Official Title: A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, EFFICACY AND SAFETY STUDY OF CRENEZUMAB IN PATIENTS WITH PRODROMAL TO MILD ALZHEIMER'S DISEASE

NCT Number: NCT03114657

Document Date: Protocol Version 2: 14-March-2018

PROTOCOL

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, EFFICACY AND SAFETY STUDY OF CRENEZUMAB IN PATIENTS WITH PRODROMAL TO MILD ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	BN29553
VERSION NUMBER:	2
EUDRACT NUMBER:	2016-003288-20
IND NUMBER:	100,839
TEST PRODUCT:	Crenezumab (RO5490245)
MEDICAL MONITOR:	[redacted] M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 15 November 2016
DATE AMENDED:	Version 2: See electronic date stamp below

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	14-Mar-2018 17:35:22

PROTOCOL AMENDMENT, VERSION BN29553: RATIONALE

Protocol BN29553 has been amended to clarify the study's secondary and exploratory objectives and planned statistical analysis. Additional minor changes have been made to improve protocol clarity.

The main changes to the protocol, along with a rationale for each change, are summarized below:

- Secondary efficacy objectives in Table 1 have been restructured into the following categories: a) cognitive, functional, and behavioral outcomes and, b) caregiver and quality-of-life endpoints (Section 3.3.9). Exploratory efficacy objectives have also been added, and endpoints have been amended, specifically:
  - The secondary endpoint, Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog 12) has been changed to ADAS-Cog 11 as it affords a more differentiated endpoint from the ADAS-Cog13 endpoint. A Mini Mental State Examination (MMSE) change from baseline to Week 105 has been added to assess severity of dementia because this scale is a widely used instrument to approximate stage of disease.
  - The time-to-clinically-evident-decline endpoint has been removed since the complex scale-based composite endpoint originally proposed is no longer considered to have clinical validity. Instead, a number of exploratory efficacy endpoints aiming to enable "time to clinically meaningful event"–type analyses have been added as they may be clinically useful yet rarer and not well studied event endpoints with which to assess and describe the drug's potential efficacy. These event endpoints will be more clearly defined in the Statistical Analysis Plan.
- The pharmacokinetic and biomarker objectives and endpoints in Table 1 have been restructured and updated for clarity.
- The protocol statistical considerations and analysis plan have been revised as follows:
  - Sample size re-estimation text has been added to Section 6.1 (Determination of Sample Size) as is commonly done in pivotal studies. In the event the variability of the Clinical Dementia Rating-Sum of Boxes (CDR-SB) endpoint is observed to be greater than planned, the proposed sample size increase will reduce the risk of an underpowered study, thereby reducing the risk of having less than 80% power to reach significance when the true relative reduction in CDR-SB equals 30%.
  - Wording has been updated at the end of Section 6 to clarify the population that will not be part of the primary analyses.
  - Additional endpoints have been added to the type 1 error control hierarchy to reflect their importance for valid hypothesis testing in the secondary efficacy endpoints analysis (Section 6.4.2).

- Exploratory Efficacy Analyses (Section 6.4.3) and Interim Analyses (Section 6.8) sections have been rewritten for greater clarity (Section 6.4.3).
- The biomarker analyses section has been updated to reflect the biomarker objectives (Section 6.7).

In addition, the following minor changes have been made and are summarized below with a rationale for each change:

- Update to Background on Alzheimer's disease section (Section 1.1) to reflect recent developments and current thinking in the field of Alzheimer's disease.
- Alignment of the following protocol sections with latest Crenezumab Investigator's Brochure (Version 10)
  - Background on Crenezumab, Summary of Nonclinical Studies, and inclusion of recent preclinical data related to crenezumab's preclinical profile and mechanism of action (Sections 1.2 and 1.2.1).
  - Summary of Clinical Studies (Section 1.2.2)
  - Safety Overview, Immunogenicity, and Pharmacokinetics (Sections 1.2.3–1.2.5).
  - Study Rationale Background (Section 1.3.1)
- Additional information describing the findings of previous studies has been added to Biomarkers section (Section 1.2.6.3).
- The Overall Benefit-Risk Summary has been updated for greater clarity (Section 1.3.6); the risk–benefit profile remains unchanged.
- The Overview of Study Design (Section 3.1.1) has been updated to reflect the changes introduced elsewhere in this amendment. The following updates have also been made to this section:
  - Clarification of the primary analysis period from the time of randomization through to Week 105.
  - Added guidance regarding long-term follow-up of patients who discontinue study drug early or complete study treatment but do not enter the open-label extension has been added.
- Wording has been updated throughout the protocol to reflect the contribution of patients from Taiwan and Hong Kong to the China extension (according to applicable Chinese regulations).
- Clarification is provided around use of medical food supplements for Alzheimer's disease not limited to Souvenaid® (Section 3.1.3).
- Requirements for the removal of no planned changes of Alzheimer's medications for 6 months post-randomization (Section 3.1.3) have been changed. Any such changes would still occur (even if unplanned) when medically indicated and have no impact on the patient's participation in the study.

- Clarification provided for the possible screening window duration to ensure patients are randomized within the protocol-defined screening window (Section 4.6.8.1).
- Clarification of the following exclusion criteria (Section 4.2):

– Patients with a history of seizures will be excluded if in the opinion of the investigator it is likely to result in cognitive impairment, which was not immediately clear in the original wording. The protocol permitted therapy regarding anticonvulsants has also been aligned accordingly.

  – The version of Diagnostic and Statistical Manual of Mental Disorders has been corrected from Version 5 to Version 4 to accurately reflect the alcohol/substance abuse or dependence exclusion criteria.
  – The cancer criterion text has been updated.
  – Screening hemoglobin A1c text has been updated.
  – Significant respiratory diseases whether or not they are likely to result in cognitive impairment.

- The exclusion criterion regarding sleep apnea has been updated on account of the relatively high prevalence of sleep apnea in this population and benefit of treatment (e.g., continues positive airway pressure). Sleep apnea that is considered by the investigator to be adequately treated and not contributing to cognitive dysfunction is allowed (treatment compliance should be documented). Patients with sleep apnea that may be contributing to cognitive impairment are excluded.
- Addition of text to recognize country variability in designation of non–Investigational Medicinal Product (NIMP)/IMP status to positron emission tomography (PET) tracers (Section 4.3.2.2). Adverse event reporting requirements for PET ligands administered in this study and associated substudies were also added (Sections 5.3.1 and 5.4.2).
- There was an update to the Permitted Therapy section to provide additional clarity and removal of duplicate text regarding antihistamines (Section 4.5.1).
- The restriction was removed of once only repeat testing of patient samples during screening (Section 4.6.7 and Appendix 1 Schedule of Activities).
- The addition of text to permit other biomarkers associated with Alzheimer's disease or study treatment to be analyzed in peripheral blood samples as pharmacodynamics markers (Section 4.6.7.2).
- Amyloid-related imaging abnormalities (ARIA) text including management of ARIA and required dose adjustments has been updated and restructured for greater clarity. New nonclinical information has also been provided (Sections 5.1.1 and 5.1.2). Additional information and guidance for the reporting of ARIA adverse events has also been included in the Selected Adverse Events section (Section 5.2.4).
- Medical Monitor contact information has been updated in the Emergency Medical Contacts to reflect the change in the secondary Medical Monitor (Section 5.4.1).

- The Schedule of Activities (Appendix 1) has been updated to correct errors and provide additional guidance and clarity in the footnotes.
- The Diagnostic Verification Form (Appendix 4) has been edited to reflect the correct process.

Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED, PARALLEL GROUP, EFFICACY AND SAFETY STUDY OF CRENEZUMAB IN PATIENTS WITH PRODROMAL TO MILD ALZHEIMER'S DISEASE**
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MEDICAL MONITOR:	[redacted] M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of this form to your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED, PARALLEL GROUP, EFFICACY AND SAFETY STUDY OF CRENEZUMAB IN PATIENTS WITH PRODROMAL TO MILD ALZHEIMER'S DISEASE**
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IND NUMBER:	100,839
TEST PRODUCT:	Crenezumab (RO5490245)
PHASE:	III
INDICATION:	Alzheimer's disease
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics of crenezumab compared with placebo in patients with prodromal to mild Alzheimer's disease (AD). Specific objectives and corresponding endpoints for the study are outlined in the table below.

Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	
• To evaluate the efficacy of crenezumab compared with placebo	• Change from baseline to Week 105 in global *outcome* as assessed by CDR-SB
Secondary Efficacy *Objectives*:	
• To evaluate the efficacy of crenezumab compared with placebo *on additional cognitive, functional, and behavioral outcomes*	• Change from baseline to Week 105 on cognition as *assessed* by ADAS-Cog-13 and *ADAS-Cog-11* • Change from baseline to Week 105 on severity of dementia, assessed *by* CDR-GS *and MMSE* • Change from baseline to Week 105 on function *as by* the ADCS-ADL total score *and its ADCS-iADL subscore and by the FAQ total score* • *Change from baseline to Week 105 on a measure of* dependence derived from the ADCS-ADL score • *Change from baseline to Week 105 on behavior* assessed *by* the *NPI-Q* total score
• *To evaluate the efficacy of crenezumab compared with placebo on caregiver and quality-of-life endpoints*	• Effect of crenezumab on HRQOL, assessed using the QOL-AD scale • Effect of crenezumab on caregiver burden, assessed using the ZCI-AD scale • Effect of crenezumab on health outcomes in patient and caregiver as measured by EQ-5D
Exploratory Efficacy Objectives:	
• *To evaluate the efficacy of crenezumab compared with placebo on events related to disease progression*	• *Effect on cognition, assessed by time to an increase from baseline at any time before or on Week 105 (i.e., worsening) on a version of the ADAS-Cog or the MMSE* • *Time to clinically evident decline since baseline, as defined by an increment on the CDR global score* • *Time to development of impairment in additional domains or worsening of impairments within a domain on the CDR-SB* • *Time to increase-of-dependence level, as derived from the ADCS-ADL scale* • *Time to decline in ability to perform one or more basic or instrumental ADL present at baseline using the ADCS-ADL scale* • *Composite time-to-event endpoint. Combination of clinical progression events including any of the following: worsening disease severity (e.g., CDR Global), increasing care needs (e.g., ADCS-ADL–derived dependence level), concomitant medications, and other events that may be indicative of disease progression*

Objectives and Corresponding Endpoints (cont.)

Safety Objective:	
• To evaluate the safety of crenezumab compared with placebo	• Nature, frequency, severity, and timing of adverse events and serious adverse events • Physical and neurologic examinations, vital signs, blood tests, ECGs, and C-SSRS • Adverse events of special interest, specifically pneumonia • Adverse events as assessed by MRI: ARIA-E and ARIA-H • The immunogenic potential of crenezumab through measurement of antibodies directed against crenezumab and other components of the drug product and assessment of their relationship with other outcome measures.
Pharmacokinetic Objectives:	
• To characterize the crenezumab PK profile	• Serum concentration of crenezumab (administered at a dose of 60 mg/kg IV) at specified timepoints • *CSF concentration of crenezumab (administered at a dose of 60 mg/kg IV) at specified timepoints in a subset of consenting patients in a substudy (BN29553-CSF longitudinal)*
Biomarker Objectives:	
• To evaluate the effect of crenezumab compared with placebo on biomarker changes	• *Brain amyloid load over time measured by amyloid-PET in a substudy (BN29552/BN29553-Amyloid PET longitudinal)* • *Brain tau load over time measured by tau-PET in a substudy (BN29552/BN29553-tau PET longitudinal)* • *CSF markers of disease over time in a substudy (BN29553-CSF longitudinal)* • MRI-derived measurements over time such as volumetric changes in whole brain, ventricles, hippocampus, or other structures • Plasma Abeta concentrations
• *To explore exposure–response relationships in patients with prodromal to mild AD based on the following endpoints:*	• *CSF biomarkers* • Plasma PD biomarkers • Imaging biomarkers • Efficacy and safety outcomes
• To conduct exploratory genetic analysis on disease progression and response to crenezumab based on the following:	• [redacted] • *APOE* genotype

Objectives and Corresponding Endpoints (cont.)

AD = Alzheimer's disease; ADAS-Cog-*11* = Alzheimer's Disease Assessment Scale-Cognition *11*; ADAS-Cog (subscale) 13 = Alzheimer's Disease Assessment Scale-Cognition (subscale) 13; ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory; ADCS-iADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory Instrumental Subscale; ADL = activity of daily living; ARIA-E = Amyloid–related imaging abnormalities-edema/effusion; ARIA-H = Amyloid–related imaging abnormalities-hemosiderin deposition; CDR-SB = Clinical Dementia Rating–Sum of Boxes; CDR-GS = Global Score; C-SSRS = Columbia Suicide Severity Rating Scale; FAQ = Functional Activities Questionnaire; HRQOL = health–related quality of life; IV = intravenous; MMSE = Mini Mental State Exam; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory Questionnaire; PD = pharmacodynamic; *PET=positron emission tomography;* PK = pharmacokinetic; QOL-AD = Quality of Life-Alzheimer's Disease Scale; ZCI-AD = Zarit Caregiver Interview for Alzheimer's Disease.

Study Design

Description of Study

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate the safety and efficacy of crenezumab in patients with prodromal AD (pAD) to mild AD (mAD).

To maintain a balanced number of patients enrolled in each treatment arm, randomization will be stratified by dementia status (pAD vs. mAD), APOE status (presence or absence of $\varepsilon 4$ allele), anti-dementia medications (present of absent) at baseline, and geographic region. Approximately 250 centers in approximately 30 countries worldwide will participate in this study.

Patients will be selected on the basis of clinical diagnosis of probable AD (according to the National Institute on Aging/Alzheimer's Association [NIAAA] Diagnostic Criteria and Guidelines for AD) OR pAD (according to the NIAAA Diagnostic Criteria and Guidelines for AD).

Eligible patients will be 50–85 years old and must have increased brain amyloid as indicated by reduced cerebrospinal fluid (CSF) amyloid beta $(A\beta)_{1\text{-}42}$ concentration (i.e., CSF-enrolled patients) or positive amyloid positron emission tomography PET scan by qualitative read (i.e., PET-enrolled patients).

At the time of screening, patients must have a Mini-Mental State Examination (MMSE) score of ≥ 22 points and a Clinical Dementia Rating Global Score (CDR-GS) of 0.5 or 1.0. To confirm objective memory impairment, patients must have a Free and Cued Selective Reminding Test–Immediate Recall (FCSRT-IR) Cueing Index * of ≤ 0.67 and a total free recall score of ≤ 27.

* FCSRT cueing index is calculated as follows:

[Free recall score – total score achieved] / [Free recall score – 48]

Neuroradiologic evaluation will use a standard magnetic resonance imaging (MRI) protocol (including T2* weighted gradient–recalled echo [GRE] and fluid–attenuated inversion recovery [FLAIR]). Screening MRIs will be read by a central reader who will exclude patients with other structural causes of dementia, significant cerebral vascular pathology, and other relevant exclusion criteria.

Patients will be eligible for the study whether or not they are receiving standard of care symptomatic medications for AD (i.e., cholinesterase inhibitors or memantine, or combination*),* or medical food *supplements (e.g., Axona or* Souvenaid). These medications must have been stable for ≥ 3 months prior to screening.

The study will consist of a screening period of up to *12* weeks for each patient who agrees to participate, signs the informed consent form, and is eligible for the study. Eligible patients will then undergo the baseline visit (Week 1), when they will receive the first dose following completion of all relevant assessments. Patients will be enrolled in a double-blind treatment period of 100 weeks (26 doses; 60 mg/kg *crenezumab or placebo* by IV infusion every 4 weeks [q4w]), and a final efficacy and safety assessment 4 weeks following the patient's last dose (Week 105). Patients will then have the option to enter the open-label extension (OLE) study if eligible. Patients who do not enter the OLE will have additional follow up visits at 16 and 52

weeks after the last dose, primarily for safety and also for limited efficacy assessments. Assessments for patients who participate in the OLE will be documented in a specific OLE protocol.

Patients will undergo brain MRI examinations for monitoring of safety and as a biomarker to assess study drug activity. Patients will also undergo tests to monitor safety (including standard safety blood tests, ECG, MRI), as well as tests for cognition, function, and quality of life assessments. Blood samples for assessment of pharmacokinetics, pharmacodynamic biomarkers, and for the measurement of antibodies directed against crenezumab and other components of the drug product will be obtained from all patients.

The incidence and nature of adverse events, serious adverse events, amyloid–related imaging abnormalities-edema/effusion and amyloid–related imaging abnormalities-hemosiderin deposition (ARIA-H) abnormalities, adverse events of special interest, and laboratory abnormalities will be assessed on a regular basis by an unblinded independent Data Monitoring Committee (iDMC).

The study consists of four distinct periods:

Screening: Up to *12* weeks in length for each eligible patient.

Double-Blind Treatment: Double-blind treatment period of 100 weeks. After screening, patients who meet all eligibility criteria will be randomly assigned to one of two arms (crenezumab 60 mg/kg or placebo) in a 1:1 ratio. Starting on Week 1 after baseline assessments, each patient will receive 26 total IV infusions of study administered Q4W.

Primary Analyses *Period*: *Randomization through* Week 105

Long Term Treatment Follow-up: *Patients who discontinue from the study drug or who complete the study treatment* and do not enter the OLE *will be asked to return for the collection of safety and efficacy data 4, 16, and 52 weeks after administration of the last dose of study treatment.*

Additionally, all patients who discontinue from study drug early will be encouraged to return for subsequent visits, especially the Week 105 visit (early discontinuation of study treatment does not imply study discontinuation).

Open-Label Extension: All eligible patients will have the opportunity to enter an OLE (documented in a separate protocol).

Number of Patients

The planned number of patients in the Global Enrollment Phase for this study is approximately 750 (375 randomized to crenezumab 60 mg/kg IV and 375 randomized to placebo). [redacted] This China subpopulation may include patients enrolled at sites in *mainland* China*, Hong Kong, and/or Taiwan (according to applicable Chinese regulations)* during both the Global Enrollment Phase and the China Extension Phase.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Able to provide written consent signed by the patient (co-signed by the patient's legally authorized representative, if required by the local regulations, guidelines, and independent ethics committee or institutional review board [IRB])
- Aged between 50 and 85 years at screening, inclusive
- Weight between 40 and 120 kg, inclusive
- Availability of a person (referred to as the "caregiver" throughout this protocol) who in the investigator's judgment:
  - Has frequent and sufficient contact with the patient to be able to provide accurate information regarding the patient's cognitive and functional abilities, agrees to provide information at clinic visits (which require partner input for scale completion), signs the

necessary consent form, and has sufficient cognitive capacity to accurately report upon the patient's behavior and cognitive and functional abilities.

- Is in sufficiently good general health to have a high likelihood of maintaining the same level of interaction with the patient and participation in study procedures throughout the study duration.

Every effort should be made to have same caregiver participate throughout the duration of the study.

- Fluency in the language used at the study site
- Willingness and ability to complete all aspects of the study (including MRI, lumbar puncture [if applicable], clinical genotyping, and PET imaging [if applicable]); the patient should be capable of completing assessments either alone or with the help of the caregiver
- Adequate visual and auditory acuity, in the investigator's judgment, sufficient to perform the neuropsychological testing (eye glasses and hearing aids are permitted)
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least 8 weeks after the last dose of study drug.

- A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
  - Examples of contraceptive methods with a failure rate of [illegible]% per year include bilateral tubal ligation, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

- With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 8 weeks after the last dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- Evidence of the AD pathological process, by a positive amyloid assessment either on CSF $A\beta_{1-42}$ levels as measured on the Elecsys β-Amyloid(1-42) Test System OR amyloid PET scan by qualitative read by the core/central PET laboratory.
- Demonstrated abnormal memory function at *FCSRT/MMSE consent* or at *main* screening [FCSRT cueing index $\leq$0.67 AND free recall $\leq$27]
- Evidence of retrospective decline confirmed by a diagnosis verification form
- Mild symptomatology, as defined by a screening MMSE score of $\geq$22 points and CDR-GS of 0.5 or 1.0. MMSE may be performed at *FCSRT/MMSE consent or main* screening.
- Meets NIAAA core clinical criteria for probable AD dementia or pAD (consistent with the NIAAA diagnostic criteria and guidelines for MCI)

- If the patient is receiving symptomatic AD medications, the dosing regimen must have been stable for 3 months prior to screening. *If the patient is taking medical food supplements (e.g., Axona® or Souvenaid®), these must also have been stable for 3 months prior to screening.*
- Inclusion is subject to review of clinical criteria at screening (diagnostic verification form)
- Patient must have completed at least 6 years of formal education after the age of 5 years
- For enrollment into the China Extension Phase, patients must have residence in *mainland China, Hong Kong, or Taiwan and be of Chinese ancestry*.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Any evidence of a condition other than AD that may affect cognition, including but not limited to, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, Parkinson's disease, corticobasal degeneration, Creutzfeldt-Jakob disease, progressive supranuclear palsy, frontotemporal degeneration, Huntington's disease, normal pressure hydrocephalus, or hypoxia.
- *Seizure history that, in the opinion of the investigator, is likely to result in cognitive impairment*
- History or presence of clinically evident vascular disease that could potentially affect the brain (e.g., clinically significant carotid, vertebral stenosis or plaque; aortic aneurysm; intracranial aneurysm; cerebral hemorrhage; arterio-venous malformation.
- History or presence of any stroke with clinical symptoms within the past 2 years, or documented history within the last 6 months of an acute event consistent, in the opinion of the investigator, with a transient ischemic attack.
- History of severe, clinically significant (persistent neurologic deficit or structural brain damage) CNS trauma (e.g., cerebral contusion)
- History or presence of intracranial tumor (e.g., glioma). History or presence of meningioma that in the opinion of the investigator is not clinically significant and is unlikely to result in cognitive impairment is not excluded.
- Presence of infections that affect brain function or history of infections that resulted in neurologic sequelae (e.g., HIV, syphilis, neuroborreliosis, viral or bacterial meningitis/encephalitis)
- History or presence of systemic autoimmune disorders that potentially cause progressive neurologic disease with associated cognitive deficits (e.g., multiple sclerosis, lupus erythematosus, anti-phospholipid antibody syndrome, Behçet disease)
- History of schizophrenia, schizoaffective disorder, major depression, or bipolar disorder
  - A history of major depression is acceptable if patient had no episode within the past year or is considered in remission or depression is controlled by treatment.
- At risk of suicide in the opinion of the investigator
- Alcohol and/or substance abuse or dependence (according to Diagnostic and Statistical Manual of Mental Disorders *v4* criteria) within the past 2 years
  - Nicotine use is allowed.
  - Marijuana use is not allowed and must be discontinued 3 months before screening.
- According to the MRI central reader, MRI evidence of a) >2 lacunar infarcts, b) any territorial infarct >1 cm^3, or c) any white matter lesion that corresponds to an overall Fazekas score of 3 that requires at least 1 confluent hyperintense lesion on the FLAIR sequence, which is $\geq$20 mm in any dimension.
- Evidence of more than 4 microbleeds and/or areas of leptomeningeal hemosiderosis (ARIA-H) as assessed by central review of T2* GRE MRI
- Presence of significant cerebral vascular pathology as assessed by MRI central reader

- Presence on MRI of any cortical stroke regardless of age.
- Inability to tolerate MRI procedures or contraindication to MRI, including, but not limited to, presence of pacemakers not compatible with MRI, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin, or body that would contraindicate an MRI scan; or any other clinical history or examination finding that, in the judgment of the investigator, would pose a potential hazard in combination with MRI

The following cardiovascular disorders:

- History or presence of atrial fibrillation except if only one episode that resolved >1 year ago and for which treatment is no longer indicated
- Within the last 2 years, unstable or clinically significant cardiovascular disease (e.g., myocardial infarction, angina pectoris, or New York Heart Association Class II or higher cardiac failure)
- Uncontrolled hypertension (e.g., blood pressure generally >160 mmHg systolic or >95 mmHg diastolic)

The following hepatic/renal disorders:

- Chronic kidney disease of Stage ≥ 4, according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines for chronic kidney disease
- Confirmed and unexplained impaired hepatic function as indicated by screening AST or ALT ≥ 3 the upper limit of normal (ULN) or total bilirubin ≥ 2 ULN

The following infections and immune disorders:

- History of or known to currently have hepatitis B or hepatitis C infection that has not been adequately treated in the opinion of the investigator
- Systemically, clinically significantly immunocompromised patients, owing to continuing effects of immune-suppressing medication
- Corticosteroids are permitted as long as the dose is <7.5 mg/day prednisolone equivalent and the condition being treated is not expected to deteriorate significantly during the study period.

The following metabolic/endocrine disorders:

- Abnormal thyroid function as indicated by abnormal screening tests that are judged to be clinically significant by the investigator, or abnormal thyroid function that requires a new treatment or an adjustment of current treatment
  - A patient may be rescreened if there is no improvement in cognition in the investigator's judgment after 3 months of adequate treatment for thyroid function.

History of cancer except:

- If considered to be cured
  OR
- If not being actively treated with anti-cancer therapy or radiotherapy and, in the opinion of the investigator, not likely to require treatment in the ensuing 5 years
- For prostate cancer or basal cell carcinoma, no significant progression over the previous 2 years

Other exclusion criteria:

- Screening folic acid or vitamin B12 levels that are sufficiently low or remain low on retest such that deficiency may be contributing to cognitive impairment
  - A patient may be rescreened if there is no improvement in cognition after 3 months of adequate treatment for folic acid or vitamin B12 deficiency.

- Screening hemoglobin A1c > 8% (retesting is permitted if slightly elevated) or poorly controlled insulin-dependent diabetes (*past* hypoglycemic episodes *are considered one example of poor control*).
  - A patient may be rescreened after 3 months to allow optimization of diabetic control.
- Pregnant or lactating, or intending to become pregnant during the study
- Poor peripheral venous access
- Other causes of intellectual disability that may account for cognitive deficits observed at screening (e.g., static encephalopathy, closed brain injury, mental retardation).

– This may be based on, for example, patient's sufficient education or work experience.

- *Clinically significant sleep apnea that may be contributing to cognitive impairment.* Sleep apnea*, which in the clinical judgment of the investigator is adequately treated,* (e.g., continuous positive airway pressure-*adequate patient treatment compliance should be documented) is allowed.*
- *Significant* respiratory diseases (e.g., severe chronic obstructive pulmonary disease – Global Initiative for Obstructive Lung Disease criteria Stage IV.
- Deformity of the lumbosacral region of the spine that in the opinion of the investigator would contraindicate lumbar puncture in those who can only be CSF-eligible due to regional lack of availability of PET ligands.
- Clinically significantly abnormal screening blood or urine that remain abnormal at retest
- Impaired coagulation (screening PT > 1.2 × the ULN that remains abnormal on retest).
- Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins
- Any other severe or unstable medical condition that, in the opinion of the investigator or Sponsor, could be expected to progress, recur, or change to such an extent that it could put the patient at special risk, bias the assessment of the clinical or mental status of the patient to a significant degree, interfere with the patient's ability to complete the study assessments, or would require the equivalent of institutional or hospital care
- Residence in a skilled nursing facility such as a convalescent home or long-term care facility: Patients who subsequently require residence in these facilities during the study may continue in the study and be followed for efficacy and safety provided that they have a caregiver who meets the minimum requirement.

The following medications are prohibited for a pre-specified duration prior to study start, as indicated, and during the entire period of study participation (patients who start these medications during the study may be withdrawn from study treatment):

- Any previous administration of crenezumab or any other therapeutic that targets Aβ
- Any investigational active immunotherapy (vaccine) that is under evaluation to prevent or postpone cognitive decline
- Any passive immunotherapy (immunoglobulin) or other long–acting biologic agent that is under evaluation to prevent or postpone cognitive decline within 1 year of screening
- Any other investigational treatment within 5 half-lives or 3 months of screening, whichever is longer
- Any previous treatment with medications specifically intended to treat Parkinsonian symptoms or any other neurodegenerative disorder within 1 year of screening

– Certain medications are acceptable if the patient is taking the medicine for a non-neurodegenerative disorder, such as restless leg disorder (e.g., pramipexole)

- Typical antipsychotic or neuroleptic medication within 6 months of screening except as brief treatment for a non-psychiatric indication (e.g., emesis)
- Atypical antipsychotics except with intermittent short-term use which is permitted except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment

- Anti-coagulation medications within 3 months of screening
  - Anti-platelet treatments (e.g., aspirin, clopidigrel, dipyridamol) are permitted.

    Short-term, peri-operative use of anti-coagulants will not result in discontinuation from the study; however, any such use must be discussed with the Sponsor.
- Chronic use of opiates or opioids (including long-acting opioid medication) within 3 months of screening
- Intermittent short-term use of short–acting opioid medications for pain is permitted except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment
- Stimulant medications (amphetamine, methylphenidate preparations, or modafinil) within 1 month of screening and throughout the study
- Chronic use of benzodiazepines, barbiturates, or hypnotics from 3 months before screening
  - Intermittent short-term use of benzodiazepines, buspirone, or short–acting hypnotic medication for sleep or anxiety is allowed except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment. However, intermittent use of barbiturates is not permitted.

End of Study

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for safety analyses or safety follow-up is received for the last patient, whichever occurs later.

Patients who discontinue from the study *drug or who complete the study treatment and do not enter the OLE will be* asked to return for the collection of safety and efficacy data 4, 16, and 52 weeks after administration of the last dose of study treatment.

Additionally, all patients who discontinue from study drug early will be encouraged to return for subsequent visits, especially the Week 105 visit (early discontinuation of study treatment does not imply study discontinuation).

Length of Study

LPLV for the double-blind treatment period is expected to occur 153 weeks after the last patient is enrolled (i.e., 52 weeks after the last dosing visit at Week 101) for those patients who do not enter the OLE.

Investigational Medicinal Products

The investigational medicinal product (IMP) for this study is crenezumab.

Crenezumab will be administered via IV infusion to all patients. Those randomized to the active arm will receive crenezumab at a dose of 60 mg/kg q4w for 26 doses.

For all infusions (crenezumab and placebo), IV infusions will be administered by appropriately trained staff in the clinic or other agreed environment (e.g., the patient's home); the first four infusions of study drug must be administered at the clinic.

Comparator

The comparator for this study is placebo.

Placebo will be administered via IV infusion to all patients.

IV infusions will be administered by appropriately trained staff in the clinic or other agreed environment (e.g., the patient's home); the first four infusions of study drug must be administered at the clinic.

Non-Investigational Medicinal Products

Adding a new medication or changing the dose of a medication after randomization should occur only for the treatment of an adverse event *or as medically indicated.*

The following medications are permitted if the dose and dose regimen have been stable for 3 months prior to screening and are expected to remain stable after screening or if required for treatment of an adverse event after randomization:

- Prescription medications that might affect cognitive function (e.g., antidepressants, anticonvulsants)
- Over-the-counter and/or herbal medications, food additive or any other agent or supplement intended to improve cognition or reduce cognitive decline
- Medications used to treat a mood or anxiety disorder given as maintenance treatment
- Medications with anticholinergic activity that may impair cognition or attention (e.g., centrally acting antihistamines, including brompheiramine, chlorpheniramine, dimenhydrinate, diphenhydramine, and doxylamine, or anti spasmodic medicines)
- Intermittent use of centrally acting antihistamines is permitted, but should not be used within 2 days or 5 half-lives (whichever is longer) of cognitive assessment
- Intermittent use of short–acting (non-extended release) opioid medications for pain is permitted except within 2 days or 5 half-lives (whichever is the longer) of any neurocognitive assessment (up to a maximum of 3 consecutive days per month)
- Intermittent short-term use of benzodiazepines, buspirone, or short–acting hypnotic medication for sleep or anxiety is allowed, except in the 2 days or 5 half-lives (whichever is the longer) prior to any cognitive assessment. However, intermittent use of barbiturates is not permitted.
- Dose of benzodiazepine for presurgical and pre-imaging sedation at appropriate visits if allowed by Ethics Committee or IRB
- Anti-platelet therapies are permitted during study conduct

  Under certain circumstances, anticoagulation therapy (e.g., temporary usage during surgery, or for treatment of deep vein thrombosis) may be permitted. In these circumstances, appropriate safety assessments should be made, e.g., prior to a lumbar puncture. The investigator should discuss with the Sponsor all individual patient cases that require anticoagulant therapy proactively whenever possible.

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

Statistical Methods

Primary Analysis

The primary efficacy outcome measure is the change in CDR-SB from baseline (Week 1) to Week 105. For this primary outcome measure, the difference in mean change from baseline to Week 105 between crenezumab- and placebo-treated patients will be estimated using mixed model repeated measures (MMRMs) adjusting for disease severity, *APOEε4* status, geographic region, and the use or non-use of anti-dementia medications at baseline will be used to estimate the mean change from baseline for the primary endpoint. The analysis will include randomized patients *during the Global Enrollment Phase*, with patients grouped according to the treatment assigned at randomization. *Data from patients enrolled after the close of Global Enrollment will be included in analyses separate from the primary analyses.*

The MMRM model will be used to estimate the mean change from baseline for the primary endpoint. The model will include the change from baseline in CDR-SB as the dependent variable. The effects in the model will include baseline score, treatment group, visit, treatment-by-visit interaction and baseline score-by-visit interaction. Visit week will be treated as the repeated variable within a patient. Patient, treatment, and visit week will be treated as class variables. An unstructured variance–covariance structure will be applied to model the within-patient errors; in case of non-convergence, compound symmetry will be used.

The difference in the changes from baseline of each dose group from placebo will be estimated at each time point. The 95% CI and p-value for treatment difference will be presented.

All efforts will be made to minimize missing data. The Sponsor plans to request patients who discontinued early from study treatment to return for collection of safety and limited efficacy data until Week 105. To explore the robustness of MMRM results for the primary efficacy conclusions, sensitivity analyses (for example, using multiple imputation and pattern mixture models) will be performed. Descriptive summaries of the number of patients with missing data

and the timing and reasons for discontinuation from study by treatment group will also be provided.

Additional details will be documented in the Statistical Analysis Plan (SAP).

Determination of Sample Size

Determination of sample size is based on patients enrolled in the Global Enrollment Phase. In this study, 750 patients will be enrolled with 375 patients per treatment arm (crenezumab or placebo) during the Global Enrollment Phase. [redacted]

The estimate of sample size required to demonstrate efficacy with regard to CDR-SB is based on the following assumptions:

- The mean change in CDR-SB from baseline to Week 105 is 2.6 points in the placebo arm
- A common standard deviation across treatment arms for change from baseline to Week 105 in CDR-SB of approximately 3.07 (this corresponds to a coefficient of variation of 118% for change in CDR-SB from baseline to Week 105 in a prodromal to mild AD population in the placebo arm)
- The dose level has a true effect of a 30% relative reduction in deterioration of CDR-SB
- 35% of randomized patients will dropout by Week 105

This sample size will have 80% power to detect a true treatment effect of 30% relative reduction in deterioration of CDR-SB at 2-sided α of 0.05.

In the event that the rescue strategy or change in dose is required, the number of patients enrolled in the new dose group and its concurrently enrolled placebo arm will be 750 patients (375 patients per treatment arm) during the Global Enrollment Phase. All patients already enrolled on 60 mg/kg *of study treatment* and corresponding concurrently enrolled placebo patients will be replaced with new patients.

A blinded assessment of the pooled standard deviation of CDR-SB change from baseline will be performed by the Sponsor at a specified timepoint prior to unblinding. As a result, the sample size may be increased from 750 up to 1126 patients (563 patients per arm). Further details will be described in the Statistical Analysis Plan. The sample size will not be reduced on the basis of this assessment. Other factors external to the study may also trigger a decision to increase sample size.

Interim Analyses

Based on information that may emerge during the course of this study, the Sponsor may choose to conduct *one or more interim analyses. Interim* analyses *would* be conducted by an independent data coordinating center and reviewed by iDMC. *The Sponsor would remain blinded.* Interactions between the iDMC and Sponsor *would* be carried out as specified in the iDMC Charter. The iDMC Charter *would* document potential recommendations the iDMC can make to the Sponsor as a result of the analyses (e.g., stop the study for futility). *Below are further specifications in place to ensure the study continues to meet the highest standards of integrity should optional interim analyses be executed.*

The Sponsor may choose to perform an optional futility analysis. No adjustment for multiple comparisons would be made to the α level for this analysis, given that the decision rules for the futility analysis would not allow for the opportunity to stop the study early for overwhelming efficacy.

At the time of *a* futility *analysis*, the threshold for declaring futility *would* be based *on* the probability of erroneously stopping the study being lower than a pre-specified level, when crenezumab has a true treatment effect on CDR-SB (false negative rate). If the observed treatment effect at the futility analysis is smaller than the derived threshold, the iDMC may recommend that the study be stopped for futility. Additional criteria for recommending that the study be stopped for futility may be added to the iDMC Charter.

In addition, the *Sponsor* may *perform an interim assessment* for positive efficacy. The type I error rate will be controlled to ensure statistical validity is maintained. Specifically, the Lan-DeMets α-spending function that approximates the O'Brien-Fleming boundary will be applied to

determine the critical value for stopping for positive efficacy at the interim analysis. If the study continues beyond the interim analysis, the critical value at the final analysis would be adjusted accordingly to maintain the protocol-specified overall type I error rate, per standard Lan-DeMets methodology. This interim analysis *would* also be reviewed by the iDMC, and the Sponsor *would remain* blinded. Additional criteria for recommending that the study be stopped for positive efficacy may be added to the iDMC Charter.

Further details (e.g., timing, data to be reviewed by the iDMC, thresholds, etc.) will be documented in the interim SAP. The interim SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of an interim analysis.

As information external to the study (e.g., from other compounds) becomes available during the conduct of the study, the Sponsor may implement changes to the protocol to incorporate such learnings into the study, if possible. Such learnings may be concerned with endpoints, biomarkers, and sample size reassessment due to the variability and size of treatment effect observed in other compounds, for example. The Sponsor could implement such learnings through a protocol amendment while being blinded, but without consultation with the iDMC.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
Aβ	amyloid β
AChE	acetylcholinesterase
AD	Alzheimer's disease
ADA	anti-*drug* antibody
ADAS-Cog-11	*Alzheimer's Disease Assessment Scale-Cognition 11*
ADAS-Cog-12	Alzheimer's Disease Assessment Scale-Cognition 12
ADAS-Cog-13	Alzheimer's Disease Assessment Scale-Cognition 13
ADCS-ADL	Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory
ADCS-iADL	Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory Instrumental Subscale
ADAD	autosomal dominant Alzheimer's disease
ADL	activity of daily living
iADL	instrumental activity of daily living
APP	amyloid precursor protein
AUC	area under the concentration–time curve
AUC_{ss}	area under the concentration–time curve at steady state
ARIA	Amyloid–related imaging abnormalities
ARIA-E	Amyloid–related imaging abnormalities-edema/effusion
ARIA-H	Amyloid–related imaging abnormalities-hemosiderin deposition
BGTS	Barkhof Grand Total Score
CDR	Clinical Dementia Rating
CDR-GS	Clinical Dementia Rating-Global Score
CDR-SB	Clinical Dementia Rating-Sum of Boxes
ChEI	cholinesterase inhibitors
C_{max}	observed maximum serum concentration
COPD	chronic obstructive pulmonary disease
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DDI	drug-drug interaction
DLT	Dose Limiting Toxicity
DSMB	*Data Safety Monitoring Board*
EC	Ethics Committee

Abbreviation	Definition
eCRF	electronic Case Report Form
EDC	electronic data capture
FACS	fluorescence-activated cell sorting
FcγR	Fcγ receptor
FCSRT	Free and Cued Selective Reminding Test
FCSRT-IR	Free and Cued Selective Reminding Test–Immediate Recall
FDA	U.S. Food and Drug Administration
FDG	^{18}F-fluordeoxyglucose
FLAIR	fluid–attenuated inversion recovery
GRE	gradient-recalled echo
hAPP	human amyloid precursor protein
HbA1c	hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
HN	Home Nursing
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IV	intravenous
IxRS	Interactive Voice/Web Response System
LPLV	last patient, last visit
mAb	monoclonal antibody
mAD	mild Alzheimer's disease
MCI	mild cognitive impairment
mH	microhemorrhage
MMRM	mixed model repeated measure
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NIAAA	National Institute on Aging/Alzheimer's Association
NMDA	N-methyl-d-aspartate
NPI-Q	Neuropsychiatric Inventory Questionnaire
OLE	open-label extension
pAD	prodromal Alzheimer's disease

Abbreviation	Definition
PD	pharmacodynamics
PET	positron emission tomography
PK	pharmacokinetic
PRO	*patient-reported outcome*
PS1	presenilin 1
PS2	presenilin 2
q2w	every 2 weeks
q4w	every 4 weeks
QTcF	QT interval corrected using Fridericia's formula
QoL	quality of life
QOL-AD	Quality of Life-Alzheimer's Disease scale
RBR	Research Biosample Repository
RPCP	randomized placebo–controlled period
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SMC	Safety Monitoring Committee
SUVR	standardized uptake value ratio
Tg	transgenic
TP	therapeutic protein
ULN	upper limit of normal
ZCI-AD	Zarit Caregiver Interview for Alzheimer's Disease

1. BACKGROUND

1.1 BACKGROUND ON ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the most common form of dementia; it affects an estimated 5.3 million individuals in the United States and 46.8 million people worldwide (Alzheimer's Association 2015; Alzheimer's Disease International 2015). The disease is characterized pathologically by the accumulation of extracellular β-amyloid (Aβ) plaques and intracellular neurofibrillary tangles in the brain. Diagnosis is made through the clinical assessment of the neurologic and neuropsychiatric signs and symptoms of AD and the exclusion of other causes of dementia. Approved medical therapies that inhibit acetylcholinesterase (AChE) activity or antagonize N-methyl-d-aspartate (NMDA) receptors in the brain may temporarily improve the symptoms of AD in some patients but do not modify progression of the disease (Cummings 2004). See the crenezumab Investigator's Brochure for further details on the pathology of AD.

AD has *until recently* been *diagnosed at the clinical dementia stage.* There is great variation in the course of the disease. However, *it has commonly been classified into stages by a brief cognitive screening examination, the Mini Mental State Examination (MMSE; Folstein et al. 1975)* which ranges from a score of 30 (cognitively normal) to 0 (fully impaired). MMSE scores of around 20–26 are typically associated with mild AD, 10–19 with moderate AD, and <10 with severe AD (Dash and Villemarete-Pittman 2005). *Although the progressive deterioration in AD is categorized into these three stages: mild, moderate, and severe, it more realistically resembles a continuum (*Alzheimer's Association 2015*).*

AD is a slowly progressive disorder with no fixed events that define its onset (Albert et al. 2011). Prior to a diagnosis of dementia, an individual may experience problems with memory, thinking, judgment, and language, but not to a degree sufficient to impact day-to-day life or normal functional activities. This pre-dementia stage is commonly referred to as mild cognitive impairment (MCI); MCI alone is not sufficient to predict AD. *According to research criteria that have recently become available (Albert et al. 2011), the diagnosis of AD can be made with more certainty at the MCI stage with the help of biomarkers, and may then be called "MCI due to AD" or "prodromal AD (pAD)".*

Biomarker assessments (including positron emission tomography [PET] imaging of amyloid and cerebrospinal fluid [CSF] assessments) have confirmed that pAD represents a relatively early stage in the continuum of AD. Mild AD (mAD) represents a stage of the disease where patients have *not only* cognitive, *but also clear* functional deficits. *The specificity of the clinical diagnosis of mild AD can also be increased by confirming biomarker changes associated with AD* (McKhann et al. 2011). *Classification schemes of AD are an area of ongoing research and are expected to evolve further (e.g., A/T/N; see Jack et al. 2016).*

*For potential patients for this clinical trial, evaluations include a thorough clinical assessment as well as measurement of disease relevant biomarkers, i.e., markers of amyloid accumulation in CSF or on brain PET scans. Patients to be enrolled may be at the clinical stage of MCI (pAD) or mild dementia and will have positive biomarkers indicative of AD. (*Albert et al. 2011*; McKhann et al. 2011).*

The rate of AD progression shows great inter-individual variability with survival dependent on many factors, including age at onset. Population studies (Brookmeyer et al. 2002; Larson et al. 2004) suggest a lag of approximately 5 years between symptom onset and diagnosis (Roberson et al. 2005; Waring et al. 2005). Thereafter, the median survival time following a diagnosis of AD depends strongly on the patient's age at diagnosis. The median survival time ranges from 8.3 years for persons diagnosed with AD at age 65 years to 3.4 years for persons diagnosed at age 90 years (Brookmeyer et al. 2002). On average, individuals live for 3–9 years after diagnosis of AD (Helzner et al. 2008), and some survive as long as 20 years.

1.2 BACKGROUND ON CRENEZUMAB

Crenezumab (RO5490245) is a fully humanized monoclonal antibody *(mAb)* based on a human IgG4 framework that contains heavy chain V_HIII and light chain V_κII subgroup sequences. *In vitro, crenezumab binds to Aβ peptides, Aβ1-40 and Aβ1-42, in multiple forms (monomers, oligomers, fibrils, and plaques). Recent results suggest higher in vitro binding to oligomers over monomers (Ultsch et al. 2016) and in vivo crenezumab binding to brain areas postulated to be high in oligomers in AD Tg mice and no binding to the dense core of plaques (data on file).*

In vitro studies demonstrated the ability of crenezumab *to block Aβ* aggregation*, promote Aβ disaggregation, and protect neurons from oligomer-induced cytotoxicity (*Adolfsson et al. 2012*). Crenezumab's* IgG4 backbone *confers* reduced *activation of* Fc*γ* receptor (Fc*γRs) in comparison with* IgG1 *and was shown to minimize FcγR-mediated activation of microglia and release of* inflammatory *cytokines upon oligomer engagement, which has also been proposed to contribute to neurotoxicity (*Xing et al. 2011*;* Heneka et al. 2015*) while preserving FcγR-mediated microglial phagocytosis of oligomers (*Adolfsson et al. 2012*). Following in vivo dosing in presenilin 2 (PS2) amyloid precursor protein (APP) Tg mice, crenezumab localizes to brain areas with putative high concentrations of Aβ oligomers, i.e., hippocampal mossy fibers and* the *periphery of* amyloid *plaques (*Koffie et al. 2009*;* Liu et al. 2015*) but not to the dense core of plaques or vascular amyloid.* The *neutralization and removal of Aβ oligomers* is a rational approach to modify disease progression in AD.

*Amyloid-related imaging abnormalities (ARIAs), indicative of vasogenic edema or effusions (ARIA-E) and microhemorrhages (mHs) or leptomeningeal hemosiderosis (ARIA-H), have been reported in recent AD trials involving mAbs that bind aggregated forms of Aβ and have IgG1 backbones with fully preserved FcγR-mediated effector function (*Salloway et al. 2009*;* Ostrowitzki et al. 2012*;* Fuller et al. 2014*;* Sevigny et al.

2015). As these molecules demonstrated increases in ARIA-E incidence with increasing dose and apolipoprotein E4 (APOE4) allele frequency, the dose levels administered in past trials have been constrained to limit these events (Salloway et al. 2009; Sperling et al. 2012; Ostrowitzki et al. 2017). Crenezumab was designed with an IgG4 backbone on the basis of the hypothesis that reducing effector function—shown to minimize FcγR-mediated activation of microglia and release of inflammatory cytokines upon oligomer engagement—would lower the risk of inducing ARIA-E and ARIA-H, possibly by minimizing inflammation at brain vasculature (Wilcock et al. 2006. A lack of binding for crenezumab to vascular amyloid, noted following in vivo dosing in PS2APP Tg mice (GNE Study 15-2817B), may additionally reduce the risk of ARIA.

The safety profile of crenezumab to date (see Section 1.2.3) allows a higher dose of crenezumab than the 300 mg SC every 2 weeks (Q2W) or the 15 mg/kg IV Q4W that were used in the Phase II studies to be used in the ongoing Phase III program (i.e., 60 mg/kg IV crenezumab). This dose selection is supported by the data from the Phase Ib GN29632 study that investigated higher doses than those in Phase II, including 60 mg/kg and 120 mg/kg IV Q4W. The aim of the high dose is to achieve higher systemic exposure and therefore higher brain concentrations, which are predicted to result in greater efficacy than seen in the completed Phase II studies.

See the Crenezumab Investigator's Brochure for details on nonclinical and clinical studies.

1.2.1 Summary of Nonclinical Studies

In vivo pharmacology and CNS distribution studies were conducted in human amyloid precursor protein (hAPP)-Tg mouse models of AD. Crenezumab was detected in both brain homogenates and CSF following a single IV dose. Administration of two weekly doses of 5 mg/kg crenezumab to hAPP-Tg mice decreased total Aβ levels in soluble fractions of brain homogenates and increased plasma total Aβ levels. An in vivo pharmacology study in PS2APP Tg mice showed via immunofluorescence microscopy that crenezumab localized to brain areas with putatively high concentrations of Aβ oligomers, i.e., hippocampal mossy fibers and the periphery of amyloid plaques but not to the dense core of plaques or vascular amyloid.

The pharmacokinetics and toxicokinetics of crenezumab were studied in hAPP-Tg mice, non-Tg mice, and cynomolgus monkeys. Studies demonstrated biphasic disposition characterized by a short distribution phase followed by a long elimination phase of crenezumab. Because of the presence of anti-drug antibody (ADA), there were less than dose-proportional increases in overall crenezumab exposure across the range of doses investigated in mice. In monkeys, repeat dosing also resulted in development of ADA in a proportion of animals that correlated with a trend toward slightly lower serum concentrations of crenezumab but did not affect dose-proportional increases in exposure. In both species, dose-related increases in plasma total Aβ levels were observed and

appeared to correlate well with serum crenezumab concentrations. In mice, following a single IV administration, crenezumab was observed in both brain and CSF.

Toxicity studies of crenezumab were conducted in cynomolgus monkeys. IV administration of crenezumab to cynomolgus monkeys for 4 weeks at one dose per week (a total of five doses) was well tolerated at doses up to 50 mg/kg. In a subsequent chronic toxicity study, SC administration of crenezumab to cynomolgus monkeys for 39 weeks (a total of 40 doses) was well tolerated at doses up to 100 mg/kg per week (the highest dose tested). No observations related to crenezumab administration were seen on expanded *histopathology* evaluation of the brain. Nonclinical safety data provide 2-, *3*-, and *6*-fold safety factors for the 60-mg/kg dose at steady-state on the basis of human equivalent dose, exposure (*area* under the concentration-time curve [AUC]), and maximum concentration (C_{max}), respectively, relative to the maximum tested dose of 100 mg/kg via SC administration in cynomolgus monkeys (see the *Crenezumab* Investigator's Brochure).

A study to further evaluate the pharmacology of crenezumab in hAPP-Tg mice included weekly or monthly intraperitoneal (IP) administration of crenezumab for 16 weeks (a total of 17 weekly doses or 5 monthly doses) at doses up to 50 mg/kg. When crenezumab was given at doses > 10 mg/kg for > 2 weekly or monthly doses, unexpected deaths were observed. No microscopic findings were identified in the CNS or peripheral tissues to explain the mortalities. A high incidence of anti-crenezumab antibodies was observed (93% of animals evaluated), which resulted in attenuation of both serum crenezumab concentrations and *pharmacodynamic (PD)* responses (plasma total $A\beta_{1-40}$ and $A\beta_{1-42}$). These data suggest that these unexpected deaths were likely the result of an adverse immunogenic response (i.e., anaphylaxis) to the xenogeneic humanized crenezumab antibody in mice and are therefore unlikely to be predictive of human safety risk.

To address potential safety concerns associated with administration of anti-Aβ antibodies in the AD population *(i.e., ARIA-E and –H*), additional studies were performed in Tg-mouse models of AD (hAPP or hAPP/presenilin 1 [PS1*]) to evaluate for vascular injury (e.g., cerebral mH).* These studies were performed with PRO300491, a human/mouse chimeric anti-*Aβ* mAb that shares a humanized variable domain with crenezumab but has the murine IgG2a constant domain with D265A and N297A mutations. This reverse chimera antibody (PRO300491) and crenezumab demonstrate comparable binding affinity to human $A\beta_{1-40}$ and $A\beta_{1-42}$ peptides. The murine IgG2a Fc was selected to decrease immunogenic potential in mice, as crenezumab appeared to be highly immunogenic in hAPP-Tg and non-Tg-wild type mice. Furthermore, the Fc mutations D265A and N297A were designed to decrease binding to murine FcγR and to approximate the reduced effector function of an IgG4 antibody (Shields et al. 2001).

A weekly repeat–dose study was conducted in hAPP/PS1-Tg mice with PRO300491 for 4 weeks (a total of four doses). At IV doses up to 60 mg/kg, PRO300491 was well tolerated and no treatment-related increases in mH were observed. In a subsequent

chronic toxicity study, weekly IP administration of PRO300491 to hAPP-Tg mice for 24 weeks (a total of 25 doses) was well tolerated at doses up to 50 mg/kg. No changes in the cerebral microvasculature (e.g., mH or amyloid deposition) were observed despite evidence of sustained antibody exposure and PD activity (plasma total $A\beta_{1-40}$). These findings support the hypothesis that Aβ antibodies with reduced effector function, such as crenezumab, are well tolerated in hAPP-Tg mice and are not associated with the development of adverse effects similar to those described in the literature for other Aβ antibodies.

Overall, the nonclinical studies demonstrated that crenezumab has an acceptable pharmacokinetic (PK) and safety profile to support long-term SC or IV dosing in patients.

1.2.2 Summary of Clinical Studies

As of 27 May 2017, crenezumab has been *or is being* investigated in a total of *11* completed or ongoing Phase I, Phase II, and Phase III clinical trials. Approximately *1051 subjects* have been exposed to crenezumab in these studies *(exposure in blinded studies is estimated using patient enrollment and study randomization scheme).*

Four Phase I studies (Studies ABE4427g, AB4662g, GP29172, [redacted]) have been completed. Study ABE4427g studied the safety, tolerability, and pharmacokinetics of single- and multiple-ascending doses of IV crenezumab in patients with mild to moderate AD who were 50–86 years of age. Study ABE4662g studied the pharmacokinetics of IV and SC dosing and the relative bioavailability of crenezumab (SC dosing) in healthy volunteers who were 18–50 years of age. Study GP29172 evaluated the pharmacokinetics of SC dosing and the bioequivalence of two formulations of crenezumab (SC dosing) in healthy volunteers who were 18-65 years of age.

[redacted]

Two Phase I studies GN29632 *and* [redacted] are ongoing. *Study* GN29632 is *a* dose-escalation study designed to assess safety and tolerability of multiple doses of crenezumab *(30, 45, 60, and 120 mg/kg IV Q4W)* in patients with mild to moderate AD *followed by an open-label extension (OLE) phase.* [redacted]

The Phase II program (ABE4869g, ABE4955g, GN28525, and GN28352), including an *OLE* study (GN28525), was designed to study safety and tolerability, and to initially assess the clinical and biomarker effects of crenezumab in two populations within the AD spectrum: an AD dementia population (50–80 years of age) with mild to moderate disease severity (MMSE, 18–26); and *an at-risk* population *for AD* (30–60 years of age) with an autosomal dominant mutation (E280A) in the presenilin (*PSEN*) 1 gene

(autosomal dominant AD [ADAD] population). The OLE study (GN28525) in patients who previously participated in either Study ABE4869g or ABE4955g is $complete$. The Phase II Study GN28352 is ongoing in an ADAD population.

The Phase III $studies$ BN29552 and $BN29553$, which $evaluate$ the efficacy, safety, and tolerability of crenezumab in pAD to mAD population (MMSE, 22–30), are ongoing.

Sections 1.2.2.1–1.2.2.10 summarize the crenezumab clinical studies to date. Refer to the $Crenezumab$ Investigator's Brochure for further information.

1.2.2.1 Study ABE4427g

Study ABE4427g was a randomized, placebo-controlled, double-blind, Phase I study. The study had a single-dose dose–escalation stage followed by a randomized, placebo-controlled, double-blind, parallel, multiple-dose stage in patients 50–86 years of age who had been diagnosed with mild to moderate AD. This study assessed four IV single dose levels with a range of 0.3–10 mg/kg and three IV multiple dose levels (four weekly doses each) with a range of 0.5–5 mg/kg.

No patients died, discontinued treatment, or withdrew from the study because of an adverse event. The incidence of adverse events was comparable across cohorts, with no evidence of a dose-related effect. No cases of ARIA-E or infusion-related toxicities were reported. Overall, crenezumab appeared to be well tolerated at the doses investigated. The maximum dose administered was 10 mg/kg IV; a maximum-tolerated dose was not achieved. Full details are provided in the crenezumab Investigator's Brochure.

1.2.2.2 Study ABE4662g

Study ABE4662g was a Phase I, single-dose, randomized, parallel-group, open-label study that evaluated the safety, tolerability, pharmacokinetics, and bioavailability of crenezumab following SC and IV administration in healthy volunteers. Subjects were randomized in a 1:1 ratio to receive a single dose of approximately 1.8 mg/kg crenezumab by either SC injection or IV infusion. Subjects were followed for 85 days post-dose. The study has $been$ completed.

All subjects received a single dose of crenezumab IV (n = 11) or SC (n = 11). Crenezumab was well tolerated, and no deaths, discontinuations due to adverse events, or serious adverse events were reported. Full details are provided in the crenezumab Investigator's Brochure.

1.2.2.3 Study ABE4869g

Study ABE4869g was a Phase II, randomized, double-blind, parallel-group, placebo-controlled study designed to evaluate the safety and efficacy of 68 weeks of crenezumab treatment in patients 50–80 years of age who had been diagnosed with mild to moderate AD (MMSE, 18–26). A total of 444 patients were enrolled and dosed in

the study: 184 patients in an SC cohort, 247 patients in the IV cohort, and 13 patients in a safety run-in cohort.

The study was conducted in two parts. In Part 1, the SC cohort, 184 patients were randomized and dosed in a 2:1 ratio (active: placebo) to receive either crenezumab 300 mg or matching placebo administered via SC injection q2w. In Part 2, the IV cohort, 247 patients were randomized and dosed in a 2:1 ratio (active: placebo) to receive either crenezumab or matching placebo administered via IV infusion q4w. Since the highest single dose assessed during the Phase I study (10 mg/kg IV) did not elicit any dose-limiting toxicities (DLTs), a run-in assessment of the safety and tolerability of multiple monthly IV administrations of 15 mg/kg crenezumab was conducted in a limited number of patients at selected sites prior to initiating full enrollment in the IV cohort in Part 2. On the basis of the outcome of the safety run-in assessment, the dose of crenezumab of 15 mg/kg IV was selected for Part 2. Safety information is provided in Section 1.2.3; full details are provided in the crenezumab Investigator's Brochure.

1.2.2.4 Study ABE4955g

Study ABE4955g, a Phase II, randomized, double-blind, parallel-group, placebo-controlled study, was designed to evaluate the effects of crenezumab on brain amyloid burden as assessed by florbetapir-PET and other biomarkers in patients 50–80 years of age who had been diagnosed with mild to moderate AD (MMSE, 18–26). This was a companion study to Study ABE4869g (see Section 1.2.2.3). The 15 mg/kg dose was selected on the basis of the outcome of the safety run-in assessment during Study ABE4869g. Thirty-nine patients were enrolled and dosed in Part 1 (SC cohort) of the study; 52 patients were enrolled and dosed in Part 2 (IV cohort). Patients were randomized to receive crenezumab or placebo in a 2:1 ratio. Safety information is provided in Section 1.2.3; full details are provided in the crenezumab Investigator's Brochure.

1.2.2.5 Study GN28525

Study GN28525 *was* an OLE study to the Phase II Studies ABE4869g and ABE4955g. The primary objective of Study GN28525 *was* to further evaluate the long-term safety and tolerability of crenezumab administered via IV or SC doses in patients with AD for up to 144 weeks. *Safety information is provided in Section 1.2.3; full details are provided in the Crenezumab Investigator's Brochure.*

1.2.2.6 Study GN29632

Study GN29632 is an ongoing, randomized, double-blind, placebo-controlled Phase Ib study to evaluate crenezumab in patients with mild to moderate AD (see the crenezumab Investigator's Brochure for further details). The primary objective is to evaluate the safety and tolerability of doses higher than that used in the Phase II studies (15 mg/kg IV *Q4W*), including 60 mg/kg IV Q4W (the dose selected for Phase III) and higher.

Study GN29632 is designed to assess increasing doses of crenezumab in separate cohorts. Dose escalation in new cohorts is governed by dose-limiting criteria and reviewed by an unblinded internal safety monitoring committee (SMC). The purpose of the study is to identify early onset and high frequency adverse events, such as ARIA-E.

If a patient experiences a dose-limiting event (defined below), he or she will not receive additional study drug. If ≥2 patients on active treatment in a dose cohort experience a dose-limiting event as assessed by the SMC, then an evaluation of all available safety data will be performed to determine whether further dosing may continue at that dose or the dose reduced to a dose level not associated with DLT.

The dose-limiting definitions are as follows:

- **DLT:** One National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE v4.0) Grade≥3 adverse event; or Grade≥2 adverse event falling in specific neurological categories or any infusion-related toxicity that occurs within 24 hours after study drug administration that is severe or serious or does not resolve promptly with a reduced infusion rate and/or supportive care.
- **Dose-limiting criteria related to ARIA-E:** A patient who exhibits ARIA-E will not receive any additional study drug until the ARIA-E has resolved. Upon resolution, the patient may resume study drug administration at the same dose level; however, upon the first recurrence of ARIA-E, the patient will be discontinued from the study.
- **Dose-limiting criteria relating to ARIA-H:** A patient who exhibits ARIA-H that meets the criteria for superficial siderosis of the CNS; exhibits one new cerebral macrohemorrhage; has an increase of ≥1 in the number of symptomatic cerebral mH compared with screening; or has an increase of ≥6 in the number of asymptomatic cerebral mH compared with screening will be discontinued from treatment.

Patients *received* double-blind treatment for 13 weeks followed by an OLE. The initial cohort received placebo or crenezumab 30 or 45 mg/kg IV q4w. There was a specified SMC meeting after all patients on the 30 and 45 mg/kg doses reached 13 weeks of treatment. No stopping criteria were met (including no ARIA-E), and no serious adverse events related to study drug were observed; no DLTs have been reported.

A second cohort included 26 patients on a crenezumab dose of 60 mg/kg IV Q4W or placebo (randomized in a 5:1 ratio). There was a specified SMC meeting after all patients on the 60 mg/kg dose reached 13 weeks of treatment. No stopping criteria were met (including no ARIA-E), and no serious adverse events related to study drug were observed.

A *third* cohort *included 23 patients on* a crenezumab dose of 120 mg/kg IV *Q4W or placebo (randomized in a 5:1 ratio), with a specified SMC meeting after all patients*

reached 13 weeks of treatment. No stopping criteria were met (including no ARIA-E), and no serious adverse events related to study drug were observed.

The majority of patients entered the OLE phase which is ongoing. *Patients in the OLE continued on the same dose as per cohort assignment, except for those in the third cohort, who by design received a dose of 60 mg/kg IV Q4W. Additionally, the protocol was subsequently amended so that patients in the first cohort are given the option to increase to 60 mg/kg IV Q4W.*

Safety data review for *all* dose groups is regularly conducted. *Safety information is provided in Section 1.2.3; full details are provided in the crenezumab Investigator's Brochure.*

1.2.2.7 Study GP29172

Study GP29172 was a Phase I, single-dose, randomized, open-label, parallel-group study to assess the relative bioavailability of two formulations of crenezumab in healthy subjects following SC administration of a single 720 mg dose. This study has been completed.

[redacted]

1.2.2.9 Study GN28352

Study GN28352 is an ongoing Phase II, randomized, double-blind, parallel-group, placebo-controlled study designed to evaluate the safety and efficacy of crenezumab in patients 30–60 years of age who are carriers of the *PSEN* 1 E280A mutation and who do not meet criteria for MCI or dementia because of AD. Safety data *are* reviewed *approximately every 6 months* by an independent Data Safety Monitoring Board *(DSMB).*

1.2.2.10 Study BN29552

Study BN29552 is an ongoing Phase III, randomized, double-blind, parallel-group, placebo-controlled trial designed to evaluate the safety and efficacy of crenezumab in patients aged 50–85 years who meet protocol-specified criteria for pAD to mAD. Patients are receiving a crenezumab dose of 60 mg/kg IV Q4W *vs. placebo;* 750 patients *were* planned to be enrolled into this study. *This study is fully enrolled.*

Data are reviewed approximately every quarter by an independent Data Monitoring Committee (iDMC).

1.2.3 Safety Overview

The clinical safety of crenezumab has been evaluated using all available clinical data from the *four* completed Phase I studies (ABE4427, ABE4662g, GP29172, [redacted]

[redacted]), three completed Phase II studies (ABE4869g,ABE4955g, and GN28525), one ongoing Phase II study (GN28352), and two ongoing Phase I studies ([redacted] and GN29632).

The safety and tolerability profile of crenezumab to date supports its continued development in both sporadic (idiopathic) AD and ADAD.

In the Phase II studies in mild to moderate AD, more fatal events and events of pneumonia were reported in crenezumab-treated patients versus placebo-treated patients. However, the rates of death and pneumonia in the crenezumab arms were within the expected rates for the enrolled population. Please refer to Sections 1.2.3.2 and 1.2.3.3, respectively, for more information.

ARIA-E and ARIA-H remain potential risks for crenezumab, even if they were not identified as a safety concern in crenezumab studies: ARIA-E and ARIA-H have been observed with other mAbs that target Aβ; specifically, ARIA-E events have been dose limiting for several anti-Aβ antibodies (see Section 1.2.3.4).

Injection and infusion site reactions have been reported at similar rates in patients receiving crenezumab SC or IV and placebo in the Phase II studies.

No clinically relevant changes have been observed in laboratory parameters, physical and neurologic examinations, vital signs, and ECG parameters.

A Phase Ib study (GN29632) to evaluate doses higher than those used in the Phase II studies, including 60 mg/kg IV Q4W and 120 mg/kg IV Q4W, is ongoing. As of the date of protocol release, no new or unexpected safety findings have been documented. Specifically, no DLTs, drug–related serious adverse events, and ARIA-E events have been reported (see Section 1.2.2.6).

Detailed safety data from all studies are reported in the crenezumab Investigator's Brochure.

The Sponsor performs regular review of blinded data from the ongoing studies and, to date, has not identified unexpected safety findings. Furthermore, Study GN29632 is overseen by an internal SMC, while an iDMC regularly reviews unblinded data from Study BN29552 (and Study BN29553) and a DSMB from study GN28352.

1.2.3.1 Overall Adverse Event Profile

The Phase II program in mild to moderate AD (Studies ABE4869g and ABE4955g) comprises the largest completed studies conducted to date with crenezumab.

The RPCP of the Phase II program in mild to moderate AD was defined as the protocol–specified reporting period of the 2:1 randomization IV and SC dose arms of Studies ABE4869g and ABE4955g. The RPCP excluded the safety run-in arm of Study ABE4869g.

In the RPCP, patients were treated over a 68-week period and monitored for safety for 4 additional weeks if they rolled over into Study GN28525 or for 16 weeks if they did not enter Study GN28525 or they discontinued treatment prematurely. The observation period included the 68–week treatment period and the safety follow-up period.

The safety evaluable database for the Phase II program included 535 patients with mild to moderate AD who received at least one dose of study drug. Of these, 522 patients had been randomized to receive crenezumab at either 300 mg q2w SC (n = 148) or 15 mg/kg q4w IV (n = 198) or to receive placebo (n = 176). During the RPCP of the Phase II program, 9 patients (2.6%) who received crenezumab and 9 patients (5.1%) who received placebo withdrew due to adverse events. There were no imbalances in the overall rates of adverse events between patients who received crenezumab and patients who receive placebo (91.1% [n = 318] vs. 90.8% [n = 157], respectively). Serious adverse events were reported in 57 patients (16.3%) who received SC or IV crenezumab and in 21 patients (12.1%) who received SC or IV placebo. The imbalance in the rate of serious adverse events was mainly due to reports of pneumonia (see Section 1.2.3.3).

In the *completed* OLE *study* of the Phase II studies (Study GN28525), a total of 93.2% of patients from the original SC cohort and 87.7% of patients from the original IV cohort experienced at least one adverse event. Reported adverse events were as expected in an elderly population with AD, with fall and urinary tract infection being the most frequently recorded adverse events.

1.2.3.2 Deaths

During the RPCP of the Phase II program, there were five deaths. All five deaths occurred in patients treated with crenezumab; none was assessed as related to study drug by the investigator. This represents 1.4% of patients who received crenezumab compared with 0% of patients who received placebo. The rate of death in the crenezumab arms was within the expected rates of death in the AD clinical trial population treated with placebo (0%–1.9%) or with Aβ–directed passive immunotherapy (2.1%–2.4%; Salloway et al. 2009, 2014; Doody et al. 2014).

During the OLE *part of the Phase II program, 15* patients *died. Ten of the 15 patients had received active* crenezumab*,* and *5 had received placebo during RPCP* of *the Phase II study.* All deaths were assessed as not related to study drug by the investigator.

1.2.3.3 Pneumonia

An imbalance in the rates of serious adverse events of pneumonia was observed in the RPCP of the Phase II program, with 6 cases (1.7%) in the crenezumab arms and 1 case (0.6%) in the placebo arms. All serious pneumonia cases occurred 7–13 months after the first study dose. Individual cases were confounded by age, smoking history, diabetes, obesity, some by previous pneumonia events, and tuberculosis, which are known risk factors for developing pneumonia. An imbalance in non-serious adverse

events of total lower respiratory tract infection, also driven by pneumonia, was observed in the RPCP of the Phase II program, with 5 cases versus 0 cases (1.4% vs. 0%) of non-serious pneumonia observed in the crenezumab and placebo arms, respectively.

The diagnosis of pneumonia was confirmed by chest radiology in 5 of the 11 cases reported in crenezumab-treated patients. The vast majority of cases resolved upon standard treatment with antibiotics and in the absence of modification of the study drug regimen.

Overall, the pneumonia rates observed in the RPCP of Studies ABE4869g and ABE4955g (3.2% total and 1.7% serious) were slightly higher than those observed among Phase III AD clinical trial populations (Henley et al. 2012; Doody et al. 2014; Henley et al. 2014; Salloway et al. 2014). The pneumonia rates in the placebo-treated population were slightly lower (0.6%; Henley et al. 2012; Doody et al. 2014; Henley et al. 2014; Salloway et al. 2014). However, the precision of these estimates is limited by the relatively smaller sample size in crenezumab Phase II data compared to Phase III safety populations in bapineuzumab, solanezumab, and semagacestat studies. The rate of pneumonia in crenezumab-treated patients (3.2%) is within the reported incidence of pneumonia in the elderly population (2.5%–4.4%; Vila-Corcoles et al. 2009).

The rate observed during the OLE part of the Phase II program was similar to that observed in the RPCP.

1.2.3.4 Amyloid–Related Imaging Abnormalities of Edema/Effusion and Hemosiderin Deposition

In the RPCP of the Phase II program in mild to moderate AD, a single case of asymptomatic ARIA-E was reported in a patient who received crenezumab. *This patient experienced asymptomatic recurrences during the OLE phase.* The proportion of patients with ARIA-H was similar in the crenezumab and placebo arms: new (incident) mHs were documented in 11.5% (N = 40) of crenezumab-treated patients versus 12.7% (N = 22) of placebo-treated patients.

1.2.3.5 Summary

The safety and tolerability profile of crenezumab to date supports its continued development in AD.

More fatal events and pneumonia cases have been observed during the RPCP of the Phase II program in crenezumab-treated versus placebo-treated patients. There was no pattern seen in the causes of death and no obvious mechanism linking crenezumab treatment with pneumonia (e.g., no evidence of immunosuppression). Importantly, there was no relationship between steady-state exposure (AUC or C_{max}) and safety events within each dose cohort. In addition, rates of deaths and pneumonia in crenezumab-treated patients were within the expected ranges for the elderly AD population.

Further details are presented in the crenezumab Investigator's Brochure.

1.2.4 Immunogenicity

The immunogenicity of crenezumab was assessed in the completed Phase I and Phase II Studies ABE4427g, ABE4662g, ABE4869g, and ABE4955g. It is being further assessed in the ongoing Phase I and II trials.

A positive anti-$drug$ antibody (ADA) sample was defined as one in which the presence of detectable $ADAs$ could be confirmed by competitive binding with crenezumab. The prevalence of $ADAs$ at baseline was calculated from the total number of patients who tested positive for $ADAs$ at baseline divided by total number of patients with sample available at the baseline timepoint. The incidence of $ADAs$ postdose with crenezumab, or treatment-emergent $ADAs$, was calculated from the total number of patients who tested positive for $ADAs$ postdose divided by the total number of crenezumab-treated patients who had post-baseline samples available for ADA analysis:

- In Study ABE4427g, a positive ADA response *(postbaseline)* was detected in 1 of 36 patients (2.8%) given crenezumab.
- In Study ABE4662g, no $ADAs$ were detected.
- In Study ABE4662g, no incidence of the formation of $ADAs$ was detected.
- In Study ABE4869g, 444 patients were enrolled (including the safety run-in cohort). Of these, 300 patients were treated with crenezumab and 144 with placebo. The prevalence of $ADAs$ at baseline was calculated as 2 of 441 (0.5%). The incidence of $ADAs$ post-baseline was 2.7% (8 of 300) in patients treated with crenezumab. Among these 8 patients, 7 of 122 (5.7%) were from the SC treatment arm, and 1 of 165 (0.6%) was from the IV treatment arm. There was no effect observed on PK and/or safety readout in ADA-positive patients.
- In Study ABE4955g, there were a total of 91 evaluable patients for immunogenicity, including 29 placebo- and 62 crenezumab-treated patients. The prevalence of $ADAs$ at baseline was 1.1% (1 of 89 patients). A single patient tested positive at baseline only and did not have any subsequent timepoints collected. Post-baseline, there were 88 immunogenicity-evaluable patients. There was no observed incidence of $ADAs$ in either placebo- or crenezumab-treated patients.
- *In the ongoing Phase I study GN29632, the baseline prevalence of ADA-positive patients was 17.6% (13/74). All baseline-positive samples had borderline positive signals. ADAs were not detected postbaseline in any of the dose cohorts. Nevertheless, the presence of circulating crenezumab could interfere with the ADA detection, and negative results cannot rule out the presence of ADAs.*

All planned and ongoing studies will assess $ADAs$ to crenezumab and components of drug product, including impurities.

Further details are presented in the crenezumab Investigator's Brochure.

1.2.5 Pharmacokinetics

The pharmacokinetics of crenezumab have been evaluated in *five* Phase I studies (ABE4427g, ABE4662g, GP29172, GN29632*, and GP29523*) and in two Phase II studies (ABE4869g and ABE4955g). Overall, the observed *and volume of distribution* in the Phase I studies have been consistent with those for other humanized IgG mAbs that exhibit kinetics in the linear-concentration range (Dirks and Meibohm 2010; Deng et al. 2011; Mould and Sweeney 2011).

In the Phase I Study ABE4427g, the serum pharmacokinetics of crenezumab in patients with mild to moderate AD were dose proportional across the dose range tested in both the single-dose (0.3–10 mg/kg) and multi-dose (0.5–5 mg/kg weekly for four doses) phases of the study. [redacted]

The Phase I Study GP29172 demonstrated that crenezumab serum PK parameters following administration of the Phase III drug product (180 mg/mL) were bioequivalent to the Phase II drug product (150 mg/mL) following a single 720 mg SC injection in healthy volunteers. These results were supportive of change of drug product in ongoing clinical studies.

In the Phase II Studies ABE4869g and ABE4955g, serum crenezumab concentrations were measured in samples collected after biweekly SC (300 mg) or monthly IV (15 mg/kg) administration in patients with mild to moderate AD. In general, serum PK concentrations were similar between patients in the two Phase II studies. The higher dose of 15 mg/kg crenezumab administered Q4W by IV infusion resulted in approximately a 1.5-, 2.5-, and 5-fold higher exposure as measured by trough concentration, AUC, and peak concentration at steady-state, respectively, than the lower dose of 300 mg crenezumab administered Q2W by SC injection. For patients in the IV and SC treatment groups, steady–state trough serum crenezumab levels appeared to have been attained between Weeks 13 and 25 in both studies (after 3–6 IV doses or 6–12 SC doses, respectively). In Study ABE4869g, after 68 weeks of dosing with IV (q4w) crenezumab, mean (SD) steady–state trough serum crenezumab levels were 118 (72) μg/mL and steady–state peak serum crenezumab concentration levels were 447 (124) μg/mL. For comparison, the equivalent steady–state trough serum crenezumab levels for SC dosing were 69 (29.6) μg/mL. The trough crenezumab levels in CSF were measured in a subset of patients in Study ABE4869g and in all patients in Study ABE4955g. At Week 69, crenezumab penetration into the CSF was similar between the two studies as well as between the SC and IV doses, with a mean crenezumab CSF/serum ratio of approximately 0.3%. [redacted]

[redacted]

In the Phase Ib study (Study GN29632*), a* preliminary PK analysis *based on data from the 13-week double-blind treatment period at doses of 30, 45, 60, and 120 mg/kg IV Q4W has been performed. Crenezumab pharmacokinetics increased proportionally* to dose *at doses up* to *120* mg/kg and was consistent with the PK findings in prior studies of crenezumab.

[redacted]

Additional PK information for Studies ABE4427g, ABE4662g, ABE4869g, GP29172, GN29632*,* [redacted] is provided in the *Crenezumab* Investigator's Brochure.

Data from Phase II studies suggest that there are no clinically significant drug-drug interactions (DDIs) with crenezumab. Therapeutic proteins (TPs) typically do not undergo metabolism or transport as their clearance pathway; therefore, the potential is limited for small molecule drugs to affect TPs through metabolism or transport pathways. Patients enrolled in the Phase II studies were permitted to continue on approved stable doses of AchE inhibitors or memantine. Stable doses of other maintenance medications were also permitted. Doses of concomitant medications were considered stable if the dose level and frequency had not been adjusted for $\geq$3 months. In Studies ABE4869g and ABE4955g, no impact on crenezumab steady−state exposure metrics (AUC at steady state and C_{max}) by concomitantly administered medications (statins, non-steroidal anti-inflammatory drugs, NMDA antagonists, or cholinesterase inhibitors [ChEIs]) was seen in patients who received crenezumab via IV administration (N = 193) or via SC administration (N = 147). This suggests that there is no PK DDI between these compounds and crenezumab.

1.2.6 Biomarkers

1.2.6.1 Summary

Plasma, CSF, florbetapir amyloid PET, ^{18}F-fluordeoxyglucose (FDG)-PET, and volumetric magnetic resonance imaging (MRI) measurements were evaluated as PD biomarkers in the Phase II studies in patients with mild to moderate AD.

1.2.6.2 Brain Imaging Pharmacodynamic Biomarkers

Florbetapir PET, FDG-PET, and volumetric MRI measurements were evaluated in Study ABE4955g. No evidence of differences was noted between the crenezumab and placebo groups based on the mean changes from baseline at Weeks 23, 47, and 73 of the hippocampal, ventricular, and whole brain volumes.

Florbetapir-Positron Emission Tomography

An evaluation of the effect of crenezumab on amyloid accumulation was conducted in Study ABE4955g. Overall, there was no evidence of a treatment effect in either the SC or IV cohorts on changes from baseline to Week 69 in fibrillary brain amyloid using prespecified imaging normalization via cerebellar gray matter reference region.

A further analysis using a subcortical white matter reference was conducted for the overall population and in the mild AD subpopulation (MMSE, 20–26). There was no evidence of a treatment effect in the SC cohort. In the IV cohort, an overall increase in the mean change in Florbetapir-PET standardized uptake value ratio (SUVR) was observed for patients in both the placebo and crenezumab treatment arms.
The estimated mean change in florbetapir-PET SUVR from baseline was less for the crenezumab arm than the placebo arm at Weeks 47 and 69. The treatment difference at Week 69 was 0.015 (95% CI, -0.005, 0.035; p=0.131). This difference represents a 58.8% reduction in the rate of amyloid accumulation relative to placebo at Week 69.

In the mild AD subpopulation, the difference in SUVR increased to 0.018 (95% CI, -0.006, 0.041; p=0.135). This difference represents a 60.4% reduction in the rate of amyloid accumulation relative to placebo at Week 69.

^{18}F-fluordeoxyglucose Positron Emission Tomography

There was no evidence of a treatment difference between crenezumab and placebo mean changes from baseline for either the SC or IV cohorts.

1.2.6.3 Plasma and Cerebrospinal Fluid Pharmacodynamic Biomarkers

Plasma and CSF biomarker measurements were evaluated in Study ABE4955g. Concentrations of $A\beta_{42}$, total tau, and phosphorylated tau (p-tau) in CSF were assessed in 55 patients with mild to moderate AD (MMSE, 18–26) who had both a baseline and Week 69 CSF sample analyzed. The treatment effects (expressed as placebo mean change from baseline – crenezumab mean change from baseline) were -127.01 pg/mL (95% CI, -197.94, -56.07; p=0.001) and -94.51 pg/mL (95% CI, -173.80, -15.22; p=0.022) for the SC and IV cohorts, respectively, which indicated an overall increase in CSF $A\beta_{42}$ concentrations in patients given crenezumab.

There was no evidence of a treatment difference between crenezumab and placebo mean changes from baseline for either the SC or IV cohorts on either CSF total tau or on p-tau.

*Preliminary data from Phase I study ABE4427g (*Adolfsson et al. 2012*), Phase II studies ABE4869g and ABE4955g, and Phase I study GN29632 show that total plasma $A\beta_{42}$ and $A\beta_{40}$ significantly increased following administration of crenezumab, demonstrating peripheral target engagement. The increase in plasma pharmacodynamics is expected on the basis that when the $A\beta_{42}$ and $A\beta_{40}$ binds to*

crenezumab it takes on the slow half-life of the antibody and therefore stays in the circulation longer. Please refer to the Investigator Brochure for further information.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.3.1 Background

Current therapies for AD focus on symptomatic approaches that target synaptic function and cognitive enhancement (Cummings 2004). *Genetic evidence (e.g., Hardy and Selkoe 2002; Jonsson et al.2012) has* linked the accumulation of Aβ peptides to progression of AD (i.e., the amyloid hypothesis). This hypothesis suggests that overproduction of Aβ or failure to effectively clear this peptide leads to AD. Thus, the targeting of Aβ and subsequent displacement of Aβ from the brain is a rational approach to modify AD progression.

After nearly a decade of research on immunologic approaches to treating AD, including both active and passive immunization programs, much has been learned about selection criteria for antibodies that may maximize efficacy and minimize safety concerns. Consequently, the key efficacy considerations for the selection of an appropriate molecule to target Aβ included the selection of a mAb that 1) binds potentially toxic forms of Aβ, 2) reduces CNS Aβ levels and*/or* amyloid plaque load, and 3) alleviates behavioral deficits in nonclinical animal models.

These criteria led to the selection of crenezumab, a fully humanized IgG4 mAb to Aβ that binds to *Aβ peptides in multiple forms, but notably with high affinity to oligomers (*Adolfsson et al. 2012*; Ultsch et al. 2016). Crenezumab's IgG4 backbone confers reduced activation of Fcγ receptor (FcγRs) in comparison to IgG1 and was shown to minimize FcγR-mediated activation of microglia and release of inflammatory cytokines upon oligomer engagement, which has also been proposed to contribute to neurotoxicity (*Xing et al. 2011*;* Heneka et al. 2015*)—while preserving FcγR-mediated microglial phagocytosis of oligomers (*Adolfsson et al. 2012*). Crenezumab was also designed as an IgG4 based on the hypothesis that reducing effector function would lower the risk of inducing ARIA-E and ARIA-H, possibly by minimizing inflammation at brain vasculature (*Wilcock et al. 2006*). A lack of binding to vascular amyloid, noted following in vivo dosing in PS2APP transgenic mice (Study 15-2817B), may similarly reduce crenezumab's risk of inducing ARIA. Thus, crenezumab was chosen with the expectation that it might combine anti-Aβ activity with a more favorable safety profile.*

The Phase II results showed a lack of consistent treatment effect at the lower dose (300 mg SC *Q2W*), and a *possible* treatment effect *signal* at the higher dose (15 mg/kg IV *Q4W*) that increased in patients with an MMSE in the *milder* range of 22–26. Taken together with the safety profile observed in the Phase II program (see Section 1.2.3) *and subsequent Phase I dose-escalation study (see Section 1.2.2.6),* these data suggest that the therapeutic window had not been explored fully. Therefore, use of a higher dose of crenezumab (60 mg/kg IV *Q4W*) is proposed for the Phase III studies to obtain greater

efficacy while maintaining a favorable benefit-risk profile (see Section 1.3.3 for further details).

Furthermore, recent advances in the field—notably data from the mAb against Aβ aducanumab (Sevigny et al. 2015) are supportive *of the notion* that higher doses than *perhaps originally postulated (Ostrowitzki et al. 2017) may be* needed *in this field* of *anti*-amyloid *antibodies.*

Thus, in this study a dose of 60 mg/kg will be used to *potentially* enable better efficacy to be demonstrated (see Section 1.3.3 for further information on dose).

1.3.2 Efficacy

Study ABE4869g did not meet its co-primary efficacy objectives. In the higher dose cohort, a 16.8% treatment effect in the Alzheimer's Disease Assessment Scale-Cognition, 12 questions (ADAS-Cog-12) change score was seen in the mild to moderate AD population (defined as an MMSE score, 18–26) at Week 73 relative to placebo (1.78 point difference; 95% CI, -0.89,4.44; p=0.190) *(Cummings et al. 2014; Mackey et al. 2016).* The observed treatment effect increased to 23.8% in a prespecified analysis in the mAD population (MMSE score, 20–26; 2.24 point difference; 95% CI, -0.66, 5.15; p=0.128) and to 35.4% in a subsequent analysis in patients with an MMSE of 22–26 (3.44 point difference; 95% CI, 0.24, 6.64).

No treatment effect was observed in the Clinical Dementia Rating-Sum of Boxes (CDR-SB) in either the mild to moderate AD population (3.1%; 0.08 point difference; 95% CI, -0.77, 0.92; p=0.853) or mild AD population (-1.0%; -0.02 point difference; 95% CI, -1.0, 0.96; p=0.964). In an exploratory analysis of a subset of patients with milder AD (MMSE, 22–26), the treatment effects for CDR-SB change from baseline to Week 73 scores relative to placebo increased to 19.6% (1.8 point difference *favoring crenezumab*; 95% CI, -0.65, 1.52).

In the lower dose (300 mg q2w) SC crenezumab cohort, no treatment effect was observed on the ADAS-Cog-12 in any analysis. A treatment effect toward benefit was observed with crenezumab on the CDR-SB at Week 73. However, in the exploratory analysis (MMSE, 22–26), the treatment effect was in the direction of greater decline. A treatment effect was also observed on the Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (ADCS-ADL); however, it was not accompanied by a clear effect on cognition, particularly in the mildest patients. More detail on Phase II results can be found in the crenezumab Investigator's Brochure. When taken together, these data showed a consistent treatment effect only when a 2.5-fold higher exposure of crenezumab was attained (see Section 1.2.5 for further information on the pharmacokinetics of crenezumab).

Data from the Phase II program also showed that patients with milder disease (i.e., MMSE, 22–26) received greater treatment benefit. Similar findings were observed in the

biomarker Study ABE4955g. In the more recent 18-month Phase III global program with anti-amyloid antibodies in mild to moderate AD, solanezumab failed to meet primary endpoints on cognition and function. However, treatment effects were observed in a prespecified secondary analysis of pooled data from patients with mild AD data from the EXPEDITION1 and EXPEDITION 2 studies (Doody et al. 2014), which showed a statistically significant effect on cognition (ADAS-Cog subscales 11 and 14) and a trend on function (ADCS-ADL). No clinical benefit was observed in patients with moderate AD on any clinical scale, which supported the hypothesis that intervention is needed early in the course of disease.

AD is a slow, progressive disorder with no fixed events that define its onset (Albert et al. 2011). As AD is symptomatic long before dementia is diagnosed, pAD is recognized as an intermediate stage between normalcy and dementia. According to this approach, Dubois et al. (2014) proposed the diagnosis of early AD on the objective evidence of significantly impaired memory and the presence of hippocampal atrophy on MRI, an abnormal pattern of CSF biomarkers, or a specific pattern on PET neuroimaging. This approach includes pAD and mAD, irrespective of the dementia diagnosis. Because the accumulation of brain amyloid begins before the onset of AD dementia, it is reasonable to postulate that the benefit of anti-amyloid therapy may be greater if initiated at this earlier stage of the disease while neuronal damage is more limited. This supports enrollment of patients who have detectable but more subtle cognitive deficits but have confirmed pathophysiology.

The use of a single endpoint across both subpopulations of pAD and mAD is consistent with the current understanding of AD. Use of the CDR-SB as the primary outcome measure for studies of prodromal to mild AD enables simultaneous demonstration of benefit on primary symptoms (e.g., cognition, function) and clinical relevance (Aisen 2009; Aisen et al. 2011) while also ensuring use of a clinical outcome assessment with adequate measurement properties (U.S. Food and Drug Administration [FDA] 2013).

The approach to population and appropriate primary endpoint is used by others and many clinical programs now target the prodromal to mild AD continuum and use the CDR-SB to measure treatment benefit (see AMARANTH [NCT02245737] and PRIME [NCT02477800]).

Collectively, the data support the rationale and strategy for conducting Phase III efficacy and safety studies with crenezumab in patients with prodromal to mild AD who have biomarker (CSF or PET) evidence of amyloid pathology.

The purpose of this study is to establish efficacy and safety of crenezumab in patients with prodromal to mild AD who may or may not be treated concurrently with approved treatments for AD.

As anti-amyloid therapy is not expected to provide acute improvement of symptoms, a minimum of a 100-week, 26–dose treatment period was selected to demonstrate enduring clinical benefit on the basis of the mechanism of action of crenezumab that is expected to delay disease progression rather than provide symptomatic improvement over baseline. The proposed trial duration is supported by data from Study ABE4869g, which demonstrated that the difference in decline between placebo- and crenezumab-treated patients' increased over time. Placebo decline is expected to be greater at 24 months relative to 18 months; this greater decline allows greater potential to demonstrate treatment effect.

The use of the OLE enables a longer assessment of benefit-risk in the target population among a large proportion of patients who enter the study and enables those who received placebo in the double-blind portion of the trial to obtain the potential benefit of active treatment.

1.3.3 Dose

Given the very limited brain penetration observed for IgGs in general (0.2%–0.3% of levels in serum; Reiber and Felgenhauer 1987), high-serum drug concentrations will be required to increase exposure to the site of action. [redacted]

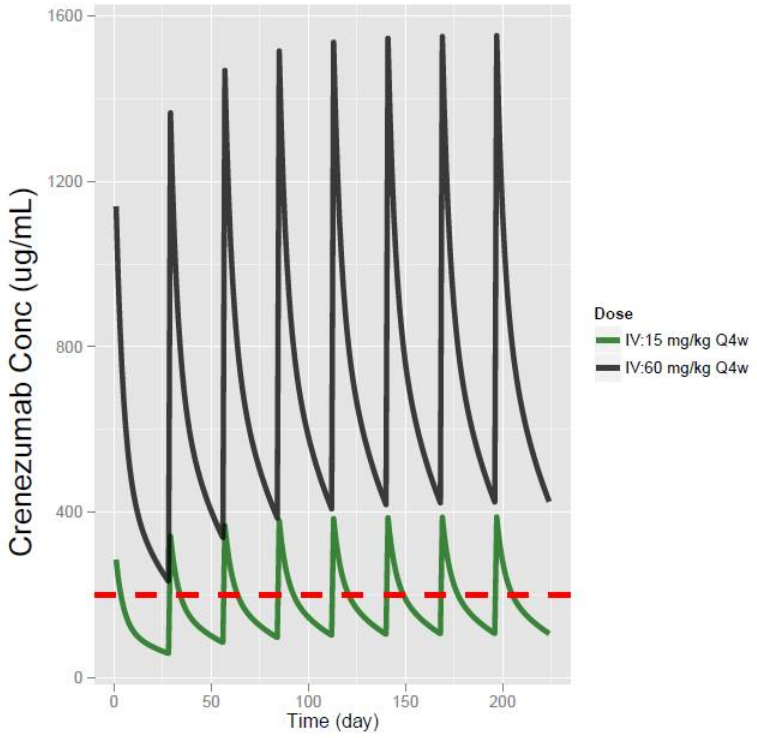
The Phase II studies demonstrated consistent treatment effects in the high-dose (15 mg/kg q4w IV) arm without eliciting dose-limiting events. The therapeutic window for crenezumab has not been fully explored; increasing the dose in this study has the potential to increase efficacy while maintaining a favorable safety profile.

Higher doses of crenezumab are predicted to increase concentrations in the brain compared with the 15 mg/kg IV dose and therefore maintain drug concentrations above the in vitro EC_{50} in the brain throughout the treatment period. In vitro, the EC_{50} for crenezumab binding to $A\beta_{1\text{-}42}$ monomers and aggregates was approximately 0.2 μg/mL and higher target engagement of soluble Aβ was observed with higher crenezumab concentrations (Adolfsson et al. 2012). Crenezumab binds both $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ with high affinity (7.3 ± 0.6 nM and 11.1 ± 1.2 nM, respectively), inhibits Aβ aggregation, and promotes Aβ disaggregation. The dose of 60 mg/kg results in a 4-fold increase in exposure in all PK parameters compared with 15 mg/kg (see Figure 1).

[redacted]

[redacted]

Figure 1 Pharmacokinetic Profile Based on Modelling and Simulation Data for 60 mg/kg of Crenezumab Administered Intravenously Every 4 Weeks Compared with 15 mg/kg Crenezumab Administered Intravenously Every 4 Weeks



Conc = concentration; Q4w = every 4 weeks; Dotted red line = EC_{50}.

Nonclinical safety data provide 2-, 6-, and 3-fold safety factors for the 60-mg/kg dose at steady state on the basis of human equivalent dose, average exposure (AUC), and C_{max}, respectively, relative to the maximum tested dose of 100 mg/kg per week via SC administration in cynomolgus monkeys (see the crenezumab Investigator's Brochure).

The dose used in this study, 60 mg/kg IV q4w, along with higher doses, is being evaluated in the ongoing Phase Ib Study GN29632 (see Section 1.2.2.6). This study was designed to provide evidence of absence of early safety signals for higher doses of crenezumab than had been used in the completed Phase II program. All patients in this study are able to continue into an OLE. Up to the date of this protocol, no stopping criteria had been met (including no occurrences of ARIA-E), and no serious adverse events related to study drug had been observed. Patients who reached 13 weeks of treatment all transitioned to an OLE.

In this Phase III study, use of a higher dose (60 mg/kg) q4w than previously used in the Phase II program has been selected as it provides the opportunity to determine the optimal benefit-risk for patients.

1.3.4 Biomarkers

In AD, core biomarkers that have been developed that reflect amyloid and neurofibrillary tangle pathology, and neuronal degeneration. Additional biomarkers that reflect other aspects of Alzheimer's pathology are also being developed.

Two imaging modalities are mainly used as secondary or exploratory endpoints in clinical trials of AD: structural MRI and amyloid PET. The change in volumes of specific brain regions as measured by structural MRI is thought to reflect neuronal loss and atrophy. PET tracers that bind to fibrillar Aβ in the brain (e.g., florbetapir, approved for use by the FDA in 2011) are thought to represent accumulation of the Aβ plaques (Joshi et al. 2012).

The CSF is in direct contact with the extracellular space of the brain and biomarkers measured in CSF can reflect biochemical changes in the brain. Low CSF $A\beta_{42}$ is well established as a biomarker of Alzheimer's pathology (Shaw et al. 2009; Le Bastard et al. 2013). Thus, CSF Aβ levels may provide information on diagnosis and disease progression and act as a biomarker for target engagement and for the impact of crenezumab on Aβ retention and aggregation. Changes in CSF total tau and p–tau-181 levels over time may provide information on the impact of crenezumab on tau pathology. Other exploratory biomarkers in CSF may provide additional understanding of the impact of crenezumab on disease progression.

1.3.5 Risk to Patients without Alzheimer's Disease Pathology

Due to rigorous screening procedures in this study, including the measurement of CSF $A\beta_{1\text{-}42}$ and amyloid-PET scan, it is expected that only patients with AD pathology will be enrolled. In the event that a patient without amyloid pathology is enrolled, no additional risk is expected. However, such a patient may experience other side effects related to the product (e.g., infusion reactions, development of $ADAs$).

1.3.6 Overall Benefit-Risk Summary

The benefit-risk profile of investigation of crenezumab at a dose of 60 mg/kg IV q4w in a population of prodromal to mild AD patients is favorable.

Overall, the benefit-risk assessment of crenezumab is based on the following:

- In Phase II studies *in patients with AD*:
  - In prespecified subanalyses, a consistent effect on ADAS-Cog-12 was observed in the subset of patients with mAD (MMSE, 22–26) who were treated with crenezumab 15 mg IV q4w versus placebo.
  - Treatment with crenezumab was associated with an increase in CSF-Aβ_{42} relative to placebo, which was suggestive of target engagement in the CNS.
- ARIA events were within the range of background events in this population. *A* single *patient experienced three events* of asymptomatic ARIA-E*, all of which were Grade 1 in severity.*
- ARIA *appears* to be manageable with MRI monitoring and dose-intervention algorithms and do not appear to lead to significant adverse outcomes (e.g., Sperling et al. 2012a)
  - While more deaths and pneumonia cases were observed with crenezumab versus placebo, there was no pattern seen in the causes of death, and no obvious common mechanism observed for pneumonia (e.g., immunosuppression). In addition, death rates are in line with background rates for the placebo-treated or untreated AD population (Henley et al. 2014) and in the variability range reported in clinical trials for compounds of this class with similar patient populations and durations of treatment (Doody et al. 2014; Salloway et al. 2014). The rate of pneumonia in crenezumab-treated patients (3.2%) is within the reported incidence of pneumonia in the elderly population (2.5%–4.4%; Chong and Street 2008), and slightly higher than the rate of pneumonia cases reported in the active and placebo arms of the solanezumab Phase III trials (2.0% and 2.1%, respectively; Doody et al. 2014). This may be attributable to the small patient numbers in the Phase II studies.
- *Until January 2018, in the ongoing clinical development program two additional ARIA-E (one symptomatic] have been observed. The benefit–risk profile remains unchanged by these adverse events.*
- Patients will undergo regular brain MRI monitoring, and discontinuation rules are in place in case of ARIA.
- Patients will be asked about prior respiratory history and any risk factors for pneumonia at screening. Those with significant respiratory disease (such as severe chronic obstructive pulmonary disease [COPD]) will be excluded. Pneumonia cases, other serious respiratory infections, and deaths will be closely monitored in the study, through the requirement to report these cases to the Sponsor within 24 hours with a full description of the case (see Section 5.4).

- An unblinded iDMC is in place to review adverse events, serious adverse events, ARIA-E and ARIA-H findings, and adverse events of special interest (including pneumonia) as well as laboratory and ECG data. Review will occur regularly (e.g., quarterly). Details of the iDMC will be provided in the iDMC Charter (available on request).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of crenezumab compared with placebo in patients with prodromal to mild AD. Specific objectives and corresponding endpoints for the study are outlined in Table 1.

Table 1 Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	
• To evaluate the efficacy of crenezumab compared with placebo	• Change from baseline to Week 105 in global *outcome* as assessed by CDR-SB
Secondary Efficacy *Objectives*:	
• To evaluate the efficacy of crenezumab compared with placebo *on additional cognitive, functional, and behavioral outcomes*	• Change from baseline to Week 105 on cognition as *assessed* by ADAS-Cog-13 and *ADAS-Cog-11* • Change from baseline to Week 105 on severity of dementia, assessed *by* CDR-GS *and MMSE* • Change from baseline to Week 105 on *function as* assessed by the ADCS-ADL total score *and its ADCS-iADL subscore and by the FAQ total score* • *Change from baseline to Week 105 on a measure of* dependence derived from the ADCS-ADL score • *Change from baseline to Week 105 on behavior* assessed *by* the *NPI-Q* total score
• *To evaluate the efficacy of crenezumab compared with placebo on caregiver and quality of life endpoints*	• Effect of crenezumab on HRQOL, assessed using the QOL-AD scale • Effect of crenezumab on caregiver burden, assessed using the ZCI-AD scale • Effect of crenezumab on health outcomes in patient and caregiver as measured by EQ-5D
Exploratory Efficacy Objectives:	
• *To evaluate the efficacy of crenezumab compared with placebo on events related to disease progression*	• *Effect on cognition, assessed by time to an increase from baseline at any time before or on Week 105 (i.e., worsening) on a version of the ADAS-Cog or the MMSE* • *Time to clinically evident decline since baseline, as defined by an increment on the CDR global score* • *Time to development of impairment in additional domains or worsening of impairment within a domain on the CDR-SB* • *Time to increase-of-dependence level, as derived from the ADCS-ADL scale* • *Time to decline in ability to perform one or more basic or instrumental ADL present at baseline using the ADCS-ADL scale* • *Composite time-to-event endpoint. Combination of clinical progression events including any of the following: worsening disease severity (e.g., CDR Global), increasing care needs (e.g., ADCS-ADL derived dependence level), concomitant medications, and other events that may be indicative of disease progression.*

Table 1 Objectives and Corresponding Endpoints (cont.)

Safety Objective:	
• To evaluate the safety of crenezumab compared with placebo	• Nature, frequency, severity, and timing of adverse events and serious adverse events • Physical and neurologic examinations, vital signs, blood tests, ECGs, and C-SSRS • Adverse events of special interest, specifically pneumonia • Adverse events as assessed by MRI: ARIA-E and ARIA-H • The immunogenic potential of crenezumab through measurement of antibodies directed against crenezumab and other components of the drug product and assessment of their relationship with other outcome measures.
Pharmacokinetic Objectives:	
• To characterize the crenezumab PK profile	• Serum concentration of crenezumab (administered at a dose of 60 mg/kg IV) at specified timepoints • *CSF concentration of crenezumab (administered at a dose of 60 mg/kg IV) at specified timepoints in a subset of consenting patients in a substudy (BN29553-CSF longitudinal)*
Biomarker Objectives:	
• To evaluate the effect of crenezumab compared with placebo on biomarker changes	• *Brain amyloid load over time measured by amyloid-PET in a substudy (BN29552/BN29553-Amyloid PET longitudinal)* • *Brain tau load over time measured by tau-PET in a substudy (BN29552/BN29553-tau PET longitudinal)* • *CSF markers of disease over time in a substudy (BN29553-CSF longitudinal)* • MRI-derived measurements over time such as volumetric changes in whole brain, ventricles, hippocampus, or other structures • Plasma Abeta concentrations
• *To explore exposure–response relationships in patients with prodromal to mild AD based on the following endpoints:*	• *CSF biomarkers* • Plasma PD biomarkers • Imaging biomarkers • Efficacy and safety outcomes
• To conduct exploratory genetic analysis on disease progression and response to crenezumab based on the following:	• [redacted] • *APOE* genotype

Table 1 Objectives and Corresponding Endpoints (cont.)

AD = Alzheimer's disease; ADAS-Cog-*11* = Alzheimer's Disease Assessment Scale-Cognition *11*; ADAS-Cog (subscale) 13 = Alzheimer's Disease Assessment Scale-Cognition (subscale) 13; ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory; ADCS-iADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory Instrumental Subscale; ADL = activity of daily living; ARIA-E = Amyloid–related imaging abnormalities-edema/effusion; ARIA-H = Amyloid–related imaging abnormalities-hemosiderin deposition; CDR-SB = Clinical Dementia Rating–Sum of Boxes; CDR-GS = Global Score; C-SSRS = Columbia Suicide Severity Rating Scale; FAQ = Functional Activities Questionnaire; HRQOL = health–related quality of life; IV = intravenous; MMSE = Mini Mental State Exam; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory Questionnaire; PD = pharmacodynamic; *PET=positron emission tomography;* PK = pharmacokinetic; QOL-AD = Quality of Life-Alzheimer's Disease Scale; ZCI-AD = Zarit Caregiver Interview for Alzheimer's Disease.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of crenezumab in patients with prodromal to mild AD.

The planned number of patients in the Global Enrollment Phase for this study is approximately 750 (375 randomized to crenezumab 60 mg/kg IV and 375 randomized to placebo). [redacted] This China subpopulation may include patients enrolled at sites in *mainland China, Hong Kong, and/or Taiwan (according to applicable Chinese regulations)* during both the Global Enrollment Phase and the China Extension Phase.

To maintain a balanced number of patients enrolled in each treatment arm, randomization will be stratified by dementia status (pAD vs. mAD), *APOE* status (presence or absence of ε4 allele), anti-dementia medications (present of absent) at baseline, and geographic region. Approximately 250 centers in approximately 30 countries worldwide will participate in this study.

Patients will be selected on the basis of clinical diagnosis of probable AD (according to the National Institute on Aging/Alzheimer's Association [NIAAA] Diagnostic Criteria and Guidelines for AD; see Appendix 2; McKhann et al. 2011) OR pAD (according to the NIAAA Diagnostic Criteria and Guidelines for AD; see Appendix 3; Albert et al. 2011).

Eligible patients will be 50–85 years old and must have increased brain amyloid as indicated by reduced CSF $A\beta_{1\text{-}42}$ concentration (i.e., CSF-enrolled patients) *or* positive amyloid PET scan by qualitative read (i.e., PET-enrolled patients).

At the time of screening, patients must have a MMSE score of ≥ 22 points and a Clinical Dementia Rating-Global Score (CDR-GS) of 0.5 or 1.0. To confirm objective memory impairment, patients must have a Free and Cued Selective Reminding Test–Immediate Recall (FCSRT-IR) Cueing Index * of ≤ 0.67 and a total free recall score of ≤ 27.

* FCSRT cueing index is calculated as follows:

[Free recall score – total score achieved] / [Free recall score – 48]

Neuroradiologic evaluation will use a standard MRI protocol (including T2*-weighted gradient–recalled echo [GRE] and fluid–attenuated inversion recovery [FLAIR]). Screening MRIs will be read by a central reader who will exclude patients with other structural causes of dementia, significant cerebral vascular pathology, and other relevant exclusion criteria (see Section 4.2).

Patients will be eligible for the study whether or not they are receiving standard-of-care symptomatic medications for AD (i.e., ChEIs or memantine, or combination*),* or medical food *supplements (e.g., Axona® or* Souvenaid®). These medications *or supplements* must have been stable for ≥ 3 months prior to screening.

The study will consist of a screening period of up to *12* weeks for each patient who agrees to participate, signs the informed consent form, and is eligible for the study. Eligible patients will then undergo the baseline visit (Week 1), when they will receive the first dose following completion of all relevant assessments. Patients will be enrolled in a double–blind treatment period of 100 weeks (26 doses; 60 mg/kg *crenezumab or placebo* by IV infusion *Q4W*), and a final efficacy and safety assessment 4 weeks following the patient's last dose (Week 105). Patients will then have the option to enter the OLE study if eligible. Patients who do not enter the OLE will have additional follow-up visits at 16 and 52 weeks after the last dose, primarily for safety and also for limited efficacy assessments. Assessments for patients who participate in the OLE will be documented in a specific OLE protocol.

Patients who discontinue treatment before Week 105 should be encouraged to return for subsequent visits, for non-infusion related assessments, especially the Week 105 visit.

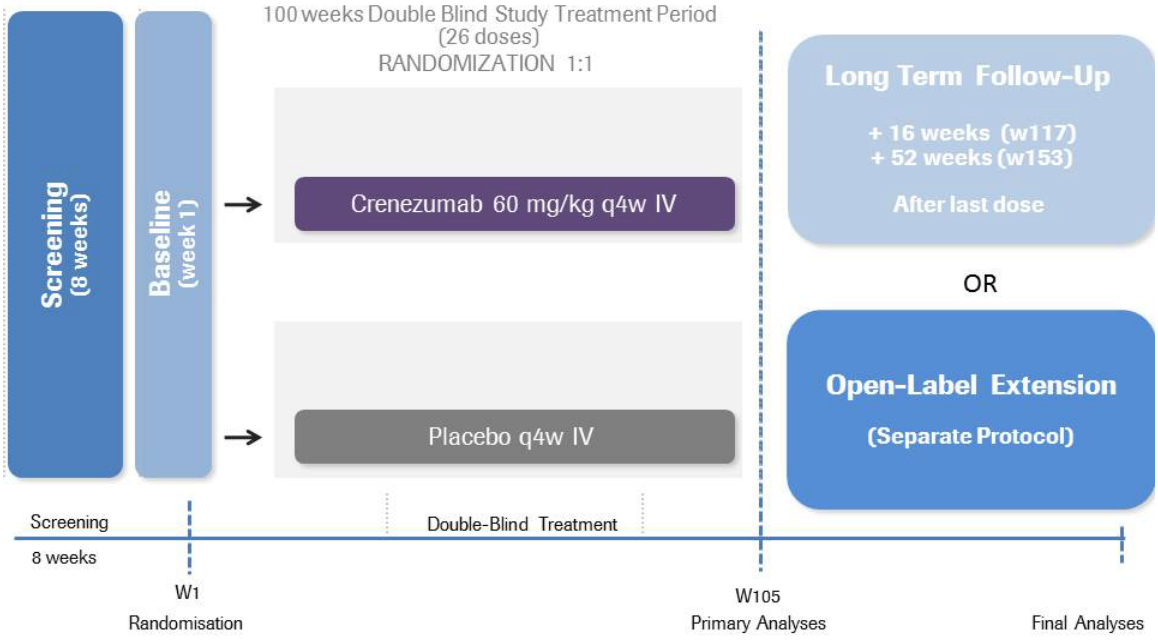
Patients will undergo brain MRI examinations for monitoring of safety and as a biomarker to assess study drug activity. Patients will also undergo tests to monitor safety (including standard safety blood tests, ECG, MRI), as well as tests for cognition, function, and quality-of-life (QOL) assessments. Blood samples for assessment of pharmacokinetics, PD biomarkers, and for the measurement of antibodies directed

against crenezumab and other components of the drug product will be obtained from all patients.

The incidence and nature of adverse events, serious adverse events, ARIA-E and ARIA-H abnormalities, adverse events of special interest, and laboratory abnormalities will be assessed on a regular basis by an unblinded iDMC.

An overview of the study design is provided in Figure 2. A schedule of assessments is provided in Appendix 1.

Figure 2 Overall Study Design



Q4W = every 4 weeks; W/w = week.

Notes: The 8-week screening period can be extended up to a total of 12 weeks. Patients who discontinue treatment early will be encouraged to return for subsequent visits, for non-infusion related assessments, especially the Week 105 visit.

The study consists of four distinct periods:

Screening: Up to *12* weeks in length for each eligible patient.

Double-Blind Treatment: Double-blind treatment period of 100 weeks. After screening, patients who meet all eligibility criteria will be randomly assigned to one of two arms (crenezumab 60 mg/kg or placebo) in a 1:1 ratio. Starting on Week 1 after baseline assessments, each patient will receive 26 total IV infusions of study administered Q4W.

Primary Analyses *Period:* *Randomization through* Week 105

Long-Term Treatment Follow-up: *Patients who discontinue from the study drug or who complete the study treatment* and do not enter the OLE *will be asked to return for the collection of safety and efficacy data 4, 16, and 52 weeks after administration of the last dose of study treatment.*

Additionally all patients who discontinue from study drug early will be encouraged to return for subsequent visits, especially the Week 105 visit (early discontinuation of study treatment does not imply study discontinuation).

Open-Label Extension: All eligible patients will have the opportunity to enter an OLE (documented in a separate protocol).

For the schedule of assessments at each visit, see Appendix 1.

3.1.2 Substudies

Substudies associated with study BN29553 will be described in separate protocols with associated informed consents. Substudy protocols may include data analysis plans that utilize assessments from the main study including, but not limited to demographic and efficacy assessments.

3.1.3 Use of Symptomatic Treatments for Alzheimer's Disease

Patients will be eligible for the study whether or not they are receiving symptomatic medications for AD (i.e., ChEIs or memantine, or combination*,* or medical food *supplements (e.g., Axona® or* Souvenaid®*).* These medications *and supplements* must have been stable for ≥ 3 months prior to screening.

3.1.4 Data Monitoring Committee

The incidence and nature of adverse events, serious adverse events, adverse events of special interest, ARIA-E and ARIA-H abnormalities, ECG findings, vital signs, laboratory abnormalities*, and limited efficacy data* will be assessed on a regular basis by an iDMC. It is anticipated that these assessments will occur approximately every 3 months (quarterly).

The details of iDMC will be provided in the iDMC Charter.

The iDMC will also undertake evaluation of any planned interim *analyses* for efficacy or futility (see Section 6.8).

3.2 END OF STUDY

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for safety analyses or safety follow-up is received for the last patient, whichever occurs later. LPLV for the double-blind treatment period is expected to occur 153 weeks after the last patient is enrolled (i.e., 52 weeks after the last dosing visit at Week 101) for those patients who do not enter the OLE.

3.2.1 Long-Term Follow-Up

Patients who discontinue from the *study drug or who complete the study treatment and do not enter the OLE will be asked to return for the collection of* safety *and* efficacy *data 4, 16, and* 52 weeks after *administration of* the *last* dose *of study treatment.*

Additionally all patients who *discontinue from study drug early will be encouraged to return for subsequent visits, especially the Week 105 visit (early discontinuation of study treatment does not imply study discontinuation).*

3.3 RATIONALE FOR STUDY DESIGN

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of crenezumab in patients with a diagnosis of prodromal to mild AD, as defined by clinically evident symptoms (consistent with the NIAAA updated diagnostic research criteria for AD dementia; Appendix 2 [mAD] and Appendix 3 [pAD]), increased amyloid burden (defined by CSF or PET criteria), and clinical symptoms.

3.3.1 Rationale for Treatment Duration

The treatment duration of 100 weeks (26 doses) for assessment of the primary endpoint has been selected on the basis of the mechanism of action of crenezumab that is expected to delay disease progression rather than provide symptomatic improvement over baseline. Any difference between treatment and control will be on the basis of a reduction in the progression of AD over time. Ongoing trials in the AD area have used durations of at least 18 months.

The proposed trial duration is supported by data from Study ABE4869g which demonstrated that the difference in decline between placebo- and crenezumab-treated patients' increased over time until 18 months (the end of the trial). Placebo decline is expected to be greater at 24 months relative to 18 months; this greater decline allows greater potential to demonstrate *a* treatment effect.

To ensure that evidence relating to *early efficacy is* captured, assessments relevant to the study objectives will be obtained at 6, 12, and 18 months.

3.3.2 Rationale for Long-Term Follow-Up

The primary objective of the long term follow-up is to estimate the long-term safety of crenezumab. Assessments performed 16 and 52 weeks after the last dose of treatment will evaluate the effects of treatment on both efficacy and safety parameters over an extended period when no study drug is administered. These assessments will be conducted in all patients who discontinue treatment *early* or who complete the study but do not enter the OLE. These assessments will allow for the exploration of the long-term effects of exposure to study drug given that continued cognitive decline is expected in this patient population.

3.3.3 Rationale for Crenezumab Dosage

The goal of dose selection in this Phase III study is to select a safe treatment regimen that also efficiently removes amyloid species from the brains of patients with AD. In the Phase II studies, 198 patients (163 in Study ABE4869g and 35 in Study ABE4955g) received the IV crenezumab dose of 15 mg/kg Q4W and demonstrated consistent treatment effects in prespecified subgroups without eliciting dose-limiting events. This suggested that the therapeutic window for crenezumab had not been fully explored.

A higher dose than that used in the Phase II program will result in increased brain exposure and thus result in increased target engagement and the potential for better efficacy (see Section 1.3.3 for further details).

3.3.4 Rationale for Patient Population

The patient selection approach is consistent with the NIAAA research diagnostic criteria and guidelines for AD as well as with the Qualification Opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use on the use of CSF biomarkers for enrichment of trials in mild to moderate AD dementia (2012), and FDA draft guidance for early AD (2013). The FDA guidance refers to the early stage of AD in which individuals present with MCI; however, there is consensus in the field that biomarkers of amyloid pathology are expected to also add value to patient selection in mAD studies.

To adequately determine the safety and tolerability of crenezumab, an antibody that targets Aβ, the study population should have documented evidence of amyloid pathology. Therefore, the study will enroll patients with prodromal to mild AD with evidence of an abnormal brain amyloid load. The rationale for selecting amyloid-positive patients in this study is to ensure that patients are enrolled with the pathology targeted by crenezumab.

The crenezumab Phase III prodromal to mild AD study will enroll patients who have biomarker evidence for β-amyloid deposition. Biomarker enrichment may be important for anti-amyloid therapy clinical trials because recent results have demonstrated that approximately 20% patients who are enrolled in trials based on a clinical diagnosis of AD may not have underlying amyloid pathology as assessed by amyloid-PET (Doody et al. 2014; Sperling et al. 2012b). These results are consistent with screening results in Study ABE4995g, in which 16.5% (18/109) of screened patients with a clinical diagnosis of AD subsequently screen-failed due to a negative florbetapir amyloid-PET scan (visual read). Lastly, biomarker evidence of amyloid pathology is consistent with recently proposed revised diagnostic criteria for AD (McKhann et al. 2011; Dubois et al. 2014).

For enrollment, biomarker evidence of β-amyloid deposition will be assessed either by decreased CSF $A\beta_{1-42}$ levels (using a prespecified cutpoint and the Roche Diagnostics Elecsys® β amyloid [1–42] immunoassay) or a centralized visual assessment of PET brain amyloid imaging. The Sponsor is proposing to enroll patients on the basis of a

positive CSF test or PET scan because both approaches have been shown to correlate with the "gold standard" of β-amyloid pathology at autopsy (Shaw et al. 2009; Clark et al. 2011; Le Bastard et al. 2013). Both methods have been widely used in the research community, and patients or physicians in the trial and in clinical practice generally may not have access to both methods.

This approach is in line with emerging evidence that indicates consistency between PET-amyloid imaging and CSF biomarkers. Low CSF $A\beta_{1\text{-}42}$ shows an inverse relationship with in vivo β–amyloid cortical load as measured with Pittsburgh Compound B amyloid PET imaging (Fagan et al. 2006; Forsberg et al. 2008; Tolboom et al. 2009). There is concordance on the information obtained via PET amyloid imaging and low CSF $A\beta_{1\text{-}42}$ in broad populations across a range of severity of AD (pre-dementia through mild to moderate AD; Jagust et al. 2009; Fagan et al. 2011; Landau et al. 2013; Zwan et al. 2014).

As the accumulation of Aβ brain amyloid begins before the onset of AD dementia, it is reasonable to postulate that the benefit of anti-amyloid therapy may be greater if initiated at an early stage of the disease. This hypothesis is supported by the Phase II data from crenezumab (see the crenezumab Investigator's Brochure for further details) and Phase III data from solanezumab in mild to moderate AD, where the treatment effects were observed in patients with mAD, but not in patients with moderate AD (Doody et al. 2014). For this reason, Roche has focused clinical development of crenezumab on the prodromal to mild segment of AD.

Patients in this study are required to meet standard research criteria for *AD* (according to the NIAAA research criteria and guidelines for AD *dementia*; Appendix 2) *in the mild dementia stage,* or pAD (according to the NIAAA research criteria and guidelines for MCI; Appendix 3). Patients with pAD will present with documented objective evidence of deficit in one cognitive domain. Patients with mAD will present with documented deficits in at least two cognitive domains and functional decline. Overall, the population will have an MMSE of ≥22 points and a CDR-GS of between 0.5 and 1.0. The MMSE score provides evidence of mild disease severity and the CDR-GS score indicates that the patients have noticeable amnestic (pAD) or cognitive and functional (mAD) deficits.

To ensure that the patients selected are likely to decline over the 2-year trial, two approaches have been included. The first is that all patients have to demonstrate amnestic deficits as measured by the cueing index of the FCSRT (e.g., Sarazin et al. 2007) and the total free recall score. The FCSRT Cueing Index of ≤0.67 AND a free recall score of ≤27 have been selected. The cueing index measures the ability of the patient to benefit from being reminded by the use of specific cue words in order to recall the target word. To prevent patients who have a high free recall who don't appear to further benefit from reminding from being included simply due to an apparent low cueing index, a free recall score of ≤27 has also been included. The cueing index *cut-off* has been generated from internal data sets *(prior to the start of this study) in*

which patients with cueing index of ≤0.67 had a greater likelihood of decline over the proposed time frame. The FCSRT index is consistent with those published by Sarazin et al. (2007) and Auriacombe et al. (2010).

The second approach to ensure decline is to verify that there is evidence of prior decline through observations made by clinician or caregiver and recorded on the diagnostic verification form (see Appendix 4). A caregiver is defined as a person who in the investigator's judgment has frequent and sufficient contact with the patient so as to be able to provide accurate information as to the patient's cognitive and functional abilities, who agrees to provide information at clinic visits that require partner input for scale completion, and who signs the necessary consent form. This person should not be a caregiver in a paid position (e.g., a healthcare professional).

To minimize the effects of confounding the cognitive assessments, anyone with a current untreated depressive episode (i.e., presence of depressive symptoms) will be excluded from the study. Current treatment for depression will be documented in the electronic Case Report Form (eCRF).

3.3.5 Rationale for Control Group

This is *a* placebo-controlled trial in which patients will be eligible for study participation whether or not they are receiving standard of care medications for AD (i.e., ChEIs, memantine, *or combinations thereof)* and/or medical *supplements (e.g., Axona® or* Souvenaid®*)*. Given that there are currently no approved disease-modifying compounds that could serve as an active control, patients will be randomized to crenezumab or placebo.

3.3.6 Rationale for Rescue Strategy

A rescue strategy may be recommended by the iDMC based on their unblinded assessment of the benefit-risk profile (see Section 3.1.4). In the event that this strategy is recommended, all ongoing patients will be switched to a lower dose of IV crenezumab. In the event that this occurs, the sample size will be adjusted so that all existing patients are replaced by new patients at the revised study dose (see Section 6.1).

3.3.7 Rationale for Diagnostic Verification

Enrollment into this trial is subject to adjudication by the Medical Monitor or designated staff. The objective of the adjudication process is to ensure that patients are enrolled on the basis of objectively ascertained and well-documented diagnosis of AD (McKhann et al. 2011) or pAD symptomatology sufficient to meet the appropriate criteria specified in Albert et al. (2011). The Medical Monitor *or assignee* may review anonymized source documents and may solicit advice from other qualified Sponsor staff or external, independent experts to support this adjudication process. The scope and detailed procedures for the diagnostic verification process will be described in the study

documents and documented for review on the diagnostic verification form (see Appendix 4).

3.3.8 Rationale for Primary Outcome Measure

AD is considered a continuous disease that passes through consecutive stages without discrete transition points. Thus, the use of a single endpoint across both subpopulations of prodromal and mild AD is consistent with the current understanding of AD.

Showing the benefit of new therapies for patients in the early stages of AD is challenging, owing to the lack of sensitive assessment tools. Use of the CDR-SB as the primary outcome measure for studies of prodromal to mild AD enables simultaneous demonstration of benefit on primary symptoms (e.g., cognition, function) and clinical relevance (Aisen 2009; Aisen et al. 2011) while also ensuring use of a clinical outcome assessment with adequate measurement properties (FDA 2013).

Assessments in clinical trials for AD should be obtained across several domains of neurologic function, including cognition—measured directly by objective tests (cognitive endpoints)—and functioning. Improved clinical outcomes in both cognitive and functional domains should translate to an overall benefit measured by global improvement score, which would demonstrate that a proportion of patients achieved a clinically meaningful benefit from this therapy.

3.3.8.1 Clinical Dementia Rating-Sum of Boxes

The Washington University CDR is a global assessment instrument that yields Global (GS) and Sum of Boxes (SB) scores. The CDR is derived from a semi-structured interview with the patient and an appropriate informant, and it rates impairment in six categories (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care) on a 5-point scale in which no impairment = 0, questionable impairment = 0.5, and mild, moderate, and severe impairment = 1, 2, and 3, respectively. From the six individual category ratings or box scores the CDR-GS is established by clinical scoring rules where CDR 0 = no dementia and CDR of 0.5, 1, 2, or 3 = questionable, mild, moderate, or severe dementia, respectively (Morris 1993). The CDR-SB score is a detailed quantitative general index that provides more information than the CDR-GS in patients with prodromal to mild dementia (O'Bryant et al. 2010). In particular, the CDR-SB has been proposed for use in longitudinal assessment of dementia and is widely used in AD studies as a global measure of disease progression (Lynch et al. 2006). Furthermore, as proposed in the FDA's draft guidance for developing drugs for the early stages of disease, the use of a composite scale, validated in early stage patients to assess both cognition and function as a single primary efficacy outcome measure, is appropriate. The CDR-SB score fulfills these criteria (FDA 2013) and is now being utilized as the sole primary endpoint in studies of patient populations that encompass prodromal to mild AD including AMARANTH (https://clinicaltrials.gov/ct2/show/NCT02245737) and PRIME (https://clinicaltrials.gov/ct2/show/NCT02477800).

The proposal for the Phase III program is to employ the CDR-SB as a primary endpoint for an integrated functional/global assessment*, and the* ADAS-Cog-13 *and ADAS-Cog-11, ADCS-iADL and ADCS-ADL* as key secondary *endpoints* to *additionally* support *assessment of* cognition *as a core symptom of this disease (ADAS-Cog)* and *function (*ADCS-ADL instrumental *function subscore and total score), separately* (see Section 3.3.9).

3.3.9 Rationale for Key Secondary Outcome Measures

The key secondary endpoints for studies in prodromal to mild AD have been chosen to reflect the treatment benefit on *cognitive and* functional endpoints. The rationale for selection of key secondary endpoints is provided in Sections 3.3.9.1 (ADAS-Cog) and 3.3.9.2 (*ADCS-iADL and ADCS-ADL total score*).

3.3.9.1 Alzheimer's Disease Assessment Scale-Cognition

The ADAS-Cog is an examiner-administered battery that assesses multiple cognitive domains, including memory, comprehension, praxis, orientation, and spontaneous speech (Rosen et al. 1984; Mohs et al. 1997). The ADAS-Cog is considered the standard primary endpoint in AD treatment studies (Mani 2004) and is generally considered the gold standard for assessing cognitive function in AD clinical studies (Cano et al. 2010; Sevigny et al. 2010). The 12-item version of the scale does not include adequate assessment of executive function particularly for patients in the early stages of AD. In the crenezumab Phase II program, the 12-item version (ADAS-Cog-12) was used in patients with mild to moderate AD (defined as screening MMSE score of 18–26), and a treatment effect was detected in a subpopulation of patients with mAD (MMSE, 22–26). Because of the expected increased sensitivity to detect a treatment effect in patients on the milder part of the AD continuum, the Sponsor proposes to use the 13-item version (ADAS-Cog-13), which is supplemented with executive measures sensitive to change in patients at the milder end of the disease spectrum (Mohs et al. 1997) as the key secondary endpoints.

3.3.9.2 *ADCS-iADL and ADCS-ADL Total Score* (Vellas et al. 2008)

*The ADCS-ADL (*Galasko et al. 1997*) is the scale most widely used to assess functional outcome in patients with AD. The ADCS-ADL covers both basic ADL (e.g., eating and toileting) and more complex "instrumental" ADL or iADL (e.g., using the telephone, managing finances, preparing a meal). The ADCS-ADL scale with its resulting total score is considered a standard (co-)primary endpoint in treatment trials in patients in the mild to moderate dementia stage of AD. Because of the expected increased sensitivity to detect a treatment effect in patients on the milder part of the AD continuum, the Sponsor will use both the ADCS-ADL total score and also the ADCS-iADL subscore as a key secondary endpoint in order to capture meaningful clinically evident decline on functional abilities.*

3.3.10 Rationale for Pharmacokinetic Sampling

A sparse sampling schedule is being utilized to minimize patient burden and still provide an adequate characterization of the population PK profile of crenezumab. The PK data may be compared with available data from other crenezumab studies and may be used to assess exposure-response relationships for relevant imaging, plasma PD biomarkers, ECG, and efficacy and safety outcomes in patients with prodromal to mild AD, as appropriate.

3.3.11 Rationale for Biomarker Assessments

The biomarker assessments described in Section 3.3.11.1 (CSF), Section 3.3.11.2 (PET imaging), and Section 3.3.11.3 (brain volumetry) will be used to investigate the effect of crenezumab on the underlying pathology of AD in the clinical trial population.

3.3.11.1 Cerebrospinal Fluid Biomarkers

Amyloid plaque deposition, neurofibrillary tangle formation, and neuronal degeneration are known pathologic features of AD. Decreased CSF $A\beta_{1-42}$ and elevated CSF total-tau (t-tau) and p-tau are considered a biochemical signature of AD. Accumulating evidence suggests that low CSF $A\beta_{1-42}$ reflects underlying amyloid plaque pathology, whereas increased t-tau and p-tau levels may be reflective of neurodegeneration and/or tau pathology. CSF assessment will be utilized as a screening biomarker for BN29553.

3.3.11.2 Positron Emission Tomography Imaging Biomarker

The definitive postmortem diagnosis of AD requires the presence of progressive dementia during life and the presence of neuropathological lesions (i.e., neuritic plaques composed of β-amyloid aggregates and neurofibrillary tangles formed from hyperphosphorylated tau protein). However, imaging approaches using ligands that demonstrate high affinity for aggregated amyloid $and\ tau$ are able to provide an assessment of deposition in vivo, which can be evaluated over time (Clark et al. 2011). PET imaging assessment will be utilized as a screening biomarker for BN29553.

3.3.11.3 Brain Volumetry

A characteristic feature of AD is neuronal destruction. Such neuronal loss is demonstrated at a macroscopic level by progressive cerebral atrophy, which can be tracked on MRI (Fox and Kennedy 2009). Multiple changes in brain anatomy beyond those associated with normal aging have been reported in patients with AD (e.g., enlarged ventricles, decreased cortical thickness, decreased total brain volume, and hippocampal atrophy), and there is evidence for strong correlations between these imaging biomarkers and functional cognitive measures (Li and Wahlund 2011). Based on volumetric MRI measurements, the two most established markers of disease progression through longitudinal observational studies are hippocampal and whole brain atrophy (Fox et al. 2000, 2005; Jack et al. 2010), with ventricular expansion a third and related quantitative marker.

Therefore, to quantify the effects of crenezumab on neurodegeneration, whole brain volume, ventricular enlargement, and regional brain volume changes will be assessed at screening and following treatment with crenezumab. All MRI reads and volume measures will be conducted by the central reader.

4. MATERIALS AND METHODS

This study will include approximately 750 male and female patients with increased amyloid burden (defined by CSF or PET criteria), objective memory impairment indicated by cognitive assessment, and a diagnosis of probable AD or pAD based on diagnostic verification (and relevant NIAAA criteria; see Appendix 2 [probable AD] and Appendix 3 [pAD]) enrolled during the Global Enrollment Phase. Additional criteria are defined in Section 4.1. [redacted]

If the patient is currently receiving medications for AD, doses must have been stable for at least 3 months prior to screening.

Patients who discontinue from this study are not permitted to be enrolled and re-randomized for a second course of treatment.

4.1 INCLUSION CRITERIA

Patients must meet the following criteria for study entry:

- Able to provide written consent signed by the patient (co-signed by the patient's legally authorized representative, if required by the local regulations, guidelines, and independent ethics committee or institutional review board [IRB])
- Aged between 50 and 85 years at screening, inclusive
- Weight between 40 and 120 kg, inclusive
- Availability of a person (referred to as the "caregiver" throughout this protocol) who in the investigator's judgment:
  - Has frequent and sufficient contact with the patient to be able to provide accurate information regarding the patient's cognitive and functional abilities, agrees to provide information at clinic visits (which require partner input for scale completion), signs the necessary consent form, and has sufficient cognitive capacity to accurately report upon the patient's behavior and cognitive and functional abilities.
  - Is in sufficiently good general health to have a high likelihood of maintaining the same level of interaction with the patient and participation in study procedures throughout the study duration.

  Every effort should be made to have same caregiver participate throughout the duration of the study.
- Fluency in the language used at the study site

- Willingness and ability to complete all aspects of the study (including MRI, lumbar puncture [if applicable], clinical genotyping, and PET imaging [if applicable]); the patient should be capable of completing assessments either alone or with the help of the caregiver
- Adequate visual and auditory acuity, in the investigator's judgment, sufficient to perform the neuropsychological testing (eye glasses and hearing aids are permitted)
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least 8 weeks after the last dose of study drug.
  - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
  - Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:
  - With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 8 weeks after the last dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- Evidence of the AD pathological process, by a positive amyloid assessment either on CSF $A\beta_{1-42}$ levels as measured on the Elecsys β-Amyloid(1-42) Test System OR amyloid PET scan by qualitative read by the core/central PET laboratory.
- Demonstrated abnormal memory function at $FCSRT/MMSE\ consent$ or at $main$ screening [FCSRT cueing index ≤ 0.67 AND free recall ≤ 27]
- Evidence of retrospective decline confirmed by a diagnosis verification form (see Appendix 4)

- Mild symptomatology, as defined by a screening MMSE score of ≥ 22 points and CDR-GS of 0.5 or 1.0. MMSE may be performed at *FCSRT/MMSE consent* or *main* screening.
- Meets NIAAA core clinical criteria for probable AD dementia (see Appendix 2; McKhann et al. 2011) or pAD (consistent with the NIAAA diagnostic criteria and guidelines for MCI; Appendix 3; Albert et al. 2011)
- If the patient is receiving symptomatic AD medications, the dosing regimen must have been stable for 3 months prior to screening. *If the patient is taking medical food supplements (e.g., Axona® or Souvenaid®), these must also have been stable for 3 months prior to screening.*
- Inclusion is subject to review of clinical criteria at screening (diagnostic verification form; see Appendix 4).
- Patient must have completed at least 6 years of formal education after the age of 5 years
- For enrollment into the China Extension Phase, patients must have residence in *mainland China, Hong Kong, or Taiwan and be of Chinese ancestry.*

4.2 EXCLUSION CRITERIA

Patients who meet any of the following criteria will be excluded from study entry:

- Any evidence of a condition other than AD that may affect cognition, including but not limited to, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, Parkinson's disease, corticobasal degeneration, Creutzfeldt-Jakob disease, progressive supranuclear palsy, frontotemporal degeneration, Huntington's disease, normal pressure hydrocephalus, or hypoxia.
- *Seizure history that, in the opinion of the investigator, is likely to result in cognitive impairment*
- History or presence of clinically evident vascular disease that could potentially affect the brain (e.g., clinically significant carotid, vertebral stenosis or plaque; aortic aneurysm; intracranial aneurysm; cerebral hemorrhage; arterio-venous malformation).
- History or presence of any stroke with clinical symptoms within the past 2 years, or documented history within the last 6 months of an acute event consistent, in the opinion of the investigator, with a transient ischemic attack.
- History of severe, clinically significant (persistent neurologic deficit or structural brain damage) CNS trauma (e.g., cerebral contusion)
- History or presence of intracranial tumor (e.g., glioma). History or presence of meningioma that, in the opinion of the investigator, is not clinically significant and is unlikely to result in cognitive impairment is not excluded.
- Presence of infections that affect brain function or history of infections that resulted in neurologic sequelae (e.g., HIV, syphilis, neuroborreliosis, viral or bacterial meningitis/encephalitis)

- History or presence of systemic autoimmune disorders that potentially cause progressive neurologic disease with associated cognitive deficits (e.g., multiple sclerosis, lupus erythematosus, anti-phospholipid antibody syndrome, Behçet disease)
- History of schizophrenia, schizoaffective disorder, major depression, or bipolar disorder
  - A history of major depression is acceptable if patient had no episode within the past year or is considered in remission or depression is controlled by treatment.
- At risk of suicide in the opinion of the investigator
- Alcohol and/or substance abuse or dependence (according to Diagnostic and Statistical Manual of Mental Disorders $v4$ criteria) within the past 2 years
  - Nicotine use is allowed.
  - Marijuana use is not allowed and must be discontinued 3 months before screening.
- According to the MRI central reader, MRI evidence of a) >2 lacunar infarcts, b) any territorial infarct >1 cm^3, or c) any white matter lesion that corresponds to an overall Fazekas score of 3 that requires at least 1 confluent hyperintense lesion on the FLAIR sequence, which is ≥ 20 mm in any dimension.
- Evidence of more than 4 microbleeds and/or areas of leptomeningeal hemosiderosis (ARIA-H) as assessed by central review of T2* GRE MRI (see MRI Charter for further details).
- Presence of significant cerebral vascular pathology as assessed by MRI central reader (see MRI Charter for further details).
- Presence on MRI of any cortical stroke regardless of age.
- Inability to tolerate MRI procedures or contraindication to MRI, including, but not limited to, presence of pacemakers not compatible with MRI, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin, or body that would contraindicate an MRI scan; or any other clinical history or examination finding that, in the judgment of the investigator, would pose a potential hazard in combination with MRI

The following cardiovascular disorders:

- History or presence of atrial fibrillation except if only one episode that resolved >1 year ago and for which treatment is no longer indicated
- Within the last 2 years, unstable or clinically significant cardiovascular disease (e.g., myocardial infarction, angina pectoris, or New York Heart Association Class II or higher cardiac failure)
- Uncontrolled hypertension (e.g., blood pressure generally >160 mmHg systolic or >95 mmHg diastolic)

The following hepatic/renal disorders:

- Chronic kidney disease of Stage ≥ 4, according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines for chronic kidney disease
- Confirmed and unexplained impaired hepatic function as indicated by screening AST or ALT ≥ 3 the upper limit of normal (ULN) or total bilirubin ≥ 2 ULN

The following infections and immune disorders:

- History of or known to currently have hepatitis B or hepatitis C infection that has not been adequately treated in the opinion of the investigator
- Systemically, clinically significantly immunocompromised patients, owing to continuing effects of immune-suppressing medication
- Corticosteroids are permitted as long as the dose is < 7.5 mg/day prednisolone equivalent and the condition being treated is not expected to deteriorate significantly during the study period.

The following metabolic/endocrine disorders:

- Abnormal thyroid function as indicated by abnormal screening tests that are judged to be clinically significant by the investigator, or abnormal thyroid function that requires a new treatment or an adjustment of current treatment
  - A patient may be rescreened if there is no improvement in cognition in the investigator's judgment after 3 months of adequate treatment for thyroid function.

History of cancer except:

- If considered to be cured

  OR

- If not being actively treated with anti-cancer therapy or radiotherapy and, in the opinion of the investigator, not likely to require treatment in the ensuing 5 years
- For prostate cancer or basal cell carcinoma, no significant progression over the previous 2 years

Other exclusion criteria:

- Screening folic acid or vitamin B12 levels that are sufficiently low or remain low on retest such that deficiency may be contributing to cognitive impairment
  - A patient may be rescreened if there is no improvement in cognition after 3 months of adequate treatment for folic acid or vitamin B12 deficiency.
- Screening hemoglobin A1c (HbA1C) $> 8\%$ (retesting is permitted if slightly elevated) or poorly controlled insulin-dependent diabetes (*past* hypoglycemic episodes *are considered one example of poor control*).
  - A patient may be rescreened after 3 months to allow optimization of diabetic control.

- Pregnant or lactating, or intending to become pregnant during the study
- Poor peripheral venous access
- Other causes of intellectual disability that may account for cognitive deficits observed at screening (e.g., static encephalopathy, closed brain injury, mental retardation).

– This may be based on, for example, patient's sufficient education or work experience.

- *Clinically significant sleep apnea that may be contributing to cognitive impairment.* Sleep apnea*, which in the clinical judgment of the investigator is adequately treated,* (e.g., continuous positive airway pressure*–adequate patient treatment compliance should be documented) is allowed.*
- *Significant* respiratory diseases (e.g., severe COPD – Global Initiative for Obstructive Lung Disease criteria Stage IV*).*
- Deformity of the lumbosacral region of the spine that in the opinion of the investigator would contraindicate lumbar puncture in those who can only be CSF-eligible due to regional lack of availability of PET ligands.
- Clinically significantly abnormal screening blood or urine that remain abnormal at retest
- Impaired coagulation (screening PT $>$ 1.2 $\times$ the ULN that remains abnormal on retest).
- Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins
- Any other severe or unstable medical condition that, in the opinion of the investigator or Sponsor, could be expected to progress, recur, or change to such an extent that it could put the patient at special risk, bias the assessment of the clinical or mental status of the patient to a significant degree, interfere with the patient's ability to complete the study assessments, or would require the equivalent of institutional or hospital care
- Residence in a skilled nursing facility such as a convalescent home or long-term care facility: Patients who subsequently require residence in these facilities during the study may continue in the study and be followed for efficacy and safety provided that they have a caregiver who meets the minimum requirement (refer to Section 4.1).

The following medications are prohibited for a pre-specified duration prior to study start, as indicated, and during the entire period of study participation (patients who start these medications during the study may be withdrawn from study treatment):

- Any previous administration of crenezumab or any other therapeutic that targets Aβ
- Any investigational active immunotherapy (vaccine) that is under evaluation to prevent or postpone cognitive decline

- Any passive immunotherapy (immunoglobulin) or other long–acting biologic agent that is under evaluation to prevent or postpone cognitive decline within 1 year of screening
- Any other investigational treatment within 5 half-lives or 3 months of screening, whichever is longer
- Any previous treatment with medications specifically intended to treat Parkinsonian symptoms or any other neurodegenerative disorder within 1 year of screening

– Certain medications are acceptable if the patient is taking the medicine for a non-neurodegenerative disorder, such as restless leg disorder (e.g., pramipexole)

- Typical antipsychotic or neuroleptic medication within 6 months of screening except as brief treatment for a non-psychiatric indication (e.g., emesis)
- Atypical antipsychotics except with intermittent short-term use which is permitted except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment
- Anti-coagulation medications within 3 months of screening

  – Anti-platelet treatments (e.g., aspirin, clopidigrel, dipyridamol) are permitted.

    Short-term, peri-operative use of anti-coagulants will not result in discontinuation from the study; however, any such use must be discussed with the Sponsor (see section 4.5.1 for further details).

- Chronic use of opiates or opioids (including long-acting opioid medication) within 3 months of screening
- Intermittent short-term use of short–acting opioid medications for pain is permitted except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment
- Stimulant medications (amphetamine, methylphenidate preparations, or modafinil) within 1 month of screening and throughout the study
- Chronic use of benzodiazepines, barbiturates, or hypnotics from 3 months before screening

– Intermittent short-term use of benzodiazepines, buspirone, or short–acting hypnotic medication for sleep or anxiety is allowed except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment. However, intermittent use of barbiturates is not permitted.

- Permitted medications are described in Section 4.5.1

4.3 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Randomization will be performed centrally using an interactive voice/Web response system (IxRS) that uses stratified block randomization. After screening, patients who meet all eligibility criteria will be randomly assigned to 1 of 2 treatment groups (crenezumab or placebo). Patients will be randomized in a drug to placebo ratio of 1:1.

Randomization to treatment allocation will also be stratified by dementia status (pAD vs. mAD), patient *APOEε4* status (presence or absence of ε4 allele), background medication at baseline (present, absent) and geographic region. Stratification factors will ensure balance of these strong prognostic factors across treatment arms and facilitate unbiased estimate of treatment effect in subgroups based on disease severity and geographic regions.

Except in circumstances in which a health authority, Ethics Committee (EC), or IRB requires the patient be told of his or her *APOE* status, patients, investigators, central MRI reader, and the cognitive test rater as well as the Sponsor *will be blinded to individual patient APOE genotype results*. *APOE* status information will be supplied directly to the IxRS vendor by the central testing laboratory so that the information can be incorporated at the time of randomization. In cases where *APOE* status is already known, these prior results will be blinded to the Sponsor and as much as possible to the site and central MRI reader.

The study is to be conducted in a double-blind manner to minimize potential bias from investigators and patients. The Sponsor will be blinded to study treatment. The Master Randomization or Master Medication List will not be available at the study center, to Roche monitors, project statisticians, or to the project team at Roche with the exception of those responsible for performing PK, PD, and *ADA* assessments. Personnel responsible for performing PK, PD and *ADA* assessments will be unblinded to patients' treatment assignments to identify appropriate samples to be analyzed. Samples from patients assigned to the placebo group will not be analyzed except by request (e.g., to evaluate a possible error in dosing).

If unblinding is necessary for patient management (e.g., in the case of a serious adverse event for which patient care might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations. If the investigator wishes to know the identity of the study treatment for any other reason, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event).

For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected suspected adverse reactions that are considered by the investigator or Sponsor to be related to study drug.

4.4 STUDY TREATMENT

The investigational medicinal product (IMP) for this study is crenezumab.

4.4.1 Formulation, Packaging, and Handling

4.4.1.1 Crenezumab and Placebo

Crenezumab and placebo will be supplied by the Sponsor as a solution buffered at pH 5.5 (using arginine succinate solution that contains polysorbate 20 and water for injection) in 6.0 mL glass vials. For information on formulation and handling of crenezumab, see the pharmacy manual and crenezumab Investigator's Brochure.

4.4.2 Dosage, Administration, and Compliance

4.4.2.1 Crenezumab and Placebo

Crenezumab or placebo will be administered via IV infusion to all patients. Those randomized to the active arm will receive crenezumab at a dose of 60 mg/kg q4w for 26 doses.

For all infusions (crenezumab and placebo), IV infusions will be administered by appropriately trained staff in the clinic or other agreed environment (e.g., the patient's home); the first four infusions of study drug must be administered at the clinic.

The IV drug will be prepared and infused from the IV bag by infusion pump. The bag size, drug preparation, and infusion rates are all described in the pharmacy manual guidance. All patients will be monitored for a minimum of 1 hour after dosing, and vital signs will be measured immediately following completion of the infusion and ≥ 60 minutes after the end of the infusion as described in the pharmacy manual.

For the IV dose calculation, the patient's screening weight (reference weight) should be used. If the current weight changes by ≥ 10%, the current weight should become the new reference weight for subsequent dosing. If the patient's weight changes again by ≥ 10% from the reference weight, the IV dose should again be recalculated. See the pharmacy manual for further information.

Crenezumab will be administered to patients under close medical supervision in a setting with access to appropriate emergency equipment and staff who are trained to monitor and respond to medical emergencies. In the event that a patient experiences a mild infusion-related reaction, the infusion will be halted. Once the reaction has resolved, the infusion rate will be resumed at half of the most recently used rate [redacted]. Patients who experience a moderate infusion-related reaction (e.g., fever or chills) should have the infusion stopped immediately and should receive aggressive symptomatic treatment. The infusion should not be restarted before all symptoms have disappeared, and then it should be restarted at half the initial rate. Patients who experience serious or severe hypersensitivity reactions (e.g., hypotension, mucosal involvement) should not receive additional study drug. In any patient who develops anaphylaxis, anaphylactoid, or serious hypersensitivity reactions, a blood sample will be collected for analyses of antibodies to crenezumab and/or other components of the drug product. In addition, for any patient suspected of developing anaphylaxis, or anaphylactoid or serious hypersensitivity reactions warranting

discontinuation of dosing, a washout *ADA* sample (16 weeks post-dose) and concurrent PK sample must be collected.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

At applicable sites, following the first four infusions, study drug may be administered by a trained home nursing (HN) professional at the patient's home or another suitable location, if the patient has given written informed consent to participate in HN visits (please refer to Section 4.6 for details).

4.4.2.2 Non-Investigational Medicinal Products

All patients who are enrolled using PET amyloid evaluation at baseline and those in any relevant substudies will be assessed by PET imaging using an appropriate PET ligand. Details of substudies are described in separate protocols.

According to EU guidance, the PET ligands used in the context of this study (and associated substudies) have been designated as non-IMPs. In some regions, according to local regulations, these PET tracers may be considered as IMPs.

Regarding the safety profile of and reporting requirements for the PET ligands administered in this study (and associated substudies) please refer to Section 5.7.

4.4.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (crenezumab or placebo) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.4.4 Post-Trial Access to Crenezumab

The Sponsor will offer post-trial access to the study drug (crenezumab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive study drug after completing the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for AD
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for AD
- Provision of study drug is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.5 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by a patient 3 months prior to screening through the study completion/early termination visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF page.

4.5.1 Permitted Therapy

Adding a new medication or changing the dose of a medication after randomization should occur only for the treatment of an adverse event *or as medically indicated*.

The following medications are permitted if the dose and dose regimen have been stable for 3 months prior to screening and are expected to remain stable after screening or if required for treatment of an adverse event after randomization:

- Prescription medications that might affect cognitive function (e.g., antidepressants*, anticonvulsants*)
- Over-the-counter and/or herbal medications, food additive or any other agent or supplement intended to improve cognition or reduce cognitive decline

- Medications used to treat a mood or anxiety disorder given as maintenance treatment
- Medications with anticholinergic activity that may impair cognition or attention (e.g., centrally acting antihistamines, including brompheiramine, chlorpheniramine, dimenhydrinate, diphenhydramine, and doxylamine, or anti spasmodic medicines)
- Intermittent use of centrally acting antihistamines is permitted, but should not be used within 2 days or 5 half-lives (whichever is longer) of cognitive assessment
- Intermittent use of short–acting (non-extended release) opioid medications for pain is permitted except within 2 days or 5 half-lives (whichever is the longer) of any neurocognitive assessment (up to a maximum of 3 consecutive days per month)
- Intermittent short-term use of benzodiazepines, buspirone, or short–acting hypnotic medication for sleep or anxiety is allowed, except in the 2 days or 5 half-lives (whichever is the longer) prior to any cognitive assessment. However, intermittent use of barbiturates is not permitted.
- Dose of benzodiazepine for presurgical and pre-imaging sedation at appropriate visits if allowed by EC or IRB
- Anti-platelet therapies are permitted during study conduct

  Under certain circumstances, anticoagulation therapy (e.g., temporary usage during surgery, or for treatment of deep vein thrombosis) may be permitted. In these circumstances, appropriate safety assessments should be made, e.g., prior to a lumbar puncture. The investigator should discuss with the Sponsor all individual patient cases that require anticoagulant therapy proactively whenever possible.

Concomitant and excluded therapies for determination of patient eligibility are described in Section 4.2.

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

4.5.2 Prohibited Therapy

Any medication that is prohibited before screening is also prohibited during conduct of the study (see Section 4.2). If a patient receives any prohibited treatment during the study, the patient may be withdrawn from study treatment.

4.6 STUDY ASSESSMENTS

Please see Appendix 1 for the schedule of activities to be performed during the study.

Patient-centered outcome instruments are to be adequately translated and adapted for the local language and culture, and where feasible, according to the International Society of Pharmacoeconomics and Outcomes good principles (Wild et al. 2005), distributed by the investigative staff, and completed in their entirety by the designated responder.

Adverse event reports will not be derived from patient–centered outcome data. For further details see Section 5.3.2.

In this study, patient-centered outcomes instruments will be completed in the order specified in Sections 4.6.8 and as specified in the schedule of assessments (see Appendix 1).

At applicable sites, certain study assessments may be performed by an HN professional at the patient's home or nursing center to improve access and convenience for patients who participate in the study. The Sponsor will select a healthcare company that will be responsible for providing HN services for participating sites (the HN vendor). The HN vendor is responsible for ensuring that all HN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that HN services are appropriate for a patient and the patient gives written informed consent to participate in HN visits, the HN network will communicate with the patient and the patient's site. HN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the HN professional. The schedule of assessments (see Appendix 1) specifies the assessments and visits that may be performed by an HN professional.

Rescue medications and equipment to treat anaphylactic and anaphylactoid reactions must be available for home nursing visits. Patients and their caregivers will be alerted to watch for signs of anaphylactic/anaphylactoid reactions and to contact the study center as soon as possible if any such signs are noted.

4.6.1 Informed Consent Forms and Screening Log

All patients and caregivers must review, sign and date the most current IRB-EC approved written informed consent for participation in the study before any study–specific screening tests or evaluations are performed. Informed Consent Forms for enrolled patients and their caregivers, and for those who are not subsequently enrolled, will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that a patient meets all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.6.2 Medical History and Demographic Data

Medical history status includes clinically significant diseases, respiratory diseases and risk factors, surgeries, cancer history (including prior cancer therapies and procedures), smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the patient within 3 months prior to the screening visit.

Demographic data will include age, sex, and self-reported race/ethnicity. Medical history and demographic data will be collected at the screening visit only. Demographics of caregiver will also be collected.

As this study is being conducted in multiple geographic regions, it is likely that patients of different ethnic origins will be enrolled in the study. Although there is currently no indication that crenezumab (RO5490245) is metabolized or eliminated differently or that the treatment effect would be different in patients with different ethnic origins, collecting this information is essential to adequately evaluate the results of this study (e.g., possible differences in PK exposure [concentration of the drug in the blood] or treatment effect).

4.6.3 Physical Examinations

A physical examination should be performed and should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems, as clinically indicated. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. At Week 105, this examination will be repeated.

At intervening visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

The schedule of assessments indicates when height and weight should be recorded.

4.6.4 Vital Signs

Blood pressure and heart rate will be taken when the patient is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements.

Body temperature will be taken at each visit.

Respiratory rate and oxygen saturation will be taken at each visit.

Heart rate will be determined by radial pulse and will be recorded as beats per minute. The pulse should be counted for a minimum of 20 seconds at each assessment.

The schedule of assessments indicates when vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation, and body temperature) are to be recorded (see Appendix 1).

4.6.5 Cognitive Assessments

Cognition will be assessed using the ADAS-Cog, FCSRT, CDR, and MMSE.

The cognitive assessments described in this section will be performed in the *recommended* order specified in Section 4.6.8 and the schedule of assessments (see Appendix 1).

The scales and assessments for this study will be provided unless otherwise specified. Whenever possible, the *same* rater and caregiver *should* complete the scales for *a given* patient throughout the study. Potential raters will receive training and be approved by the rating scale contract research organization (CRO) prior to being allowed to administer any cognitive assessments/rating scales in the study.

Raters who are rating secondary scales do not need approval but do need to have completed appropriate training. In addition, given that the primary outcome measure in this trial involves subjective judgment, the adequacy of patient interviews and ratings will be monitored by an endpoint reliability program administered by the rating scale CRO; this is considered to be an essential part of good research methodology. Prior studies have clearly demonstrated that the failure to adequately monitor such ratings can substantially increase the risks of failed trials (Becker and Greig 2008; Kobak 2010).

4.6.5.1 Clinical Dementia Rating Scale

Washington University's CDR is a global assessment instrument that yields global scores (i.e., CDR-GS). The sum of boxes (i.e., CDR-SB) score is a detailed quantitative general index that provides more information than the CDR-GS in patients with mild dementia (O'Bryant et al. 2010). The CDR characterizes six domains of cognitive and functional performance applicable to AD and related dementias: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The necessary information to make each rating is obtained through a semi-structured interview of the patient and a reliable informant or collateral source (e.g., a caregiver). Details of the CDR can be found at the website: http://knightadrc.wustl.edu/CDR/CDR.htm.

As much as feasible, the CDR should be administered to an individual patient by the same assessor throughout the study and that assessor should not perform the MMSE, ADAS-Cog, or ADCS-ADL. However, if in exceptional circumstances only this assessor is available to perform these other scales, then the CDR patient interview must be completed after the caregiver interview but before ADAS-COG, MMSE and other cognitive scales are completed.

Raters who assess the CDR should not be involved in any other aspects of patient care for the person that they are rating, including assessment of adverse events and preparation or infusion of study drug.

4.6.5.2 Alzheimer's Disease Assessment Scale-Cognition

The ADAS-Cog is the most frequently used scale to assess cognition in clinical trials for mild to moderate AD (Rozzini et al. 2007; Connor and Sabbagh 2008; Ihl et al. 2012). The modified version will be used; it has 13 items and includes the addition of 1) delayed word recall, and 2) number cancellation, as well as use of only one trial for word recognition. This is the version used in the Alzheimer's Disease Neuroimaging Initiative protocol (http://www.adni-info.org/Scientists/ADNIStudyProcedures.html). Equivalent alternate forms of the word recall, word recognition, and number cancellation subtests will be used in successive test administrations.

The *11*-item version of ADAS-COG will also be analyzed.

4.6.5.3 Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory

The ADCS-ADL (Galasko et al. 1997) is the scale most widely used to assess functional outcome in patients with AD (Vellas et al. 2008). The ADCS-ADL covers both basic ADL (e.g., eating and toileting) and more complex ADL or iADL (e.g., using the telephone, managing finances, preparing a meal).

4.6.5.4 Mini-Mental State Examination

The MMSE (v9.8 including serial 7s) is a set of standardized questions used to evaluate possible cognitive impairment and help stage the severity level of this impairment. The questions target six areas: orientation, registration, attention, short-term recall, language, and constructional praxis/visuospatial abilities.

4.6.5.5 Free and Cued Selective Reminding Test –Immediate Recall

The FCSRT-IR is a measure of memory under conditions that control attention and cognitive processing in order to obtain an assessment of memory. Impairments in FCSRT-IR performance have been associated with preclinical and early dementia in several longitudinal epidemiological studies (Grober and Buschke 1987; Sarazin et al. 2007).

Free and total recall are the two measures from this assessment. Cued recall and the cueing index can be calculated from these two scores. Lower scores imply poorer performance on all aspects of the test.

4.6.5.6 Functional Activities Questionnaire

Impairments in daily functioning is a key clinical feature of AD. Early in AD, impairments are seen in so-called iADLs (e.g., handling of finances, using transportation). This loss of iADLs leads to a loss in resulting in increased burden to caregivers and increased costs independence (Marshall et al. 2011).

The Functional Activities Questionnaire (FAQ) is an informant-based assessment that presents a forced choice of four levels of functioning for 10 ADLs. The FAQ total score

is calculated by adding together the scores of each item – higher scores indicate worsening function (Pfeffer et al. 1982).

4.6.5.7 Neuropsychiatric Inventory Questionnaire

The Neuropsychiatric Inventory Questionnaire (NPI-Q; Cummings et al. 1994; Cummings 2009) was developed to assess a range of behaviors encountered in dementia patients, to provide a means of distinguishing severity of behavioral changes, and to facilitate rapid behavioral assessment through the use of screening questions. It is an informant-based instrument that evaluates 12 neuropsychiatric disturbances common in dementia: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, night-time behavioral disturbances, and appetite and eating abnormalities. The severity of each neuropsychiatric symptom is rated on a 3-point scale (mild, moderate, and marked) while the distress is rated on a 6-point scale (no distress, minimal, mild, moderate, severe, extreme, or very severe).

4.6.5.8 Columbia−Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS; http://www.cssrs.columbia.edu) is an assessment tool used to assess the lifetime suicidality of a patient (C-SSRS at baseline) as well as any new instances of suicidality (C-SSRS since last visit). The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual/potential lethality. The baseline C-SSRS will be collected at baseline and the C-SSRS since last visit will be collected at subsequent visits as indicated in the schedule of assessments (Appendix 1). The assessment will be completed by a certified C-SSRS rater after he or she interviews the patient and *if necessary,* the patient's caregiver during the study visit.

4.6.5.9 Zarit Caregiver Interview for Alzheimer's Disease

The Zarit Caregiver Interview for AD (ZCI-AD) is a modified version of the Zarit Burden Interview, which was originally designed to reflect the stresses experienced by caregivers of people with dementia (Zarit and Zarit 1990). The modified version includes slight modifications in item and title wording (e.g., removal of "your relative" to refer directly to the patient, removal of "burden" from title) and the use of 11-point numerical rating scales. The ZCI-AD scale consists of a total of 30 items and is completed by the caregiver without involvement from the site staff. Total and domain scores will be calculated (higher scores indicate higher levels of distress). Documentation of the questionnaire's psychometric properties will be performed as exploratory analyses.

If a patient's caregiver is replaced during the study, the ZCI-AD will not be completed by his or her new caregiver.

4.6.5.10 Quality of Life–Alzheimer's Dementia

The Quality of Life-AD (QOL-AD) was developed to assess QOL in patients who have dementia (Logsdon et al. 1999, 2002). The QOL-AD consists of 13 items that cover

aspects of patients' relationships with friends and family, physical condition, mood, concerns about finances, and overall assessment of QOL. Items are rated on 4–point Likert-type scales.

In this study, the QOL-AD will be administered in a standardized, structured interview format to the patient by investigative staff in order to gather patient responses on QOL. The caregiver will also complete the caregiver version of the questionnaire to enable proxy responses from the caregiver. A global score will be generated, with a higher score indicating better QOL. Documentation of the questionnaire's psychometric properties in the study population will be performed as exploratory analyses.

4.6.5.11 EQ-5D

The EQ-5D is a standardized measure of health status designed to provide a simple generic measure of health for clinical and economic appraisal. It is broadly applicable across a wide range of health conditions and treatment.

The EQ-5D assesses five domains to provide a health state index. These are anxiety/depression, pain/discomfort, usual activities, mobility, and self-care.

Two versions are used in this study: EQ-5D-5L proxy v1, reported on behalf of the patient and the EQ-5D-5L patient version provided to caregivers to assess caregiver health status.

4.6.6 Electronic Assessment of Rating Scales

The following rating scales will be captured electronically and transferred to the database directly from the core laboratory: ADAS-Cog, ADCS-ADL, CDR, FAQ, FCSRT MMSE, NPI-Q, QOL-AD, ZCI-AD, and C-SSRS. The diagnostic verification will also be included on the device used for scales and submitted electronically.

4.6.7 Laboratory, Biomarker, and Other Biological Samples

4.6.7.1 Standard Laboratory Samples

Samples for the following laboratory tests will be sent to a central laboratory for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments.

For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

- Serum chemistry: AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, CPK, sodium, potassium, calcium, BUN/UREA, and serum creatinine (and creatinine clearance calculated by the central laboratory)
- HbA1c, folic acid, and vitamin B12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed as per the schedule of assessments

- Hematology: hemoglobin, hematocrit, RBC (with morphology), WBC counts, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC–other total counts
- Screening serologies: HIV, hepatitis B, hepatitis C
- Coagulation: PT
- Immunophenotyping: including CD4, CD8, CD3, CD19, CD16+56.
- Urine for drugs of abuse: At screening only, urine samples will be analyzed for the presence of the following drugs: amphetamine, benzodiazepines, cannabinoids, opiates, cocaine, barbiturates, and methadone.
- Results will be used to verify patient eligibility pertaining to drugs of abuse. Inconclusive results may be repeated during the screening period. Investigators should use their best clinical judgment in cases where results may be erroneous (e.g., permitted use of opiates or ingestion of food/food supplements).
- Urinalysis will be performed at the site by dipstick for blood, protein, glucose, and pH. Microscopic examination performed at the central laboratory if blood and/or protein results are positive or strongly positive. Results do not need to be recorded on the eCRF.
- Urine for pregnancy: Urine pregnancy testing will be performed at each dosing visit for women of childbearing potential (including those who have had a tubal ligation), and at the site for any other female participants if required by local regulations. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory.

4.6.7.2 Biomarker Sampling

Samples will be collected from all patients and will be used for research purposes to identify dynamic biomarkers that may be predictive of response to treatment with crenezumab (in terms of dose, safety, and tolerability) and will help to better understand the pathogenesis, course, and outcome of AD and related diseases.

For patients who consent to the optional Research Biosample Repository (RBR), residual biomarker samples will be kept for future biomarker research (see Section 4.6.12).

The procedures for the collection, handling, and shipping of biomarker samples are specified in the Sample Handling and Logistics Manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.6.12), biomarker samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Cerebrospinal Fluid Sampling

CSF samples will be collected in those patients who chose this approach for confirmation of Aβ levels for eligibility purposes (CSF-enrolled patients). Samples will be collected according to the schedule of assessments (see Appendix 1). Lumbar puncture will be performed by an individual who meets all local requirements and is proficient in the procedure. Lumbar puncture procedures and post−lumbar puncture care will be performed in accordance with local practice. CSF sampling should be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters.

Approximately 12 mL of CSF will be collected at screening from patients who are enrolled using CSF Aβ (see Appendix 1). The sample will be divided into aliquots onsite and used for the following:

- Biomarker analysis, including $A\beta_{1-42}$, t-tau, and p-tau. This sample may also be used to support the development of biomarker assays for diagnostic use.

Clinical Genotyping

During screening, three mandatory whole blood samples will be obtained for DNA extraction from every patient who has consented to participate in the study. All patients will be evaluated for *APOE* [redacted], an exploratory diagnostic biomarker. Except in circumstances in which a health authority, EC, or IRB requires the patient be told of his or her *APOE* status [redacted], results will be blinded to patients, investigators, and the Sponsor in order to maintain the blind in the event that dose reduction is implemented. Data arising from these analyses will be subject to the same confidentiality as the rest of the study.

RNA Sampling

During screening, two whole blood samples will be obtained for RNA extraction from every patient who has consented to participate in the study. [redacted]

Plasma Sampling

Plasma sampling will be conducted during screening, at baseline, and at subsequent visits as detailed in the schedule of assessments (see Appendix 1). One whole blood sample will be obtained for plasma extraction from every patient who has consented to participate in the study.

This sample will be used to evaluate plasma Aβ levels *and other biomarkers associated with AD or study treatment* in peripheral blood as pharmacodynamics markers.

4.6.7.3 Immunogenicity Sampling

Blood samples will be collected to assess the possible development of *ADAs* in all patients as noted in the schedule of assessments (see Appendix 1) and in case of

anaphylaxis, anaphylactoid, or serious hypersensitivity reactions and at wash out in the case of discontinuation for anaphylaxis. Serum samples will be analyzed for antibodies to crenezumab using a bridging ELISA. Samples may be tested for antibodies against other drug product substances.

The procedures for the collection, handling, and shipping of *ADA* samples are specified in the Sample Handling and Logistics Manual supplied to the site by the Sponsor.

4.6.7.4 Pharmacokinetic Sampling (Serum Crenezumab)

Blood samples will be collected to evaluate the pharmacokinetics of crenezumab in serum as noted in the schedule of assessments (see Appendix 1). An additional PK sample for the assessment of serum concentrations of crenezumab may be obtained if the patient makes an unscheduled visit. Unscheduled PK samples should be taken in the event of anaphylaxis, anaphylactoid, or serious hypersensitivity reactions, and at wash out in the case of discontinuation for anaphylaxis.

Processing, storage, and shipping instructions for these PK blood samples are presented in a separate laboratory manual provided by the Sponsor to the clinical research unit.

Serum concentrations of crenezumab will be determined using validated analytical procedures.

Samples from patients who receive placebo may not be measured initially but will be retained for subsequent analysis if appropriate.

4.6.8 Timing of Study Assessments

4.6.8.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

After giving written informed consent, patients who are willing to participate in the study will undergo thorough screening assessments within *12* weeks prior to the baseline visit, as detailed in the schedule of assessments (Appendix 1). Patients must fulfill all the entry criteria for participation in the study and the results must be available prior to the baseline visit.

If the FCSRT and MMSE are completed following FCSRT/MMSE consent, and the patient is not excluded, these assessments would not need to be repeated during the screening period. If a patient completes *the* FCSRT *following FCSRT/MMSE consent*, the patient may be asked to perform the MMSE scale even if they do not meet FCSRT related eligibility criteria.

In case of an abnormal laboratory or ECG result at screening that may normalize upon retest, investigators have the option to repeat the tests (prior to baseline and within the screening window) to confirm the test results before randomizing a patient at baseline.

Unexpected logistical or technical *issues* may necessitate *an extension to* the *8-week* screening period. *However, all* screening *assessments, including the FCSRT/MMSE scales if done following* the *FCSRT/MMSE consent,* should *completed within a maximum of 12 weeks prior to baseline. (Exception: MRI scans must be conducted within 8 weeks prior to baseline.) As* careful scheduling *must* remain a priority*, an assessment of progress through the screening period will be made at 8 weeks from first start of screening (inclusive of screening assessments related to the FCSRT/MMSE consent). Any extension beyond 12 weeks requires review and approval by the Sponsor.*

The recommended order of clinical assessments/rating scales at screening is as follows:

Patient	Caregiver
1. FCSRT/MMSE *may be done following the FCSRT/MMSE consent*) 2. CDR (patient interview) 3. MMSE (if not completed *at FCSRT/MMSE consent*) 4. ADAS-Cog-13	~~1.~~ *1.* CDR (caregiver input)

ADAS-Cog-13 = Alzheimer's Disease Activity Scale-Cognitive (subscale) 13; CDR = Clinical Dementia Rating; FCSRT = Free and Cued Serial Recall Task; MMSE = Mini Mental State Examination.

Following the patient assessments on the screening visit, the clinician should complete the diagnosis verification form (see Appendix 4) and submit this within 48 hours of visit. The patient may not continue through screening, including any further invasive screening procedures (e.g., new CSF, MRI, PET scan), until patient eligibility has been confirmed. If a patient does not qualify on the basis of eligibility tests, the patient may be rescreened again after at least 3 months have elapsed if recruitment for the study is still ongoing (see Sections 4.1 and 4.2).

In the event that a patient has an alternative PET scan available (e.g., from a prior clinical investigation), this may be used for confirmation of eligibility, subject to meeting criteria as defined in the PET Imaging Charter.

As noted in the exclusion criteria (see Section 4.2), patients may be rescreened after appropriate treatment if they were originally excluded for abnormal thyroid, folic acid, vitamin B12, or HbA1c results. Other laboratory tests that would exclude the patient may be repeated (as an unscheduled laboratory assessment) if it is suspected that the

abnormal result is transient and likely to be normal at repeat. The Sponsor will monitor the number of repeat laboratory tests during Screening.

Patients may be rescreened if the protocol is amended such that they would satisfy the amended criteria and if recruitment for the study is still ongoing. In this case, all screening assessments must be repeated other than the *MRI (if performed within 8 weeks of randomization),* lumbar puncture and prior PET testing if within eligible ranges.

Patients may be rescreened if there is a substantial change in the patient's condition (e.g., a disallowed medication was stopped) and if recruitment for the study is still ongoing and all eligibility criteria are met.

If FCSRT (and MMSE) are completed following FCSRT/MMSE consent, and the patient is not excluded, these assessments would not need to repeated during the screening period. It is suggested that the remaining screening tests with the exception of the lumbar puncture and MRI and PET scan be done within 1 to 2 weeks of signing the *main* informed consent (to allow adequate time for the remaining tests). As soon as all these results are available, and none exclude the patient from the trial, the CSF collection and/or PET scan and MRI scan should be done if required. It will take several days to receive the results of the MRI or CSF, and, on occasion, the originally scheduled MRI or CSF collection day may need to be postponed and in the case of the MRI, it may need to be repeated. Therefore, the scheduling of these tests needs to be done carefully and should begin as soon as possible.

It is recommended that the MRI appointment should be scheduled to occur no more than 3 weeks after the beginning of the screening period. This is to allow sufficient time for the *amyloid assessment (*PET *or LP)* to be performed and evaluated before the end of the screening period.

A Patient Eligibility Checklist that documents the investigator's assessment of each screened patient with regard to the study's inclusion and exclusion criteria is to be completed by the investigator. A screen failure log must be maintained by the investigator.

4.6.8.2 Study Assessments

In order to be randomized to receive double-blind treatment, patients must have no significant change in medical, psychiatric or neurological conditions or change in medication since screening. The recommended order of assessments and rating scales is as follows:

- Clinical assessments (e.g., QoL-AD, ZCI-AD, MMSE; ADAS-Cog-13; ADCS-ADL; CDR), including all those that require caregiver input, should be completed before any invasive safety assessments

- Vital signs; ECGs; blood draws for clinical laboratory assessments, pharmacokinetics, ADA, and plasma biomarkers; and urine samples are recommended to be collected following scale assessments and must be collected before study drug administration.

The recommended order of clinical assessments/rating scales at baseline, on treatment, and at the Week 105 (or early termination) visit is as follows:

Patient	Caregiver
1. ADAS-Cog-13 2. CDR (patient interview) 3. MMSE 4. FCSRT 5. QoL-AD (if appropriate) 6. C-SSRS	1. CDR (caregiver input) 2. ADCS-ADL 3. FAQ 4. EQ-5D 5. ZCI-AD (if appropriate) 6. QoL-AD(if appropriate) 7. NPI-Q(if appropriate)

ADAS-Cog-13 = Alzheimer's Disease Activity Scale-Cognitive (subscale) 13;
ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living;
C-SSRS = Columbia-Suicide Severity Rating Scale; CDR = Clinical Dementia Rating;
FAQ = Functional Activities Questionnaire; FCSRT = Free and Cued Serial Recall Task;
MMSE = Mini Mental State Examination; NPI-Q = Neuropsychiatric Inventory-Questionnaire;
QoL-AD = Quality of Life-Alzheimer's Disease; ZCI-AD = Zarit Caregiver Interview-Alzheimer's Disease.

Vital signs, ECGs, blood draws for clinical laboratory assessments, pharmacokinetics, ADA, plasma biomarkers, and urine samples are recommended to be collected following scale assessments and must be collected before study drug administration.

If assessments are split over 2 days, all safety assessments must be done on same day as the infusion.

4.6.9 Confidentiality

Data arising from clinical genotyping will be subject to the confidentiality standards described in Section 8.4.

4.6.10 Brain Magnetic Resonance Imaging

The MRI should be performed using a scanner with a field strength of 1.5 T or higher and where practical the same scanner should be used for an individual patient for the entire duration of the study. MRI will be conducted at patient screening to provide a baseline for future safety monitoring, as a baseline measure of structural brain volumes, and as baseline information for the PET substudy concordance analysis (for the schedule of assessments, see Appendix 1). In addition, the screening MRI will be used to help determine whether the exclusion criteria have been met (number of microbleeds, presence of mass lesions, etc.). MRI will be used during the study to help assess safety such as the occurrence of microbleeds or signs potentially indicative of inflammation or ARIA-E. Additional unscheduled MRI scans may be utilized to better understand

relevant CNS–related adverse events (such as increased confusion) or to follow a sign that emerges at a scheduled scan; contrast agent may be used in such a case of follow-up if administration of contrast agent is considered safe for the patient according to local standards. Finally, MRI will be performed at multiple timepoints to determine potential treatment effects on various MRI outcome measures (see Appendix 1).

Patients who are enrolled using CSF-amyloid criteria should either undergo lumbar puncture for CSF sample and then wait for 3 days before having MRI or, ideally, undergo MRI before the CSF sample is taken.

During study conduct, within 3 days prior to the scheduled MRI visit, site staff should contact the patient or caregiver to prospectively determine whether the patient is experiencing any CNS-related symptoms. MRI results must be available for review by site staff before dosing can occur.

Details regarding image acquisition and data transfer by the scanning facilities, and the procedures, clinical assessments, and quantitative measurements performed by the core laboratory can be found in the MRI Charter and Scanning Manuals.

4.6.11 Electrocardiograms

In all patients a routine ECG monitoring approach will be used. Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of assessments (see Appendix 1) and may be obtained at unscheduled timepoints as clinically indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 5 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Digital recordings will be analyzed at the central ECG laboratory and data transmitted to Roche.

The following should be recorded by the electrocardiograph machine: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QT interval corrected using Fridericia's formula (QTcF) and Bazett's formula based on the machine readings of the individual ECG tracings.

If the QTcF is > 500 ms and/or > 60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard of care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. When 12-lead ECGs are scheduled at the same time as blood draws, the blood draws will be obtained at the scheduled timepoint, and the ECGs will be obtained prior to but as close to the scheduled blood draw as possible.

4.6.12 Samples for Research Biosample Repository

4.6.12.1 Overview of the Research Biosample Repository

The RBR is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

In this study, all specimens for the RBR will come from retaining the residual samples remaining after the protocol-specified analysis has been performed on protocol-specified mandatory samples, including those collected in the associated substudy protocols. These residual samples will be retained from patients who give specific consent to participate in this optional research.

RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.6.12.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.6.12) will not be applicable at that site.

4.6.12.3 Sample Collection

Three types of residual samples will be retained by the RBR for identification of dynamic (non-inherited) biomarkers: CSF, plasma, and RNA.

- Plasma and CSF samples may be used for exploratory biomarker assays, including but not limited to determination of markers of amyloid deposition and/or clearance, markers of oxidative stress, neurodegeneration, inflammation, or other processes implicated in the pathogenesis of AD. These samples will be used to further the Sponsor's understanding of AD and the response to treatment and may also be used to support the development of biomarker and diagnostic assays.
- RNA samples may be tested using techniques such as RNAseq, microarray profiling and/or quantitative reverse transcription polymerase chain reaction to study the expression profile of genes known to be involved in AD. These samples will be used to further our understanding of AD and the response to treatment and may also be used to support the development of biomarker and diagnostic assays.

The following sample type will be retained by the RBR for identification of inherited genetic biomarkers:

- DNA extracted from whole blood: DNA samples may be used to explore the associations of specific variants of genes implicated in susceptibility and pathogenesis of AD with therapy response. DNA samples in the RBR may also be used for whole genome sequencing to explore how genetic changes affect diseases or response to treatment.

Whole blood samples may be sent to one or more laboratories for DNA extraction to enable analysis of germline mutations, somatic mutations via whole genome sequencing (WGS), next-generation sequencing (NGS), or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

RBR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

For all samples, dates of consent should be recorded on the associated RBR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

4.6.12.4 Confidentiality

Specimens and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses, data derived from RBR specimens will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

[redacted]

4.6.12.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

4.6.12.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the

RBR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study BN29553 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study BN29553.

4.6.12.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.7 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.7.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. *Study treatment discontinuation does not imply discontinuation from the study as described in Section* 4.7.2. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

Patients should be informed of circumstances under which their participation may be terminated by the investigator without the patient's consent. Any administrative or other reasons for withdrawal must be explained to the patient.

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.7.2 Study Treatment Discontinuation

Patients must discontinue study treatment permanently if they experience any of the following:

- Pregnancy

- Evidence of more than 10 microbleeds and/or areas of leptomeningeal hemosiderosis (ARIA-H), including any present at baseline, as assessed by central review of MRI.
- Diagnosed with three recurrent, symptomatic ARIA-E events or exacerbations of previous events.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Patients who discontinue from the study *drug or who complete the study* treatment *and do not enter* the *OLE will be asked to return* for *the* collection of safety and efficacy data 4, 16, and 52 weeks *after administration* of the last dose of study treatment.

Additionally all patients who discontinue from study drug early will be encouraged to return for subsequent visits, especially the Week 105 visit (early discontinuation of study treatment does not imply study discontinuation).

4.7.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Futility analyses from this or other studies with crenezumab suggest that treatment with crenezumab is likely not effective
- Sponsor determines it is in the best interest of the patients.

The Sponsor will notify the investigator if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Crenezumab is not approved, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with crenezumab in completed and ongoing studies. The anticipated important safety risks for crenezumab are outlined below. Please refer to the crenezumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

Investigators will assess the occurrence of adverse events and serious adverse events at all patient evaluation timepoints during the study. All adverse events and serious adverse events, whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means, will be recorded in the patient's medical record and on the appropriate adverse event eCRF. Each recorded adverse event or serious adverse event will include a description of its duration (i.e., start and end dates), severity, seriousness according to regulatory criteria, if applicable, and suspected relationship to the investigational product, as well as any actions taken. Patients will be carefully followed for adverse events during the study, including a safety follow-up period of 52 weeks after the last dose of study drug.

An iDMC will review unblinded safety and limited efficacy data at regular intervals (see Section 3.1.4 and the iDMC charter for further details).

5.1.1 Amyloid-Related Imaging Abnormalities-Edema/Effusion and Amyloid-Related Imaging Abnormalities-Hemosiderin Deposition

The occurrence of imaging abnormalities believed to represent amyloid–related imaging abnormalities-edema/effusion has been reported in association with the investigational use of compounds that are intended to treat Alzheimer's disease through the reduction of amyloid β in the brain. These imaging abnormalities have, in the majority of instances, been asymptomatic, and their presence has been detected by brain magnetic resonance imaging (Salloway et al. 2009; Sperling et al. 2011).

These magnetic resonance imaging signal hyperintensities seen in the parenchyma and leptomeninges are named **amyloid–related imaging abnormalities-edema/effusion** to cover the magnetic resonance imaging alterations seen in the fluid–attenuated inversion

recovery sequence thought to represent edema in the gray and white matter and effusion or extravasated fluid in the sulcal space (Sperling et al. 2011). Symptoms, when present in association with such imaging abnormalities, have been reported to include headache, worsening cognitive function, alteration of consciousness, seizures, unsteadiness, and vomiting.

Cerebral microhemorrhages in Alzheimer's disease have a point prevalence of 23% (Vernooij et al. 2008). One longitudinal study found that in patients with Alzheimer's disease the incidence of ≥1 microhemorrhage after a mean follow-up of 2 years was 12% (Goos et al. 2010). Recently, the occurrence of microhemorrhage has also been identified as an adverse event in anti-amyloid vaccination trials, and together with superficial siderosis, these events have been termed **amyloid–related imaging abnormalities-hemosiderin deposition** (Sperling et al. 2011). Limited data on amyloid–related imaging abnormalities-hemosiderin deposition occurrence are available, but a retrospective analysis in patients with Alzheimer's disease who were treated with anti-amyloid β antibodies with full effector function reported that 24 out of 207 patients (11.6%) developed amyloid–related imaging abnormalities-hemosiderin deposition (Sperling et al. 2012a). Acute occurrence of cerebral microhemorrhage is not always considered clinically significant (Greenberg et al. 2009). Study patients who received bapineuzamab and developed amyloid–related imaging abnormalities-hemosiderin deposition without amyloid–related imaging abnormalities-edema/effusion were clinically asymptomatic (Sperling et al. 2012a). However, the clinical significance of cerebral microhemorrhage is not yet fully understood.

Recent population-based studies have shown that cerebral microhemorrhages are common in community-dwelling elderly people, with high prevalence ranging from 10%–25% (Greenberg et al. 2009). Among those patients, approximately 70%–80% had 1 or 2 cerebral microhemorrhages (Cordonnier et al. 2011) and high numbers of cerebral microhemorrhages have been associated with future risk of ischemic and hemorrhagic strokes (Greenberg et al. 2009). In a longitudinal study in patients visiting a memory clinic, the incidence of new cerebral microhemorrhages (range, 1–19 per patient) within 2 years of that visit was approximately 12%, and the incidence was not related to diagnosis (type of dementia or disease severity) or *APOEε4* status (Goos et al. 2010). Taken together, accumulating evidence suggests that cerebral mHs are common in cross-sectional observational studies of healthy elderly subjects, and the increase in prevalence over time may be part of the natural history of aging, which indicates a specific underlying vascular pathologic state, in particular hypertensive vasculopathy or cerebral amyloid angiopathy.

When anti-amyloid β antibodies bind to amyloid deposited around blood vessels, an FcγR–mediated immune response may be elicited. This compromises vascular integrity and results in amyloid–related imaging abnormalities-edema/effusion or amyloid–related imaging abnormalities-hemosiderin deposition. The hypothesis that FcγR–mediated immune response may contribute to the occurrence of amyloid–related imaging

abnormalities-edema/effusion and/or amyloid–related imaging abnormalities-hemosiderin deposition is supported by results from clinical studies that have shown that patients with Alzheimer's disease who were treated with anti-amyloid β antibodies with full effector function developed amyloid–related imaging abnormalities-edema/effusion (symptomatic and asymptomatic*). In these patients ARIA events tend to occur early after treatment initiation and are dose and APOEε4 dependent.*

Crenezumab, a human IgG4, has reduced FcR binding compared with IgG1/IgG2 and, thus, has reduced effector function that theoretically might lower the risk of amyloid-related imaging abnormalities-edema/effusion. *A lack of binding to vascular amyloid, noted following in vivo dosing in PS2APP transgenic mice (Study 15-2817B), may similarly reduce crenezumab's risk of inducing ARIA.* This has been supported by emergent safety data observed in both clinical and nonclinical studies.

In the completed Phase I and II studies, only a single case of amyloid-related imaging abnormalities-effusion/edema has been observed as of 27 May *2017* (a case of asymptomatic sulcal effusion observed in the intravenous cohort of Study ABE4869g in a patient treated with crenezumab). This same patient had recurrences of amyloid-related imaging abnormalities-edema/effusion during the open-label extension.

Since development of asymptomatic cerebral microhemorrhages may occur within the natural history of Alzheimer's disease at a rate of approximately 10% per year, the appearance of new cerebral microhemorrhages should not automatically disqualify a patient from further treatment. However, as the occurrence of new cerebral microhemorrhages may also result from amyloid clearance associated with amyloid-lowering therapy and high numbers of new cerebral microhemorrhages might impose a risk for future ischemic and hemorrhagic strokes, study drug must be discontinued in specific circumstances (refer to Section 5.1.2 for details of withdrawal rules).

In this Phase III study, a safety monitoring plan has been designed to monitor the potential risk of amyloid–related imaging abnormalities-edema/effusion and amyloid–related imaging abnormalities-hemosiderin deposition. This plan consists of the following key elements:

- Exclusion criteria:
  - According to the magnetic resonance imaging central reader, magnetic resonance imaging evidence of a) >2 lacunar infarcts, b) any territorial infarct >1 cm^3, or c) any white matter lesion that corresponds to an overall Fazekas score of 3 that requires at least one confluent hyperintense lesion on the fluid–attenuated inversion recovery sequence, which is ≥ 20 mm in any dimension
  - Evidence of >4 microbleeds and/or areas of leptomeningeal hemosiderosis (amyloid–related imaging abnormalities-hemosiderin deposition) as assessed

by central review of T2* gradient-recalled echo magnetic resonance imaging (see Magnetic Resonance Imaging Charter for further details)

- Prior to all magnetic-resonance imaging evaluations, the patient and caregiver will be contacted to determine if the patient has any CNS-related symptoms. If present, a symptom-led assessment will be performed at the visit
- Brain magnetic resonance imaging (including fluid–attenuated inversion recovery sequence and T2*-weighted gradient-recalled echo sequences) will be performed every 3 months in the first year and at least every 6 months in subsequent years to detect amyloid–related imaging abnormalities-edema/effusion and amyloid–related imaging abnormalities-hemosiderin deposition (see Appendix 1)
- All magnetic resonance imaging scans will be read in a timely fashion and will evaluate amyloid–related imaging abnormalities-edema/effusion and amyloid–related imaging abnormalities-hemosiderin deposition as well as other abnormalities. Assessments will be made by independent blinded radiologists at a central contract imaging vendor.
- Patients who exhibit new amyloid–related imaging abnormalities-edema/effusion or amyloid–related imaging abnormalities-hemosiderin deposition (but do not qualify for treatment discontinuation as defined below) will be rescanned within approximately 4 weeks after the last magnetic resonance imaging scan to evaluate the evolution of the findings.

Amyloid–related imaging abnormalities-edema/effusion or amyloid–related imaging abnormalities-hemosiderin deposition findings *may require* dose modification or treatment discontinuation. *The* rules *to be applied* in specific cases are detailed in Section 5.1.2.

5.1.2 *Management of* Amyloid-Related Imaging Abnormalities *including Required* Dose Adjustments

To date, there has been limited clinical experience of ARIAs with crenezumab; however, data from studies on other mAb treatments reveal that ARIA events tend to occur early after treatment initiation, are dose and APOE&4 dependent, are manageable with MRI monitoring, and do not lead to significant adverse outcomes (see Section 5.1.1).

All clinical trials with crenezumab include APOE&4 genotyping, MRI safety monitoring, and an ARIA-based dose intervention algorithm.

The following dose adjustments and discontinuation rules for magnetic resonance imaging–related findings will apply:

5.1.2.1 Amyloid–Related Imaging Abnormalities-Edema/Effusion *(ARIA-E)*

Asymptomatic amyloid–related imaging abnormalities-edema/effusion with Barkhof Grand Total Score *<4* (Barkhof et al. 2013):

- Continue study drug at the same dose (i.e., 60 mg/kg crenezumab)

- Repeat magnetic resonance imaging 4 weeks later

– If amyloid–related imaging abnormalities-edema/effusion is stable or decreased, continue study drug and monthly magnetic resonance imaging monitoring until event resolves. Once amyloid–related imaging abnormalities-edema/effusion completely resolves, conduct magnetic resonance imaging monitoring as per Appendix 1.

– If amyloid–related imaging abnormalities-edema/effusion increases (Barkhof Grand Total Score ≥ 4) or symptoms develop, refer to the rule below.

Symptomatic amyloid–related imaging abnormalities-edema/effusion (any size) or asymptomatic amyloid–related imaging abnormalities-edema/effusion with Barkhof Grand Total Score *≥4*:

- Temporarily interrupt study drug and implement monthly magnetic resonance imaging monitoring
- Once symptoms and amyloid–related imaging abnormalities-edema/effusion resolve, reintroduce study drug *at the same dose* and perform an magnetic resonance imaging after 4 weeks of dosing. If no new magnetic resonance imaging is detected, resume magnetic resonance imaging monitoring as per Appendix 1.

Any new onset of amyloid–related imaging abnormalities-edema/effusion: Treat the same as the first event, based on symptoms and Barkhof Grand Total Score. However, in the case where a patient is diagnosed with three recurrent, symptomatic amyloid–related imaging abnormalities-edema/effusion events or exacerbations of previous events, permanently discontinue the study drug. Implement monthly magnetic resonance imaging monitoring until resolution of both symptoms and amyloid–related imaging abnormalities-edema/effusion. As per the protocol (please refer to Section 4.6.2), maintain the patient in the study until study end and perform assessments as per the schedule of assessments.

5.1.2.2 Amyloid–Related Imaging Abnormalities-Hemosiderin Deposition *(ARIA-H)*

Dose reduction: Patients who develop > 8 amyloid–related imaging abnormalities-hemosiderin deposition cumulatively* will receive a lower dose of the study drug *(i.e., 30 mg/kg) at any dosing visits for the rest of the study*.

Study drug discontinuation: Patients who develop > 10 amyloid–related imaging abnormalities-hemosiderin deposition cumulatively* will be permanently discontinued from the study drug.

*Sum of amyloid–related imaging abnormalities-hemosiderin deposition at baseline and newly detected amyloid–related imaging abnormalities-hemosiderin deposition during the study.

5.1.3 *Prevention* and Management of Hypersensitivity and Infusion Reactions

Crenezumab will be administered to patients under close medical supervision in a setting with access to appropriate emergency equipment and staff who are trained to monitor and respond to medical emergencies. In the event that a patient experiences a mild infusion related reaction, the infusion will be halted. Once the reaction has resolved, the infusion rate will be resumed at half of the most recently used rate [redacted]. Patients who experience a moderate infusion-related reaction (e.g., fever or chills) should have the infusion stopped immediately and should receive aggressive symptomatic treatment. The infusion should not be restarted before all symptoms have disappeared, and then it should be restarted at half the initial rate. Patients who experience serious or severe hypersensitivity reactions (e.g., hypotension, mucosal involvement) should not receive additional study drug.

5.1.4 Additional Safety Monitoring

Laboratory tests, including hematology and chemistry, will be performed throughout the study. ECGs will be recorded regularly (see Appendix 1). Symptom-led examinations will be performed as required during the study to assess physical and neurologic events that are not consistent with normal disease progression. The Columbia-Suicide Severity Rating Scale will be used for prospective suicidality assessment. Pregnancy testing will be performed at each visit in women of child-bearing potential. Samples to assess immunogenicity will be collected prior to and throughout the treatment and follow-up periods.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

- Pneumonia: In the Phase II program, a numerical imbalance in pneumonia cases was observed, with more events reported in crenezumab-treated patients versus placebo-treated patients. It is of paramount importance to carefully document any pneumonia cases and other serious respiratory infections that occur in this study, by means of providing all relevant information required by the eCRF. A chest X-ray is required under the following circumstances:

– Serious and non-serious pneumonia

– Serious and non-serious lower respiratory tract infections

– Serious upper respiratory infections.

- In addition, whenever possible, additional relevant investigations should be conducted (e.g., WBC counts, pathogen identification by means of hemocultures, bronchoalveolar lavage).
- When a pneumonia case is diagnosed, a blood sample for fluorescence-activated cell sorting analysis must be collected as soon as feasible for the site and the patient.

– In addition, in order to investigate any potential effects of study drug on the immune system, blood samples for B and T cells' phenotyping (i.e., fluorescence-activated cell sorting analysis) will be collected in all enrolled patients at Baseline and Week 25.

5.2.4 Selected Adverse Events

To further elucidate potential clinical implications of amyloid–related imaging abnormalities findings, patients will be asked if they experience CNS adverse events up to 1 week before each magnetic resonance imaging assessment is performed. The eliciting of these adverse events should be according to Section 5.3.2. The adverse events collected in this prospective fashion will be distinct from other adverse events and

summarized separately in the clinical study report. Additional data on associated symptoms (as defined on the eCRF) and safety magnetic resonance imaging scans will be collected for the following selected adverse events:

- Amyloid–related imaging abnormalities-edema/effusion: Amyloid-related imaging abnormalities suggestive of vasogenic edema and sulcal effusions
- Amyloid–related imaging abnormalities-hemosiderin deposition: Amyloid-related imaging abnormalities suggestive of microhemorrhage and hemosiderin deposits.

New amyloid-related imaging abnormalities-edema/effusion or amyloid-related imaging abnormalities-hemosiderin deposition noted on study-related MRI scans should be reported as adverse events in these circumstances:

- *They are symptomatic (i.e., accompanied by CNS symptoms)*

  AND/OR

- *They result in a change in study treatment (dose modification, interruption, or discontinuation; see Section 5.1.2)*

Any accompanying symptoms should also be captured as separate adverse events.

ARIA-E should be reported separately from ARIA-H.

It is possible that more than one new area of ARIA-H is identified on the same MRI. If meeting the criteria above, these should be reported collectively as one new adverse event, and the number of areas should be specified. The same should be done separately for ARIA-E.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4 –5.6

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive

procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

In addition, after initiation of a PET ligand but prior to initiation of study drug, all serious adverse events occurring within 48 hours of PET ligand administration should be reported regardless of relatedness to the PET ligand (see Section 5.4.2). After this 48-hour timepoint, only serious adverse events s considered related to the PET ligand should be reported. Non-serious adverse events (occurring at any timepoint) considered to be related to the PET ligand should also be reported.

After initiation of study drug, all adverse events will be reported until 2 elimination half-lives after the last dose of study drug (8 weeks) after the last dose of study drug.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

Table 2 provides guidance for assessing adverse event severity.

Table 2 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration.

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)

- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction" on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of AD.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

If the death is attributed to progression of Alzheimer's disease, "Alzheimer's disease progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Alzheimer's Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on guidelines (e.g., NIAAA New Diagnostic Criteria and Guidelines for AD; see Appendix 2 and Appendix 3). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event.

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.3.5.13 Patient-*Reported* Outcome Data

Adverse event reports will not be derived from *PRO* data by the Sponsor, and safety analyses will not be performed using *PRO* data. *Investigators and site staff* are not expected to review *PRO* data *for* adverse *events*.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor:	[redacted] M.D. (Primary)
Telephone No.:	[redacted]
Mobile Telephone No.:	[redacted]
Medical Monitor:	[redacted] M.D. (Secondary)
Telephone No.:	[redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all

calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events, Adverse Events of Special Interest, *and PET Ligand Adverse Events*

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, serious adverse events caused by a protocol-mandated intervention *as well as all serious adverse events that occur within 48 hours of PET ligand administration regardless of causality* should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting *paper* Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

For PET ligand-related adverse events, the clinical site will complete a PET ligand-specific non-serious adverse event reporting paper form and submit it to the Sponsor or its designee by scanning and emailing the form using the email address provided on the form.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 8 weeks after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur >8 weeks after the last dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 8 weeks after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and

submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 8 weeks after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 8 weeks after the last dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Crenezumab Investigator's Brochure

To determine reporting requirements for PET ligands used, in those countries that have health authority approval of the PET ligands the approved local product information will be used. In countries where the PET ligand does not have health authority approval, the Investigator's Brochure will be used.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The purpose of this study is to investigate the treatment effect of crenezumab relative to placebo. The primary efficacy analysis will be based on an intent-to-treat (ITT) population, which will include all randomized patients who receive at least one dose of study drug, with patients grouped according to their randomly assigned treatment.

Approximately 750 patients will be randomized in the Global Enrollment Phase of this study. [redacted]. The China subpopulation will include patients enrolled at sites in *mainland China, Hong Kong, and/or Taiwan (according to applicable Chinese regulations)* during both the Global Enrollment Phase and the China Extension Phase.

The primary analyses of this study will include patients enrolled during the Global Enrollment Phase; data from patients enrolled *after the close of Global Enrollment* will be included in analyses separate from the primary analyses.

6.1 *DETERMINATION OF SAMPLE SIZE*

Determination of sample size is based on patients enrolled in the Global Enrollment Phase. In this study, 750 patients will be enrolled with 375 patients per treatment arm (crenezumab or placebo) during the Global Enrollment Phase. [redacted]

The estimate of sample size required to demonstrate efficacy with regard to CDR-SB is based on the following assumptions:

- The mean change in CDR-SB from baseline to Week 105 is 2.6 points in the placebo arm

- A common SD across treatment arms for change from baseline to Week 105 in CDR-SB of approximately 3.07 (this corresponds to a coefficient of variation of 118% for change in CDR-SB from baseline to Week 105 in a prodromal to mild AD population in the placebo arm)
- The dose level has a true effect of a 30% relative reduction in deterioration of CDR-SB
- 35% of randomized patients will dropout by Week 105

This sample size will have 80% power to detect a true treatment effect of 30% relative reduction in deterioration of CDR-SB at 2-sided α of 0.05.

In the event that the rescue strategy or change in dose is required, the number of patients enrolled in the new dose group and its concurrently enrolled placebo arm will be 750 patients (375 patients per treatment arm) during the Global Enrollment Phase. All patients already enrolled on 60 mg/kg *of study treatment* and corresponding concurrently enrolled placebo patients will be replaced with new patients.

A blinded assessment of the pooled standard deviation of CDR-SB change from baseline will be performed by the Sponsor at a specified timepoint prior to unblinding. As a result, the sample size may be increased from 750 up to 1126 patients (563 patients per arm). Further details will be described in the Statistical Analysis Plan (SAP). The sample size will not be reduced on the basis of this assessment. Other factors external to the study may also trigger a decision to increase sample size.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, patient disposition, and incidence of protocol deviations will be summarized for *all randomized patients and grouped* according to *randomized* treatment *assignment*.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (such as age, sex, race, disease severity, *APOEε4* status, use and non-use of background therapy for AD) will be summarized descriptively for the ITT population, grouped according to the assigned treatment arm.

Descriptive summaries of continuous data will present the mean, SD, median, minimum, and maximum. Descriptive summaries of discrete data will include frequencies expressed in terms of number and percentage of patients.

The primary and secondary efficacy analyses will include all randomized patients, with patients grouped according to the treatment assigned at randomization.

6.4 *EFFICACY ANALYSES*

6.4.1 Primary Efficacy Endpoint

The primary efficacy outcome measure is the change in CDR-SB from baseline (Week 1) to Week 105. For this primary outcome measure, the difference in mean change from

baseline to Week 105 between crenezumab- and placebo-treated patients will be estimated. Mixed model repeated measures (MMRMs) adjusting for disease severity, *APOEε4* status, geographic region, and the use or non-use of anti-dementia medications at baseline will be used to estimate the mean change from baseline for the primary endpoint. The analysis will include all randomized patients, with patients grouped according to the treatment assigned at randomization.

The MMRM model will be used to estimate the mean change from baseline for the primary endpoint. The model will include the change from baseline in CDR-SB as the dependent variable. The effects in the model will include baseline score, treatment group, visit, treatment-by-visit interaction and baseline score-by-visit interaction. Visit week will be treated as the repeated variable within a patient. Patient, treatment, and visit week will be treated as class variables. An unstructured variance–covariance structure will be applied to model the within-patient errors; in case of non-convergence, compound symmetry will be used.

The difference in the changes from baseline of each dose group from placebo will be estimated at each time point. The 95% CI and p-value for treatment difference will be presented.

All efforts will be made to minimize missing data. The Sponsor plans to request patients who discontinued early from study treatment to return for collection of safety and limited efficacy data until Week 105. To explore the robustness of MMRM results for the primary efficacy conclusions, sensitivity analyses (for example, using multiple imputation and pattern mixture models) will be performed. Descriptive summaries of the number of patients with missing data and the timing and reasons for discontinuation from study by treatment group will also be provided.

Additional details will be documented in the SAP.

6.4.2 Secondary Efficacy Endpoints

The absolute change from baseline in the continuous secondary efficacy endpoints listed in Section 2 (including cognition endpoints, global endpoints, disease pathology biomarkers, and endpoints that measure other AD symptoms and effects) will be analyzed using an MMRM analysis model similar to that described above for the primary efficacy endpoint.

In order to protect the overall type I error rate for the study when incorporating the hypothesis testing of the primary endpoints and the key secondary endpoints into the analysis, the fixed sequence testing procedure (Westfall and Krishen 2001) will be used to adjust for multiple comparisons. These endpoints will be tested in the following order:

1) Change from baseline to Week 105 in CDR-SB
2) Change from baseline to Week 105 in ADAS-Cog-13 and $ADAS\text{-}Cog\text{-}11$

3) Change from baseline to Week 105 in iADL

4) Change from baseline to Week 105 in ADCS-ADL total score

The treatment difference in the primary endpoint (change from baseline to Week 105 in CDR-SB) will be tested at a 2-sided 5% overall significance level using the O'Brien−Fleming boundary. If this test result is statistically significant at either the interim or the final analysis, the treatment difference in change from baseline to Week 105 in ADAS-Cog-13 will be tested at a two-sided 5% significance level. If the treatment effect on ADAS-Cog-13 is statistically significant, the treatment effect on *ADCS-iADL total score* will be tested at a two-sided 5% significance level *and likewise for ADL if iADL is significant*. If any test result is not statistically significant, testing of the subsequent endpoints will not occur.

6.4.3 Exploratory Efficacy Analyses

For time-to-event endpoints, the Kaplan−Meier method will be used to estimate the median time-to-event for each treatment arm. Cox proportional hazard model stratified by the randomization stratification factors will be used to estimate the hazard ratio and its 95% CI. The two-sided log-rank test, stratified by the randomization stratification factors, will be used to perform hypothesis testing for assessing treatment difference between the two treatment arms at a 5% significance level.

Subgroup *analyses* of efficacy results *may* also be performed *based on clinically relevant baseline factors. Subgroups will be* defined by *factors which may include one or more of the following:* age, sex, race, dementia status (pAD vs. mAD), *APOEε4* status, geographic region, use and non-use of background therapies for AD, *or* other clinically relevant factors at baseline.

6.5 SAFETY ANALYSES

The safety analysis population will include all randomized patients who received at least one dose of study drug, with patients grouped according to the treatment actually received.

- Incidence and nature of MRI safety findings: ARIA-E and ARIA-H
- Incidence, nature, and severity of serious adverse events
- Incidence, nature, and severity of adverse events
- Incidence of adverse events of special interest
- Incidence of treatment discontinuations due to adverse events
- Mean changes in clinical laboratory tests from baseline over time; incidence of treatment-emergent abnormal laboratory values and abnormal laboratory values reported as adverse events
- Mean change in ECG assessments from baseline over time and incidence of abnormal ECG assessments

- Incidence of immunogenicity as evidenced by antibodies to crenezumab or other components of drug product
- Physical and neurologic examination abnormalities
- Mean change in vital signs (blood pressure, heart rate) from baseline over time and incidence of abnormal vital sign measurements
- Changes in CSSR-S scores from baseline over time.

6.6 PHARMACOKINETIC ANALYSES

Serum concentration data for crenezumab will be tabulated and summarized. Descriptive summary statistics will include the arithmetic mean, median, range, SD, and coefficient of variation, as appropriate. Since a sparse PK sampling design is being used, population (non-linear mixed-effects) modeling will be used to analyze the dose concentration-time data of crenezumab. Information from other clinical studies may be incorporated to establish the PK model. The influence of patient characteristics (e.g., demographics, disease stage) and background medication on the pharmacokinetics of crenezumab will be explored using the PK model. The selection of parameters and the derivation of individual measures of exposure, such as AUC, C_{max}, and trough serum concentration, will depend on the final PK model used for this analysis. The results of this modeling analysis may be reported separately from the clinical study report.

CSF concentrations data for crenezumab and the ratio between CSF and serum crenezumab will be tabulated and summarized as appropriate from the substudy (BN29553-CSF longitudinal).

6.7 *BIOMARKER* ANALYSES

Plasma Abeta concentrations and MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, will be analyzed using the same methods used for the primary analysis. Brain amyloid load, brain tau load, and CSF markers of disease will be analyzed in their respective substudies (BN29552/BN29553-Amyloid PET longitudinal, BN29552/BN29553-tau PET longitudinal, and BN29553-CSF longitudinal). Further details can be found in the pertinent substudy protocol.

[redacted]

Exploratory analyses of the relationship between crenezumab exposure and biomarker (imaging, plasma PD, CSF PD*, or genetic*), efficacy, or safety measures will be performed as appropriate. The results of these analyses may be reported separately from the clinical study report.

6.8 INTERIM ANALYSIS

Based on information that may emerge during the course of this study, the Sponsor may choose to conduct *one or more interim analyses. Interim* analyses *would* be conducted by an independent data coordinating center and reviewed by iDMC. *The Sponsor would remain blinded.* Interactions between the iDMC and Sponsor *would* be carried out as specified in the iDMC Charter. The iDMC Charter *would* document potential recommendations the iDMC can make to the Sponsor as a result of the analyses (e.g., stop the study for futility). *Below are further specifications in place to ensure the study continues to meet the highest standards of integrity should optional interim analyses be executed.*

The Sponsor may choose to perform an optional futility analysis. No adjustment for multiple comparisons would be made to the α level for this analysis, given that the decision rules for the futility analysis would not allow for the opportunity to stop the study early for overwhelming efficacy. At the time of *a* futility *analysis*, the threshold for declaring futility *would* be based *on* the probability of erroneously stopping the study being lower than a pre-specified level, when crenezumab has a true treatment effect on CDR-SB (false negative rate). If the observed treatment effect at the futility analysis is smaller than the derived threshold, the iDMC may recommend that the study be stopped for futility. Additional criteria for recommending that the study be stopped for futility may be added to the iDMC Charter.

In addition, the *Sponsor* may *perform an interim assessment* for positive efficacy. The type I error rate will be controlled to ensure statistical validity is maintained. Specifically, the Lan-DeMets α-spending function that approximates the O'Brien-Fleming boundary will be applied to determine the critical value for stopping for positive efficacy at the interim analysis (DeMets and Lan 1994). If the study continues beyond the interim analysis, the critical value at the final analysis would be adjusted accordingly to maintain the protocol-specified overall type I error rate, per standard Lan-DeMets methodology. Control of overall type I error in multiple comparisons of primary and key secondary endpoints are described in Section 6.4. This interim analysis *would* also be reviewed by the iDMC, and the Sponsor *would remain* blinded. Additional criteria for recommending that the study be stopped for positive efficacy may be added to the iDMC Charter.

Further details (e.g., timing, data to be reviewed by the iDMC, thresholds, etc.) will be documented in the interim SAP. The interim SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of an interim analysis.

As information external to the study (e.g., from other compounds) becomes available during the conduct of the study, the Sponsor may implement changes to the protocol to incorporate such learnings into the study, if possible. Such learnings may be concerned with endpoints, biomarkers, and sample size reassessment due to the variability and size of treatment effect observed in other compounds, for example. The Sponsor could

implement such learnings through a protocol amendment while being blinded, but without consultation with the iDMC.

6.9 CHINA SUBPOPULATION ANALYSIS

Approximately 750 patients will be randomized during the Global Enrollment Phase of this study. [redacted] The China subpopulation will include patients enrolled at sites in *mainland China, Hong Kong, and/or Taiwan (according to applicable Chinese regulations)* during both the Global Enrollment Phase and the China Extension Phase.

The objective of the China Extension Phase and the China subpopulation analyses is to assess the treatment effects of crenezumab in a population of patients in *mainland* China*, Hong Kong, and/or Taiwan* and to investigate the consistency in treatment effects between the China subpopulation and the global population for the purpose of registration in China.

Methods for analyzing data from the China subpopulation will be provided in the SAP. Results from these analyses will be summarized in a separate report.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data, ECG, and other data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO and ObsRO data will be collected through the use of an electronic device provided by a vendor. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR Part 11). The electronic data are available for view access only via secure access to a

web server. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related

monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO and ObsRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and

approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of the analyses, data derived from exploratory biomarker specimens will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, subjects' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

The overall procedures for quality assurance of clinical study data are described in the Roche standard operating procedures. This study will be sponsored by F. Hoffmann-La Roche Ltd. Roche will provide clinical operations oversight, site monitoring and management, data management support, and medical monitoring.

Drug distribution may occur through an IxRS (see Section 4.3). Central facilities may be used for study assessments (i.e., ECG, MRI, lumbar puncture, specified laboratory tests, pharmacokinetics, rating scales evaluation, and PET, as applicable).

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

[redacted]

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to

eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

Adolfsson O, Pihlgren M, Toni N, et al. An effector-reduced anti-β-amyloid (Aβ) antibody with unique aβ binding properties promotes neuroprotection and glial engulfment of Aβ. J Neurosci 2012;32:9677–89.

Aisen PS. Alzheimer's disease therapeutic research: the path forward. Alzheimers Res Ther 2009;1:2.

Aisen PS, Andrieu S, Sampaio C, et al. Report of the task force on designing clinical trials in early (predementia) AD. Neurology 2011;76:280–6.

Albert MS, DeKosky ST, Dickson B, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dement 2011;7:270–279.

Alzheimer's Association. 2015 Alzheimer's disease facts and figures. Alzheimers Dement 2015;11:332–84.

Alzheimer's Disease International. World Alzheimer report 2015: The global impact of dementia. 2015.

Auriacombe S, Helmer C, Amieva H, et al. Validity of the Free and Cued Selective Reminding Task in predicting dementia. Neurology 2010;74:1760–67.

Barkhof F, Daams M, Scheltens P, et al. An MRI rating scale for amyloid-related imaging abnormalities with edema or effusion. AJNR Am J Neuroradiol. 2013;34(8):1550–5.

Becker RE, Greig NH. Alzheimer's disease drug development: old problems require new priorities. CNS Neurol Disord Drug Targets 2008;7:499−511.

Brookmeyer R, Corrada MM, Curriero, et al. Survival following a diagnosis of Alzheimer's disease. Arch Neurology 2002;59:1764–67.

Cano SJ, Posner HB, Moline ML, et al. The ADAS-cog in Alzheimer's disease clinical trials: psychometric evaluation of the sum and its parts. J Neurol Neurosurg Psychiatry 2010;81:1363–68.

Chong CP, Street PR. Pneumonia in the elderly: A review of the epidemiology, pathogenesis, microbiology, and clinical features. South Med J 2008;101:1141–5.

Clark CM, Schneider JA, Bedell BJ, et al. Use of Florbetapir-PET for Imaging β-Amyloid Pathology. JAMA 2011;305:275–83.

Connor DJ, Sabbagh MN. Administration and scoring variance on the ADAS-Cog. Journal of Alzheimer Disease. 2008;15(3):461–4.

Cordonnier C, van der Flier WM. Brain microbleeds and Alzheimer's disease: innocent observation or key player? Brain 2011;134(Pt 2):335–44.

Cummings JL. Defining and labeling disease-modifying treatments for Alzheimer's disease. Alzheimer Dement 2009;5:406–18.

Cummings JL. Alzheimer's disease. N Engl J Med 2004;351:56−67.

Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;44:2308–14.

Cummings JL, Cho W, Ward M, et al. A randomized, double-blind, placebo controlled Phase 2 study to evaluate the efficacy and safety of crenezumab in patients with mild to moderate Alzheimer's disease. Alzheimer Dement 2014;10:275.

Dash P, Villemarette-Pittman N. Alzheimer's Disease. American Academy of Neurology Press 2005.

DeMets DL, Lan KK. Interim analysis: the alpha spending function approach. Stat Med 1994;13:1341–52.

Deng R, Iyer S, Theil FP, Mortensen D, et al. Projecting human pharmacokinetics of therapeutic antibodies from nonclinical data. What have we learned? mABs 2011;3:61–6.

Dirks NL, Meibohm B. Population pharmacokinetics of therapeutic monoclonal antibodies. Clin Pharmakinet 2010;49:633−59.

Doody RS, Thomas RG, Farlow M, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med 2014;370:311–21.

Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol 2014;13:614–29.

European Medicines Agency Committee for Medicinal Products for Human Use. Qualification opinion of Alzheimer's disease novel methodologies/biomarkers for the use of CSF AB_{1-42} and t-tau and/or PET-amyloid imaging (positive/ negative) as biomarkers for enrichment, for use in regulatory clinical trials in mild and moderate Alzheimer's disease. Resource on the Internet [16 February 2012; accessed 23 August 2015]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/04/WC500125019.pdf.

Fagan AM, Mintun MA, Mach RH, et al. Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid $A\beta_{1-42}$ in humans. Ann Neurol 2006;59:512–19.

Fagan AM, Shaw LM, Xiong C, et al. Comparison of Analytical Platforms for Cerebrospinal Fluid Measures of β-$Amyloid_{1-42}$, Total τ, and P-τ181 for Identifying Alzheimer Disease Amyloid Plaque Pathology. Arch Neurol 2011;68:1137–44.

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.

Food and Drug Administration (FDA), U.S. Department of Health and Human Services, Center for Drug Evaluation and Research. Draft guidance for industry, Alzheimer's disease: developing drugs for the treatment of early stage disease. February 2013. Resource on the Internet [accessed 23 August 2015]. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM338287.pdf.

Forsberg A, Engler H, Almkvist O, et al. PET imaging of amyloid deposition in patients with mild cognitive impairment. Neurobiol Aging 2008;29:1456–65.

Fox NC, Black RS, Gilman S, et al. Effects of Aβ immunization (AN1792) on MRI measures of cerebral volume in Alzheimer disease. Neurology 2005;64:1563–72.

Fox NC, Cousens S, Scahill R, et al. Using serial registered brain magnetic resonance imaging to measure disease progression in Alzheimer disease: power calculations and estimates of sample size to detect treatment effects. Arch Neurol 2000;57:339–44.

Fox NC, Kennedy J. Structural imaging markers for therapeutic trials in Alzheimer's disease. J Nutr Health Aging 2009;13:350–2.

Galasko D, Bennett D, Ferris S. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer"s Disease Cooperative Study. Alzheimer Dis Assoc Disord 1997;11(Suppl 2):S33–9.

Goos JD, Henneman WJ, Sluimer JD et al. Incidence of cerebral microbleeds: a longitudinal study in a memory clinic population. Neurology 2010;74:1954−60.

Greenberg SM, Vernooij MW, Cordonnier C, et al. Ceerebral microbleeds: a guide to detection and interpretation. Lancel Neurol 2009;8:165−74.

Grober E, Buschke H. Genuine memory deficits in dementia. Dev Neuropsychol 1987;3:13–36.

Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 2002;297:353–6.

Helzner EP, Scarmeas N, Cosentino S, et al. Survival in Alzheimer's disease: A multiethnic, population-based study of incident cases. Neurology 2008;71:1489−95.

Henley DB, Sundell KL, Sethuraman G, et al. Adverse events and dropouts in alzheimer's disease studies: What can we learn? Alzheimer's Dement 2014;10:1−8.

Henley DB, Sundell KL, Sethuraman G, et al. Safety profile of Alzheimer's disease populations in Alzheimer's disease neuroimaging initiative and other 18-month studies. Alzheimer's Dement 2012;8:407−16.

Ihl R, Ferris S, Robert P, et al. Detecting treatment effects with combinations of the ADAS-Cog items in patients with mild and moderate Alzheimer's disease. International Journal of Geriatric Psychiatry 2012;27(1):15–21.

Jack CR Jr, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010;9:119–28.

Jack CR Jr, Bennett DA, Blennow K, et al. A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers. Neurology 2016;87:539–47.

Jagust WJ, Landau SM, Shaw LM, et al. Relationships between biomarkers in aging and dementia. Neurology 2009;73:1193–9.

Jonsson T, Atwal JK, Steinberg S, et al. A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. Nature 2012;488:96–9.

Joshi AD, Pontecorvo ML, Clark CM, et al. Performance characteristics of amyloid PET with florbetapir F 18 in Patients with Alzheimer's disease and cognitively normal subjects. J Nucl Med 2012;53:378–84.

Kobak KA. Inaccuracy in clinical trials: effects and methods to control inaccuracy. Curr Alzheimer Res 2010;7:637–41.

Landau SM, Lu M, Joshi AD, et al. Comparing Positron Emission Tomography Imaging and Cerebrospinal Fluid Measurements of β-Amyloid. Ann Neurol 2013;74:826–36.

Larson EB, Shadlen M-F, Wang L, et al. Survival after initial diagnosis of Alzheimer disease. Ann Intern Med 2004;140:501–9.

Le Bastard N, Coart E, Vanderstichele H, et al. Comparison of two analytical platforms for the clinical qualification of Alzheimer's disease biomarkers in pathologically confirmed dementia. J Alzheimer's Dis 2013;33:117–31.

Li T-Q, Wahlund L-O. The search for neuroimaging biomarkers of Alzheimer's disease with advanced MRI techniques. Acta Radiol 2011;52:211–22.

Logsdon RG, Gibbons, LE, McCurry SM, et al. Quality of life in Alzheimer's disease: patient and caregiver reports. J Mental Health Aging 1999;5:21–32.

Logsdon RG, Gibbons LE, McCurry SM, et al. Assessing quality of life in older adults with cognitive impairment. Psychosomatic Med 2002;64:510–9.

Lynch CA, Walsh C, Blanco A, et al. The clinical dementia rating sum of box score in mild dementia. Dement Geriatr Cogn Disord 2006;21:40–3.

Mackey H, Cho W, Ward M, et al. Exploratory analyses of cognitive effects of crenezumab in a mild alzheimer's disease subpopulation of a randomized, double-blind, placebo-controlled, parallel-group Phase 2 study (ABBY). Alzheimer Dement 2016;12:610.

Mani RB. The evaluation of disease modifying therapies in Alzheimer's disease: a regulatory viewpoint. Stat Med 2004;23:305–14.

Marshall GA, Rentz DM, Frey MT, et al. Executive function and instrumental activities of daily living in mild cognitive impairment and Alzheimer's disease. Alzheimer's & Dement 2011;7:300-308.

McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dement 2011;7:263–9.

Mohs RC, Doody RS, Morris JC, et al. A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. Neurology 2001;57:481–88.

Mohs RC, Knopman D, Petersen RC, et al. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's disease assessment scale that broaden its scope. The Alzheimer's Disease Cooperative Study. Alz Dis Assoc Dis 1997;11(Suppl 2):S13–21.

Morris JC. The clinical dementia rating (CDR): Current version and scoring rules. Neurology 1993;43:2412–14.

Mould DR, Sweeney KR. The pharmacokinetics and pharmacodynamics of monoclonal antibodies–mechanistic modeling applied to drug development. Curr Opin Drug Discov Devel 2011;10:84−96.

O'Bryant SE, Lacritz LH, Hall J, et al. Validation of the new interpretive guidelines for the clinical dementia rating scale sum of boxes score in the national Alzheimer's coordinating center database. Arch Neurol 2010;67:746–49.

Ostrowitzki S, Lasser RA, Dorflinger E, et al. A Phase III randomized trial of gantenerumab in prodromal Alzheimer's disease. Alzheimers Res Ther 2017;9:95.

Pfeffer RI, Kurosaki TT, Harrah CH Jr, et al. Measurement of functional activities in older adults in the community. J Gerontol 1982;37:323–9.

Reiber H, Felgenhauer K. Protein transfer at the blood cerebrospinal fluid barrier and the quantitation of the humoral immune response within the central nervous system. Clin Chim Acta 1987;163:319–28.

Roberson ED, Hesse JH, Rose KD, et al. Frontotemporal dementia progresses to death faster than Alzheimer's disease. Neurology 2005;65:719–25.

Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984;141:1356–64.

Rozzini L, Chilovi BV, Conti M, et al. Conversion of amnestic Mild Cognitive Impairment to dementia of Alzheimer type is independent to memory deterioration. Int J Geriatr Psychiatry 2007;22(12):1217–22.

Salloway S, Sperling R, Gilman S, et al. A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease. Neurology 2009;73:2061–70.

Salloway S, Sperling R, Fox NC, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N Engl J Med 2014;370:322–33.

Sarazin M, Berr C, De Rotrou J, et al. Amnestic syndrome of the medial temporal type identifies prodromal AD. Neurology 2007;69:1859–67.

Sevigny J, Chiao P, Williams L, et al. Randomized, Double-blind, Placebo-controlled, Phase 1b Study of Aducanumab (BIIB037), an Anti-Aβ Monoclonal Antibody, in Patients With Prodromal or Mild Alzheimer's Disease: Interim Results by Disease Stage and ApoE ε4 status. 67th Meeting of the American Academy of Neurology. April 18–25, 2015, Washington, DC. Resource on the Internet [accessed 23 August 2015]. http://biogenidecconferences.com/AAN2015/BART/BART_Sevigny_PhIB_subgp_IA2.pdf.

Sevigny JJ, Peng Y, Liu L, et al. Review: Item analysis of ADAS-Cog: Effect of baseline cognitive impairment in a clinical AD trial. Am J Alzheimers Dis Other Demen 2010;25:119–24.

Shaw ML, Vanderstichele H, Knapik-Czajka M, et al. Cerebrospinal Fluid Biomarker Signature in Alzheimer's Disease Neuroimaging Initiative Subjects. Ann Neurol 2009:65;403–13.

Shields RL, Namenuk AK, Hong K, et al. High resolution mapping of the binding site on human IgG1 for FcγRI, FcγRII, FcγRIII, and FcRn and design of IgG1 variants with improved binding to the FcγR. J Biol Chem 2001;276:6591–604.

Sperling RA, Jack Jr CR, Black SE, et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: Recommendations from the Alzheimer's Association research roundtable workgroup. Alzheimer's Dement 2011;7:367–85.

Sperling R, Salloway S, Brooks DJ, et al. Amyloid-related imaging abnormalities in patients with Alzheimer's disease treated with bapineuzumab: a retrospective analysis. Lancet Neurol 2012b;11:241–9.

Sperling R, Salloway S, Raskind M, et al. Bapineuzumab Phase 3 trials in mild tomoderate Alzheimer's disease dementia in apolipoprotein E-4 carriers (Study 302) and non-carriers (Study 301) [Presentation]. Clinical Trials on Alzheimer's Disease Meeting: 2012a Oct 29-31; Monte Carlo.

Tolboom N, van der Flier WM, Yaqub M, et al. Relationship of Cerebrospinal Fluid Markers to 11C-PiB and 18F-FDDNP Binding. J Nucl Med 2009;50:1464–70.

Ultsch M, Li B, Maurer T, et al. Structure of crenezumab complex with Aβ shows loss of β-hairpin. Sci Rep 2016;6:39374.

Vellas B, Andrieu S, Sampaio C, et al. Endpoints for trials in Alzheimer's disease: a European task force consensus. Lancet Neurol 2008;7:436–50.

Vernooij MW, van der Lugt A, Ikram MA, et al. Prevalence and risk factors of cerebral microbleeds: the Rotterdam Scan Study. Neurology 2008;70:1208–14.

Vila-Corcoles A, Ochoa-Gondar O, Rodriguez-Blanco T, et al. Epidemiology of community-acquired pneumonia in older adults: a population-based study. Respir Med. 2009 Feb;103(2):309−16.

Waring SC, Doody RS, Pavlik VN, et al. Survival among patients with dementia from a large multi-ethnic population. Alzheimer Dis Assoc Disord 2005;19:178−83.

Westfall PH, Krishen A. Optimally weighted, fixed sequence, and gatekeeping multiple testing procedures. J Stat Plan Inference 2001;99;25–40.

Wilcock DM, Alamed J, Gottschall PE, et al. Deglycosylated anti amyloid β antibodies eliminate cognitive deficits and reduce parenchymal amyloid with minimal vascular consequences in aged amyloid precursor protein transgenic mice. J Neurosci 2006;26:5340−6.

Wild D, Grove A, Martin M, et al. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: Report of the ISPOR Task Force for Translation and Cultural Adaptation. Value in Health 2005;8(2):94−104.

Zarit SH, Zarit JM. The memory and behavior problems checklist and the burden interview. Gerontology Center, Penn State University, 1990.

Zwan M, van Harten A, Ossenkoppele R, et al. Concordance Between Cerebrospinal Fluid Biomarkers and [11C]PIB PET in a Memory Clinic Cohort. J. Alzheimer's Disease 2014;41:801−7.

Appendix 1
Schedule of Assessments

Table 1 Year 1 Assessments

Assessment/ Procedure	Screen	BL		Treatment Period													ET
	Wk-8 to Wk-1	Day 1 Wk1	Day 2 Wk 1	Wk 5	Wk 9	Wk 13	Wk 17	Wk 21	Wk 25	Wk 29	Wk 33	Wk 37	Wk 41	Wk 45	Wk 49	Wk 53	
Dose Number		1 [a]	☎	2	3	4	5 [b]	6 [b]	7 [a]	8 [b]	9 [b]	10	11 [b]	12 [b]	13 [b]	14 [a]	[a]
Informed consents	x																
Review of inclusion/ exclusion criteria	x	x															
Medical history, AD history, personal status, and demographics [c]	x																
Diagnosis Verification Form	x																
Vital signs [d]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
PK serum sample [e]		x [i]		x		x			x [i]			x				x	x
Clinical genotyping sample	x [f]																
Clinical RNA sample	x [g]																
12-lead ECG [h]	x	x				x			x							x	x
Immunogenicity sample [j]		x		x		x			x			x				x	x
Plasma biomarker sample [e]	x	x		x					x							x	x
Serum chemistry and hematology [k, l]	x	x							x							x	x
Urinalysis [m]	x																
Urine sample for drugs of abuse [n]	x																
Urine pregnancy test [o]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Coagulation (PT)	x																
Physical / neurological exam [p]	x															x	

Appendix 1
Schedule of Assessments (cont.)

Assessment/ Procedure	Screen	BL		Treatment Period													ET
	Wk-8 to Wk-1	Day 1 Wk1	Day 2 Wk 1	Wk 5	Wk 9	Wk 13	Wk 17	Wk 21	Wk 25	Wk 29	Wk 33	Wk 37	Wk 41	Wk 45	Wk 49	Wk 53	
Dose Number		1 [a]	☎	2	3	4	5 [b]	6 [b]	7 [a]	8 [b]	9 [b]	10	11 [b]	12 [b]	13 [b]	14 [a]	[a]
MRI [q]	x					x[r]			x[r]			x[r]				x[r]	x
PET / CSF sample [q, s]	x															x [w, x]	x [w, x]
CDR	x	x							x							x	x
ADAS-Cog-13	x	x							x							x	x
ADCS-ADL; FAQ		x							x							x	x
MMSE	x [t]	x							x							x	x
NPI-Q		x														x	x
FCSRT-IR	x [t]	x							x							x	x
EQ-5D		x							x							x	x
QOL-AD		x														x	x
ZCI-AD		x														x	x
C-SSRS BL/SLV [u]		x							x							x	x
Concomitant medications		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
Study drug administration [v]		x		x	x	x	x	x	x	x	x	x	x	x	x	x	

ACDS-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living; AD = Alzheimer's disease; ADAS-Cog13 = Alzheimer's Disease Activity Scale Cognition (subscale) 13; BL = baseline; CDR = Clinical Dementia Rating; CSF = cerebrospinal fluid; C-SSRS= Columbia Suicide Severity Rating Scale; ET = early termination; FAQ = Functional activities Questionnaire ; FCSRT-IR = Free and Cued Selective Reminding Test–Immediate Recall; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; SLV = since last visit; Wk = week; ZCI-AD = Zarit Caregiver Interview for Alzheimer's Disease.

Note: The visit window is ± 7 days for dosing days and ± 3 days for all other visits. Patients should return to initial planned schedule per randomization for subsequent visits. For patients who terminate early, assessments listed in the ET visit (week 105) should be completed.

Appendix 1
Schedule of Assessments (cont.)

In case of rescreening a patient, all screening assessments must be repeated other than the *MRI (if performed within 8 weeks of randomization),* lumbar puncture and amyloid PET scan if previous results were within eligible ranges.

☎ Does not have to be a site visit – telephone call to patient following first infusion

[a] Visit may be split over 2 days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vitals, blood tests and ECGs) should be completed prior to dosing on the day of dosing.

[b] Visit suitable for home administration of crenezumab.

[c] Medical history includes clinically significant diseases, surgeries, respiratory diseases and risk factors, surgeries, cancer history (including prior cancer therapies and procedures), smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the patient within 3 months prior to the screening visit. Demographic data will include age, sex, and self-reported race/ethnicity. Demographics of caregiver will also be collected.

[d] Vital signs include measurements of weight, pulse rate, systolic and diastolic blood pressure, respiratory rate, oxygen saturation, and body temperature. The same arm should be used for all blood pressure measurements. Heart rate and blood pressure should not be measured unless 15 minutes have passed since the last blood draw. Vital sign assessments should be performed just prior to study drug administration, at the end of infusion, and 60−90 minutes after the end of infusion. Weight need only be measured prior to study drug administration. All vitals should be recorded in the eCRF. Height should be recorded at the screening visit only. Vital sign assessments should be performed at the site or by the health care provider who is administering study drug; such assessments should not be captured separately at the site if such administration is done at a different location (e.g. by a home nurse).

[e] All scheduled PK and plasma biomarker samples should be obtained just prior to study drug administration, if possible. Accurate recording of the time of study drug administration, and PK or PD sample is critical. Unscheduled PK samples should be taken in the event anaphylaxis, anaphylactoid, or serious hypersensitivity reactions.

[f] At screening, three mandatory whole blood samples will be obtained for DNA extraction for analysis of *APOE* status [redacted]

[g] At screening, two mandatory RNA samples will be taken [redacted] (paxgene tubes).

[h] Perform after the patient has been in a supine position for 5 minutes. ECGs for each patient should be obtained from the same machine whenever possible and performed prior to any blood draws, brain MRI scans, and lumbar puncture.

[i] PK samples will be taken pre- and 60-90 minutes post-infusion.

[j] Immunogenicity samples should be obtained prior to study drug administration. Samples are taken to measure antibody development to crenezumab ($ADAs$) and other drug component products. Unscheduled samples should be taken in the event anaphylaxis, anaphylactoid, or serious hypersensitivity reactions. For any patient suspected of developing anaphylaxis, or anaphylactoid or serious hypersensitivity reactions warranting discontinuation of dosing, a washout ADA sample (16 weeks post-dose) and concurrent PK sample must be collected.

[k] Serum chemistry includes AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, CPK, sodium, potassium, calcium, BUN/urea, and serum creatinine (and creatinine clearance calculated by the central laboratory). At the screening, and Week 53, hemoglobin A1C, folic acid, vitamin B12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed. At screening only, serum samples will be tested for HIV and hepatitis B and C virus.

Appendix 1
Schedule of Assessments (cont.)

[l] Hematology includes hemoglobin, hematocrit, RBC (with morphology), WBC counts, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC-other total counts. At baseline and Week 25, immunophenotyping analysis of peripheral blood cells. In the event of a pneumonia diagnosis, immunophenotyping analysis of peripheral blood cells should be repeated.

[m] Urinalysis will be performed at the site by dipstick for blood, protein, glucose, and pH. Microscopic examination performed at the central laboratory if blood and/or protein results are positive or strongly positive. Results do not need to be recorded on the eCRF.

[n] At screening only, urine samples will be analyzed for the presence of the following drugs: amphetamine, benzodiazepines, cannabinoids, opiates, cocaine, barbiturates, and methadone. Results will be used to verify patient eligibility pertaining to drugs of abuse. Inconclusive results may be repeated during the screening period. Investigators should use their best clinical judgment in cases where results may be erroneous (e.g., permitted use of opiates or ingestion of food/food supplements).

[o] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents. *Urine pregnancy testing must also be performed and a negative result obtained prior to receiving injection of a PET radioligand.*

[p] At visits between Week 5 and Week 101, assessment of neurological or physical adverse events will be symptom-led.

[q] CSF sampling, new PET and MRI scans at screening should be performed once all other screening results are available and none exclude the patient from the trial.

[r] MRI must be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture. The patient must be called in advance of the MRI to ask whether he or she is experiencing any CNS symptoms.

[s] Lumbar puncture must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters. For post baseline visits, lumbar puncture should be performed prior to dosing but on the same day as predose plasma biomarker and serum PK samples are taken. During screening, lumbar puncture should be performed 3 days before MRI – or after MRI has been done for screening. Post-baseline, if a patient is participating in any CSF substudy, the MRI must be completed before the CSF sample is taken.

[t] If FCSRT and MMSE are completed *following FCSRT/MMSE consent*, and patient is not excluded, these assessments *would* not need to be *repeated during* the *screening period.*

[u] C-SSRS-Baseline form should be used on the baseline visit; subsequent visits should use the “since-last-visit” form.

[v] Study drug administration should be performed only after all assessments/rating scales for the patient are completed (unless indicated otherwise). Study drug will be administered to patients as infusion (full details in the pharmacy manual). Patients should be observed for a minimum of 1 hour after dosing and vitals should be assessed immediately after infusion is completed, and then ≥60 minutes post-infusion.

[w] *CSF sample only in those who have consented to participate in the BN29553-CSF longitudinal substudy.*

[x] *PET assessment only in those who have consented to participate in the BN29552/BN29553-Amyloid PET longitudinal substudy or BN29552/BN29553-tau PET longitudinal substudy.*

Appendix 1
Schedule of Assessments (cont.)

Table 2 Year 2 Assessments

Assessment/Procedure	Treatment Period													Follow-up for those not entering OLE	
	Wk 57	Wk 61	Wk 65	Wk 69	Wk 73	Wk 77	Wk 81	Wk 85	Wk 89	Wk 93	Wk 97	Wk 101	Wk 105 +4 wks (or ET)	Wk 117 +16 wks	Wk 153 +52 wks
Dose number	15 [a]	16 [a]	17 [a]	18 [a]	19 [a]	20 [b]	21 [a]	22 [a]	23 [a]	24 [a]	25 [a]	26 [a]	[b, c]		
Vital signs [d]	x	x	x	x	x	x	x	x	x	x	x	x	x		
Urinalysis [e]													x		
Urine pregnancy test [f]	x	x	x	x	x	x	x	x	x	x	x	x	x		
Plasma biomarker sample [g]						x							x	x	
PK serum sample [g]						x							x	x	
Immunogenicity sample [h]						x							x	x	
12-lead ECG [i]						x							x	x	
Physical / neurological exam [j]													x		
Serum chemistry and hematology [k, l]						x							x		
MRI [n]						x							x		
PET/CSF sample													*x* [o, p]		
CDR						x							x	x	x
ADAS-Cog-13						x							x	x	x
ADCS-ADL; FAQ						x							x	x	x
MMSE						x							x	x	x
NPI-Q													x		x
FCSRT-IR						x							x		
EQ-5D						x							x	x	x
QOL-AD						x							x	x	x
ZCI-AD													x		x

Appendix 1
Schedule of Assessments (cont.)

Assessment/Procedure	Treatment Period													Follow-up for those not entering OLE	
	Wk 57	Wk 61	Wk 65	Wk 69	Wk 73	Wk 77	Wk 81	Wk 85	Wk 89	Wk 93	Wk 97	Wk 101	Wk 105 +4 wks (or ET)	Wk 117 +16 wks	Wk 153 +52 wks
Dose number	15 [a]	16 [a]	17 [a]	18 [a]	19 [a]	20 [b]	21 [a]	22 [a]	23 [a]	24 [a]	25 [a]	26 [a]	[b, c]		
C-SSRS SLV						x							x		
Concomitant medications	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		
Study drug administration [m]	x	x	x	x	x	x	x	x	x	x	x	x			

ACDS-ADL=Alzheimer's Disease Cooperative Study – Activities of Daily Living; ADAS-Cog13 = Alzheimer's Disease Activity Scale Cognition (subscale) 13; CDR = Clinical Dementia Rating; C-SSRS= Columbia Suicide Severity Rating Scale; ET = early termination; FAQ = Functional activities Questionnaire; FCSRT-IR = Free and Cued Selective Reminding Test–Immediate Recall; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory-Questionnaire; OLE = open-label extension; QOL-AD = Quality of Life–Alzheimer's Disease; SLV = since last visit; Wk = week; ZCI-AD = Zarit Caregiver Interview for Alzheimer's Disease.

Note: The visit window is ± 7 days for dosing days and ± 3 days for all other visits. Patients should return to initial planned schedule per randomization for subsequent visits. For patients who terminate early, assessments listed in the ET visit should be completed.

In case of rescreening a patient, all screening assessments must be repeated other than the *MRI (if performed within 8 weeks of randomization),* lumbar puncture and amyloid PET scan if previous results were within eligible ranges.

[a] Visit suitable for home administration of crenezumab.

[b] Visit may be split over 2 days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., visits, blood tests, and ECGs) should be completed on the day of dosing.

[c] Transition to OLE protocol for those eligible to participate.

[d] Vital signs include measurements of weight, pulse rate, systolic and diastolic blood pressure, respiratory rate, oxygen saturation, and body temperature. The same arm should be used for all blood pressure measurements. Heart rate and blood pressure should not be measured unless 15 minutes have passed since the last blood draw. Vital sign assessments should be performed just prior to study drug administration, at the end of infusion, and 60−90 minutes after the end of infusion. All vitals should be recorded in the eCRF. Vital sign assessments should be performed at the site or by the health care provider who is administering study drug; such assessments should not be captured separately at the site if such administration is done at a different location (e.g., by a home nurse).

[e] Urinalysis will be performed at the site by dipstick for blood, protein, glucose, and pH. Microscopic examination performed at the central laboratory if blood and/or protein results are positive or strongly positive. Results do not need to be recorded on the eCRF.

Appendix 1
Schedule of Assessments (cont.)

[f] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory. Results are to be recorded only in the source documents. *Urine pregnancy testing must also be performed and a negative result obtained prior to receiving injection of a PET radioligand,*

[g] All scheduled PK samples and plasma PD should be obtained just prior to study drug administration, if possible. Accurate recording of the time of study drug administration and PK or PD sample is critical. Unscheduled PK samples should be taken in the event of anaphylaxis, anaphylactoid, or serious hypersensitivity reactions.

[h] Immunogenicity samples should be obtained prior to study drug administration; samples are taken to measure antibody development to crenezumab (*ADAs*) and other drug component products. Unscheduled samples should be taken in the event of anaphylaxis, anaphylactoid, or serious hypersensitivity reactions. For any patient suspected of developing anaphylaxis, or anaphylactoid or serious hypersensitivity reactions warranting discontinuation of dosing, a washout *ADA* sample (16 weeks post-dose) and concurrent PK sample must be collected.

[i] Perform after the patient has been in a supine position for 5 minutes. ECGs for each patient should be obtained from the same machine whenever possible and performed prior to any blood draws, brain MRI scans, and lumbar puncture.

[j] At visits between Week 5 and Week 101, assessment of neurological or physical adverse events will be symptom-led.

[k] Serum chemistry includes AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, CPK, sodium, potassium, calcium, BUN/urea, and serum creatinine (and creatinine clearance calculated by the central laboratory).

[l] Hematology includes hemoglobin, hematocrit, RBC (with morphology), WBC counts, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC–other total counts. In the event of a pneumonia diagnosis, immunophenotyping analysis of peripheral blood cells should be repeated.

[m] Study drug administration should be performed only after all assessments/rating scales for the patient are completed (unless indicated otherwise). Study drug will be administered to patients as infusion (full details in the pharmacy manual). Patients should be observed for a minimum of 1 hour after dosing and vitals should be assessed immediately after infusion is completed, and then ≥60 minutes post infusion.

[n] MRI must be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. The patient will be called in advance of the MRI regarding any CNS symptoms experienced.

[o] *CSF sample only in those who have consented to participate in the BN29553-CSF longitudinal substudy.*

[p] *PET assessment only in those who have consented to participate in the BN29552/BN29553-Amyloid PET longitudinal substudy or BN29552/BN29553-tau PET longitudinal substudy.*

Appendix 2
National Institute on Aging/Alzheimer's Association Criteria for *Dementia due to* Alzheimer's Disease

NIA-AA category	Description
Probable Dementia: core Clinical Criteria Meets criteria for dementia described earlier in the text, and in addition, has the following characteristics:	A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days; B. Clear-cut history of worsening of cognition by report or observation; and C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories. a. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text. b. Non-amnestic presentations: Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present. Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present. Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present. D. The diagnosis of probable AD dementia should not be applied when there is evidence of (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) core features of Dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.
Probable AD dementia with increased level of certainty	Probable AD dementia with documented decline In persons who meet the core clinical criteria for probable AD dementia, documented cognitive decline increases the certainty that the condition represents an active, evolving pathologic process, but it does not specifically increase the certainty that the process is that of AD pathophysiology. Probable AD dementia with documented decline is defined as follows: evidence of progressive cognitive decline on subsequent evaluations based on information from informants and cognitive testing in the context of either formal neuropsychological evaluation or standardized mental status examinations.

Appendix 2
National Institute on Aging/Alzheimer's Association Criteria for *Dementia due to* Alzheimer's Disease (cont.)

	Probable AD dementia in a carrier of a causative AD genetic mutation In persons who meet the core clinical criteria for probable AD dementia, evidence of a causative genetic mutation (in APP, PSEN1, or PSEN2), increases the certainty that the condition is caused by AD pathology. The workgroup noted that carriage of the ε4 allele of the apolipoprotein E gene was not sufficiently specific to be considered in this category.
Probable AD dementia with evidence of the AD pathophysiological process	AD dementia is part of a continuum of clinical and biological phenomena. AD dementia is fundamentally a clinical diagnosis. To make a diagnosis of AD dementia with biomarker support, the core clinical diagnosis of AD dementia must first be satisfied. Relevant biomarkers include amyloid-β(CSF or PET); tau (CSF or PET)

Source: McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dement 2011;7:263–9.

Appendix 3
National Institute on Aging/Alzheimer's Association Criteria for Prodromal Alzheimer's Disease (Mild Cognitive Impairment due to Alzheimer's Disease)

NIA-AA category	Clinical and cognitive criteria
Clinical Criteria :	Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time) Objective evidence of Impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains) Preservation of independence in functional abilities Not demented
Etiology of MCI consistent with AD pathophysiological process	Rule out vascular, traumatic, medical causes of cognitive decline, where possible Provide evidence of longitudinal decline in cognition, when feasible Report history consistent with AD genetic factors, where relevant
Prodromal AD dementia with evidence of the AD pathophysiological process	pAD is part of a continuum of clinical and biological phenomena. pAD is fundamentally a clinical diagnosis. To make a diagnosis of pAD with biomarker support, the core clinical diagnosis of pAD must first be satisfied. Relevant biomarkers include amyloid-β(CSF or PET); tau (CSF or PET)

Source: Albert MS, DeKosky ST, Dickson B, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dement 2011;7:270-279

Appendix 4
Diagnostic Verification Form

Instructions

The Medical Monitor or assignee will review the form and indicate whether a subject may continue with screening. Confirmation of review must be given before any invasive procedures are conducted. The clinical team *or assignee* will *confirm eligibility based on* the *diagnostic verification* form *with* the site.

Date Please list all dates as DD-MMM-YYYY	
Subject Screening Number	
Name of Person submitting request	
Email of Person submitting request	
Principal Investigator email	
Investigator Direct Contact Number	
Site Telephone Number	
Site Fax Number	
I have evaluated this patient and confirm that the information documented on this form represents the best information (based on clinical evaluation and other information sources) available at this time	
Investigator *(or Sub-Investigator or CDR Rater)* Name	
Investigator *(or Sub-Investigator or CDR Rater)* (Electronic signature)	

Appendix 5
Diagnostic Verification Form (cont.)

Verification of diagnosis Based upon the review of the screening information made available by the site, I confirm the above noted patient has been reviewed and conclude: ☐ Yes, the patient may continue with screening ☐ No, the patient cannot continue with screening	
Reviewer (electronic signature)	
Date of confirmation	

CLINICAL HISTORY	
1	By patient, caregiver, clinician report, when did the patient first experience or exhibit symptoms of cognitive dysfunction (month/year)?
AFFECTED COGNITIVE DOMAINS NIA-AA criteria require the involvement of at least one cognitive domain for mild cognitive impairment, or at least two domains for dementia. Please indicate which of the following cognitive domains are affected AND which test(s) was/were used; if known please provide dates of assessment.	
	☐ Memory (impaired ability to acquire and remember new information) ☐ Executive function / complex attention (e.g. impaired reasoning, impaired problem solving, inability to plan and organize): ☐ Visuospatial function (inability to recognize faces or common objects, to find objects in direct view despite adequate visual acuity, to operate simple tools, or to orient clothes on the body): ☐ Language (impairments in comprehension, naming, word retrieval, verbal fluency, grammar; disturbances in understanding emotional content of speech): ☐ Praxis

Appendix 6
Diagnostic Verification Form (cont.)

2	Does the patient currently have Dementia [☐] or Mild Cognitive Impairment? [☐].When was the diagnosis in (2) first made (month/year)?
3	If the patient has dementia, please detail how functional impairment has been established (include patient/caregiver history, and any standardized assessment, e.g., CDR) and which areas of the patient's life have been affected:
4	Has there been cognitive or functional decline in the past 12 months? [yes ☐ /no ☐] If yes, please give examples of specific deficits that have emerged or deteriorated in the past year as reported by the caregiver or clinician: If yes, please report any available objective evidence of progression (e.g., MMSE or MoCA scores at two time points, with dates):
5	SUPPORTIVE INFORMATION Please provide details of any other supportive diagnostic information (e.g., MRI, amyloid-PET, tau-PET, FDG-PET, CSF biomarkers, etc.)