the recently updated NIA-AA criteria, the study population will include patients diagnosed with "MCI due to AD" and patients diagnosed with "probable AD dementia" (of mild severity based on cognitive testing) (Albert et al. 2011; McKhann et al. 2011). Patients from the 2 early AD subgroups will be enrolled to represent the early disease continuum.

A clearly defined transition point between the symptomatic pre-dementia stage and the mild dementia stage is generally difficult to define in individual patients (Albert et al 2011). The range of cognitive scores used to classify MCI and AD dementia cohorts overlaps between the 2 disease stages (eg, in the Alzheimer's Disease Neuroimaging Initiative [ADNI] study, the MMSE score range for patients with MCI was 24 to 30, while the range for patients with mild AD dementia was 20 to 26; Shaw et al 2009). There is a general consensus among clinical experts that progression from MCI due to AD to probable AD dementia does not occur as a discrete event and that the precision for defining such transition points is likely to be made even more difficult in the context of large international clinical studies (Aisen 2009; Dubois et al 2007). For these clinical reasons, it is logical to test these overlapping patient groups in a single study.

The inclusion requirement for evidence of abnormal brain amyloid levels, either by CSF $A\beta_{1-42}$ measurement or by amyloid PET, will increase diagnostic accuracy by ensuring that the patients with less severe symptoms still have underlying amyloidosis that is required for a diagnosis of AD pathology.

Study design

This study will be randomized, double blind, and placebo controlled. Randomization and blinding of the patient, the patient's study partner, the investigator, and the Sponsor to the patient's treatment assignment are intended to minimize the potential for bias in the analysis of AZD3293 treatment effects. The placebo comparator will provide a reference for the changes in cognition and biomarkers due to disease progression as well as inform the safety profile of AZD3293 in patients with early AD.

Dosing and study duration

The AZD3293 doses selected for this study (20 mg and 50 mg, administered once daily) represent the projected therapeutic dose range based on their levels of inhibition of BACE1 in the CNS as calculated from the multiple-ascending-dose study CSF Aβ data. It is anticipated that 20-mg and 50-mg AZD3293 doses should achieve clinically relevant CSF Aβ reductions,

and the projected mean exposures at those doses should be well within the range of exposures shown to be safe and well tolerated in the Phase 1 studies. The 20-mg dose provided >50% mean reduction in CSF Aβ1-42 concentrations over the dosing interval, and the 50-mg dose provided approximately 75% reduction in CSF Aβ1-42 concentrations over the dosing interval. Thus, these 2 doses are deemed sufficient to demonstrate the efficacy of AZD3293 in this study. The PK variability is expected to be sufficiently low to ensure that individual patient exposures at these doses will also not exceed the levels already demonstrated to be safe and well tolerated.

The 104-week study duration is deemed adequate to detect the effects of AZD3293 on cognition, function, and biomarkers relevant to AD in the selected patient population. The potential for debilitating disease progression in the placebo-treated patients will be mitigated by the fact that all study patients will be maintained on standard of care.

Primary endpoint

The primary endpoint in this study is the change from baseline to Week 104 in the ADAS-Cog$_{13}$. The ADAS-Cog is a widely accepted, validated clinical outcome measure. The scale reflects domains and abilities that are central to the characterization of an AD patient's deficits in a clinical setting and its items are linked to meaningful aspects of the lives of patients and caregivers. Furthermore, the scale has demonstrated its ability to detect treatment differences in the span of MCI and mild AD (Orgogozo et al. 2004; Salloway et al. 2004; Aronson et al. 2009).

Safety monitoring

The current study has been designed as a seamless Phase 2/3 study to take account of the need for Phase 2 evaluation of AZD3293. The advantages of this approach include earlier acquisition of long-term safety data while collecting comparable safety data to a conventional Phase 2 study; a reduction in the duration of clinical development program, thereby fulfilling an unmet clinical need sooner; and greater efficiency from the use of patients from both Phase 2 and 3 stages, thus requiring fewer patients. The initial Phase 2 stage of the study spans the time from study initiation to the first interim analysis (IA1), when 70 patients per group will have had the opportunity to complete 13 weeks of treatment. In addition to IA1, an IDMC will review safety data on a quarterly basis, both before and after IA1. This schedule of safety reviews should provide the same degree of oversight and risk mitigation as a conventional Phase 2 study.

The study will include standard safety assessments, ie, spontaneously reported AEs, clinical laboratory tests, vital sign and body weight measurements, 12-lead ECGs, and physical examinations. Additional safety assessments will include neurological examinations, comprehensive eye examinations performed by an ophthalmologist, skin examinations performed by a dermatologist, serial MRI examinations, and suicidality evaluations using the C-SSRS.

3.4. Role of the patient's study partner

Every patient in the study must have a study partner, who must sign an ICF. As several of the outcome measures require input from the study partner, the study partner should be willing to actively participate in the study and must have sufficient patient interaction to be able to provide

meaningful input. The study partner should be willing to participate in every study visit that requires their input for efficacy measures as outlined in Table 2. The study partner is not required to attend all study procedures; examples include but are not limited to MRI, PET or lumbar procedures, skin or eye examinations. As outlined in inclusion criterion 21 (Section 4.1), the study partner must either co-habit with or have regular contact with the enrolled patient. As guidance, the study partner's ability to meet his/her expected responsibilities for this study would normally be possible when the study partner spends no less than 10 hours per week with the patient, divided over multiple days. While every effort should be made to maintain the same study partner for a given patient throughout the study, in the event of an unavoidable change in study partner, the new study partner should be thoroughly oriented to the purpose and requirements of the study and must sign an ICF. An identification code will be assigned to each study partner and recorded at each in-clinic study visit. Demographic data, including date of birth, sex, and relationship to the patient, will be collected for every study partner.

3.5. Discontinuation of the study

The study will be discontinued if the sponsor judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP).

The IDMC (see Section 12.4) will monitor the general safety of the patients in this study and provide ongoing review to confirm that the risks subjects face are not unreasonable in comparison to the potential benefits. The IDMC will do this by reviewing all safety events quarterly and at the formal interim analyses to determine evidence of any potential safety signals and their relative significance in terms of the overall benefit-risk profile of the drug. After each safety data review meeting, the IDMC will provide recommendations to the sponsor Executive Committee. The sponsor Executive Committee will be responsible for receiving and promptly acting on the IDMC recommendations. A potential outcome based upon the review of the IDMC recommendations includes stopping the study for safety reasons.

4. SUBJECT SELECTION CRITERIA

Study patients will be recruited by specialist clinics with extensive referral networks.

Investigators must keep a record of patients who were considered for enrollment (those that signed informed consent) but were never randomized. This information is necessary to establish that the patient population was selected without bias.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. In general, there can be no exceptions to this rule. However, provision is made for rescreening of patients who did not meet entry criteria (see Section 3.2).

4.1. Inclusion criteria

For inclusion in the study, patients should fulfill the following criteria:

General

[1] Provision of signed, written, and dated informed consent from patient and from study partner prior to any study specific procedures

[2] Male or female, aged 55 to 85 years inclusive at signing of informed consent form (ICF)

[3] For inclusion in optional genetic research, provision of specific signed, written, and dated informed consent

Diagnostic

[4] Gradual and progressive change in the patient's memory function over more than 6 months, reported by patient and study partner

[5] MMSE score of 20 to 30 inclusive at screening visit

[6] Score of ≤85 on the Delayed Memory Index of the Repeatable Battery for the Assessment of Neuropsychological Status at screening visit

[7] Inclusion criterion [7] has been deleted.

[8] Inclusion criterion [8] has been deleted.

[9] For a diagnosis of mild AD, patient (1) meets the National Institute on Aging (NIA) and the Alzheimer's Association (AA) (NIA-AA) criteria for probable AD and (2) has a CDR global score of 0.5 or 1, with the memory box score ≥0.5 at the screening visit

[10] For a diagnosis of MCI due to AD, patient (1) meets NIA-AA criteria for MCI due to AD and (2) has a CDR global score of 0.5, with the memory box score ≥0.5 at the screening visit

[11] Inclusion criterion [11] has been deleted.

[12] Laboratory tests show no evidence of other etiologies for MCI or dementia, including but not limited to vitamin B12 level. Patients may be enrolled if the investigator considers that the abnormal values are not the cause of cognitive symptoms.

[13] PET visual reading or CSF $A\beta_{1-42}$ concentration positive for presence of amyloid. Please see the laboratory manual for further details.

Note: For inclusion, amyloid positivity criteria must be met by either amyloid PET imaging or by CSF $A\beta_{1-42}$ concentration (both are not required). If a patient does not meet amyloid positivity criteria according to the first test applied (either amyloid PET or CSF $A\beta_{1-42}$ concentration), the other amyloid test cannot be performed.

Contraception and concomitant medication

[14] Women must be postmenopausal or surgically sterile or infertile due to congenital anomaly. A postmenopausal woman is defined as having an intact uterus, who has not taken hormones or oral contraceptives within 1 year, and who has had either cessation of menses for at least 1 year, or 6 months of spontaneous amenorrhea with follicle-stimulating hormone (FSH) value that indicates the woman is postmenopausal. Surgically sterile women are defined as those who have had a hysterectomy, bilateral ovariectomy (oophorectomy), or bilateral tubal ligation.

[15] Men must abstain or be willing to use barrier contraception (ie, condoms), from the first day of dosing until 3 months after the last dose of study treatment. They must also be willing to abstain for 24 hours after PET scans. For this protocol, sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. True abstinence is only acceptable when it is in line with the patient's usual and preferred lifestyle. Given the length of the study, the reliability of patients to adhere to this provision should be considered by the investigator.

[16] All medication dosing should be stable for at least 30 days before screening, and between screening and randomization (does not apply to medications discontinued during screening, medications taken as needed, and/or medications not expected to substantially influence safety or efficacy assessments, in the opinion of the investigator, at baseline).

[17] Treatment with memantine must be discontinued at least 3 weeks before randomization.

Procedural

[18] Patient agrees to undergo APOE genotyping

[19] For patients undergoing florbetapir F 18 amyloid PET for entry or as part of the PET sub-study: able and willing to travel to a PET imaging center and complete the planned scanning sessions, and with past and planned exposure to ionizing radiation not exceeding safe and permissible levels

[20] Must have completed 6 years of formal education and/or have a history of academic achievement and/or employment sufficient to exclude intellectual disability

[21] The patient must have a reliable study partner with whom he/she cohabits or has regular contact (combination of face-to-face visits/ telephone contact acceptable). If at all possible, the same study partner should be willing to participate throughout the study and must have sufficient patient interaction to be able to provide meaningful input into the rating scales administered in this study, where study partner input is required, in particular for the CDR. As guidance, the ability for a study partner to meet his/her expected responsibilities for this study would normally be possible when the study partner spends no less than 10 hours per week with the subject, divided over multiple days. Evidence for adequacy of the study partner should be documented in source documentation.

[22] Patient and study partner must be able to read, write, and speak the language in which psychometric tests are provided, with acceptable visual and auditory acuity (corrected).

[23] Study partner must be cognitively able to fulfill the requirements of the study.

[24] In the opinion of the investigator, the patient and study partner will be compliant with, and have a high probability of completing, the study

4.2. Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

General

[1] Patients should not have participated or currently participate in any other clinical trial or any other type of medical research judged not to be scientifically or medically compatible with this study at screening or for the duration of their participation in the current study.

[2] Investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted. Employees or study partner of AstraZeneca, Lilly, or any third-party organizations involved in the study.

Medical

[3] Significant and/or current neurological disease affecting the CNS, other than AD, that may affect cognition or ability to complete the study, including but not limited to, other dementias, serious infection of the brain, Parkinson's disease, or epilepsy or recurrent seizures (except febrile childhood seizures)

[4] History of clinically evident stroke, or multiple strokes based on history or imaging results.

[5] History of clinically important carotid or vertebrobasilar stenosis or plaque. Patients with evidence of a carotid bruit at screening should undergo an ultrasound prior to randomization.

[6] History of multiple concussions or a concussion with sustained cognitive complaints or objective change in neuropsychological function in the last 5 years

[7] Patients with a current Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) diagnosis of Major Depressive Disorder (MDD) or any current primary psychiatric diagnosis other than AD (as per DSM-V) if, in the judgment of the investigator, the psychiatric disorder or symptom is likely to confound interpretation of drug effect, affect cognitive assessment, or affect the patient's ability to complete the study. Patients with history of schizophrenia or other chronic psychosis are excluded.

[8] History of alcohol, drug abuse or dependence (except nicotine dependence) (as per DSM-V) within 2 years before the screening visit

[9] Within 1 year before the screening visit or between screening and baseline, any of the following: myocardial infarction; moderate or severe congestive heart failure, NYHA class III or IV; hospitalization for, or symptoms of, unstable angina; syncope due to orthostatic hypotension or unexplained syncope; known significant structural heart disease (eg, significant valvular disease, hypertrophic cardiomyopathy); or hospitalization for arrhythmia

[10] Congenital QT prolongation

[11] Intermittent second- or third-degree atrioventricular (AV) heart block or AV dissociation or history of ventricular tachycardia

[12] Exclusion criterion [12] has been deleted.

[13] History of cancer within the last 5 years, with the exception of non-metastatic basal and/or squamous cell carcinoma of the skin, in situ cervical cancer, non-progressive prostate cancer or other cancers with low-risk of recurrence or spread.

[14] Current serious or unstable clinically important systemic illness that, in the judgment of the investigator, is likely to affect cognitive assessment, deteriorate, or affect the patient's safety or ability to complete the study, including hepatic, renal, gastroenterologic, respiratory, cardiovascular, endocrinologic, immunologic, or hematologic disorders

[15] History of vitiligo and/or current evidence of post-inflammatory hypopigmentation or exposure to depigmenting agents, eg, hydroquinone, in the 6 months prior to screening

[16] History of 2 or more clinically important drug allergies, eg, severe drug-induced rash or anaphylaxis

MRI, vital signs, electrocardiogram, and laboratory tests, physical examination

[17] Screening MRI shows evidence of significant abnormality that would suggest another potential etiology for MCI or dementia, such as >5 microhemorrhages; prior macrohemorrhage (>1 cm^3); ≥4 lacunar infarcts, or single infarct >1 cm^3; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformation, or clinically significant space-occupying lesions

[18] Uncontrolled hypertension, ie, supine systolic blood pressure >165 mmHg or diastolic blood pressure >95 mmHg. If an initial blood pressure reading is higher than this, the lowest value from 3 additional attempts to get a rested (>5 min), supine blood pressure reading should be used before excluding a patient for uncontrolled hypertension.

[19] A corrected QT (QTcF) interval measurement >470 msec (men and women) at screening (as determined at the investigational site). The site may request a central read prior making determination of this exclusion.

[20] Known positive serologic findings for human immunodeficiency virus (HIV) antibodies

[21] Positive hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) antibodies. Note: Patients with positive HCV antibodies may have a follow-up polymerase chain reaction (PCR) test ordered. If the PCR is negative, they are not excluded.

[22] Urine drug screen positive for inappropriate drug use.

[23] Any clinically important abnormality at screening, as determined by investigator, in physical or neurological examination, vital sign, ECG, or clinical laboratory test results that could be detrimental to the patient or could compromise the study

[24] Calculated creatinine clearance <30 mL/min (Cockcroft-Gault formula; Cockcroft and Gault 1976)

[25] ALT ≥2 × the upper limit of normal (ULN) of the performing laboratory, AST ≥2 × ULN, total bilirubin ≥1.5 × ULN, or ALP ≥1.5x ULN at screening

Concomitant medications

[26] Clinician impression of use of medications (eg, sleep aids, narcotics, anxiolytics etc.) in a manner that would interfere with cognitive testing.

[27] Use of strong inhibitors of CYP3A4 within 14 days or 5 half-lives, whichever is longer, before randomization, or of strong inducers of CYP3A4 within 30 days before randomization.

[28] Use of strong inhibitors of Pgp or BCRP within 14 days or 5 half-lives, whichever is longer, prior to randomization, or inducers of Pgp within 30 days before baseline.

[29] Exclusion criterion [29] has been deleted.

[30] For patients who will undergo lumbar puncture for CSF collection, use of medications known to significantly influence coagulation, such as warfarin or heparin. Anti-platelet inhibitors, such as aspirin, dipyridamole, or clopidogrel, are allowed, but they may require washout prior to lumbar puncture, at the investigator's discretion.

[31] Treatment with any investigational drug or device within 60 days or 5 half-lives prior to screening (whichever is longer) or between screening and randomization.

[32] Prior treatment with an AD vaccine. Prior treatment with a passive anti-amyloid immunotherapy is allowed if completed at least 5 half-lives prior to randomization.

Procedural

[33] Presence of any of the following MRI contraindications: pacemaker; cardiac defibrillator; spinal cord or vagus nerve stimulator; aneurysm clip; artificial heart valve; coronary or carotid stents that are not compatible with MRI; ear implant; CSF shunt; other implanted medical device (eg, Swan Ganz catheter, insulin pump); metal fragments or foreign objects in the eyes, skin, or body; severe claustrophobia that would contraindicate a brain MRI scan; or other contraindications due to local requirements

Additional exclusion criteria for patients undergoing CSF sampling at inclusion or participating in the CSF sub-study are as follows:

[34] Any spinal malformations or other aspects (eg, tattoos) or other clinical findings (eg, papilledema seen with ophthalmoscopy) that may complicate or contraindicate lumbar puncture, as judged by the investigator

[35] Current blood-clotting or bleeding disorder, including clinically significant abnormal findings in laboratory assessments of coagulation or hematology

Additional exclusion criteria for patients using amyloid PET for inclusion or participating in the florbetapir F 18 amyloid PET sub-study are as follows:

[36] Present or planned participation in a research and/or medical protocol involving PET ligands or radioactive agents, judged not to be scientifically or medically compatible with this study

[37] Have planned or are planning to have exposure to ionizing radiation that, in combination with the planned administration of study amyloid PET ligand, would result in a cumulative exposure that exceeds local recommended exposure limits

[38] For patients who will obtain a florbetapir F 18 scan: hypersensitivity to the active substance or any of the excipients of florbetapir F 18.

For procedures for withdrawal of incorrectly enrolled patients, see Section 5.3.

5. STUDY CONDUCT

5.1. Restrictions during the study

Patients will be required to:

1. Refrain from donating blood from the screening visit until 3 months after the follow-up visit
2. Follow restrictions regarding concomitant medications according to Section 5.6
3. Avoid use of tanning beds and self-tanning products
4. Wear a hat and appropriate clothing when exposed to sunlight; use a sunscreen with a sun protection factor (SPF) of at least 15; and protect the lips with a lip balm containing sun block
5. Men must abstain or be willing to use barrier contraception (ie, condoms) and not donate sperm during the study participation, through 3 months after study participation ends. Men must also agree to abstain for 24 hours after PET scans.
6. Avoid excessive use of alcohol during study participation. Excessive alcohol consumption is defined for men as consuming an average of more than 3 drinks per day, or more than 21 drinks per week. For women, excessive use of alcohol is defined as consuming an average of more than 2 drinks per day, or more than 14 drinks per week.

5.2. Patient enrollment and randomization

5.2.1. Procedures for enrollment

Additional information for the procedures for enrollment can be found in Section 3.2.1 and the Study Plan (Table 2)

5.2.2. Procedures for randomization

Patient eligibility will be established before randomized treatment assignment (see Section 4 for inclusion and exclusion criteria). The randomization will be stratified for disease status at baseline (MCI due to AD or mild AD).

The stratified randomization schedule will be prepared by the CCI Biostatistics Department on behalf of the sponsor. Randomization codes will be allocated in blocks within strata to AZD3293 20 mg, AZD3293 50 mg, or placebo in a ratio of 1:1:1, stratified by MCI due to AD and mild AD dementia. Enrollment rates in MCI due to AD and mild AD strata will be monitored.

If a patient withdraws from the study, the patient's study identifier and randomization code will not be reused, and the patient will not be allowed to re-enter the study.

5.3. Procedures for handling subjects incorrectly enrolled or entered

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule.

Patients who are incorrectly entered but are not yet randomized or initiated on treatment should not participate in any further study-related procedures and should be withdrawn from the study.

Where patients who do not meet the study inclusion and/or exclusion criteria are enrolled in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, the investigator should inform the CCI medical monitor immediately. The CCI medical monitor is to ensure all such contacts are appropriately documented. The CCI medical monitor, the sponsor's clinical research physician/scientist, and the investigator will determine whether the patient may continue in the study, with or without investigational product. Inadvertently enrolled patients may be maintained in the study and on investigational product when the CCI medical monitor and sponsor's clinical research physician/scientist agree with the investigator that it is medically appropriate for that patient. The patient may not continue in the study with or without investigational product if the CCI medical monitor and sponsor's clinical research physician/scientist do not agree with the investigator's determination it is medically appropriate for the subject to continue. The investigator must obtain documented approval from the sponsor's clinical research physician/scientist to allow the inadvertently enrolled patient to continue in the study with or without investigational product.

Safety information may be collected for 30 days after treatment discontinuation to ensure adequate follow-up.

5.4. Blinding and procedures for unblinding the study

5.4.1. Methods for ensuring blinding

The AZD3293 and placebo tablets used in the study will be identical in appearance, smell, and taste. Equal numbers of tablets will be dispensed to patients in each of the 3 treatment groups.

Packaging, labeling, and preparation of study medication will be performed in a way that will ensure blinding throughout the study.

Patients and their study partners will be unaware of the patient's randomized treatment assignment. No staff of the sponsor, CCI, the investigational centers, or any other personnel involved in the conduct of the study on behalf of the sponsor will have access to the randomization scheme during the conduct of the study, except the personnel analyzing the PK and PD samples, responsible for the IVRS system, or preparing/managing the blinded study treatment kits or the Independent Statistical Center preparing the reports for the IDMC. The randomization list will be kept in a secure location until the end of the study and until all regulatory obligations have been met.

5.4.2. Methods for unblinding the study

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the investigator(s) or pharmacists from the IVRS/IWRS for use in emergency situations as described below. Routines for this situation will be described in detail in the IVRS/IWRS materials that will be provided to each center.

If a patient receives a treatment kit other than the one randomly assigned by the IVRS/IWRS, the site clinical research associate should be notified and the IVRS/IWRS should be notified and the site inventory updated.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization, unless otherwise specified in this Clinical Study Protocol. In the case of a medical emergency, the investigator should make all attempts to contact the sponsor-designated medical monitor or designee prior to unblinding. However, if this is not possible, it is still required to document and report the action to the sponsor.

The sponsor, or its pharmacovigilance agent, retains the right to have the treatment allocation code broken for SAEs that are unexpected and are suspected to be causally related to study medication and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data, unless otherwise specified for the interim analyses of this study (see Section 12.2.2) until all decisions on the evaluability of the data from each individual patient have been made and documented.

If the treatment allocation is unblinded, the patient will be discontinued from study participation. However, the patient should continue to be followed for safety follow-up as appropriate.

5.5. Treatments

5.5.1. Identity of study medication

AZD3293 (investigational product) will be provided as immediate-release tablets. Matching placebo will be provided (Table 3).

Table 3. Study Medication

Study medication	Dosage form and strength
AZD3293 (investigational product)	Tablets (20 mg, 50 mg)
Placebo	Tablets to match AZD3293

Study medication will be dispensed at Visits 2 through 19 (see Study Plan in Table 2). Each kit box will have a unique kit number, and enough tablets will be dispensed for daily dosing until the patient returns for the next study visit. All study medication will be provided in blister packs and must be stored as per storage conditions in a secured area with limited access.

5.5.2. Doses and treatment regimens

Study medication is to be taken once daily, in the morning (Note: it is not a protocol violation if patient cannot or does not take study medication in the morning).

Study treatments (blinded) are as follows:

AZD3293 20 mg

AZD3293 50 mg

Placebo to match AZD3293

Patients should not take the morning dose of study treatment at home on the days of Visit 4 (Week 4), Visit 7 (Week 19), Visit 10 (Week 39), Visit 11 (Week 45), and Visit 14 (Week 65) because a blood sample for analysis of plasma AZD3293 and AZ13569724 concentrations will be drawn at the clinic before dose intake. Patients should not take the morning dose of study treatment until late afternoon on the day prior to Visits 7 and 14 (that is, at least 14 hours before the clinic visit). Patients should bring all study medication and kit boxes/blister packs to each study visit.

5.5.3. Labeling

Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. Label text will be translated into local language where required.

5.5.4. Storage

All study medication must be kept in a secure place under appropriate storage conditions. Appropriate storage conditions are specified on the study medication pack label.

5.6. Concomitant treatment(s)

Prior to randomization and during the screening period, medications should be stable to avoid confounding safety and efficacy assessments for baseline measures. In general, discontinuation of medications is permissible and switching between formulations of the same medication is permissible. Switching within a class of medications and other conditions may be permissible if they are unlikely to impact safety and efficacy assessments and should be approved by the medical monitor prior to randomization. Patients with medication changes considered significant prior to randomization (also see cognition medication below) may be rescreened once this inclusion criterion is met (see Section 3.2.3).

Concomitant medications with the potential to affect cognition are permitted, provided the patient has been maintained on a stable dose regimen for at least 30 days before screening, and between screening and randomization. These include, but are not limited to, cholinesterase inhibitors, opiates, ginkgo biloba and other approved nootropics, anxiolytics, antidepressants, sedative-hypnotics, hormone replacement therapy, sleeping aids, sedating anti-allergy medications, thyroid supplements, and vitamin E and vitamin B12 supplements (by injection). If a patient is taking these medications intermittently (eg, as needed for insomnia, anxiety, etc.)

he/she should be strongly discouraged from taking them the night before or morning of a study visit/testing session, unless he/she also did this for the Visit 2 (eg, he/she always does so before a stressful engagement). Maintaining consistency in testing conditions should be emphasized with respect to taking as-needed medication.

Patients may receive premedication for the MRI or PET assessments, but this medication should not be administered within 24 hours of any efficacy assessments.

After randomization, initiation, discontinuation, or dose adjustment of any therapy appropriate to the patient's condition is permitted, with the exception of those listed as prohibited. The medical monitor should be consulted as needed. Concomitant medications taken during the study must be recorded on the electronic case report form (eCRF), along with indication, daily dose, and start and stop dates of administration. All patients will be questioned about concomitant medications at every study visit.

5.6.1. Initiation of post-randomization symptomatic AD treatments

Over the period of this trial patients may have progression of symptoms/disease (patients may progress to mild or moderate/severe stages of disease). For patients for whom treatment becomes medically indicated during the trial, initiation of cholinesterase inhibitors and memantine (moderate stages) is permitted. This initiation must only occur when medically indicated and documenting rationale or indication for initiation will be required. In order to adequately capture any decline as well as stable improvements, these symptomatic treatments should be initiated within approximately four weeks after the completion of cognitive testing at Visit 8, Visit 12, Visit 16, and Visit 20 (see Figure 1). Initiation at time outside of these windows is discouraged, but the medical monitor should be contacted if a clinical need arises outside of the protocol-specified windows and will not be deemed a protocol violation if approved.

5.6.2. Other medication considerations post-randomization

Initiation of treatment with medications that may affect cognition are permitted if medically indicated. Attempts to limit use or establish reasonable routines with respect to consistency of cognitive testing periods are desired. Low-dose benzodiazepine use is allowed, such as lorazepam if required, for treatment of anxiety associated with study procedures such as lumbar puncture, MRI, or PET.

Use of hormone-replacement therapy is permitted.

Treatment with photosensitizing drugs is allowed, but patients should be advised on appropriate precautions.

Permitted concomitant medications should be maintained on a stable dose regimen during the study whenever possible.

As there is a potential for AZD3293 to influence digoxin levels due to effects of Pgp, it is recommended that digoxin levels be monitored when initiating and discontinuing test drug to

avoid possible over- or under-digitalization. Other Pgp sensitive medications with very narrow therapeutic margins may also require monitoring or use with caution.

The following are prohibited during the study:

- Use of any investigational drug or device not specified in this study judged to be scientifically or medically incompatible with this study.
- Use of any drugs of abuse, including but not limited to, illicit amphetamine, cannabis, cocaine, illicit opiates, propoxyphene, methadone, methaqualone, phencyclidine, or barbiturates
- Use of depigmenting agents, eg, hydroquinone, during double-blind treatment
- Use of strong inhibitors or inducers of CYP3A4 (topical may be permitted).
- Use of strong inhibitors of Pgp or BCRP or inducers of Pgp (topical may be permitted).

5.7. Treatment compliance

5.7.1. Assessment of compliance

The administration of all study medication should be recorded in the appropriate sections of the eCRF.

Compliance will be assessed at in-clinic visits via tablet counts when study medication packaging and any unused study medication are returned at study visits. The patient should be instructed retain all empty drug kits after using up the medication in the kit and to bring the empty kits and any unused medication to the clinic at each visit so that the clinic staff can record the amount of medication used since the last visit.

Compliance will be assessed at telephone visits via questioning of the patient and/or study partner.

Only patients who consume at least 80% of the prescribed daily dose during this study will be considered compliant. Patients regarded as non-compliant may be discontinued in consultation with the medical monitor.

5.7.2. Accountability

It is the investigator's responsibility to establish a system for handling the study medication to ensure that:

- Deliveries of such products are correctly received by a responsible person (eg, pharmacist)
- Such deliveries are recorded
- Study treatments are handled and stored safely and properly

- The study medication provided for this study will be used only as directed in the study protocol

The study personnel will account for all medication received at the site, dispensed for the patient, and returned to the site. Any discrepancies should be documented, investigated, and appropriately resolved.

At the end of the study, site personnel will account for all unused study medication and for appropriate handling with the sponsor's approval. Certificates of delivery, return, and/or destruction should be signed.

5.8. Discontinuation of study treatment

Patients **must** be discontinued from study treatment in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further routine clinical care.
- Adverse event or clinically significant laboratory value, ECG result, or vital sign measurement of such severity that, in the opinion of the investigator or medical monitor, continued treatment is not in the best interest of the patient
- Severe non-compliance to the study protocol that results in a safety concern, in the judgment of the investigator
- The patient, for any reason, requires a treatment with an excluded therapeutic agent for which temporary suspension of study treatment cannot be achieved (see Section 5.9). In this case, discontinuation from study drug occurs prior to introduction of the new agent.
- The patient develops a significant uncontrolled medical condition, such as a neuropsychiatric disorder that meets one of the exclusion criteria that in the opinion of the investigator after appropriate medical assessment, would pose an unacceptable risk to the patient if they were to continue receiving study drug.

Patients **may** be discontinued from study treatment in the following situations:

- An individual patient enrolled in the study may be discontinued from dosing based on a specific AE profile, as recommended by the IDMC, the CCI medical monitor, and/or the sponsor Global Study Physician/Scientist, in discussions with the Principal Investigator.
- Incorrect enrollment (Section 5.3)
- Vasogenic edema (Section 6.4.3.7)
- Elevated liver enzymes (Section 6.4.5.1)

The study may be paused or stopped by either the IDMC or the sponsor at any time.

Procedures for discontinuation

A patient who decides to discontinue study treatment will always be asked about the reason(s) and the presence of any AEs. Any reported AEs will be followed up (See Sections 6.4.3 and 6.4.4).

All study medication should be returned to the investigational site.

Patients should be encouraged to remain in the study until Week 104 (Visit 20), even if study treatment has been discontinued, and they should continue to participate in scheduled visits as described in Table 2. Patients who agree to remain in the study after discontinuing study treatment should continue to participate in scheduled visits and assessments, as appropriate, with the exception of PK measurements and PET scans, after completing the early discontinuation assessments described in Table 2, as appropriate. The CCI medical monitor may be consulted regarding the details of managing a specific patient who discontinues treatment but remains in the study.

Only patients on study treatment through Week 104 (Visit 20) are eligible to participate in the extension Study AZFD. For those who continue into Study AZFD, the follow-up visit in Study AZES is not required. However, Study AZES study must be completed prior to entering Study AZFD.

Patients in Study AZES who complete Week 104 procedures (Visit 20) will be considered study completers; any statements regarding early discontinuation requirements do not apply to these patients.

Patients who choose to withdraw from the study upon discontinuing study treatment and after completing the early discontinuation Visit assessments, as appropriate, should be asked to return for a follow-up visit (Visit 21) within 4 to 6 weeks of discontinuing treatment. If a patient withdraws his or her consent to participate in the study, see Section 5.10.

5.9. Suspension of study treatment

Treatment suspension and re-dosing of study drug can be considered based on the Principal Investigator's judgment, if clinical symptoms have resolved or a short-course of a prohibited medication is required. The maximum cumulative permissible treatment suspension is 6 weeks. Please contact your sponsor-designated medical monitor or designee for assistance.

5.10. Withdrawal from study

Patients are at any time free to withdraw from the study (study treatment and assessments), without prejudice to further routine clinical care (ie, withdrawal of consent). Such patients will always be asked about the reason(s) for withdrawal and the presence of any AEs.

Any reported AEs will be followed up (See Sections 6.4.3 and 6.4.4), and all study medication should be returned by the patient and early discontinuation procedures along with Visit 21 should be completed as described in Table 2.

If possible, patients who withdraw from the study after the start of dosing and before study completion will be seen and assessed by an investigator and undergo final study assessments as described in Section 5.8 for patients who discontinue study treatment.

Patients who withdraw from study treatment or study will not be eligible to re-enter this trial, any other potential trial with this compound, or the extension study.

6. COLLECTION OF STUDY VARIABLES

The study assessments are described in the sections that follow, and the timing of these assessments is detailed in the Study Plan (Table 2).

It is recommended that cognitive and functional assessments and vital sign assessments are performed before any blood samples are collected (unless otherwise noted in PK Section 6.5.1). It is recommended that cognitive efficacy assessments be performed as the first activity at baseline and subsequent visits.

Assessments should be scheduled to allow the cognitive testing to be performed at approximately the same time of the day at all the visits to avoid the known circadian variation of cognitive performance wherever possible (Higuchi et al 2000).

6.1. Recording of data

A Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRF as specified in this study protocol and in accordance with the instructions provided.

The investigator will ensure the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The investigator will sign the completed eCRF, and a copy of the completed eCRF will be archived at the study site.

6.2. Screening assessments

This section describes specific assessments that are performed at screening and are not described elsewhere in in Section 6.

6.2.1. NIA-AA criteria review

NIA-AA criteria will be reviewed at screening to assess the patient's diagnostic status for study inclusion and will be reviewed for diagnostic accuracy. This assessment will also be performed at Weeks 45 and 97 (Visits 11 and 19) to monitor for changes in the patient's diagnostic status during the course of the study.

The NIA-AA criteria for "MCI due to AD" and "probable AD dementia" are listed below. The ranges for cognitive testing results overlap between these diagnoses, consistent with the prevailing view of the diagnostic continuum of early AD. The ultimate distinction between these diagnoses is, therefore, inherently clinical and will be based heavily on the CDR rating and the overall clinical impression.

MCI due to AD (Albert et al 2011)

The process for diagnosing MCI is divided into 2 broad steps:

1. Establish clinical and cognitive criteria

- Objective evidence of impairment in 1 or more cognitive domains, typically including memory (ie, formal or bedside testing to measure cognitive function in multiple domains);
- Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (ie, historical or observed evidence of decline over time);
- Preservation of independence in functional abilities; and
- Not demented (see criteria for all-cause dementia below).
- Examine etiology of MCI to ensure it is consistent with AD pathophysiology
- Rule out vascular, traumatic, medical causes of cognitive decline (by history and/or by relevant laboratory tests (such as vitamin B12 levels) and imaging studies (such as MRI), if available;
- Provide evidence of longitudinal decline in cognition; and
- Report history consistent with AD genetic factors, where relevant.

Probable AD dementia (McKhann et al 2011)

Patients must first satisfy clinical criteria for **all-cause dementia**, which require cognitive or behavioral changes that:

1. Interfere with the ability to function at work or perform usual activities – *the significance of this functional impact differentiates dementia from MCI, which is an inherently clinical judgment*;
2. Represent a decline from previous levels of functioning;
3. Cannot be explained by delirium or a major psychiatric disorder;
4. Can be detected and diagnosed by a combination of:
   - History taking from both the patient and a knowledgeable informant
   - Objective cognitive assessment – either "bedside" mental status examination or neuropsychological testing, if needed; and
5. Involve a minimum of 2 domains, ie, has impairments in:
   - Acquiring and remembering new information – eg, repetitive questions
   - Reasoning and handling of complex tasks – eg, poor finances
   - Visuospatial abilities – eg, inability to recognize faces

- Language functions – eg, difficulty with common words
- Personality, behavior, or comportment – eg, mood fluctuations

For a clinical diagnosis of **probable AD dementia**, patients must meet criteria for all-cause dementia PLUS have:

1. Insidious onset (ie, no sudden changes that may suggest a cerebrovascular etiology)
2. Clear-cut history of worsening of cognition by report or observation (progression)
3. Initial and most prominent cognitive deficits in either:
   - **Amnestic** presentation:

     Most prominent deficits in learning and recall of recent information

     Evidence of cognitive dysfunction in at least 1 other domain
   - **Non-amnestic** presentation:

     Language presentation – eg, word-finding deficits

     Visuospatial presentation – eg, object agnosia, facial recognition

     Executive dysfunction – eg, impaired judgment, problem-solving

     Evidence of cognitive dysfunction in at least 1 other domain
4. No evidence of findings that do not suggest AD
   - Cerebrovascular disease – eg, stroke history or MRI with multiple infarcts or severe white matter disease
   - Core features of dementia with Lewy bodies (other than dementia)
   - Prominent features of behavioral variant frontotemporal dementia
   - Prominent features of semantic variant primary progressive aphasia or non-fluent/ agrammatic variant primary progressive aphasia
   - Evidence for other neurological or medical disease or medication use that could affect cognition

6.2.2. APOE genotyping

A blood sample will be taken at screening for APOE genotyping. Individual results will not be given to study patients, except as required by law or by an Ethics Committee (EC) or Institutional Review Board (IRB).

6.3. Efficacy

This section describes the primary and secondary efficacy variables to be collected in the study. The appropriateness of the efficacy measurements and variables is addressed in Section 3.3. The schedule of assessments is provided in the Study Plan (Table 2).

All efficacy assessments must be performed by trained and certified raters (see Section 6.3.4.2). In general, there should be a minimum of 2 raters per site: 1 rater for the global scales (see Section 6.3.1) and 1 rater for the remaining assessments. The CDR scale is included in the global scales. The CDR rater must, as much as possible, not have access to AE information to avoid bias in the CDR assessments. It is recommended that the same rater administer a particular scale at each visit, if possible, to minimize variability.

Cognitive and functional assessments should be performed in the order specified in Table 4. It is strongly recommended that any assessments that are administered to both the patient and study partner are performed separately, because the presence of the other person may potentially influence the results of an assessment.

6.3.1. Primary efficacy variable

Cognitive function will be assessed using a 13-item version of ADAS-Cog. The ADAS-Cog_{13} measures severity of impairment in various cognitive domains (memory, language, orientation, praxis and executive functioning). The ADAS-Cog has been designed specifically for the evaluation of the severity of major dysfunctions in the cognitive behavior characteristics of patients with AD. It has frequently been used in drug studies in AD of mild-to-moderate severity and is recognized by regulatory authorities. Most item scores are based on the number of words not recalled or the number of errors: Word Recall, Commands, Constructional Praxis, Delayed Word Recall, Naming, Ideational Praxis, Orientation and Word Recognition. Remembering Test Instructions is rated based on the number of reminders during the Word Recognition task. Spoken Language Ability, Comprehension of Spoken Language, and Word-finding Difficulty are rated on a scale of severity of dysfunction ranging from 0 to 5, where 0 = no impairment, 1 = very mild, 2 = mild, 3 = moderate, 4 = moderately severe, and 5 = severe. The score for the Number Cancellation item ranges from 0 to 5, based on ranges of numbers of target items correctly crossed off by the patient within the time limit; the fewer correct responses, the higher the score.

The ADAS-Cog_{13} is composed of the original 11-item ADAS-Cog (Rosen et al. 1984) as well as Delayed Word Recall and Number Cancellation items. The Number Cancellation task has been shown to be reliable and sensitive to a broad range of dementia severity and, therefore, is a useful addition to the 11-item ADAS-Cog (Mohs et al. 1997). The additional items in ADAS-Cog_{13} demonstrate good psychometric properties, even in subjects without AD. These items show excellent retest reliability and no ceiling effects observed on Delayed Word Recall and Number Cancellation items (Raghavan 2013; Wessels et al. 2015)

The maximum score for the ADAS-Cog$_{13}$ is 85 points. A lower score indicates a better performance.

The ADAS-Cog$_{13}$ word lists and number cancellation will not be the same at consecutive visits, that is, word lists and number cancellation will be alternated and thus vary by visit.

ADAS-Cog$_{13}$ assessment results will be recorded on worksheets. Administration of the ADAS-Cog$_{13}$ will be audio-recorded for quality-control and training purposes where permitted by local law. Item-level scores from the worksheet will be transcribed into the eCRF. A sample of the ADAS-Cog$_{13}$ worksheets and audio recordings will be centrally reviewed and monitored where permitted by local law. Follow-up with raters will occur if concerns about administration and/or scoring practices are observed in central monitoring.

6.3.2. Secondary efficacy variables

Secondary efficacy variables in this study are the changes from baseline (Visit 2) to Week 104 in FAQ score, ADCS-ADL score, CDR-SB, iADRS, MMSE, NPI total score; and CDR global score.

6.3.2.1. Functional Activities Questionnaire

The FAQ measures functional activities that may be impaired in the early stages of AD (eg, ability to shop, cook, and pay bills) (Pfeffer et al 1982). The FAQ is a study partner/ informant rating of the performance changes in 10 complex activities of daily living.

The ratings are obtained from a brief, approximately 5-minute, clinician interview with the patient's study partner to evaluate the patient's ability to carry out the following activities of daily living: 1) manage finances, 2) complete forms, 3) shop, 4) perform games of skill or hobbies, 5) prepare hot beverages, 6) prepare a balanced meal, 7) follow current events, 8) attend to television programs, books or magazines, 9) remember appointments, and 10) travel out of the neighborhood. Each activity is rated on a scale from 0 to 3 (Never did and would have difficulty now = 1, Never did [the activity] but could do now = 0, Normal = 0, Has difficulty but does by self = 1, Requires assistance = 2, Dependent = 3).

The maximum FAQ total score is 30, with higher scores indicating greater impairment.

The FAQ assessment results will be recorded on worksheets. Administration of the FAQ will be audio-recorded for quality-control and training purposes where permitted by local law. Item-level scores from the worksheet will be transcribed into the eCRF. A sample of the FAQ worksheets and audio recordings will be centrally reviewed and monitored where permitted by local law. Follow-up with raters will occur if concerns about administration and/or scoring practices are observed in central monitoring.

6.3.2.2. The Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory

The ADCS-ADL measures 6 basic and 17 instrumental activities of daily living and was specifically developed as a sensitive tool to track changes in functional performance in AD over time (Galasko et al 1997, Galasko et al 2004). The basic activities include self-care tasks such as

eating, walking, toileting, bathing, and grooming. The instrumental activities are more complex skills that are required to successfully live independently and include shopping, keeping appointments, traveling outside of home, making a meal or snack, reading, and writing. These instrumental skills are often compromised in early AD.

For each activity on the ADCS-ADL, the score ranges from 0 (not able to perform the activity or needs extensive help) to the highest score (independently performs the activity).

The maximum ADCS-ADL total score is 78, with lower scores indicating greater impairment. The maximum basic items score (sum of individual basic item scores) is 22, and the maximum instrumental items score (sum of individual instrumental item scores) is 56 (Galasko et al 2004).

The ADCS-ADL is a study partner/informant rating, and the administration of the scale takes approximately 15 minutes.

The ADCS-ADL assessment results will be recorded on worksheets. Administration of the ADCS-ADL will be audio-recorded for quality-control and training purposes where permitted by local law. Item-level scores from the worksheet will be transcribed into the eCRF. A sample of the ADCS-ADL worksheets and audio recordings will be centrally reviewed and monitored where permitted by local law. Follow-up with raters will occur if concerns about administration and/or scoring practices are observed in central monitoring.

6.3.2.3. Clinical Dementia Rating Scale

The CDR (Hughes et al. 1982) is a global rating system widely used in clinical studies of AD as a measure of dementia severity and disease progression. The CDR ratings are based on a semi-structured and in-depth interview with both the patient and the patient's study partner. The CDR rates decline in cognition and its impact on functioning relative to the patient's own premorbid ability levels. Although the rater may administer selected cognitive tasks during the interview to further estimate the patient's cognitive and functional abilities, the CDR ratings do not rely directly on psychometric test performance. The interview takes approximately 45 minutes to administer and requires a trained and experienced rater. The CDR rater should, as much as possible, not have access to information regarding AEs.

The CDR includes assessment of 6 independent domains: Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care. Each independent domain is rated at each assessment time point on a scale from 0 to 3 (0 = none, 0.5 = questionable, 1 = mild, 2 = moderate, 3 = severe). These domain ratings are also known as "box" scores. The Sum of Boxes score is derived by adding the individual box scores at a given time point. The maximum Sum of Boxes score is 18, with higher scores indicating greater impairment. The CDR global score is a composite score calculated using the Washington University CDR-assignment algorithm applied to the 6 individual domain box scores (Morris 1993). The memory domain is considered the primary category that drives the CDR global outcome, and all other domains are secondary. The CDR global score ranges from 0 to 3 (0 = no dementia, 0.5 = questionable dementia, 1 = mild dementia, 2 = moderate dementia, 3 = severe dementia). The CDR global score and memory box score will be used to determine patient

eligibility for the study and categorize patients as having either MCI due to AD or mild AD, as described in Section 4.1, inclusion criteria.

The CDR assessment results will be recorded on worksheets. Administration of the CDR will be audio-recorded for quality-control and training purposes where permitted by local law. The box scores and global scores from the worksheet will be transcribed into the eCRF. A sample of the CDR worksheets and audio recordings will be centrally reviewed and monitored where permitted by local law. Follow-up with raters will occur if concerns about administration and/or scoring practices are observed in central monitoring.

Time in the current disease state will be assessed in terms of time to loss of 1 global stage on the CDR global score through Week 104.

6.3.2.4. Integrated Alzheimer's Disease Rating Scale (iADRS) [calculated assessment, not a separately administered scale]

The iADRS (Wessels et al 2015) is a composite that measures both cognition and function. The iADRS is a simple linear combination of scores from two well-established, therapeutically sensitive, widely accepted measures in AD, the ADAS-Cog_{13} and the instrumental activities within the ADCS-ADL (ADCS-iADL), measuring the core domains of AD. All items of these two scales are included without additional weighting of items, yielding face validity and ease of interpretation of the composite relative to its components.

The iADRS provides an overall measure of AD impairment (total score) and can also provide individual subscores for cognition and function based on standard, accepted instruments. The iADRS demonstrated acceptable psychometric properties (established through principal component analysis, estimation of the contributions of domain scores to the iADRS total score, and estimation of the contributions of individual item scores to the iADRS total score) and was effective in capturing disease progression and treatment effects (both beneficial and detrimental) across a broad range of the symptomatic disease spectrum – MCI/prodromal, mild AD dementia, and moderate AD dementia populations.

The iADRS score ranges from 0-141; with higher scores indicating greater impairment.

6.3.2.5. Mini-Mental State Examination

The MMSE (Folstein et al 1975) is a brief test used to screen for cognitive impairment. It is routinely used for estimating the severity of cognitive impairment and tracking cognitive changes in an individual over time. The MMSE assesses orientation to time and place, immediate and delayed recall of words, attention and calculation, language (naming, comprehension and repetition), and spatial ability (copying a figure). The maximum total score is 30, with a higher score indicating better cognitive performance. The range of permissible scores at screening for enrollment of patients is 20 to 30, inclusive.

The MMSE assessment results will be recorded on worksheets. Administration of the MMSE will be audio-recorded for quality-control and training purposes where permitted by local law. Item-level scores from the worksheet will be transcribed into the eCRF. A sample of the MMSE worksheets and audio recordings will be centrally reviewed and monitored where permitted by

local law. Follow-up with raters will occur if concerns about administration and/or scoring practices are observed in central monitoring.

6.3.2.6. Neuropsychiatric Inventory

The Neuropsychiatric Inventory (NPI) is a well-validated clinical rating instrument designed specifically to assess a wide range of abnormal behaviors encountered in dementia patients (Cummings 1997, Cummings et al 1994). The NPI is an informant-based interview that utilizes scripted questions to explore 12 different symptom domains: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor activity, night-time behavioral disturbances, and appetite and eating abnormalities. For each domain, the study partner is asked a screening question to determine whether the abnormal behavior has been present within the previous 4 weeks and represents a change in the patient since the onset of illness. If the behavior has been present, then a series of sub-questions are asked to obtain more detailed information about the specific features of the behavioral disturbance. For any behavior that has been present in the past 4 weeks, the study partner is asked to rate the frequency of the behavior on a 4-point scale (Rarely – less than once per week, Sometimes – about once per week, Often – several times per week but less than every day, Very often – once or more per day or continuously present), and the severity of the behavior on a 3-point scale (Mild – produces little distress in the patient, Moderate – more disturbing to the patient but can be redirected by the caregiver, Severe – very disturbing to the patient and difficult to redirect). A total score for each symptom is calculated by multiplying the frequency rating by the severity rating. The total NPI score is the sum of all symptom scores and has a possible range of 0 to 144, with higher scores indicating a greater degree of symptomatology.

The NPI also contains a Caregiver Distress Scale (NPI-D) that was designed to quantitate the distress experienced by caregivers as it relates specifically to the individual symptoms assessed in the patient by the NPI. For each symptom deemed to be present in the past 4 weeks, the study partner is asked to rate the distress the symptom has caused him or her on a 6-point scale (based on response to the question "How emotionally distressing do you find this behavior?"): 0 = not at all, 1 = minimally, 2 = mildly, 3 = moderately, 4 = severely, 5 = very severely or extremely. The maximum score for the Caregiver Distress Scale is 60.

The NPI assessment results will be recorded on worksheets, and item-level scores will be transcribed into the eCRF.

6.3.3. Exploratory efficacy variables

Exploratory efficacy variables in this study are the changes from screening/baseline that include but are not limited to: the Letter Fluency, Category Fluency, and Digit Symbol-Coding test scores, the NPI-D score, as well as the changes from screening in the RBANS score.

6.3.3.1. Letter Fluency, Category Fluency, and Digit Symbol-Coding tests

The Letter Fluency test is a measure of phonemic verbal fluency and executive functioning. The test consists of 3 trials. For each trial, the patient is asked to name as many words that start with a specific letter as he/she can in 60 seconds. Each trial is scored for the number of words

correctly generated and number of errors. The total number of correct words and total errors are derived by summing the scores across the 3 trials.

The Category Fluency test is a measure of semantic verbal fluency and executive functioning. The patient is asked to name as many animals as he/she can in 60 seconds. The test yields scores for the number of correct animal names generated and the number of errors.

The Digit Symbol-Coding test from the Wechsler Adult Intelligence Scale-III (Wechsler 1997) engages multiple cognitive abilities, including attention, psychomotor speed, complex scanning, visual tracking, and immediate memory. The test instrument is composed of 140 small blank squares presented in 7 rows. Each blank square is randomly paired with a number (1 to 9) printed directly above it. A key printed above the rows of blank squares pairs each number with an unfamiliar symbol. After completing 7 practice items, the patient must use the key to fill in the blank squares in order (working left to right across the rows) with the symbol that is paired with the number above it, working as quickly as possible within the time limit of 90 seconds. The test score is the number of blank squares filled in correctly within the time limit.

The Letter Fluency, Category Fluency, and Digit Symbol-Coding assessment results will be recorded on worksheets. Item-level scores from the worksheets will be transcribed into the eCRF.

6.3.3.2. Repeatable Battery for the Assessment of Neuropsychological Status

The RBANS is a collection of 12 subtests representing 5 neurocognitive domains: Immediate Memory, Visuospatial/Constructional, Language, Attention, and Delayed Memory. The RBANS administration generally requires 20 to 30 minutes.

The raw scores from each subtest within a domain are converted to a summary score, or Index Score, for the domain by consulting normative data tables. The RBANS also provides an overall Index Score that summarizes the patient's overall level of performance on this measure.

A Delayed Memory Index score of ≤85 at screening (Visit 1) is required for study eligibility.

The RBANS assessment results will be recorded on worksheets. Administration of the RBANS will be audio-recorded for quality-control and training purposes where permitted by local law. Subtest scores and Index scores from the worksheet will be transcribed into the eCRF. A sample of the worksheets for these assessments and audio recordings will be centrally reviewed and monitored where permitted by local law. Follow-up with raters will occur if concerns about administration and/or scoring practices are observed in central monitoring.

6.3.4. Order of efficacy assessments and rater qualifications

6.3.4.1. Order of efficacy assessments

The screening cognitive scales in Visit 1 should be administered before performing any imaging.

Assessments administered to the patient are the MMSE; RBANS; ADAS-Cog_{13}; Letter Fluency, Category Fluency, and Digit Symbol-Coding tests; EQ-5D-5L; and CDR. Assessments administered to the study partner include the FAQ, ADCS-ADL, CDR, NPI, and RUD-Lite.

Refer to Table 4 for the relative sequencing of tests for both patient and study partner. It is recommended that efficacy assessments be performed as the first activity at the baseline and subsequent visits. Additionally, it is recommended that, during these visits, cognitive and functional tests are performed in the sequence shown in Table 4. The CDR should always be administered to the study partner first and then to the patient; the study partner and patient must be interviewed separately.

It is important to maintain the same test sequence at each visit for each patient throughout the study. Assessments should be scheduled to allow the cognitive testing to be performed at approximately the same time of the day at all the visits to avoid the known circadian variation of cognitive performance (Higuchi et al 2000).

It is strongly recommended that patients and study partners be assessed separately, because the presence of the other person may potentially contaminate the results of an assessment. When necessary, patients should be allowed a rest break between cognitive tests. Based on rater judgment, other non-stressful study procedures may be conducted during these breaks.

Where there are multiple raters, ie, a psychometric rater and a global rater, the recommended sequence of tests allows for simultaneous testing. Table 4 describes the testing flow and respective rater responsibilities in this situation.

Table 4. Order of Test Administration for Patient and Study Partner and Rater Responsibilities

Psychometric rater	Global rater
Patient	**Study partner**
1) MMSE	
2) RBANS	1) FAQ
3) ADAS-Cog$_{13}$	2) ADCS-ADL
4) Letter & Category Fluency tests	3) CDR[a]
5) Digit Symbol-Coding test	
6) EQ-5D-5L	
Study partner	**Patient**
4) NPI	7) CDR[a]
5) RUD-Lite	

All tests may not be administered at each visit; the relative order of tests is maintained for any tests that are administered at the same visit.

[a] The CDR must always be administered to the study partner first and then to the patient. It is recommended that both sections be administered on the same day.

Abbreviations: ADAS-Cog$_{13}$ 13-item Alzheimer's Disease Assessment Scale - Cognitive subscale; ADCS-ADL The Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory; CDR Clinical Dementia Rating; FAQ Functional Activities Questionnaire; MMSE Mini-mental State Examination; NPI Neuropsychiatric Inventory; RBANS Repeatable Battery for the Assessment of Neuropsychological Status; RUD Resource Utilization in Dementia.

6.3.4.2. Rater qualifications and blinding

Raters will be selected based on experience appropriate for the measures and will be trained so that variability in ratings is minimized. Two separate types of trained and qualified raters will administer the cognitive/functional and functional/global scales unless a single rater is approved by the sponsor. A psychometric rater will administer measures such as the MMSE, RBANS, ADAS-Cog$_{13}$, NPI, EQ-5D-5L, and RUD-Lite (see Table 4). A separate, global rater will administer the FAQ, the ADCS-ADL, and the CDR. If possible, the CDR should be administered by the same rater for a given patient. It is preferred that the same rater who administers the screening tests also performs all post-screening administrations of those tests for a given patient.

Every effort should be made to prevent the CDR rater from becoming aware of any AEs the patient may experience during the study. CDR raters should, as much as possible, not have access to this information and should instruct patients and their study partners not to discuss AEs during the CDR interview. The rater should sign a statement to this effect on the CDR worksheet. Site personnel who are involved in reviewing medical data or who may have access to AE information must refrain from discussing this information with the CDR rater.

6.4. Safety

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.4.1. Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation if symptomatic or clinically significant (Section 6.4.3.6 for abnormal results; eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.4.2. Definitions of serious adverse event

A serious AE is an AE occurring during any study phase (ie, screening, double-blind treatment, and follow-up), that fulfills 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of an SAE, see Appendix B to the Clinical Study Protocol.

Note: Cases where a patient shows an AST **or** ALT ≥3xULN **and** total bilirubin ≥ 2xULN may need to be reported as SAEs. Refer to Appendix D "Actions required in cases of combined increase of aminotransferase and total bilirubin – Hy's Law," for further instructions.

6.4.3. Recording of adverse events

6.4.3.1. Time period for collection of adverse events

Adverse events (including SAEs) will be collected from screening (Visit 1) throughout the treatment period (Visits 2 through 20) and including the follow-up period (Visit 21).

6.4.3.2. Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last study visit are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. The sponsor or its designated safety representative retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.4.3.3. Intensity of adverse events

The following ratings will be used by the investigator to judge AE intensity:

- Mild: awareness of sign or symptom, but easily tolerated
- Moderate: discomfort sufficient to cause interference with normal activities
- Severe: incapacitating, with inability to perform normal activities

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

6.4.3.4. Causality collection

The investigator will assess causal relationship of all AEs.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

6.4.3.5. Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or study partner or reported in response to the open question from the study personnel: "Have you had any health problems since you were last asked?" or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known, and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.4.3.6. Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests, vital sign measurements, ECG results, and other safety assessments will be summarized in the clinical study report.

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory, term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-protocol-

mandated laboratory tests, vital sign measurements, ECG results, and other safety assessments should be reported as AE(s).

Any new or aggravated, clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.4.3.7. Vasogenic edema

If a patient develops symptoms believed to be suggestive of vasogenic edema, such as headache, confusion, gait disturbance, or visual disturbance, these should be recorded as AEs and an MRI should be obtained. Study treatment should be discontinued if clinically significant symptomatic vasogenic edema, clinically significant symptomatic superficial siderosis, or clinically significant symptomatic incident microhemorrhage is seen (see Section 5.9 for suspension of study treatment). Following the study treatment discontinuation, the MRI scan should be repeated within 4 weeks to evaluate the status of the finding and then performed every 4 to 6 weeks (or as clinically indicated) until the finding resolves or stabilizes. Treatment with high-dose dexamethasone is to be considered, should symptoms be severe.

6.4.3.8. Rash

In the event a patient experiences a suspected drug-induced rash, the following procedures should be followed:

- The patient should be referred to a dermatologist for an expert opinion.
- A photograph of the rash should be taken.
- A blood sample should be drawn for PK analysis.
- A punch biopsy may be obtained at the discretion of the dermatologist.

If treatment is discontinued due to a suspected drug-induced rash, the CCI medical monitor should be notified as soon as possible, even if the rash did not meet the definition of an SAE.

6.4.3.9. Depression

In the event a patient experiences a clinically significant worsening of depression or a new onset major depression, the following procedures should be followed:

- The investigator or another qualified study physician should assess the patient clinically as soon as it is possible, and any appropriate emergency measures should be undertaken.
- Assuming an evaluation by a psychiatric emergency service is not required, the patient should be referred to a psychiatrist for an expert opinion.
- The investigator may initiate psychiatric management, including the use of psychiatric medication, as clinically needed.

- If study treatment is discontinued due to depression, the CCI medical monitor should be notified as soon as possible, even if the event did not meet the definition of an SAE.

6.4.3.10. Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. Gradual deterioration of cognition and/or function consistent with the usual course of AD should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression should not be reported as AEs during the study.

6.4.4. Reporting of serious adverse events

All SAEs must be reported, whether or not considered causally related to the study medication or to the study procedure(s). All SAEs will be recorded in the source documents and in the eCRF.

If any SAE occurs in the course of the study, then the investigator or other site personnel will inform the designated sponsor or representative within 1 day of when he or she becomes aware of it, ie, immediately, but **no later than 24 hours from the time he or she becomes aware of it**, using the SAE Report Form. Telephone reports must be confirmed promptly by submitting the completed SAE Report Form by facsimile.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. The investigator or other site personnel will inform sponsor or representatives of any follow-up information on a previously reported SAE within 1 calendar day of when he or she becomes aware of it, ie, immediately, but **no later than 24 hours from the time he or she becomes aware of it**.

6.4.5. Laboratory safety assessment

Blood and urine samples for determination of hematology and clinical chemistry parameters, electrolytes, thyroid-stimulating hormone, total thyroxine, and urinalysis will be taken at the times indicated in the Study Plan (see Table 2). The date of collection of all laboratory tests will be recorded in the eCRF.

At screening, the clinical chemistry tests will include a lipid panel and creatinine clearance. At this visit, all patients will be tested for HbA1c, vitamin B12 level, folic acid, rapid plasma reagin (RPR), hepatitis B surface antigen, antibodies to hepatitis C, prothrombin time, partial thromboplastin time, and international normalized ratio (INR). Urine will be tested for drugs of abuse at screening. Human immunodeficiency virus may be tested at the discretion of the investigator or if mandated by local regulatory authority. This test may require a separate informed consent.

A follicle-stimulating hormone test will be performed at screening for female patients who report 6 to 12 months of spontaneous amenorrhea. The results of this test will be used to determine if the patient meets criteria for exclusion from the study.

The laboratory variables to be measured are listed in Table 5.

Table 5. Safety Laboratory Variables

Variables in serum/blood and urine	
Hematology (blood)	**Electrolytes (serum)**
Hematocrit	Bicarbonate
Hemoglobin	Chloride
Leukocyte (white blood cell count, WBC) count	Phosphate
Absolute leukocyte differential count (neutrophils, basophils, monocytes, eosinophils and lymphocytes)	Potassium
Platelet count	Sodium
Coagulation	**Urinalysis**
Prothrombin time[a]	Blood
Partial thromboplastin time[a]	Color
International normalized ratio (INR)[a]	Glucose
	Ketones
Clinical chemistry (serum)	Leukocyte esterase
Alanine aminotransferase (ALT)	pH
Albumin	Protein
Alkaline phosphatase	Specific gravity
Aspartate aminotransferase (AST)	
Bilirubin, total	**Screening tests[a]**
Blood urea nitrogen (BUN)	Folic acid
Cholesterol (total, HDL, LDL) and triglycerides[a]	Hepatitis B surface antigen
Calcium, total	Hepatitis C antibodies
C-reactive protein	RPR
Creatine kinase (CK)	Vitamin B12
Creatinine	Urine test for drugs of abuse
Creatinine clearance[a]	
Glucose	**Other**
	Hemoglobin A1c (HbA1c)[c]
Endocrinology	
Follicle-stimulating hormone (FSH)[a,b]	**Optional/Confirmatory Testing**
Thyroid-stimulating hormone[c]	Human immunodeficiency virus[a]
Total thyroxine[c]	Hepatitis C PCR[d]

[a] At screening only.

[b] Only for female patients for whom the investigator believes menopausal status is uncertain who report between6 and 12 months of spontaneous amenorrhea

[c] At screening, Week 52, and Week 104 (or final study visit) only.

[d] Patients with positive HCV antibodies may have a follow-up PCR test ordered.

Abbreviations: HDL High-density lipoproteins; LDL Low-density lipoproteins; PCR polymerase chain reaction; RPR Rapid Plasma Reagin.

Laboratory values outside the reference limit suspected to be of any clinical significance will be repeated. Patients for whom suspected clinical significance is confirmed will either not be enrolled or, if already enrolled, will be followed until normalization or for as long as the

Investigator considers necessary. Additional laboratory tests may be performed for safety reasons if judged appropriate by the investigator. See Section 6.4.3 for information regarding the recording of AEs based on laboratory tests. All laboratory samples will be analyzed using routine methods per the central laboratory, as referenced in the Laboratory Manual for this study.

For blood volume, see Section 7.1.

6.4.5.1. Elevation in Liver Tests

If a patient experiences AST or ALT ≥3 x ULN, total bilirubin ≥2 x ULN, or ALP ≥2x ULN, the investigator is to consult with the designated medical monitor regarding collection of specific recommended clinical information and follow-up laboratory tests. The Liver Assessment CRFs should be completed for these patients as information becomes available.

Note: If a patient shows an AST **or** ALT level ≥3 × ULN **or** total bilirubin ≥2 × ULN, please also refer to Appendix D "Actions required in cases of combined increase of aminotransferase and Total Bilirubin – Hy's Law," for further instructions.

Discontinuation of study drug for abnormal liver tests should be considered by the investigator in consultation with the designated medical monitor if the patient meets one of the following criteria:

- ALT or AST ≥8x ULN
- ALT or AST ≥5x ULN for more than 2 weeks
- ALT or AST ≥3x ULN and either total bilirubin >2x ULN or INR >1.5
- ALT or AST ≥3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP elevations, if deemed of liver origin and drug-related as follows:
    - ALP >3x ULN
    - ALP >2.5x ULN and total bilirubin >2x ULN
    - ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

In all the above situations involving elevations in liver enzymes, every attempt should be made to obtain the following:

- Viral hepatitis serology including:
    - Hepatitis A antibody (total and IgM)
    - Hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis B core antibody
    - Hepatitis C RNA PCR
    - Cytomegalovirus IgG and IgM antibody

  - Epstein-Barr viral capsid antigen IgG and IgM antibody (or if unavailable, obtain heterophile antibody of monospot testing)
  - Hepatitis E IgG and IgM antibody
- Blood sample for plasma PK analysis. The date and time of the PK blood sample collection and dates and times of the 2 previous doses of study medication must be recorded.
- Serum creatine phosphokinase (CPK)
- Fractionate bilirubin, if total bilirubin is ≥1.5 x ULN
- Anti-nuclear antibody, anti-smooth muscle antibody, and Type I anti-liver kidney microsomal antibodies
- Liver imaging (ultrasound, MR or CT) to evaluate liver disease
- Complete the Liver Assessment CRFs as information becomes available
- Record of the appearance or worsening of clinical symptoms of hepatitis if applicable
- Record of the use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, putative hepatotoxins, or alcohol
- Consultation with a gastrointestinal or hepatology specialist should be considered

6.4.6. Physical and neurological examinations

Complete physical examinations will be performed at screening, baseline, and Weeks 13, 52, and 104 as indicated in the Study Plan (see Table 2). Brief physical examinations will be performed at Weeks 4, 26, 39, 65, 78, and 91. The complete physical examination will include assessment of the following: general appearance; skin, head and neck; lymph nodes; thyroid; abdomen (bowel sounds, liver and spleen palpation); back (costovertebral angle tenderness); and musculoskeletal, cardiovascular, and respiratory systems. The brief physical examination will include assessments of the skin, lungs, cardiovascular system, and abdomen (bowel sounds, liver and spleen palpation).

Complete neurological examinations will be performed as indicated in the Study Plan (see Table 2). The examinations will include a thorough assessment of gait, balance, coordination, cranial nerves, sensory and motor systems, and reflexes.

See Section 6.4.3 for information regarding the recording of AEs based on examinations.

6.4.7. 12-lead ECG

Digital 12-lead ECG files will be collected using continuous 12-lead digital recorders at the times indicated in the Study Plan (see Table 2) after the patient has been resting in supine position for at least 10 minutes.

The 12-lead ECG equipment will be supplied and supported by CCI [redacted]

For each ECG time point shown in the Study Plan, a 90-second continuous 12-lead digital ECG file will be collected. A 12-lead safety ECG will be printed at the site and the digital data will be transmitted to CCI . The safety ECG data will be reviewed for quality and alerts by CCI , and this information will be transmitted back to the study site. The Principal Investigator or physician delegate is responsible for reviewing the safety ECG to determine if a patient meets eligibility criteria with respect to cardiac inclusion/exclusion criteria at the time of the screening.

The ECG data sent to CCI will be stored in a centralized safety ECG database. The digital 90-second ECGs will be converted to International Society for Holter and Noninvasive Electrocardiology (ISHNE) format and transmitted to the AstraZeneca ECG Center for ECG analysis and interpretation according to the Core laboratory's standard procedures. The PR, QRS, QT, and RR intervals will be measured and reported. Heart rate and QTcF interval will be calculated by the study statistician.

From the 90-second continuous ECG recording, the site will print a safety ECG that will be evaluated for heart rate and PR, RR, QRS, QT and QTcF intervals, and the investigator will judge the overall interpretation as normal or abnormal. If the ECG is interpreted as abnormal, it will be decided whether or not the abnormality is clinically significant or not clinically significant, and the reason for the abnormality will be recorded. The recording date and time and the investigator interpretation (normal, abnormal clinically significant, abnormal not clinically significant) will be recorded in the eCRF, and the paper printouts will be stored as source documents. The investigator (or delegate) will evaluate the printout of the ECG in real time, with particular attention to the effects of clinical importance on the QRS and QTcF intervals.

The investigator may add and print extra 12-lead ECG safety assessments if there are any abnormal findings or if the investigator considers it is required for any other safety reason. In this event, concurrent blood samples should be collected for PK and electrolyte analyses. Additional ECGs may also be performed, at the discretion of the investigator, whenever a significant change in the patient's clinical status occurs (eg, significant deterioration in cardiac, renal, or liver function or salt-water balance).

Safety ECG results should be reviewed by the investigator (or delegate) for potential clinical significance, and the clinical significance should be determined by the investigator in consultation with the cardiologist at the AstraZeneca ECG Center, if necessary. Note that new findings on ECG after enrollment that do not meet entry criteria do not automatically indicate that subject should be discontinued. In many cases discontinuation will not be necessary and will depend on clinical significance and implications (eg, QTcF > 470 ms). See Section 6.4.3 for information regarding the recording of AEs based on ECG results.

6.4.8. Vital signs

Vital signs, including supine and standing blood pressures and pulse rates, and temperature will be recorded at each in-clinic study visit (see the Study Plan in Table 2).

See Section 6.4.3 for information regarding the recording of AEs based on tests and examinations.

6.4.8.1. Pulse rate and blood pressure

Supine blood pressure and pulse rate should be taken after at least 5 minutes of supine rest. Standing blood pressure and pulse rate should be taken after the respective supine measurements, approximately 2 and 5 minutes after patient achieves a standing position.

6.4.8.2. Height, body weight, and body temperature

Height will be measured in centimeters, and body weight will be measured in kilograms. Measurements should be taken without shoes and, when possible, the same scale should be used for all measurements. Body mass index (BMI) will be calculated from the height and body weight. Temperature will be recorded using an oral or tympanic (or other acceptable route) thermometer.

Body weight will be collected on the laboratory requisition for creatinine clearance calculations. Any body weight data entered into the eCRF will be used for the overall data analysis.

6.4.9. Other safety assessments

6.4.9.1. Eye and skin examinations

The principal investigator will make all final determinations of AEs in consultation with the dermatologist or optometrist/ophthalmologist. Any clinically significant findings that result in a diagnosis should be recorded to the Sponsor or its designee as a pre-existing condition or AE via eCRF.

Eye examination

A comprehensive eye examination, to include corrected visual acuity, intraocular pressure, a slit lamp examination, and a dilated fundus examination, will be performed at the times shown in the Study Plan (Table 2). Note, patients with acute angle closure glaucoma or other contraindications to dilation should have a fundoscopic exam without dilation. The eye examinations must be supervised and reviewed and/or performed by an ophthalmologist or optometrist where permitted by local law.

Skin examination

A complete skin examination will be performed at the times shown in the Study Plan (Table 2). Only the initial examination will include Fitzpatrick scale rating.

All skin examinations must be supervised and reviewed and/or performed by a dermatologist.

The skin examinations will preferably be completed for a given patient by the same dermatologist who will inspect the patient's unclothed full body using a UV lamp.

At each examination, abnormal hypopigmentation will be assessed by location, percentage of body surface area involvement, degree (partial/decreased pigmentation to complete depigmentation), and other findings in or around the hypopigmentation area (eg, redness or induration). A static physician's global assessment (sPGA) will be used to determine the

patient's overall hypopigmentation severity at a given time point using a visual analog scale (VAS) ranging from 0 to 100. In addition, patients noted to have evidence of hypopigmentation will be asked to record how bothersome they find the hypopigmentation to be on a VAS ranging from 0 to 100. Skin photographs may be taken as appropriate for generating supporting documentation, but not for the purpose of primary clinical dermatologic evaluation or for data generation or analysis. A punch biopsy may be obtained at the discretion of the dermatologist.

Data management and evaluation

Data from both the eye and skin examinations will be captured in case report forms which will be entered into the WBDC system at the primary study site in order to enable ongoing cumulative review and signal detection.

The ophthalmologist/optometrist or dermatologist will not make any determinations regarding whether the findings observed represent AEs or are causally related to the study medication and will not make decisions regarding whether the patient should discontinue study treatment. Instead, all information gathered by the ophthalmologist/optometrist or dermatologist should be reviewed by the site investigator, who will decide if an AE is present and who should take action, as appropriate.

See Section 6.4.3 for information regarding the recording of AEs based on examinations.

6.4.9.2. C-SSRS

The C-SSRS will be performed to determine of the presence of suicidality. The assessment schedule is indicated in the Study Plan (see Table 2).

The C-SSRS is a unique, simple and short method of assessing both behavior and ideation that tracks all suicidal events and provides a summary of suicidality. It assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation and deterrents), all of which are significantly predictive of completed suicide.

If, during the performance of the C-SSRS assessment, the patient makes a statement indicating acute risk of suicide, the rater will immediately alert the site physician, and will stay with the patient until the site physician is physically present. The site physician will then make a complete risk assessment and refer to or initiate treatment as required.

6.4.9.3. Magnetic resonance imaging

MRI will be used to screen and monitor patients for ARIA. All patients will be required to, and thus must be able to, have an MRI scan during screening and for subsequent safety monitoring at Week 52 and Week 104 as shown in the Study Plan (Table 2).

MRI screening scans should be performed during the screening period as outlined in Section 3.2.1. The central radiologist review of the screening MRI scan must be available before randomization to evaluate the inclusion/exclusion criteria. The scans will be reviewed by the investigator or qualified designee for immediate patient management.

MRI scanning will be conducted under the management of a central imaging vendor. The MRI scans will be acquired at imaging sites using a standardized protocol.

The imaging vendor will assist with the identification and qualification of the imaging centers, create a detailed procedure manual to be used by the study sites to ensure proper image acquisition and image transfer from the study sites to the imaging vendor, and provide training for imaging center staff.

The MRI scans will be transmitted to the imaging vendor for amyloid-related imaging abnormalities (ARIA) evaluation and for automated derivation of volumetric brain biomarker data (See Section 6.6.2.2).

All scans will be subject to quality control checks by specially trained technicians/technologists. Sites that encounter repeated problems with image quality or protocol adherence will be contacted directly by the imaging vendor to discuss the problem and potential solutions.

The scans will be evaluated by 1 independent neuroradiologist. MRI findings believed to have potential clinical significance (eg, ARIA or other, incidental findings) will be reported to the investigator and to the sponsor. See Section 6.4.3 for information regarding the recording of AEs based on tests and examinations.

6.4.10. Safety areas of specific interest

Specific safety topics of interest for this study include, but are not limited to, the following:

- Adverse eye effects (see Section 6.4.9.1)
- Adverse skin effects including rash and hypopigmentation (see Sections 6.4.3 and 6.4.9.1)
- Peripheral nervous system, central nervous system and muscle effects (see Section 6.4.6)
- Liver toxicity (see Section 6.4.5.1)
- Cardiovascular (CV) -type events (including, but not limited to, orthostatic hypotension and QT prolongation; see Sections 6.4.7 and 6.4.8.1)

Alzheimer's disease occurs mainly in elderly people, who may have established CV disease or CV risk factors and constitute a population of patients at increased risk of CV events. Serious CV events, as well as particular arrhythmic events related to QTcF prolongation, are therefore of potential special interest. SAEs that, according to the Investigator, may be CV events of the major adverse CV event (MACE) type (myocardial infarction, stroke, or CV death) or may be potential QT prolongation-related arrhythmic events, eg, syncope, ventricular tachycardia/torsades des pointes/fibrillation or cardiac arrest, will be carefully documented and sent for adjudication. The events will be blindly evaluated by external independent adjudication consultants and adjudicated as MACE events or ventricular arrhythmias/cardiac arrest related to QT prolongation or to other mechanisms.

The topics listed above, as well as other topics which may be subsequently determined by the sponsor, will be subject to enhanced surveillance activities. Additionally, the topics above will

be analyzed for presentation in the Clinical Study Report in accordance with the Statistical Analysis Plan.

6.5. Pharmacokinetics

6.5.1. Collection of samples

Blood samples (3 mL) for determination of plasma AZD3293 and metabolite AZ13569724 concentrations will be collected as follows: 2 samples will be collected just after arrival at, and just prior to departure from, the clinic at Week 4 (Visit 4), Week 45 (Visit 11), and Week 91 (Visit 18); 1 sample will be collected at Week 19 (Visit 7), Week 39 (Visit 10), and Week 65 (Visit 14) or final study visit.

Patients (or their study partners) will receive a telephone call prior to each visit at which AZD3293 PK sampling will be performed, instructing them as to when the patient should take study medication prior to the clinic visit.

CSF samples (up to 18 mL unless prohibited by local regulations) for determination of AZD3293 and AZ13569724 concentrations will be obtained from CSF sub-study participants at Week 52 (Visit 12) and at Week 97 (Visit 19) or final study visit.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

For blood volumes, see Section 7.

Every effort should be made to collect the PK samples as described in the Study Plan (Table 2). Failure to do so would not be considered a protocol violation. The accurate date and time of each sample collection must be recorded as detailed in the Laboratory Manual.

6.5.2. Determination of drug concentration

Plasma and CSF samples for determination of AZD3293 and AZ13569724 concentrations will be analyzed on behalf of the sponsor by Covance or its designate, using appropriate bioanalytical methods. Full details of the analytical methods used will be described in a separate bioanalytical report. Samples from patients who received placebo may not be assayed for AZD3293 and AZ13569724 concentrations.

Additional analyses may be conducted on the biological samples to further investigate the presence and/or identity of drug metabolites or to investigate any potential dosing issues. Any results from such analyses may be reported separately from the Clinical Study Report.

6.6. Pharmacodynamics

Pharmacodynamic outcome variables in this study include changes from baseline to the end of treatment in CSF biomarkers (concentrations of $A\beta_{1-40}$, $A\beta_{1-42}$, total tau, phosphorylated tau concentrations, and other, exploratory biomarkers [eg, sAPPβ]), imaging biomarkers (amyloid PET and volumetric MRI), and plasma biomarkers relevant to AD.

6.6.1. Cerebrospinal fluid biomarkers

Participants in the CSF longitudinal biomarker sub-study will have post-baseline CSF samples collected at Week 52 and Week 97 (or at discontinuation of study treatment if it has been at least 24 weeks since previous collection) for analysis of concentrations of $A\beta_{1-40}$, $A\beta_{1-42}$, total tau, phosphorylated tau, and exploratory biomarkers (eg, sAPPβ, sAPPα, 5-x amyloid) (see Study Plan in Table 2). If a post-baseline CSF sample cannot be obtained because of procedural complications, patient issues, or patient request, it will not be considered a protocol violation.

Lumbar punctures should be scheduled at approximately the same time of the day at all visits to avoid the known circadian variation of CSF amyloid levels (Lucey and Bateman 2014). It is recommended that CSF samples be collected by insertion of an atraumatic spinal needle between vertebrae L3 and L5 (Vanderstichele et al 2012). Before performing the lumbar puncture procedure, the physician must take into account the overall assessment of the patient and bleeding risk.

CSF $A\beta_{1-40}$ and $A\beta_{1-42}$ are biomarkers for BACE inhibition that enable direct measure of the central PD of AZD3293.

CSF tau and phosphorylated tau concentrations are elevated in patients with AD. Elevations in concentrations of tau, as well as specific phosphorylated tau species, are thought to be markers for progressive neurodegeneration in AD. Accordingly, reductions from baseline in concentrations of CSF tau in patients who receive AZD3293 compared with patients who receive placebo may be indicative of reduced neuronal loss in AZD3293-treated patients.

Other CSF metabolites and/or protein species, including processed forms of APP such as sAPPβ, inflammatory biomarkers, other recognized or as-yet unrecognized biomarkers, and, if appropriate, proteomics assessments may be examined. Biochemical signatures may help to explain differences in efficacy, safety, or tolerability and/or PK/PD related to AZD3293 treatment.

Detailed sample collection and handling procedures are provided in the Laboratory Manual.

CSF aliquots from patients in the CSF sub-study will be retained for future analysis for up to 15 years from the date of the last patient's last visit. CSF samples from patients who undergo CSF sampling at screening but fail other aspects of the screening process before CSF analysis will also be retained for future analysis, if the patient has provided appropriate consent. In countries prohibiting sample storage, it will not be considered a protocol violation if CSF is not collected for storage and future analysis.

For CSF sample volumes, see Section 6.5.1.

6.6.2. Imaging biomarkers

6.6.2.1. Positron emission tomography

Florbetapir F 18 amyloid PET will be used to evaluate changes in amyloid binding from screening to end of treatment. A decrease in the rate of accumulation of brain amyloid load as measured by florbetapir F 18 PET in AD patients taking AZD3293 may be an indicator of the

ability of AZD3293 to affect the underlying pathology. In addition, the regional distribution of cerebral amyloid may be related to differences in efficacy/safety/tolerability and/or PK/PD with AZD3293 treatment.

Florbetapir F 18 amyloid PET scanning will be conducted under the management of a central PET vendor. The PET imaging data will be acquired after injection of the ^{18}F amyloid ligand florbetapir F 18 injection.

The PET imaging vendor will provide visual interpretation and quantitative analysis of all florbetapir F 18 PET imaging data acquired at the imaging centers for both eligibility and monitoring disease progression (amyloid PET substudy).

The details of florbetapir F 18 image acquisition methodology, analysis, quality control, and reader training will be documented in the technical operations manual and the image review charter.

Qualitative amyloid PET results for patient eligibility will indicate "positive" or "negative." Amyloid PET images from those patients who do not meet screening amyloid burden criteria for enrollment will be retained for future research, if the patient has provided appropriate consent.

The primary quantitative florbetapir F 18 PET outcome variables will be regional estimates of amyloid binding (distribution volume ratio [DVR], standard uptake value ratio [SUVR]). The average of the binding estimates from areas typically involved in AD, ie, the frontal, lateral temporal, posterior cingulate and medial parietal (precuneal) cortices, will be calculated to estimate the global amyloid load.

The PET imaging vendor will provide quantitative florbetapir F 18 PET data for integration with the CCI clinical database and, as requested, will provide the PET images to the sponsor. The details of data and images to be transferred are specified in the respective data transfer agreements.

6.6.2.2. Magnetic resonance imaging

MRI scans will be obtained as described in Section 6.4.9.3 under the management of the central imaging vendor and transferred to the vendor for volumetric analysis. The images will be used to assess cerebral atrophy (hippocampal, temporal, ventricular, entorhinal cortex and whole brain volume changes) from baseline to end of treatment.

Atrophy represents a marker of neurodegeneration that is estimated to diverge from normal about 5.5 years and 4 years prior to AD diagnosis in the hippocampus and the whole brain, respectively. Rates of change in structural measures correlate closely with the gradual cognitive decline in AD and can be visualized by MRI. Atrophy rates would generally be expected to be lower if the underlying disease is attenuated by effective treatment. Thus, demonstrating an effect of AZD3293 on cerebral atrophy may support a disease-modifying effect of AZD3293.

The following volumetric measures will be derived from the MRI scans using automated methods: hippocampus volume, hippocampus atrophy, whole brain volume, whole brain

atrophy, ventricular volume, ventricular enlargement, entorhinal cortex volume, entorhinal cortex atrophy, temporal lobe volumes, and temporal lobe atrophy.

6.6.3. Plasma biomarkers

Blood samples for exploratory analysis of plasma biomarkers relevant to AD ($A\beta_{1-40}$, $A\beta_{1-42}$, inflammatory markers, and other markers of interest) will be collected from all patients at baseline (Visit 2), Week 52, and Week 97 (or final study visit) (see Study Plan in Table 2).

These samples will support characterization of the PD effects of AZD3293 on plasma biomarkers, which have not previously been studied in this patient population. The samples will also enable exploratory evaluation of as-yet-unrecognized plasma biomarkers relevant to the diagnosis and prognosis of AD.

The vendor and methodology to analyze the plasma samples will be chosen prior to database lock, given the rapid technological development in this field.

Detailed sample collection and handling procedures are provided in the Laboratory Manual.

Plasma aliquots for future analysis will be retained for up to 15 years from the date of the last patient's last visit or for a shorter period if local regulations and/or ethical review boards (ERBs) /IRBs impose shorter time limits, at a facility selected by the Sponsor or its designee.

For blood sample volumes, see Section 7.1.

6.7. Pharmacogenetics

A blood sample will be obtained at screening for mandatory APOE genotyping.

An optional sample will be collected and stored for future exploratory genetic research from patients who have given specific consent.

Samples will be collected, labeled, stored and shipped as detailed in the Laboratory Manual. The samples for future exploratory genetic research from consenting patients may be retained for up to 15 years or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits, at a facility selected by the Sponsor or its designee. If a patient does not consent to the optional genetic research, the blood sample will be discarded after the mandatory APOE genotyping is performed.

For blood sample volumes, see Section 7.1.

6.8. Pharmacogenomics

Blood samples for future pharmacogenomics research will be collected at baseline (Visit 2), Week 52, and Week 97 (or final study visit) (see Study Plan in Table 2) from patients who have given consent for this optional sampling.

Samples will be collected, labeled, stored and shipped as detailed in the Laboratory Manual. The samples may be retained for up to 15 years from the date of the last patient's last visit or for a

shorter period if local regulations and/or ERBs/IRBs impose shorter time limits, at a facility selected by the Sponsor or its designee.

For blood sample volumes, see Section 7.1.

6.9. Health economics

Health economics variables included in this study to address an exploratory objective are the changes from baseline (Visit 2) to Week 104 in the RUD-Lite and EQ-5D-5L scores. The results of analyses of these variables may not be included in the Clinical Study Report, but may be described in supplementary reports as appropriate.

6.9.1. RUD-Lite

The RUD Lite is a short version of Resource Utilization in Dementia (RUD; Wimo and Winblad 2003) interview to assess formal resource utilization of patients with dementia as well as informal resource use (ie, time caregivers spend assisting the patient) during a specific time period. These data make it possible to estimate costs of dementia care from a societal perspective. The administration of the RUD Lite interview takes approximately 10 minutes and captures the following dimensions with regard to the patient: long-term living accommodation, temporary changes in living situation (eg, respite care), and healthcare utilization to include hospital care, emergency room care, practitioner visits, and other resource use (eg, home healthcare, day care, care-related transportation). In addition, the interview assesses time spent by the study partner providing care for the patient in the form of basic activities of daily living (eg, eating, grooming, dressing), instrumental activities of daily living (eg, shopping, food preparation, managing financial matters), and safety surveillance, as well as any time missed from work for caregiving responsibilities if the study partner is still working.

A baseline version of the RUD-Lite questionnaire, given at the initial assessment, inquires about all dimensions of resource utilization over the previous 30 days. The follow-up version of the questionnaire, administered at all subsequent assessments, assesses patient resource use since the last visit and caregiver time over the previous 30 days.

6.9.2. EQ-5D-5L

The EQ-5D-5L (patient) provides a single index value for health status and is relevant to a wide range of health conditions and treatments. It is administered to the patient in only a few minutes and consists of 2 pages: the EQ-5D-5L descriptive system and the EQ Visual Analogue scale (EQ VAS). The descriptive system covers 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each rated on 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.

The EQ VAS records the patient's estimation of his/her health on a visual analogue scale with endpoints labeled "the best health you can imagine" and "the worst health you can imagine." This information can be used as a quantitative measure of patient health. The EQ-5D-5L asks the patient to mark an "X" on the scale to indicate his/her current health status.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1. Volume of blood

The approximate volume of blood that will be drawn from each patient in this study is shown in Table 6.

Table 6. Volume of Blood to be Drawn From Each Patient

Assessment		Panel volume (mL)	No. of time points	Total volume (mL)
Safety	Clinical chemistry/Electrolytes	2.5	12	30
	Hematology	2	12	24
	Coagulation	1.8	1	1.8
	Endocrinology	3.5*	3	8.5
	Screening tests	8.5	1	8.5
	Optional/Confirmatory Testing	11	1	11
Pharmacokinetics				
	AZD3293 and AZ13569724	3	9**	27
Plasma biomarkers		12	3	36
Pharmacogenetics				
Mandatory APOE genetic sampling		2	1	2
Optional genetic sampling		6	1	6
Pharmacogenomics		5	3	15
Total				**169.8**

Note: Total volume does not include unscheduled Hepatic testing, early discontinuation, or unscheduled/follow-up visit

*3.5 mL collected at screening (Visit 1) and 2.5 mL collected at the other 2 visits (Visit 12 and Visit 20).

**Visits 4, 11, and 18 collects 2 time points. See Section 6.5.1.

7.2. Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use as described here.

The results from future analyses will not be reported in the Clinical Study Report but separately in a scientific report and/or scientific publication.

7.2.1. Pharmacokinetic and/or pharmacodynamic samples

Blood and CSF samples collected for PK analysis will be disposed of after the Bioanalytical Report is finalized or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless retained for future analyses.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test PK samples. The results from the evaluation will not be reported in the Clinical Study Report but separately in a Bioanalytical Report.

Selected PK samples may be used for additional metabolite identification and/or quantification or to investigate any potential dosing issues.

Key blood and CSF samples collected for biomarker analysis may be retained for future investigations. These samples will be retained for a maximum of 15 years following last patient's last visit or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits, at a facility selected by the Sponsor or its designee. The results from investigations involving retained samples will be provided in separate reports and not in the Clinical Study Report.

7.2.2. Pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years from the date of the last patient's last visit or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples, irrespective of the type of coding used, the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the at the designated contract laboratory. No personal details identifying the individual will be available to any person

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrollment/randomization code and the DNA number will be maintained and stored in a secure environment, with restricted access. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analyzed.

7.3. Labeling and shipment of biohazard samples

The Principal Investigator ensures that samples are labeled and shipped in accordance with the Laboratory Manual for this study and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria).

Any samples identified as Infectious Category A materials are not shipped, and no further samples will be taken from the patient unless agreed with sponsor and appropriate labeling, shipment and containment provisions are approved.

7.4. Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each center keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

The sponsor keeps oversight of the entire lifecycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the system during the entire lifecycle.

7.5. Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples for genetic or biomarker research, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, the sponsor is not obliged to destroy the results of this research.

As collection of the biological samples for genetic or biomarker research is an optional part of the study, then the patient may continue in the main study.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to the sponsor
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and the sponsor are informed about the sample disposal.

The sponsor ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1. Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonization/Good Clinical Practice, applicable regulatory requirements and the sponsor policy on Bioethics and Human Biological Samples.

8.2. Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

The sponsor will not provide individual genotype results to the patient or study partner, any insurance company, any employer, the patient's family members or general physician, or any other third party, unless required to do so by law**.**

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, a sponsor Physician or an investigator might know a patient's identity and also have access to his or her genetic data. Also, Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

8.3. Ethics and regulatory review

As used in this protocol, the term "informed consent" includes all consent and assent given by patients or their legal representatives and by caregivers/partners.

An IRB or EC should approve the final study protocol, including the final versions of the Informed Consent Forms and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable IRB/EC, and to the study site staff.

The opinion of the IRB/EC should be given in writing. The investigator should submit the written approval to the sponsor before enrollment of any patient into the study.

The IRB/EC should approve all advertising used to recruit patients for the study.

The sponsor should approve any modifications to the Informed Consent Forms that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB/EC annually.

Before enrollment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

The sponsor will handle the distribution of any of these documents to the national regulatory authorities.

The sponsor will provide Regulatory Authorities, IRBs and ECs and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

Each Principal Investigator is responsible for providing the IRB/EC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. The sponsor will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

8.4. Informed consent

The Principal Investigator(s) at each center will:

- Ensure each patient and his or her study partner are given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure that each patient and study partner is informed of the optional pharmacogenetic/pharmacogenomic sampling and will ask the patient to consider providing consent for the sampling
- Ensure each patient and study partner are notified that the patient is free to discontinue from the study at any time
- Ensure that each patient and his or her study partner are given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient and study partner (and, where appropriate, legally authorized representative) provide signed and dated informed consent before any study-specific procedure is conducted
- Ensure the original, signed and dated Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the relevant signed and dated Informed Consent Form is given to the patient and study partner
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the Informed Consent Form that is approved by an IRB/EC.

8.5. Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International Co-ordinating Investigator, the Principal Investigator at each site, and the sponsor.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and, where required, in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant IRB/EC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

The sponsor (or its representative) will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to IRBs and ECs, see Section 8.3.

If a protocol amendment requires a change to a center's Informed Consent Form, the sponsor (or its representative) and the center's IRB/EC are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each IRB/EC.

8.6. Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, or an IRB/EC may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. The investigator will contact the sponsor immediately if contacted by a regulatory agency about an inspection at the center.

9. STUDY MANAGEMENT

Study management activities will be performed by CCI on behalf of the sponsor.

This study will be conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations

9.1. Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of the sponsor to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of the sponsor or its representatives. This will be documented in a CSA between the sponsor and the investigator.
- Discuss where the identification of the data will be recorded, eg, medical record(s), eCRF, or other associated documents. This will be documented in the CSA.
- Discuss the specific requirements of all genetic research performed in this study with the investigator(s) (and other personnel involved with the study)
- Confirm that appropriate raters are certified for all required study assessments

9.2. Training of study site personnel

The Principal Investigator will ensure that appropriate training relevant to the study is given to all investigational staff, and that any new information relevant to the performance of this study is forwarded to the staff involved. The Principal Investigator will also maintain a record of all individuals involved in the study (medical, nursing and other staff).

Training and information on all study-related processes will take place at the investigator meetings, at local initiation and monitoring meetings, and using web-based methods for remote training. The sponsor or delegates will supply more detailed instructions to center personnel as necessary before and during the study.

Before the site's first patient visit, the investigational staff will be trained to use the WBDC system by sponsor personnel or delegates.

In addition, before the first patient is entered into the study the investigational staff will have an opportunity to discuss the procedures associated with the collection of blood samples, extraction of DNA, and optional and mandatory genetic research with sponsor personnel or delegates. The ethical considerations specific to genotyping and the importance of the informed consent process for participation in the optional genetic exploratory research will be made clear. The requirements for the collections of the patients' samples will also be made clear.

Investigators and other staff who will be responsible for administering cognition and other rating scales (eg, CDR) must be certified and have an appropriate educational background and/or experience. Rater training and certification will be provided by a specialized vendor.

Training for staff at the MRI and PET imaging centers will be provided by the respective central imaging vendors.

Investigators should be instructed on the importance of retaining patients in the study, even if study treatment is discontinued (see Section 5.8), and minimizing the amount of missing data.

9.3. Monitoring of the study

During the study, a CCI monitor, on behalf of the sponsor, will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual, and that study medication accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient and/or study partner.

The sponsor representative will be available between visits if the investigator(s) or other staff at the center need information and advice about the study conduct.

9.3.1. Source data

Refer to the Source Document Agreement for the location of source data.

9.4. Study agreements

The Principal Investigator at each center should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between the sponsor and the Principal Investigator should be in place before any study-related procedures can take place, or subjects are enrolled.

9.4.1. Archiving of study documents

The Investigator must follow the principles of ICH-GCP and applicable regulatory requirements regarding the archiving of study documents.

9.5. Study timetable and end of study

The end of the study is defined as "the last visit of the last patient undergoing the study." This definition applies to the entire study and is not region specific.

The study is expected to start in Q4 of 2014 and to end by Q3 of 2019.

The study may be terminated at individual centers if the study procedures are not being performed according to Good Clinical Practice, or if recruitment is slow. The sponsor may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD3293.

The Principal Investigators will be notified by the sponsor when patient recruitment is complete.

10. DATA MANAGEMENT

10.1. General principles

Data management will be performed by CCI . Data will be entered in the WBDC system at the investigational site. The WBDC system will be authorized and approved by the sponsor or its delegate and will be set up and maintained by CCI .

The data management plan will describe in detail the methods used to collect, check, validate and process clinical data. It will also clarify the roles and responsibilities for the different functions and personnel involved in the data management process. Furthermore, the data management plan will describe the data flow and timelines within the study.

Data captured electronically will be immediately saved to the applicable database. The data collected through third party sources will be obtained and reconciled against study data. Data queries will be raised for inconsistent, impossible or missing data. All entries and changes to the study database will be available in an audit trail.

Data associated with biological samples (blood and CSF) will be transferred to laboratories internal or external to the sponsor. For information on genetic data management see Section 10.2.

MRI and PET imaging data will be managed by the respective central imaging vendors. The imaging datasets will be transferred to CCI .

Adverse events and medical/surgical history will be classified according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the latest World Health Organization (WHO) Drug Dictionary. All coding will be performed by CCI .

The data will be validated as defined in the data management plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, and signed, the final database will be locked.

10.2. Genetic data

Any genotype data generated in this study will be stored in an appropriate secure system within the sponsor and/or third party contracted to work with the sponsor to analyze samples. The results from this genetic research may be reported in the clinical study report for the main study, or in a separate report as appropriate.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

11. EVALUATION AND CALCULATION OF VARIABLES

11.1. Calculation or derivation of efficacy variable(s)

11.1.1. ADAS-Cog$_{13}$

A summary score will be computed across all dimensions of the 13-item ADAS-Cog scale.

Changes from baseline ADAS-Cog$_{13}$ score at each post-baseline time point will be calculated as the post-baseline score minus the baseline score.

11.1.2. Clinical Dementia Rating – Sum of Boxes

The CDR-SB score will be calculated as the sum of the individual CDR domain scores. The global score summarizing the 6 domains of cognition and function will be calculated using the Washington University CDR-assignment algorithm (Morris 1993).

Changes from screening CDR-SB and global scores at each post-baseline time point will be calculated as the post-baseline score minus the baseline score.

Time in the current disease state will be assessed in terms of time to loss of 1 global stage on CDR global score through Week 104.

11.1.3. Functional Activities Questionnaire

The FAQ total score will be calculated as the sum of the 10 individual FAQ item scores.

Changes from baseline FAQ total score at each post-baseline time point will be calculated as the post-baseline score minus the baseline score.

11.1.4. The Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory

The ADCS-ADL instrumental items score will be calculated as the sum of the 17 individual instrumental item scores (maximum total score of 56).

Additionally, for exploratory analysis, the ADCS-ADL basic items score will be calculated as the sum of the individual 6 basic item scores (maximum total score of 22), and the ADCS-ADL total score will be calculated as the sum of all 23 instrumental and basic item scores (maximum total score of 78).

Changes from baseline in the ADCS-ADL instrumental items score, basic items score, and total score at each post-baseline time point will be calculated as the post-baseline score minus the baseline score.

11.1.5. Neuropsychiatric Inventory

The NPI total score will be calculated as the sum of the individual NPI item (frequency x severity) scores (maximum total score of 144).

The total NPI-D score will be calculated as the sum of the individual distress scores for each neuropsychiatric symptom (maximum score of 60).

Changes from baseline NPI total score and the total NPI-D score at each post-baseline time point will be calculated as the post-baseline score minus the baseline score.

11.1.6. Mini-mental State Examination

A total score will be computed across all dimensions of the MMSE and used as an outcome variable in the statistical analysis.

Changes from screening MMSE total score at each post-baseline time point will be calculated as the post-baseline score minus the screening score.

11.1.7. iADRS cognitive/functional composite measure

For additional details regarding the iADRS scale see Section 6.3.2.4.

Changes from baseline iADRS total score at each post-baseline time point will be calculated as the post-baseline score minus the baseline score.

11.1.8. Letter and Category Fluency and Digit Symbol-Coding tests

For the Letter Fluency test, a total words score will be calculated by adding the total correct score from the 3 trials to the total errors score. Changes from baseline total correct score at each post-baseline time point will be calculated as the post-baseline score minus the baseline score. Changes from baseline total words score will be calculated as the post-baseline score minus the baseline score.

For each administration of the Category Fluency test, a total words score will be calculated by adding the total correct score to the total errors score. Changes from baseline total correct score at each post-baseline time point will be calculated as the post-baseline score minus the baseline score. Changes from baseline total words score will be calculated as the post-baseline score minus the baseline score.

Changes from baseline Digit Symbol-Coding test score at each post-baseline time point will be calculated as the post-baseline score minus the baseline score.

11.1.9. Repeatable Battery for the Assessment of Neuropsychological Status

There are 12 subtests within the RBANS. Pre- to post-treatment changes for each subtest score will be calculated as the final visit (Week 97) score minus the pre-treatment score obtained at screening (Visit 1). Similarly, pre- to post-treatment changes in the 5 domain-specific Index scores (Immediate Memory, Visuospatial/Constructional, Language, Attention, and Delayed Memory) and RBANS total score will also be calculated. Savings scores represent the amount of information that has been retained after a delay in time from the initial learning of information on a memory test. The classic savings score will be calculated as a percent retention score for List Learning, Story Memory, and Figure Recall.

11.2. Calculation or derivation of safety variable(s)

The onset of an AE relative to treatment will be calculated as the difference between the onset date of the AE and the date of the first dose of study treatment.

The duration of a resolved AE will be calculated as the difference between the resolution date of the AE and the onset date of the AE. If an AE is unresolved at the time of the last contact with the patient, the resolution date will be entered in the database as missing and duration of the AE will not be calculated.

11.2.1. Other significant adverse events (OAE)

During the evaluation of the AE data, a sponsor medically qualified expert will review the list of AEs that were not reported as SAEs and discontinuation AEs. Based on the expert's judgment, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory, vital sign, and ECG data will be performed for identification of OAEs.

Examples of these are marked hematological and other laboratory abnormalities and certain events that lead to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

11.2.2. Laboratory tests (hematology, chemistry and urinalysis)

Changes in laboratory test results at each post-baseline time point will be calculated as the post-baseline value minus the baseline value (Visit 2). Individual patient data will be assessed for PCS values according to predetermined criteria as described in the statistical analysis plan.

11.2.3. Vital signs

Changes in supine blood pressure and pulse rate at each post-baseline time point will be calculated as the post-baseline measurement minus the baseline measurement (Visit 2). Orthostatic changes in blood pressure and pulse rate will be calculated as the difference in vital signs after 2 and 5 minutes of standing from a supine position (ie, as the t+2 minute or t+5 minute standing measurement minus the supine measurement at time t).

Individual patient data will be assessed for PCS values according to predetermined criteria as described in the statistical analysis plan.

11.2.4. ECG results

Changes in ECG parameters at each post-baseline time point will be calculated as the post-baseline value minus the baseline value (Visit 2). Individual patient data will be assessed for PCS values according to predetermined criteria as described in the statistical analysis plan.

For digital ECG data, smoothing of the RR and QT intervals will be performed first, before the derivation of the heart rate and the correction of the QT interval for heart rate (QTc interval). The data will be smoothed on an individual basis before descriptive and/or statistical analyses are

performed. These derived parameters will be calculated by the study statistician or designee. For each patient, and for each target time point the mean QT and RR intervals will be calculated based on sampling for that time point. The QT correction will be calculated according to the Fridericia method as $QTcF = QT \times RR(sec)^{-1/3}$. The ventricular heart rate will be calculated based on the smoothed RR interval as 60.000/RR(msec).

11.2.5. Body weight and body mass index

Body mass index (BMI) will be calculated as body weight (kg) /[height (meters)]^2.

Changes in body weight and BMI at each post-baseline time point will be calculated as the post-baseline value minus the baseline value (Visit 2).

11.2.6. Magnetic resonance imaging

Individual patient data will be assessed for treatment-emergent ARIA.

11.3. Calculation or derivation of pharmacokinetic variables

A population PK analysis of plasma AZD3293 and AZ13569724 concentration data will be performed. The population PK analysis will involve standard PK structural modelling techniques using nonlinear mixed effects modelling to obtain population mean and variance values of specific PK parameters for AZD3293 and AZ13569724. Potential covariate effects will be investigated as predictors of variability in AZD3293 and AZ13569724 PK. Plasma AZD3293 and AZ13569724 concentration-time data from previous AZD3293 clinical pharmacology studies may be combined with data from this study. The results of the population PK analysis will be provided in a separate report.

11.4. Calculation or derivation of pharmacodynamic variable(s)

11.4.1. Cerebrospinal fluid biomarkers

Changes from screening in CSF biomarker concentrations of $A\beta_{1-40}$, $A\beta_{1-42}$, total tau, phosphorylated tau and other, exploratory biomarkers (eg, sAPPβ) will be calculated for each post-baseline time point.

Changes in biomarker concentration will be calculated as the post-baseline value minus the predose value.

11.4.2. Imaging biomarkers

Volumetric MRI and PET imaging variables will be derived by the respective central imaging vendors and provided in agreed database format.

Changes from screening/baseline will be calculated as the post-baseline value minus the predose value.

11.4.3. Relationship between pharmacokinetic and pharmacodynamic variables

Plasma and CSF AZD3293 concentrations in relation to PD (biomarkers and cognitive markers) and other measures as appropriate will be examined graphically using plots showing predicted exposure to AZD3293 (AUC) and PD measures/markers.

11.4.4. Population analysis of pharmacokinetic/pharmacodynamic variables

A population PK/PD analysis implementing appropriate structural models will be conducted following completion of the study to examine the relationships between AZD3293 and/or AZ13569724 and selected measures of efficacy (eg, the primary efficacy endpoint) or tolerability (eg, AE incidence) using nonlinear mixed effects modelling. The results of the population PK/PD analysis will be provided in a separate report.

11.5. Calculation or derivation of pharmacogenetic variables

Pharmacogenetic outcomes for mRNA and miRNA in selected species will be calculated as change from baseline quantified with reverse transcription polymerase chain reaction (RT-PCR) or equivalent technology. Genetic variation in baseline DNA will be measured by direct resequencing of selected genes, including intronic and promoter regions. Techniques may be modified as scientific advances are made.

11.6. Calculation or derivation of health economic variables

Changes in RUD-Lite and EQ-5D-5L scores at each post-baseline timepoint will be calculated as the post-baseline value minus the baseline value (Visit 2).

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1. Description of analysis sets

12.1.1. Efficacy

The Full Analysis Set will group patients according to randomized treatment assignment, even if the patient does not take the assigned treatment, does not receive the correct treatment, switches to a different treatment group if the assigned treatment group is dropped at an interim analysis, or otherwise does not follow the protocol. When change from baseline is assessed, patients will be included in the analysis only if both a baseline and at least 1 valid post-baseline measure are available.

For the longitudinal CSF biomarker and PET (amyloid) sub-studies, the analysis sets will include all those patients whose eligibility was determined by the respective biomarker, who signed consent for the respective sub-studies, and who have a baseline and at least 1 valid post-baseline CSF assessment or PET scan.

12.1.2. Safety

All patients who received at least 1 dose of randomized study treatment (AZD3293 or placebo) will be included in the safety analysis set. In safety data presentations, erroneously treated patients (eg, those randomized to "Treatment A" but actually given "Treatment B") will be accounted for in their actual treatment groups. If an AZD3293 dose group is dropped following an interim analysis (see Section 12.2.2), patients switched to the remaining AZD3293 dose and remaining on treatment will be accounted for as a separate group.

12.1.3. Pharmacokinetics

The PK analysis set is defined as all patients in the safety population who have at least 1 post-dose PK assessment. The population PK analyses will be performed using this analysis set.

12.2. Methods of statistical analyses

12.2.1. General principles

The aim of the primary analysis is to evaluate whether at least 1 dose of AZD3293 is superior to placebo in slowing disease progression in patients with early AD (ie, the continuum of patients with MCI due to AD and patients diagnosed with mild dementia of the Alzheimer's type), as measured by change from baseline in ADAS-Cog_{13} total score at Week 104.

The aim of the secondary analyses are to evaluate whether AZD3293 is superior to placebo for other outcomes as measured by the secondary endpoints: FAQ score, ADCS-ADL score, CDR-SB score, iADRS, MMSE, time in the current disease state (CDR global score), NPI total score, to evaluate the clinical worsening and need for symptomatic treatments, and biomarkers that may be indicative of disease modification.

A comprehensive Statistical Analysis Plan (SAP; including biomarker analyses), as well as separate population PK and PK/PD analysis plans, will be prepared and finalized before the study data are unblinded. An interim analysis SAP will be prepared and finalized before each interim analysis.

12.2.2. Interim analyses

Four interim analyses may be conducted during this study. The IDMC charter will specify the final details of the interim analyses. Every effort will be made to implement this study in such a way that only IDMC members (see Section 12.4) and a ring-fenced external Independent Statistical Center will have access to unblinded data emerging from the study. Furthermore, every effort will be made to conceal any of the predefined design adaptations during the course of the study to any party involved in the conduct of the study. Maintaining validity and integrity of the study is of paramount importance to ensure its acceptability to the sponsor, the scientific community, and health authorities. The sponsor Executive Committee will be established to review the IDMC recommendations in accordance with the prespecified objectives of the interim analyses. Sponsor staff with direct roles in study conduct will not have access to the results of the interim data analyses.

12.2.2.1. Interim analysis 1

The first interim analysis (IA1) will be performed when approximately 70 patients per group have 13 weeks' worth of data. It is expected that, at IA1, approximately 500 patients will have been randomized globally. The objective of IA1 is to assess the viability of continuing with AZD3293 with regard to safety.

One of the following IDMC recommendations will result from IA1:

- Continue the study unmodified
- Discontinue enrollment in 1 or both AZD3293 treatment groups for reasons of an unacceptable safety profile.
  - If 1 AZD3293 treatment group is discontinued for enrollment at IA1, the randomization ratio for newly enrolled patients will remain 2:1 (active:placebo). Patients in the discontinued AZD3293 treatment group will be switched to the other AZD3293 treatment group; for analysis purposes, these patients will be included in their originally assigned AZD3293 treatment group.
  - Stop the study if enrollment in both AZD3293 treatment groups is discontinued

12.2.2.2. Interim analysis 2

The second interim analysis (IA2) will be performed when approximately 80% of patients have been randomized. IA2 will assess the viability of continuing AZD3293 treatment groups with regard to safety and will re-assess the total sample size based on the Bayesian posterior predictive probabilities of the ADAS-Cog_{13}, ADCS-iADL, and/or FAQ. Further details will be described in the interim analysis SAP and finalized prior to unblinding of efficacy data.

Any necessary sample-size adjustment will be recommended to the sponsor Executive Committee.

One or more of the following IDMC recommendations will result from IA2:

- Continue the study unmodified
- If neither AZD3293 treatment group was discontinued at IA1 and, therefore, both AZD3293 treatment groups remain in the study at IA2:
  - Discontinue enrollment in 1 or both AZD3293 treatment groups for reasons of an unacceptable safety profile. If 1 dose is discontinued for enrollment at IA2, the randomization ratio for newly enrolled patients will remain 2:1 (active:placebo). Patients in the discontinued AZD3293 treatment group will be switched to the other AZD3293 treatment group; for analysis purposes, these patients will be included in their originally assigned AZD3293 treatment group.
  - Stop the study if both AZD3293 treatment groups are discontinued
- If 1 AZD3293 treatment group was discontinued at IA1 and, therefore, 1 AZD3293 treatment group remains in the study at IA2:
  - Discontinue enrollment in the remaining AZD3293 treatment group for reasons of an unacceptable safety profile
  - Stop the study if the remaining AZD3293 treatment group is discontinued
- Increase the sample size

12.2.2.3. Interim analysis 3

A maximum of 2 additional interim analyses may occur following IA2. A futility interim analysis (IA3) may be performed if the study sample size does not increase at IA2 or there is decreased confidence in current clinical trial design based on external data.

12.2.2.4. Interim analysis 4

An additional interim analysis (IA4) may be performed to assess for futility and for early stopping of the study for efficacy. Data cut-off for IA4 would occur approximately 52 weeks after the last patient is randomized; however, it may occur later or earlier than this expected date if external data warrant.

To control for the remote possibility that the study will be stopped for efficacy, a Haybittle-Peto adjustment (Haybittle 1971, Peto et al 1976) will be used if efficacy is tested at IA4. A significance level of α=0.001, will be used for treatment comparisons at the start of the multiplicity graph. The final analysis will use a significance level of α=0.05 for treatment comparisons between the AZD3293 treatment groups and the placebo group at the start of the multiplicity graph (see Section 12.2.3). Further details will be described in the interim analysis SAP.

12.2.3. Multiplicity adjustments

The proposed study design contains several elements that require multiplicity adjustments to strongly control the family-wise error rate (FWER):

- Comparison of 2 AZD3293 treatment groups with the placebo group
- Changing the randomization ratio to 2:1 if a dose is dropped at the first or second interim analysis
- Sample size re-estimation at the second interim analysis

The first element, comparisons of the 2 AZD3293 treatment groups with the placebo group, is addressed by the use of a multiplicity graph. A graphical multiplicity strategy will be used for testing key secondary hypotheses to protect against Type I error of falsely rejecting a null hypothesis. The use of a prespecified analysis plan that employs Bretz' graphical approach will provide strong control of the study-wise Type I error rate for the primary and key secondary hypotheses at level α=0.05 (Bretz et al. 2009, 2011). The specific multiplicity graph will be detailed in the SAP.

In addition, to strongly control the FWER, a confirmatory adaptive design should satisfy the conditional invariance principle (Brannath et al 2007): separate test statistics will be calculated from the 2 patient cohorts (those patients enrolled prior to the second interim analysis [IA2], and those enrolled after IA2) and combined in a prespecified way (using the weighted inverse normal p-value combination method) for the final test decisions. Hence, any design modification that preserves the distributional properties of the separate test statistics under a given null hypothesis of interest will not lead to an inflation of the FWER. The p-value combination test principle combines the 2 p-values using a prespecified combination function and by construction satisfies the invariance principle. Details on the implementation of the measures to strongly control the FWER will be provided in the statistical analysis plan

A separate family of biomarkers will be tested at α=0.05. The family will include the biochemical biomarkers (CSF Aβ1-42, total tau, and phosphorylated tau), as well as imaging biomarkers (amyloid PET and volumetric MRI).

12.2.4. Efficacy

All analyses will be performed in a manner that is consistent with the intent-to-treat (ITT) principle. An ITT analysis is an analysis of data by the groups to which patients are assigned by random allocation, even if a patient does not take the assigned treatment or does not receive the correct treatment, or otherwise does not follow the protocol or is not followed to the end of the study (ie, Week 104). If a treatment group is dropped at an interim analysis, the data from those patients will be analyzed according to the treatment group to which the patients were originally randomized. When change from baseline is assessed, a modified ITT (mITT) approach will be used; patients will be included in the analysis only if both a baseline and a post-baseline measure are available.

12.2.4.1. Primary analysis

The primary efficacy endpoint, change from baseline at Week 104 in ADAS-Cog_{13} total score, will be analyzed using an MMRM model that includes the fixed effects of treatment, visit (categorical covariate), treatment-by-visit interaction, disease status at baseline (MCI due to AD or mild AD), APOE4 status (carrier versus non-carrier), baseline ADAS-Cog_{13} total score (continuous covariate), concomitant AChEI use at baseline (yes/no), age at baseline, country, and baseline ADAS-Cog_{13} total score-by-visit interaction. An unstructured variance-covariance matrix will be used.

For each of the 2 AZD3293 treatment groups, the null hypothesis is that the change from baseline in ADAS-Cog_{13} total score at Week 104 is equal to the change from baseline in ADASCog$_{13}$ total score at Week 104 for the placebo treatment group. The alternative hypothesis is that the change from baseline in ADAS-Cog_{13} total score at Week 104 for an AZD3293 treatment group ($\mu_{AZD3293}$) is not equal to the change from baseline in ADAS-Cog_{13} total score at Week 104 for the placebo treatment group ($\mu_{Placebo}$). These hypotheses can be represented as follows:

$$H_{Null}: \mu_{AZD3293} = \mu_{Placebo}$$

$$H_{Alternative}: \mu_{AZD3293} \neq \mu_{Placebo}$$

The primary analysis will evaluate whether there is a difference between treatment groups in the mean change from baseline in ADAS-Cog_{13} total score at Week 104 and will be based on the treatment difference at Week 104 using least-squares means. This will be accomplished by using appropriate linear contrasts of the parameters in the model described above.

As a sensitivity analysis, a method for missing value imputation based on pattern mixture models will be implemented. It is assumed that after discontinuation from the study, patients receiving the AZD3293 doses will exhibit the same future evolution of the disease as patients on placebo treatment. This method uses sequential regression and multiple imputation methodology to impute missing values for visits after a patient's discontinuation from the study. Based on the available data from placebo-treated patients, the missing values from the placebo and AZD3293 treatment groups will be imputed sequentially using a procedure for monotone missing data patterns until all visits are imputed.

12.2.4.2. Secondary analyses

When a comparison between an AZD3293 dose group and the placebo group is statistically significant on the primary efficacy endpoint, the secondary efficacy endpoints for the AZD3293 dose group will be tested through a graphical approach. The specific graph is detailed in the end-of-study analysis SAP prior to the end-of-study database lock.

Categorical analyses of slowing cognitive and functional decline will be conducted comparing proportions of patients reaching certain levels of decline between AZD3293 treatment groups and the placebo group. The precise definitions of cognitive and functional decline and analysis methods will be detailed in the SAP prior to database lock.

The ADAS-Cog_{13} total score results for change from baseline at Week 104 will be assessed for consistency among subgroups defined by disease status at baseline (MCI due to AD or mild AD), APOE4 status (carrier versus non-carrier), age, race, sex, region, and acetylcholinesterase inhibitor use at baseline (yes or no).

Exploratory analyses of the NPI total score will be conducted; some of these analyses will be limited to the domains that are most prevalent at baseline. Exploratory analyses of the ADCS-ADL basic items score and total score will also be conducted. In an additional exploratory analysis, the proportion of patients with MCI due to AD who progress to mild AD, as assessed by the NIA-AA diagnostic criteria, over 1 year and 2 years, will be examined. The Statistical Analysis Plan will provide further details of these analyses.

Exploratory efficacy variables (see Section 6.3.3) will be analyzed using the MMRM models described above as well as with descriptive statistical analyses. These variables include changes from screening/baseline to Week 104 that include but are not limited to: the Letter Fluency, Category Fluency, and Digit Symbol-Coding test scores, the NPI-D score, as well as the changes over time from screening to Week 97 in the RBANS score.

12.2.5. Biomarkers

Changes from screening to Week 97 in CSF biomarkers (eg, $A\beta_{1-42}$, total tau, and phosphorylated tau) will be analyzed using an MMRM analysis that includes the fixed effects of treatment, visit (categorical covariate), treatment-by-visit interaction, disease status at baseline (MCI due to AD or mild AD), APOE4 status (carrier versus noncarrier), and predose biomarker value (continuous covariate). An unstructured variance-covariance matrix will be used. The primary analysis is based on the treatment difference at Week 97 using least-squares means. The null hypothesis is that the difference in means between the AZD3293 group and placebo equals zero.

The primary analyses of estimates of global cortical load from amyloid PET and volumetric brain measures from MRI will be analyzed using the same methodology as described above for the CSF biomarker data.

In addition, amyloid PET data, including inter-individual patterns of baseline cortical load and intra-individual patterns of regional amyloid deposition, as well as eventual patient-level or regional differences in the longitudinal change of amyloid, will be explored in relation to AZD3293 treatment. Multivariate regression analysis will be performed on the level of global cortical amyloid load, the level of regional measures of amyloid binding and, potentially, on the level of single volume elements (voxels) of amyloid binding (parametric) images. Other imaging (ie, volumetric MRI) and non-imaging (eg, CSF biomarker, cognitive, demographic) data may also be explored as covariates in the analysis model.

12.2.6. Health economics

For the RUD-Lite, the individual item responses and the total study partner time spent in assisting the patient, as well as changes from baseline in these variables, will be summarized by treatment group and time point using descriptive statistics.

For the EQ-5D-5L and EQ VAS responses and changes from baseline will be summarized by treatment group and time point using descriptive statistics.

12.2.7. Pharmacokinetics

Plasma and CSF AZD3293 and AZ13569724 concentrations will be summarized by treatment and time point using descriptive statistics.

The results of the population PK analyses described in Section 11.3 will be summarized in a separate report.

12.2.8. Pharmacokinetics-pharmacodynamics

It is intended that an early lock of the PK data will be conducted to allow PK modeling to begin before the end of the treatment period and to ensure that exposure estimates from this study are available for use in exposure-response models examining the influence of PK on either efficacy or safety endpoints at the completion of the study. It is intended that the PK data will be locked after all patients complete Visit 16 (78 weeks of treatment). No safety or efficacy data will be included in the 78-week PK lock. An Early PK Lock Plan will be developed and implemented prior to this lock, which will specify the safeguards to be taken to ensure the integrity of the study. The results of the population PK/PD analysis described in Section 11.4.4 will be summarized in a separate report.

12.2.9. Pharmacogenomics

The analysis of pharmacogenomics (DNA) outcomes will consist of an analysis of the association of baseline variation with chosen outcome parameters, including efficacy and biomarker outcomes. The analysis of mRNA and miRNA outcomes will consist of descriptive statistics regarding change from baseline, including stratification by endpoints. Pharmacogenomics outcomes will be tested in a prioritized list of genes for which a scientific hypothesis for interaction with the pharmacology of AZD3293 and/or the pathophysiology of AD can be formulated, based on knowledge in the field. The results will be summarized in a separate report. Both univariate statistics and multivariate models may be applied.

12.2.10. Safety

The incidence and severity of treatment-emergent AEs will be summarized by treatment group. The results of clinical laboratory tests; 12-lead ECGs; physical, eye, skin, and neurological examinations; safety MRIs; suicidality evaluations (C-SSRS), body weight and body mass index; and vital sign measurements will be summarized with descriptive statistics, by treatment group, for all time points at which these variables are collected. In addition, visual displays of the time course of AEs will be generated, and analyses that account for time on study will be conducted.

Individual patient data for vital signs, ECG results, and laboratory test results will be assessed for PCS values according to predetermined criteria. Any PCS values identified will be summarized by treatment group.

12.3. Determination of sample size

12.3.1. Efficacy

The sample size for this study, 734 randomized patients in each of 3 treatment groups, was selected to be consistent with the hypothesis described in Section 1.2. The sample-size calculations are based on the primary efficacy endpoint, change from baseline in ADAS-Cog$_{13}$ total score at Week 104.

Assumptions about minimally clinically significant differences as measured by the ADAS-Cog total score were based on 18 month solanezumab results extrapolated to 24 months. In this database, the least-squares treatment difference from placebo in mean change in ADAS-Cog total score from baseline at 80 weeks in the mild AD population of APOE4 carriers with CDR global score = 0.5 was 1.68 units with a standard deviation (SD) of 9.72. A linear extrapolation using these results coupled with results at 28 and 52 weeks resulted in 104 week estimates of 2.24 (12.96). Using these estimates to approximate an MCI population, this expected difference translates into an effect size of 0.17.

Compared with the MCI population, deterioration of cognition in patients with mild AD has been observed to be somewhat faster. The least-squares treatment difference from placebo in mean change in ADAS-Cog total score from baseline at 80 weeks in the solanezumab mild AD population (enriched by restricting to APOE4 carriers) was 2.87 (10.16) units. A linear extrapolation using these results coupled with results at 28 and 52 weeks resulted in 104 week estimates of 3.83 (13.54). This expected difference translates into an effect size of 0.28.

Similar calculations were made for the key secondary endpoint ADCS-iADL. The least-squares mean change in ADCS-iADL score from baseline at 80 weeks in the mild placebo-treated population of APOE4 carriers with CDR global score = 0.5 was 0.31 (8.39) units. A linear extrapolation using these results coupled with results at 28 and 52 weeks resulted in 104 week estimates of 0.41 (11.19). Using these estimates to approximate an MCI population, this expected difference translates into an effect size of 0.04. The least-squares mean change in ADCS iADL score from baseline at 80 weeks in the mild AD population (enriched by restricting to APOE4 carriers) was 2.14 (9.81) units. A linear extrapolation using these results coupled with results at 28 and 52 weeks resulted in 104 week estimates of 2.85 (13.08). This expected difference translates into an effect size of 0.22.

The study will enroll a total of 2202 patients (734 patients per group). Assuming α=0.025 and the effect size among the patients who discontinue without completing the study is 50% of the effect size of the completers, the power for the mixture of MCI and mild AD patients for a single dose is 96% for ADAS-Cog (adjusted effect size is 0.21); for iADL it is 60% (adjusted effect size is 0.13). The power to show statistical significance for the mild AD subpopulation is 93% (adjusted effect size is 0.24) and 75% (adjusted effect size is 0.19) for ADAS-Cog and iADL, respectively. The power to show statistical significance for the MCI subpopulation is 26% (adjusted effect size is 0.14) and 3% (adjusted effect size is 0.03) for ADAS-Cog and iADL, respectively (Table 7).

Table 7. Effect Size and Power per Dose for Mild AD and MCI Patient Populations

Population	ADAS-Cog ES per Dose	ADAS-Cog Power per Dose	ADCS-iADL ES per Dose	ADCS-iADL Power per Dose
Overall*	0.21	96%	0.13	60%
Mild AD	0.24	93%	0.19	75%
MCI	0.14	26%	0.03	3%

*The overall population effect sizes and power calculations use a distribution of 65% mild AD patients and 35% MCI patients.

Abbreviations: AD Alzheimer's Disease; ADAS-Cog Alzheimer's Disease Assessment Scale-Cognition; ADCS-iADL The Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory - instrumental items score; ES Effect size; MCI Mild cognitive impairment.

12.3.2. Biomarkers

This section summarizes the sample-size estimates and power calculations for biomarkers arising from the CSF and PET sub-studies and for volumetric MRI data. All biomarker analyses will use α=0.05 (2-sided).

12.3.2.1. CSF biomarkers

It is expected that at least 175 patients will be included in the CSF sub-study. Three CSF biomarkers will be assessed: $A\beta_{1-42}$, total tau, and phosphorylated tau. Assuming a 40% missed post-baseline test rate, approximately 35 patients per treatment group will have a baseline value and a post-randomization value. Estimated treatment differences are based on data from the Alzheimer's Disease Neuroimaging Initiative Pool C (www.adni-info.org). CCI [redacted]

The expected mean (SD) change in CSF $A\beta_{1-42}$ over 104 weeks is -164 (63.25) units. The minimum detectable AZD3293 difference from placebo is 49.72 units (30% reduction) with 90% power and 43 units (26% reduction) with 80% power, α=0.05 (2-sided, t-test).

The expected mean (SD) change in CSF total tau over 104 weeks is -103 (61) units. The minimum detectable AZD3293 difference from placebo is 41.4 units (47% reduction) with 90% power and 43 units (40% reduction) with 80% power, α=0.05 (2-sided, t-test).

The expected mean (SD) change in CSF phosphorylated tau over 104 weeks is -36 (18) units. The minimum detectable AZD3293 difference from placebo is 14 units (39% reduction) with 90% power and 12 units (33% reduction) with 80% power, α=0.05 (2-sided, t-test).

12.3.2.2. PET biomarkers

To explore the effect of AZD3293 on brain amyloid plaque using PET, 900 patients will be enrolled in the florbetapir F 18 amyloid PET sub-study to yield 540 patients with a baseline and post-randomization value (assuming a 40% missed post-baseline test rate). Based on the ADNI

study results, using florbetapir as the radioligand, the expected mean ± SD change in amyloid load over 104 weeks is 0.0484 ± 0.0979 in SUVR-equivalent units (for patients with a baseline amyloid load of 1.15 to 1.38) in the placebo treatment group. Accordingly, the minimum detectable AZD3293 difference from placebo is 0.036 units (a 75% reduction) in the slope of Aβ accumulation with 92.1% power, and .041 units (a 85% reduction) with 97.5% power; α=0.05 (2-sided, t-test). Estimated treatment differences are based on data from the Alzheimer's Disease Neuroimaging Initiative (www.adni-info.org): University of Berkeley analysis of florbetapir longitudinal data, only including subjects who have moderately positive amyloid load in brain (SUVR in cortex was 1.15 to 1.38 at baseline).

12.3.2.3. MRI biomarkers

Volumetric MRI data will be obtained from all 2202 patients enrolled in the study. Assuming a 30% dropout rate, it is expected that 1541 patients (approximately 514 per treatment group) will complete the study. Assuming a mean (SD) decrease of 7.565 (5.242) units in MRI brain volume by Week 104 in the placebo group, the minimum detectable AZD3293 difference from placebo is 1.367 units (an 18% reduction) with greater than 99% power and α=0.05 (2-sided, t-test). Estimated treatment differences are based on data from the Alzheimer's Disease Neuroimaging Initiative Pool C (www.adni-info.org). CCI [redacted]

12.3.3. Pharmacogenetics

The number of patients who will agree to participate in the optional genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A separate Statistical Analysis Plan will be prepared where appropriate.

12.4. Data monitoring committee

This study will use an IDMC to monitor data on an ongoing basis to ensure the continuing safety of patients enrolled in the study, to ensure the integrity of the blinded nature of the study, and to oversee the interim analyses (see Section 12.2.2). The IDMC will be composed of individuals external to the sponsor and will consist of a Chair, plus at least 1 medical expert in the relevant therapeutic area and at least 1 statistician. The IDMC recommendations may include, but will not be limited to, the following:

- Continue the study as designed
- Modify the study and continue (including discontinuation of an AZD3293 dose group)
- Stop the study (for reasons of safety, conduct, or external information)

An IDMC charter will be developed which will specify the Committee's responsibilities, authorities, and procedures along with details of the interim analysis planning, decision-making guidance, and dissemination of the results as well as the recommendations and decisions after the interim analyses (see Section 12.2.2). Formal implementation and communication of IDMC

recommendations will be managed by the sponsor Executive Committee, chaired by the sponsor Chief Medical Officer and unrelated to the AZD3293 project team, will receive and act on the recommendations from the IDMC. A firewall will be established to ensure the maintenance of the study blind for the sponsor, the investigational site staff, and study patients and their study partners.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1. Medical emergencies and sponsor contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.4.4**

In the case of a medical emergency the Investigator may contact the CCI Study Physician.

The treatment code may not be broken except in an emergency situation when the appropriate management of the patient necessitates knowledge of the treatment allocation. In such an emergency, the investigator will, if time and circumstances permit, contact the local sponsor representative prior to breaking the treatment code (see Section 5.4.2).

13.2. Overdose

If a patient takes more than 2 total daily doses of study medication in a 24-hour period, it will be considered an overdose.

There are currently no data regarding overdosing of AZD3293, and there is no known antidote for AZD3293. In case of overdose, monitoring of cardiac, hepatic and hematological effects is essential, and appropriate standard support therapy should be initiated where clinically indicated.

If an overdose on study medication occurs in the course of the study, then investigators or other site personnel must inform appropriate sponsor representatives including the sponsor-designated medical monitor. A blood sample for determination of plasma AZD3293 concentration should be obtained if at all possible, and as soon as possible after the overdose becomes known, if associated with an AE.

An overdose without associated symptoms is only recorded on the Overdose CRF.

An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF.

For overdoses associated with SAEs, standard reporting timelines and procedures apply, see Section 6.4.4. The Overdose CRF is also completed.

13.3. Pregnancy

All outcomes of pregnancy either in a study patient or pregnant partner should be reported to the sponsor.

13.3.1. Maternal exposure

Women of childbearing potential are not allowed to be included in this study. Should a pregnancy still occur during study treatment, the patient should be discontinued from the study immediately (as described in Section 5.3) and the pregnancy reported to the sponsor. Any pregnancy occurring from the date of the first dose of study treatment until 90 days after the last

dose and any pregnancy occurring within 90 days after amyloid PET scan should be reported to the sponsor and followed up for its outcome as described below.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel inform appropriate sponsor representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it. Pregnancies are to be reported to the sponsor representatives using the Pregnancy Notification provided.

The same timelines apply when outcome information is available.

13.3.2. Paternal exposure

Pregnancy of a patient's sexual partner is not considered to be an AE. However, any conception occurring from the date of the first dose until 90 days after the last dose and any pregnancy occurring within 90 days after amyloid PET scan should be reported to the sponsor and followed up for its outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality).

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Appendix A. Signatures

Revised Clinical Study Protocol Appendix A

Drug Substance	AZD3293 [LY3314814]
Study Code	D5010C00009 [I8D-MC-AZES]
Edition Number	7.1
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Appendix A
Signatures

Please see electronic signature appended to this document.

Appendix B. Additional Safety Information

Clinical Study Protocol Appendix B	
Drug Substance	AZD3293 [LY3314814]
Study Code	D5010C00009 [I8D-MC-AZES]
Edition Number	7.1
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FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

"Life-threatening" means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. "Life-threatening" does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine

- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?
- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? The sponsor would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases

where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix C. International Airline Transportation Association (IATA) 6.2 Guidance Document

Clinical Study Protocol Appendix C	
Drug Substance	AZD3293 [LY3314814]
Study Code	D5010C00009 [I8D-MC-AZES]
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Content from Appendix C is being removed from the protocol to allow for potential changes in guidelines and local laws. The confirmation that study sample shipping materials are aligned with International Airline Transportation Association (IATA) certification is contained in the Study Laboratory Manual. The confirmation that the site has at least one IATA certified individual is covered during the site selection process and monitoring.

Appendix D. Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

Clinical Study Protocol Appendix D	
Drug Substance	AZD3293 [LY3314814]
Study Code	D5010C00009 [I8D-MC-AZES]
Edition Number	7.1
Date	See Cover Page

1. Introduction

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a subject meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with the sponsor's clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥ 2xULN at any point during the study irrespective of an increase in Alkaline Phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)

AST or ALT ≥ 3x ULN **and** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevations do not have to occur at the same time or within a specified time frame.

3. Identification of potential Hy's law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the sponsor representative
- Determine whether the subject meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits

4. Follow-up

4.1. Potential Hy's Law Criteria not met

If the subject does not meet PHL criteria the Investigator will:

- Inform the sponsor representative that the subject has not met PHL criteria.
- Perform follow-up on subsequent laboratory results in consultation with the designated medical monitor.
- Complete the Liver Assessment CRFs as information becomes available

4.2. Potential Hy's Law Criteria met

If the subject does meet PHL criteria the Investigator will:

- Notify the sponsor representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the Liver Assessment CRFs as information becomes available

- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

5. Review and Assessment of potential Hy's law cases

The instructions in this Section should be followed for all cases where PHL criteria were met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The sponsor will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there **is** an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the Liver Assessment CRF.

- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term "Hy's Law") according to standard processes.

  – The "Medically Important" serious criterion should be used if no other serious criteria apply

  – As there is no alternative explanation for the HL case, a causality assessment of "related" should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term "Potential Hy's Law") applying serious criteria and causality assessment as per above

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

6. Actions required for repeat episodes of potential Hy's law

This section is applicable when a subject meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met chronic or progressing malignant disease?

If No: follow the process described in Section 4.2 of this Appendix.

If Yes:

Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section 4.2 of this Appendix

[#] A "significant" change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

7. References

FDA Guidance for Industry (issued July 2009) "Drug-induced liver injury: Premarketing clinical evaluation": http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Leo Document ID = 2dd4e3a4-3648-4412-ab8a-b6a367c39866

Approver: PPD
Approval Date & Time: 17-Jul-2017 19:12:14 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 17-Jul-2017 21:56:00 GMT
Signature meaning: Approved