Official Title: A Multicenter, Open-Label, Long-Term Extension of Phase III Studies (BN29552/BN29553) of Crenezumab in Patients With Alzheimer's Disease

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PROTOCOL

TITLE:	**A MULTICENTER, OPEN-LABEL, LONG-TERM EXTENSION OF PHASE III STUDIES (BN29552/BN29553) OF CRENEZUMAB IN PATIENTS WITH ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	BN40031
VERSION NUMBER:	2
EUDRACT NUMBER:	*2017-002702-12*
IND NUMBER:	100,839
TEST PRODUCT:	Crenezumab (RO5490245)
MEDICAL MONITOR:	[redacted], M.D., M.A.S.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 18 September 2017
DATE AMENDED:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	05-Aug-2018 10:16:20

PROTOCOL AMENDMENT, VERSION 2: RATIONALE

Protocol BN40031 has been amended primarily to align with recent CREAD (BN29552/BN29553) protocol amendment completed in March 2018. Changes to the protocol, along with a rationale for each change, are summarized below:

- The amendment improves alignment with the recently amended CREAD and CREAD2 studies for the purpose of harmonization across studies. This includes the following main changes:
  - Coagulation abnormalities have been added as an exclusion criterion (Section 4.1.2).
  - The magnetic resonance imaging requirement after amyloid-related imaging abnormalities-hemosiderin findings has been removed (Section 5.1.1).
  - Pharmacokinetic and anti-drug antibody samples have been added at Week 13 (Appendix 1).
- Since the China Extension has been activated in the parent studies, language has been updated for this region (Sections 1.2.2, 3.1, and 6.6).
- Information has been updated to align with latest Crenezumab Investigator's Brochure (Version 10) (Sections 1.2.2, 1.2.3, 1.2.3.1, 1.2.3.2, 1.2.5, 1.2.6.3, and 1.3.1).
- Exploratory efficacy objectives have been updated to specify that efficacy analyses may not be limited to Week 53 (Section 2).
- The number of sites has been amended to 350 centers in approximately 40 countries (Section 3.1).
- The recruitment periods in the parent studies (BN29552 and BN29553) were reduced from initial timelines. Because the time between first and last participants in the OLE has been shortened, the maximum treatment time in the OLE is now approximately 4 years for the first patients in. The protocol has been updated to reflect this change (Section 3.3).
- The first dose window has been increased from 4 to 8 weeks from the parent study Week 105 visit to allow sites more time to confirm patient eligibility and to allow more flexibility to schedule first dose (Sections 3.2 and 4.5.11).
- The inclusion criteria that address female contraception have been modified to specify when women must refrain from donating eggs and to specify that the definition of childbearing potential may be adapted for alignment with local guidelines (Section 4.1.1).
- Text has been added to recognize country variability in designation of non-investigational medicinal product/investigational medicinal product status to positron emission tomography (PET) tracers (Sections 4.3 and 4.3.2.2), and PET Ligand Investigator's Brochures have been added as reference documents for assessing and reporting adverse events (Section 5.7).

- The physical and neurologic examination assessment has been modified to specify that a complete examination must be performed, and the elements comprising a complete examination have been specified. These changes ensure consistency of examinations across visits and allow for more thorough identification of changes in findings over time (Sections 4.5.3 and 5.1.4 and Appendix 1).
- Vitals language has been harmonized throughout protocol (Section 4.5.8 and Appendix 1).
- A set of standard laboratory samples (screening serology [HIV, Hepatitis B and C], hemoglobin A_{1c}, folic acid, vitamin B12, thyroxine 4, free thyroxine, and thyroid-stimulating hormone levels) have been removed as these assessments were already performed at the screening of the parent studies (Section 4.5.7.1).
- The plasma pharmacodynamic (PD) biomarker sampling schedule has been updated to allow collection at the early termination visit if the patient discontinues treatment prior to the Week 53 visit. This change aligns the plasma PD and CSF PD sampling schedules (Section 4.5.7.3 and Appendix 1).
- Safety data from ongoing and completed clinical studies with [^{18}F]GTP1 have been updated (Section 4.5.7.4).
- Instructions about patient withdrawal from the Research Biosample Repository after site closure have been modified to indicate that the investigator must inform the Sponsor of patient withdrawal by emailing the study number and patient number to global_rcr-withdrawal@roche.com (Section 4.5.10.6).
- The recommended order of clinical assessments/rating scales for patients and caregivers has been clarified (Section 4.5.11.1).
- Timing of brain MRI to detect ARIA-edema/effusion and ARIA-H deposition has been clarified (Section 5.1.1 and Appendix 1).
- Instructions regarding the assessment of fluorescence-activated cell sorting (FACS) have been updated to specify that the assessment will not be performed at baseline and Week 25, as this analysis has already been performed in the parent studies (Section 5.2.3). FACS remains a requested sample/assessment in the event of pneumonia.
- An analysis of the change from baseline in Clinical Dementia Rating-Sum of Boxes values recorded during the double-blind treatment period in Studies BN29552 and BN29553 and at specified timepoints of the open-label extension study has been clarified (Section 6.5.2).
- Language has been added for consistency with Roche's current data retention policy and to accommodate more stringent local requirements (if applicable) (Section 7.6).
- The schedule of activities (Appendix 1) has been updated to provide additional guidance and clarity in the footnotes as mentioned above and as follows: Week 73 has been corrected as Week 77. It has been clarified that Functional Activities Questionnaire is for caregivers of Study BN29553, not patients.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL ACCEPTANCE FORM

TITLE:	**A MULTICENTER, OPEN-LABEL, LONG-TERM EXTENSION OF PHASE III STUDIES (BN29552/BN29553) OF CRENEZUMAB IN PATIENTS WITH ALZHEIMER'S DISEASE**
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MEDICAL MONITOR:	[redacted], M.D., M.A.S.
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 the signed form to your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**A MULTICENTER, OPEN-LABEL, LONG-TERM EXTENSION OF PHASE III STUDIES (BN29552/BN29553) OF CRENEZUMAB IN PATIENTS WITH ALZHEIMER'S DISEASE**
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PHASE:	Phase III
INDICATION:	Alzheimer's Disease
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will assess the long-term safety and tolerability of crenezumab administered to all patients with Alzheimer's disease (AD) who completed Studies BN29552 (CREAD) and BN29553 (CREAD2) and who meet the eligibility criteria for this open-label extension (OLE) study. An exploratory objective of this OLE study is to investigate the effect of crenezumab on the underlying disease process and course. Specific objectives and corresponding endpoints for the study are outlined below.

Primary Safety Objective	Corresponding Endpoints
To assess the long-term safety and tolerability of crenezumab (60 mg/kg IV Q4W) in eligible patients with AD who participated in Study BN29552 or BN29553 and completed the Week 105 study visit	• Nature, frequency, severity, and timing of adverse events and serious adverse events • 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

Exploratory Efficacy Objectives	Corresponding Endpoints
To evaluate the long-term effect of crenezumab on global outcomes of disease progression	• Change from baseline during the OLE in CDR-SB
To evaluate the long-term effect of crenezumab on cognition	• Change from baseline during the OLE as measured by the ADAS-Cog13 • Change from baseline *during the OLE* using the MMSE • Change from baseline *during the OLE* using ADAS-Cog12
To evaluate the long-term effect of crenezumab on disease severity	• Change from baseline during the OLE using CDR-GS
To evaluate the long-term effect of crenezumab on patient dependence	• Change from baseline during the OLE using scores derived from the ADCS-ADL total scale
To evaluate the long-term effect of crenezumab on patient function	• Change from baseline during the OLE using the ADCS-ADL, the instrumental subscale, and/or the FAQ
To evaluate the long-term effect of crenezumab on behavior and neuropsychological symptoms	• Change from baseline during the OLE using the Neuropsychiatric Inventory Questionnaire
To evaluate the long-term effect of crenezumab on health-related quality of life	• Change from baseline during the OLE using the Quality of Life-AD scale
To evaluate the long-term effect of crenezumab on caregiver burden	• Change from baseline during the OLE *using* the Zarit Caregiver Interview for AD scale
Exploratory Pharmacokinetic Objectives	**Corresponding Endpoints**
To evaluate the serum PK characteristics of crenezumab	• Serum concentration of crenezumab at specified timepoints
To evaluate the CSF PK characteristics of crenezumab	• CSF concentrations of crenezumab at specified timepoints *(only in patients who previously enrolled in substudy BN29552-CSF Longitudinal or BN29553-CSF Longitudinal)*
To explore exposure-response relationships in patients with prodromal to mild AD	• Correlation between crenezumab concentration and biomarkers as well as safety and efficacy outcomes

Exploratory Biomarker Objectives	Corresponding Endpoints
To evaluate the effect of crenezumab on biomarkers	• Brain amyloid load over time measured by amyloid PET (only in patients who previously enrolled in substudy BN29552-Amyloid PET Longitudinal or BN29553-Amyloid PET Longitudinal) • Brain tau load and spread over time measured by tau-PET (only in patients who previously enrolled in substudy BN29552-Tau PET Longitudinal or BN29553-Tau PET Longitudinal) • CSF markers of disease over time (only in patients who previously enrolled in substudy BN29552-CSF Longitudinal or BN29553-CSF Longitudinal) • Plasma PD markers of disease over time • MRI-derived measurements over time such as volumetric changes in whole brain, ventricles, hippocampus, or other structures

AD=Alzheimer's disease; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognition 12 or 13; ADCS-ADL=Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory; ARIA-E=amyloid-related imaging abnormalities-edema/effusion; ARIA-H=amyloid-related imaging abnormalities-hemosiderin deposition; CDR-GS=Clinical Dementia Rating-Global Score; CDR-SB=Clinical Dementia Rating-Sum of Boxes; CSF=cerebrospinal fluid; C-SSRS=Columbia-Suicide Severity Rating Scale; FAQ=Functional Activities Questionnaire; MMSE=Mini Mental State Examination; MRI=magnetic resonance imaging; OLE=open-label extension; PD=pharmacodynamic; PET=positron emission tomography; PK=pharmacokinetic; Q4W=every 4 weeks.

Study Design

Description of Study

Study BN40031 is a Phase III, OLE, multicenter study to evaluate the long-term safety and tolerability of crenezumab at a dose of 60 mg/kg IV every 4 weeks (Q4W) in patients with AD who have participated in one *of the* Phase III *parent studies* (BN29552 or BN29553). Efficacy will also be assessed. Patients who discontinued early from study treatment during Study BN29552 or BN29553 but remained in the study for safety and additional efficacy evaluations and completed the Week 105 study visit can enter the OLE study and begin open-label treatment. Patients from Study BN29552 or BN29553 who discontinued the study prior to completion of the Week 105 study visit are not eligible for this OLE study.

Studies BN29552 and BN29553 are ongoing Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety studies of crenezumab in patients with prodromal AD to mild AD.

Patients and all clinical site staff will remain blinded to the original treatment assignment in Studies BN29552 and BN29553 on entry into the OLE study and until a later time which will be determined by the Sponsor.

Following completion of the global enrollment phase of *Study BN29553*, additional patients *will continue to* be enrolled in a China extension phase (i.e., China extension to *the main Phase III study BN29553*) to ensure a total enrollment sufficient to support registration in the People's Republic of China. This China subpopulation may include patients enrolled at sites in China during both the global enrollment phase and the China extension phase *and could be included in this OLE, if applicable*.

Number of Patients

The planned number of patients for this OLE study is not expected to exceed 1500 (approximately 750 randomized to crenezumab 60 mg/kg IV and 750 randomized to placebo, i.e., the total planned number of patients in *the parent s*tudies BN29552 and BN29553, not including patients from the China extension study). An estimate for the actual number of patients in this OLE study is approximately 925 patients *(not including patients from the China*

extension study) based on 1500 patients enrolled in both Phase III studies and an estimated reduction by 35% (i.e., withdrawals from double-blind treatment) and by a further 5% of completers who may not opt to enroll in this OLE study. Approximately *350* centers in approximately *40* countries worldwide will participate in this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Previous participation in Study BN29552 or BN29553 and completion of the Week 105 visit.

  Patients who discontinued from one of these studies prior to completion of the Week 105 visit are not eligible. Temporary halting of study drug (e.g., because of an adverse event) in Study BN29552 or BN29553 is not exclusionary.

- *W*ritten *informed* 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 [EC] or Institutional Review Board [IRB]) or the patient's authorized representative under applicable local law

  In the course of the study, assessment of a subject's capacity to re-consent *should be done, and written informed re-consent signed by the patient* (co-signed by the patient's legally authorized representative if required by the local regulations, guidelines, or independent EC/IRB) or the patient's authorized representative should be *obtained,* as per applicable local law and requirements.

- Every effort should be made to have the same caregiver participate throughout the duration of the OLE study who also participated in Study BN29552 or BN29553

  The caregiver, in the investigator's judgment, should fulfill the following:

  Have frequent and sufficient contact with the patient to be able to provide accurate information regarding the patient's cognitive and functional abilities, agree to provide information at clinic visits (which require partner input for scale completion), sign the necessary consent form, and have sufficient cognitive capacity to accurately report upon the patient's behavior and cognitive and functional abilities

  Be 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

  If the caregiver cannot continue to participate in the OLE study and cannot be replaced, the patient can continue in the OLE so long as patient safety can be assured.

- Willingness and ability to complete all aspects of the study (including magnetic resonance imaging [MRI], lumbar puncture [if applicable], and positron emission tomography [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 measures, and agreement to refrain from donating eggs, as defined below:*

  Women must remain abstinent 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 *final* dose of study drug. *Women must refrain from donating eggs during this same period.*

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). *The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.*

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 *a* female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for at least 8 weeks after the *final* 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 *preventing drug exposure*.

Exclusion Criteria

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

- Patients who discontinued treatment permanently in Study BN29552 or BN29553 for safety reasons
- *Impaired coagulation (screening PT >1.2 ×the upper limit of normal (ULN) that remains abnormal on retest)*
- Evidence of more than 10 *ARIA-H (*microbleeds and/or *leptomeningeal hemosiderin deposits)* at the Study BN29552 or BN29553 Week 105 visit, as assessed by central review of MRI
- Diagnosed with three recurrent, symptomatic amyloid-related imaging abnormalities-edema/effusion (ARIA-E) events or exacerbations of previous events
- Presence of intracranial lesion that could potentially increase the risk of CNS bleeding (e.g., intracranial aneurysm; arteriovenous malformation)
- 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 Version 5 criteria) within the past 2 years and during the study

  Nicotine use is allowed.

  Marijuana use is not allowed within the past 2 years.
- 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
- Pregnant or lactating, or intending to become pregnant during the study

- 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, or interfere with the patient's ability to complete the study assessments
- Chronic use of anticoagulants or participation in any other investigational drug treatment trial

See the protocol for further details and other concomitant medication restrictions.

End of Study

The end of this study is defined as the date when the last patient, last visit occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately 28 months after the last patient is enrolled.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately *4* years.

Investigational Medicinal Products

Test Product (Investigational Drug)

Crenezumab will be administered via IV infusion to all patients at a dose of 60 mg/kg Q4W until the end of the study.

Statistical Methods

Primary Analysis

The safety analysis population will include all patients who completed the double-blind treatment period and received at least one dose of study drug in either Study BN29552 or BN29553 and entered the OLE study. Patients will be grouped according to the treatment actually received until the first visit of the OLE study.

- Incidence, nature, and severity of adverse events
- Incidence, nature, and severity of serious adverse events
- Incidence of adverse events of special interest
- Incidence and nature of MRI safety findings: ARIA-E and ARIA-H
- 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
- 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.

Determination of Sample Size

This study is open to all patients who completed Study BN29552 or BN29553 and who meet the eligibility criteria. Accordingly, the sample size for this study is not based on a formal sample size calculation. The planned number of patients for this OLE study is not expected to exceed 1500 (approximately 750 randomized to crenezumab 60 mg/kg IV and 750 randomized to placebo, that is, the total planned number of patients in *the parent s*tudies BN29552 and BN29553, not including patients from the China extension study). An estimate for the actual number of patients in this OLE study is approximately 925 patients *(not including patients from*

the China extension study) based on 1500 patients enrolled in both Phase III studies and an estimated reduction by 35% (i.e., withdrawals from double-blind treatment) and by a further 5% of completers who may not opt to enroll in this OLE study.

Interim Analyses

No formal interim analysis of the efficacy results is planned for the OLE study. In the event that an interim efficacy analysis is performed prior to the primary analysis, it will be described in the Statistical Analysis Plan and will include specifications for adjustment of the Type I error level at the time of the primary analysis.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
Aβ	β–amyloid
AChE	acetylcholinesterase
AD	Alzheimer's disease
ADA	anti-drug antibody
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
ADAD	autosomal dominant Alzheimer's disease
ADL	activity of daily living
APOE4	apolipoprotein E4
APP	amyloid precursor protein
AUC	area under the concentration–time curve
ARIA	amyloid–related imaging abnormalities
ARIA-E	amyloid–related imaging abnormalities-edema/effusion
ARIA-H	amyloid–related imaging abnormalities-hemosiderin deposition
CDR	Clinical Dementia Rating
CDR-GS	Clinical Dementia Rating-Global Score
CDR-SB	Clinical Dementia Rating-Sum of Boxes
CL	clearance
C_{max}	observed maximum serum concentration
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DDI	drug–drug interaction
DBTP	double-blind treatment period
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EQ-5D	EuroQOL 5-Dimension questionnaire
EQ-5D-5L	EuroQOL 5-Dimension, 5-Level questionnaire
FAQ	Functional Activities Questionnaire
FcγR	Fcγ receptor
FCSRT	Free and Cued Selective Reminding Test

Abbreviation	Definition
FCSRT-IR	Free and Cued Selective Reminding Test–Immediate Recall
FDA	U.S. Food and Drug Administration
FDG	fluordeoxyglucose
hAPP	human amyloid precursor protein
HIPAA	Health Insurance Portability and Accountability Act
HN	home nursing
iADL	instrumental activity of daily living
ICF	Informed Consent Form
ICH	International Council *for* Harmonisation
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IP	intraperitoneal
IRB	Institutional Review Board
ITT	intent to treat
IxRS	interactive voice *or* web-based *response* system
LPLV	last patient, last visit
MAb	monoclonal antibody
mAD	mild Alzheimer's disease
mH	microhemorrhage
MMRM	mixed-effect model for repeated measures
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
NIAAA	National Institute on Aging/Alzheimer's Association
NMDA	N-methyl-D-aspartate
NPI-Q	Neuropsychiatric Inventory Questionnaire
ObsRO	observer-reported outcome
OLE	open-label extension
pAD	prodromal Alzheimer's disease
PD	pharmacodynamic
PET	positron emission tomography
PK	pharmacokinetic
PRO	patient-reported outcome
PS1	presenilin 1
PS2	presenilin 2
p-tau	phosphorylated tau

Abbreviation	Definition
Q2W	every 2 weeks
Q4W	every 4 weeks
QoL	quality of life
QTcF	QT interval corrected through use of Fridericia's formula
QoL-AD	Quality of Life–Alzheimer's Disease
RBR	Research Biosample Repository
SAP	Statistical Analysis Plan
SUVR	standardized uptake value ratio
$t_{1/2}$	half-life
Tg	transgenic
TP	therapeutic protein
t-tau	total tau
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 47 million people worldwide (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, with use of biomarkers to aid the diagnostic process increasing (Albert et al. 2011; McKhann et al. 2011). Recent research suggests that AD likely represents a continuum of disease stages from an asymptomatic stage (changes in biomarkers such as amyloid only) through the prodromal AD (pAD) stage, which is clinically characterized by mild cognitive impairment, to the dementia stage (mild, moderate, severe dementia).

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.

Approved medical therapies for AD dementia that inhibit acetylcholinesterase (AChE) activity or antagonize N-methyl-D-aspartate (NMDA) receptors in the brain may temporarily improve the symptoms in some patients but do not modify progression of the disease (Cummings 2004). A number of investigational treatments are under study, among them antibodies against Aβ. The hypothesis is that treatment with an anti-amyloid antibody may interfere with key events in the disease pathophysiology and may therefore have an impact on the progression of disease or may modify the disease process. Moreover, it is postulated that intervention early in the course of the disease, that is, before moderate dementia has developed, may have a higher efficacy potential than later intervention and may allow meaningful preservation of cognition and function.

Study BN40031 is an open-label extension (OLE) study (dosing crenezumab at 60 mg/kg IV every 4 weeks [Q4W] for all participants) to the two randomized, double-blind, multinational, *parent* Phase III efficacy studies BN29552 (CREAD) and BN29553 (CREAD2) that investigate crenezumab at a dose of 60 mg/kg IV Q4W compared with placebo over a 2-year treatment period in patients with pAD or mild AD (mAD) dementia.

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), and notably with high affinity to oligomers.

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). Its IgG4 backbone confers reduced activation of Fcγ receptor (FcγRs) 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) transgenic (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 (*together referred to as* 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). Crenezumab was designed as an IgG4 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 *parent BN29552 and BN29553* Phase III *studies* (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 cerebrospinal fluid (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. Due to 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 [PS-1]) 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

To date, crenezumab has been investigated in a total of *12* completed or ongoing *Roche-sponsored* Phase I, Phase II, and Phase III clinical trials. Approximately

1051 patients and healthy volunteers have been exposed to crenezumab in these studies.

Four Phase I studies (Studies ABE4427g, AB4662g, GP29172, and [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 P*hase I *studies* (GN29632 *and* [redacted] *are* ongoing. Study GN29632 is a dose-escalation study with a 13-week double-blind treatment period (DBTP) followed by an ongoing open-label all-to-active extension designed to assess safety, tolerability, and pharmacokinetics of multiple doses of crenezumab in patients with mild to moderate AD with doses of 30, 45, 60, and 120 mg/kg IV Q4W. [redacted]

The Phase II program (ABE4869g *and* ABE4955g), including an OLE study (GN28525), was designed to study safety and tolerability and to assess the clinical and biomarker effects of crenezumab in an AD dementia population (50–80 years of age) with mild to moderate disease severity (Mini Mental State Examination [MMSE] score, 18–26) (completed Studies ABE4869g and ABE4955g tested two doses of crenezumab [300 mg SC Q2W and 15 mg/kg IV Q4W versus placebo over 18 months]). The OLE study (GN28525) in patients who previously participated in either Study ABE4869g or ABE4955g *is complete*.

Another *Phase II* efficacy study in a different population within the AD spectrum (Study GN28352) is also ongoing. This study is conducted in a pre-symptomatic at-risk-for-AD population (30–60 years of age) with an autosomal dominant mutation (E280A) in the *PS1* gene (autosomal dominant AD [ADAD] population). This study initially dosed crenezumab at 300 mg SC Q2W. (Following results from the above-mentioned Phase II studies, the dose was increased to 720 mg SC Q2W.) In order to maintain the blind for the mutation, a group of mutation non-carriers who only receive placebo is also included.

There are two ongoing Phase III studies evaluating the efficacy, safety, and tolerability of crenezumab at a dose of 60 mg/kg IV Q4W versus placebo in a pAD to mAD population (MMSE score, 22–30). Study BN29552 (CREAD) and BN29553 (CREAD2) are randomized, double-blind, parallel-group, placebo-controlled trials designed to evaluate the safety and efficacy of crenezumab in patients aged 50–85 years who meet protocol-specified criteria for pAD or mAD.

China Extension Phase (DBTP)

Following completion of the global enrollment phase of *Study* BN29553, additional patients *will continue to* be enrolled in a China extension phase (i.e., *China extension to the main Phase III study BN29553*) to ensure *a total enrollment sufficient to support registration in the People's Republic of* China. *This* China subpopulation *may* include patients enrolled at sites in China during both the global enrollment phase and the China extension phase *and could be included in this OLE, if applicable*.

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 the People's Republic of China and to investigate the consistency in treatment effects between the China subpopulation and the global population for the purpose of registration in the People's Republic of China.

For a summary and details of the clinical studies to date refer to the Crenezumab Investigator's Brochure for further information.

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, and [redacted] *three* completed Phase II studies (ABE4869g*,* ABE4955g*, and GN28525*), *two* ongoing Phase I stud*ies* ([redacted] *and* GN29632), *one* ongoing Phase II stud*y* (GN28352), and two ongoing Phase III studies (BN29552 and BN29553).

In the Phase II studies in mild to moderate AD, more fatal events and *events of* pneumonia were reported in crenezumab-treated patients than in 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).

- In the crenezumab Phase II program, the overall rate of ARIA-E in the DBTP was 1/349 (0.3%) in crenezumab-treated versus 0/173 in placebo-treated patients. The incidence of ARIA-H was similar between crenezumab- and placebo-treated patients: The number of patients with incident mH was 40/349 (11.5%) in crenezumab-treated and 22/173 (12.7%) in placebo-treated patients, while superficial siderosis of CNS was reported in 3 patients (1.7%) receiving placebo. The rate of ARIA-E and ARIA-H in the DBTP of the Phase II program is similar to the background rate in the mild to moderate AD population (0.2% – 0.4%) (Doody et al. 2014; Salloway et al. 2014).
- *As of the date of release of this protocol, 4 patients have developed ARIA-E across the crenezumab program. In one patient, ARIA-E was considered symptomatic (headache).*

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*.

Three serious infusion-related reactions were reported in the ongoing Phase III studies BN29552 and BN29553 as of the date of release of this protocol. One reaction was reported as "anaphylaxis." The patient recovered rapidly after administration of epinephrine via auto-injector (EpiPen®). Two additional patients experienced serious acute hypotension during infusion with the blinded study drug. Both patients recovered within the next hour without the need for additional treatment. In all three cases, the study treatment was discontinued (see the Crenezumab Investigator's Brochure for additional details on these cases).

No population trend or pattern in clinically relevant changes has been observed in laboratory parameters, physical and neurologic examinations, vital signs, and ECG parameters.

An ongoing Phase Ib study (GN29632) is evaluating doses higher than those used in the Phase II studies, including 60 *mg/kg IV Q4W* and 120 mg/kg IV Q4W. This study is now in the OLE phase. The 60 mg/kg IV Q4W dose is also being used in both Phase III studies (BN29552 and BN29553). As of the date of the release of this protocol (BN40031), no new or unexpected safety findings *were observed in Study GN29632.* Specifically, no dose-limiting toxicities, drug–related serious adverse events, *or* ARIA-E events have been reported in *S*tudy *GN29632*.

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

The Sponsor performs a regular review of blinded data from the ongoing studies to identify any new or unexpected safety findings. Furthermore, Study GN29632 is overseen by an internal Safety Monitoring Committee, while independent Data Monitoring Committees (iDMCs) regularly review unblinded data from Studies GN28352, BN29552, and BN29553.

1.2.3.1 Adverse Event Profile

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

The DBTP 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 DBTP excluded the safety run-in arm of Study ABE4869g.

In the DBTP, 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 DBTP of the Phase II program, 9 patients (2.6%) who received crenezumab and 9 patients (5.1%) who received placebo withdrew because of adverse events. There were no imbalances in the overall rates of adverse events between patients who received crenezumab and patients who received 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 *program* (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 falls and urinary tract infections being the most frequently recorded adverse events.*

Details on the safety data from all completed and ongoing trials with crenezumab are provided in the most recent version of the Crenezumab Investigator's Brochure.

1.2.3.2 Deaths

During the DBTP of the Phase II program, 5 patients died. All five deaths occurred in patients treated with crenezumab; none was assessed by the investigator as related to study drug. 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).

In the OLE study GN28525, *15 patients (4.2%) died. Ten of the 15 patients had received active crenezumab, and 5 patients had received placebo. This represents 4.0% of patients who received crenezumab compared with 4.5% of patients who received placebo during DBTP of the Phase II study. All deaths were assessed as not related to study drug by the investigator.*

Details on deaths reported in the completed and ongoing clinical studies with crenezumab are presented in the most recent Crenezumab Investigator's Brochure.

1.2.3.3 Pneumonia

An imbalance in the rates of serious adverse events of pneumonia was observed in the DBTP 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 DBTP 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 DBTP 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; Salloway et al. 2014; Henley et al. 2015). The pneumonia rates in the placebo-treated population were slightly lower (0.6%; Henley et al. 2012; Doody et al. 2014; Salloway et al. 2014; Henley et al. 2015). However, the precision of these estimates is limited by the relatively smaller sample size in crenezumab Phase II data compared with 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 frequency and details of pneumonia events from all ongoing and completed studies is provided in the most recent version of the Crenezumab Investigator's Brochure.

1.2.3.4 ARIA-E and ARIA-H

In the DBTP 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 and 12.7%

(N = 22) of placebo-treated patients. The proportion of patients with superficial siderosis of CNS was 0% in crenezumab-treated patients versus 1.7% (N = 3) in placebo-treated patients. All findings in crenezumab-treated patients were asymptomatic.

An overview of ARIA-H and ARIA-E cases from all ongoing and completed studies is provided in the most recent version of the Crenezumab Investigator's Brochure.

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 *were* observed during the DBTP 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 death 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, ABE4955g, GP29172, and [redacted] It is being further assessed in the ongoing Phase I, II, and III trials.

A positive 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 the total number of patients with a 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 postbaseline samples available for ADA analysis.

- In Study ABE4427g, a positive ADA response was detected in 1 of 36 patients (2.8%) given crenezumab. Presence of ADAs had no apparent impact on pharmacokinetics and safety in this patient.
- 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 postbaseline 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 pharmacokinetics or in the 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). ADAs were not observed at postbaseline in *either placebo or* crenezumab-treated patients.

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, [redacted] and GN29632) and in two Phase II studies (ABE4869g and ABE4955g). Overall, the observed serum pharmacokinetics in the Phase I and II studies have appeared to be dose proportional (IV: 0.3–10 mg/kg single dose and 15–120 mg/kg Q4W; SC: 1.8 mg/kg single dose and 600–7200 mg single dose) and the PK parameters (e.g., clearance [CL], half-life [$t_{1/2}$]) in the Phase I studies have been consistent with those for other humanized IgG MAbs that exhibit kinetics in the linear concentration range (Mould and Sweeney 2007; Dirks and Meibohm 2010; Deng et al. 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. Crenezumab CL was slow (2.5–3.3 mL/day/kg) with a long terminal $t_{1/2}$ (17–26 days) following a single IV dose. With weekly administration, there did not appear to be any time-dependent change in crenezumab pharmacokinetics relative to single-dose administration, as evidenced by similar terminal elimination $t_{1/2}$ estimates (18–23 days) relative to the single-dose arm. [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 a change of drug product in ongoing clinical studies.

[redacted]

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]

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

Additional PK information 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 >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) 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 *F 18* amyloid–positron emission tomography (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 *F 18*-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 (MRI).

Florbetapir *F 18*-PET

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 mAD subpopulation (MMSE score, 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 *F 18*-PET standardized uptake value ratio (SUVR) was observed for patients in both the placebo and crenezumab treatment arms.
The estimated mean change in florbetapir *F 18*-PET SUVR from baseline was less for the crenezumab arm than for 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 mAD 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-PET

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 CSF Pharmacodynamic Biomarkers

Plasma and CSF biomarker measurements were evaluated in Study ABE4955g. Concentrations of $A\beta_{42}$, total tau (t-tau), and phosphorylated tau (p-tau) in CSF were assessed in 55 patients with mild to moderate AD (MMSE score, 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 indicate 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 t-tau or on p-tau.

Data from the 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 $A\beta_{42}$ and $A\beta_{40}$ bind to crenezumab, it takes on the slow half-life of the antibody and therefore stays in the circulation longer. Please refer to the Crenezumab 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 slow AD progression and potentially modify the disease course.

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 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 (GN29632), 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 in order to investigate whether greater efficacy can be obtained while maintaining a favorable benefit–risk profile (see Section 1.3.4 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.

Crenezumab is currently being studied at a dose of 60 mg/kg IV Q4W (compared with placebo) in two randomized, placebo-controlled multinational Phase III studies (BN29552 and BN29553) in patients with pAD or mAD dementia (for details, see Section 1.2 and the Crenezumab Investigator's Brochure). The primary endpoint in these 24-month treatment studies is the Clinical Dementia Rating-Sum of Boxes (CDR-SB), a clinical scale assessing cognition and function.

In this OLE study, a dose of crenezumab of 60 mg/kg IV Q4W will be offered to all patients who complete *one of the parent studies* BN29552 or BN29553 and who meet eligibility criteria for this study in order to evaluate safety in patients on long-term crenezumab treatment and to investigate the effect of crenezumab on the underlying disease process and disease course as an exploratory efficacy objective.

1.3.2 Safety Rationale

AD is a chronic condition with any efficacious therapy likely necessitating many years of treatment. Therefore, it is important to understand the long-term safety of any potential AD treatment beyond the 2-year DBTP in Studies BN29552 and BN29553.

Safety assessments in this OLE study will be the same as in Studies BN29552 and BN29553 including adverse event reporting, regular MRIs, close monitoring for pneumonia-related events, and assessment of immunogenicity. As patients who received placebo in Studies BN29552 and BN29553 will receive crenezumab for the first time in the OLE, the schedule of events has an MRI approximately 12 weeks after the first dose.

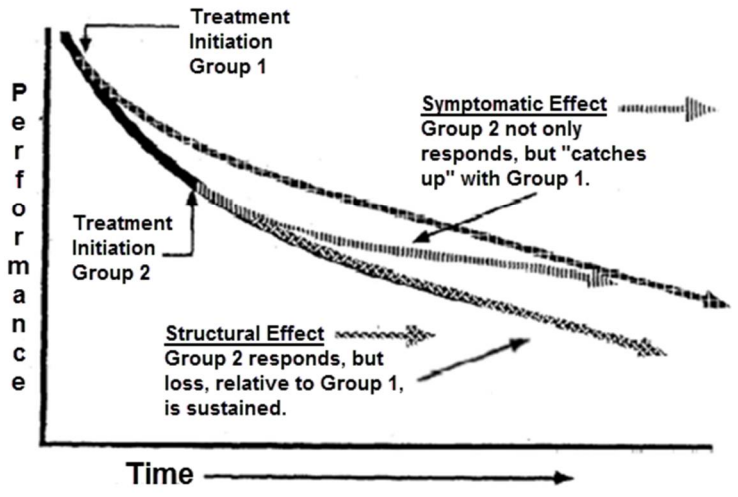
1.3.3 Efficacy

An exploratory objective of this OLE study is to investigate the effect of crenezumab on the underlying disease process and course.

The purpose of Studies BN29552 and BN29553 is to establish the efficacy and safety of crenezumab in patients with pAD to mAD who may or may not be treated concurrently with approved symptomatic treatments for AD, over a treatment period of 104 weeks (26 doses). This DBTP was selected to demonstrate an enduring clinical benefit of crenezumab treatment on the basis of the mechanism of action and available data to date. Crenezumab may slow clinical decline rather than provide improvement over baseline.

There is considerable scientific and clinical interest in understanding the impact of the intervention under study on the underlying disease process. It has been proposed that demonstration of a disease-modifying effect (rather than a reversible "symptomatic" effect) may be achieved in studies using a two-period design (Leber 1997; see Figure 1).

Figure 1 Randomized Start Design



Therefore, an exploratory randomized start analysis is proposed, using the 2-year DBTP in Studies BN29552 and BN29553 as Period 1 (i.e., Treatment Initiation Group 1 in the

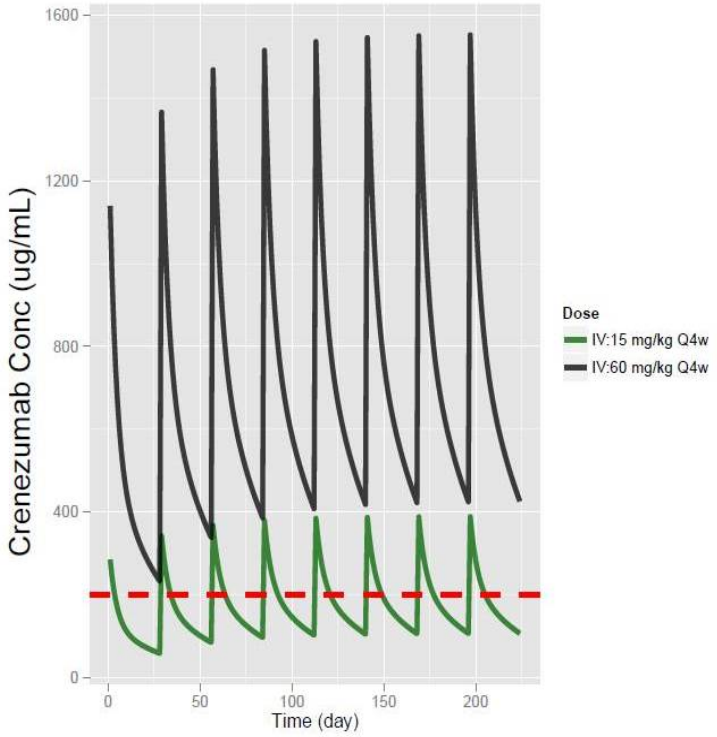
above diagram), and 1 or 2 year(s) of treatment in Study BN40031 as Period 2 (i.e., Treatment Initiation Group 2 in the above diagram). The intent is to demonstrate that patients who received placebo treatment in Period 1 will not achieve in the medium term the same clinical benefit as those patients who received active drug treatment in Period 1. Period 2 has to provide sufficient time for crenezumab to exert its effect on the patient group who previously received placebo. At the same time, it is important to keep the amount of missing data low to enable a robust analysis. The duration of Period 2 (1 or 2 years) is to be confirmed in the Statistical Analysis Plan (SAP).

The efficacy assessments in Study BN40031 will use the same scales as in the prior Phase III studies with the CDR-SB being the primary efficacy endpoint for this exploratory two-period design.

1.3.4 Dose

Considering the evidence from the Phase II studies and clinical modeling, and based on supportive safety data from Study GN29632, the dose of 60 mg/kg IV Q4W was selected for the global Phase III program (60 mg/kg IV Q4W is a dose resulting in exposure approximately 4-fold higher than the high dose in the Phase II program, see Figure 2). A higher dose than that used in the Phase II program is expected to result in increased brain exposure and thus in increased target engagement and has the potential for better efficacy. This dose is currently used in Studies BN29552 and BN29553, and it is also the planned dose in this OLE.

Figure 2 Pharmacokinetic Profile Based on Modeling 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; EC_{50} = 50% effective concentration; Q4W = every 4 weeks;
Note: Dashed red line = EC_{50}.

1.3.5 Biomarkers

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

Two imaging modalities are mainly used as secondary or exploratory endpoints in clinical trials of AD: MRI and 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 *F 18*, approved for use by the U.S. Food and Drug Administration [FDA] in *2012 and European Medicines Agency in 2013*) are thought to represent accumulation of the Aβ plaques (Joshi et al. 2012). PET tracers that have more recently become available and may bind to tau in the brain (e.g., [^{18}F]GTP1, an investigational radiotracer) are thought to enable assessment of local tau burden as well as its spreading throughout the brain.

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 AD pathology (Shaw et al. 2009; Le Bastard et al. 2013). Thus, CSF $A\beta$ levels may provide information relevant to diagnosis and could potentially act as a biomarker for target engagement and for the impact of crenezumab on $A\beta$ retention and aggregation. Changes in CSF t-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.

1.3.6 Risk to Patients without Alzheimer's Disease Pathology

On account of the rigorous screening procedures in *the parent studies BN29552 and BN29553*, including the measurement of CSF $A\beta_{1\text{-}42}$ and/or 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 side effects related to the product (e.g., infusion reactions, development of ADAs)*, similar to patients with AD pathology*.

1.3.7 Overall Benefit–Risk Summary

The overall benefit–risk profile of investigation of crenezumab at a dose of 60 mg/kg IV Q4W in a population of pAD to mAD patients is favorable.

Overall, the benefit–risk assessment of crenezumab is based on the following.

In Phase II studies (DBTP):

- The primary endpoints were not met.
- In further analyses, a consistent effect on cognitive scales including the Alzheimer's Disease Assessment Scale–Cognition 12 (ADAS-Cog12) scale was observed in patient subsets with mild disease who were treated with crenezumab 15 mg*/kg* IV Q4W versus placebo.

  A 4-fold higher dose is being investigated in Phase III studies, including this OLE. A higher dose than that used in the Phase II program is expected to result in increased brain exposure and thus in increased target engagement and has the potential for better efficacy.
- Treatment with crenezumab was associated with an increase in CSF-$A\beta_{42}$ relative to placebo, which was suggestive of target engagement in the CNS.
- While more deaths and pneumonia cases were observed with crenezumab than with 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. 2015) 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 is 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.

The benefit–risk assessment of crenezumab is also based on the following.

- Pneumonia cases, other serious respiratory infections, and deaths will be closely monitored in the study, with the requirement to report these cases to the Sponsor within 24 hours with a full description of the case (see Section 5.3.5).
- In the DBTP 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. 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 and 12.7% (N=22) of placebo-treated patients. The proportion of patients with superficial siderosis of CNS was 0 in crenezumab-treated patients versus 1.7% (N=3) in placebo-treated patients. All findings in crenezumab-treated patients were asymptomatic.
- In the other ongoing or completed studies of crenezumab, the majority of ARIA-H cases were asymptomatic and their incidence is within the rate observed in the Phase II program. Cases of ARIA-E were mostly asymptomatic. An overview of ARIA-H and ARIA-E cases from all ongoing and completed studies is provided in the most recent version of the Crenezumab Investigator's Brochure.
- ARIA events appear 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. 2012).

  Patients will undergo regular brain MRI monitoring, and discontinuation rules are in place in case of ARIA.
- Per the Crenezumab Investigator's Brochure (*Version 10,* August 2017), one event of a serious hypersensitivity reaction (adverse event verbatim term "anaphylaxis") considered related to the study drug was reported in the ongoing Phase III study BN29552. This case concerns a patient who, upon further investigation of this adverse event, reported a history of allergy to bee sting (requiring epinephrine treatment) and reactions of pruritus and fatigue to unspecified medications. No signs and/or symptoms were reported after the first administration of blinded study drug. At the second infusion visit (approximately 4 weeks after the first visit), the patient reported dizziness and subjective sensation of "throat closing up" 2 minutes after initiation of the infusion. The patient was noted to be diaphoretic and anxious and to have bright red flushing of the face, neck, and chest. The infusion was stopped immediately and epinephrine via autoinjector (EpiPen®) was administered 1 minute after onset of symptoms, followed by immediate resolution of the subjective symptom and complete resolution of the flushing within 23 minutes. No antihistamines, steroids, oxygen, or other treatments were administered, and the patient was not hospitalized.

Crenezumab should be administered to subjects under close medical supervision in a setting with access to emergency equipment and staff who are trained to monitor and respond to medical emergencies.

Please refer to the latest version of the Crenezumab Investigator's Brochure for additional information on serious infusion-related reactions.

2. OBJECTIVES AND ENDPOINTS

This study will assess the long-term safety and tolerability of crenezumab administered to all patients who completed Studies BN29552 (CREAD) and BN29553 (CREAD2) and who meet the eligibility criteria for this OLE study. An exploratory objective of this OLE study is to investigate the effect of crenezumab on the underlying disease process and course. Specific objectives and corresponding endpoints for the study are outlined in Table 1.

Table 1 Objectives and Corresponding Endpoints

Primary Safety Objective	Corresponding Endpoints
To assess the long-term safety and tolerability of crenezumab (60 mg/kg IV Q4W) in eligible patients with AD who participated in Study BN29552 or BN29553 and completed the Week 105 study visit	• Nature, frequency, severity, and timing of adverse events and serious adverse events • 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
Exploratory Efficacy Objectives	**Corresponding Endpoints**
To evaluate the long-term effect of crenezumab on global outcomes of disease progression	• Change from baseline during the OLE in CDR-SB
To evaluate the long-term effect of crenezumab on cognition	• Change from baseline during the OLE as measured by the ADAS-Cog-13 • Change from baseline *during the OLE* using the MMSE • Change from baseline *during the OLE* using ADAS-Cog-12
To evaluate the long-term effect of crenezumab on disease severity	• Change from baseline during the OLE using CDR-GS
To evaluate the long-term effect of crenezumab on patient dependence	• Change from baseline during the OLE using scores derived from the ADCS-ADL total scale
To evaluate the long-term effect of crenezumab on patient function	• Change from baseline during the OLE using the ADCS-ADL, the instrumental subscale, and/or the FAQ
To evaluate the long-term effect of crenezumab on behavior and neuropsychological symptoms	• Change from baseline during the OLE using the Neuropsychiatric Inventory Questionnaire
To evaluate the long-term effect of crenezumab on health-related quality of life	• Change from baseline during the OLE using the Quality of Life-AD scale

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Efficacy Objective (cont.)	Corresponding Endpoints (cont.)
To evaluate the long-term effect of crenezumab on caregiver burden	• Change from baseline during the OLE *using* the Zarit Caregiver Interview for AD scale
Exploratory Pharmacokinetic Objectives	**Corresponding Endpoints**
To evaluate the serum PK characteristics of crenezumab	• Serum concentration of crenezumab at specified timepoints
To evaluate the CSF PK characteristics of crenezumab	• CSF concentrations of crenezumab at specified timepoints *(only in patients who previously enrolled in substudy BN29552-CSF Longitudinal or BN29553-CSF Longitudinal)*
To explore exposure-response relationships in patients with prodromal to mild AD	• Correlation between crenezumab concentration and biomarkers as well as safety and efficacy outcomes
Exploratory Biomarker Objectives	**Corresponding Endpoints**
To evaluate the effect of crenezumab on biomarkers	• Brain amyloid load over time measured by amyloid PET (only in patients who previously enrolled in substudy BN29552-Amyloid PET Longitudinal or BN29553-Amyloid PET Longitudinal) • Brain tau load and spread over time measured by tau-PET (only in patients who previously enrolled in substudy BN29552-Tau PET Longitudinal or BN29553-Tau PET Longitudinal) • CSF markers of disease over time (only in patients who previously enrolled in substudy BN29552-CSF Longitudinal or BN29553-CSF Longitudinal) • Plasma PD markers of disease over time • MRI-derived measurements over time such as volumetric changes in whole brain, ventricles, hippocampus, or other structures

AD=Alzheimer's disease; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognition 12 or 13; ADCS-ADL=Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory; ARIA-E=amyloid-related imaging abnormalities-edema/effusion; ARIA-H=amyloid-related imaging abnormalities-hemosiderin deposition; CDR-GS=Clinical Dementia Rating-Global Score; CDR-SB=Clinical Dementia Rating-Sum of Boxes; CSF=cerebrospinal fluid; C-SSRS=Columbia-Suicide Severity Rating Scale; FAQ=Functional Activities Questionnaire; MMSE=Mini Mental State Examination; MRI=magnetic resonance imaging; OLE=open-label extension; PD=pharmacodynamic; PET=positron emission tomography; PK=pharmacokinetic; Q4W=every 4 weeks.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

Study BN40031 is a Phase III, OLE, multicenter study to evaluate the long-term safety and tolerability of crenezumab at a dose of 60 mg/kg IV Q4W in patients with AD who have participated in one *of the* Phase III *parent studies* (BN29552 or BN29553). Efficacy will also be assessed. Patients who discontinued early from study treatment during Study BN29552 or BN29553 but remained in the study for safety and additional efficacy evaluations and completed the Week 105 study visit can enter the OLE study and begin open-label treatment. Patients from Study BN29552 or BN29553 who discontinued the study prior to completion of the Week 105 study visit are not eligible for this OLE study.

Studies BN29552 and BN29553 are ongoing Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety studies of crenezumab in patients with pAD to mAD. The planned number of patients for this OLE study is not expected to exceed 1500 (approximately 750 randomized to crenezumab 60 mg/kg IV and 750 randomized to placebo, i.e., the total planned number of patients in *the parent s*tudies BN29552 and BN29553, not including patients from the China extension study). An estimate for the actual number of patients in this OLE study is approximately 925 patients *(not including patients from the China extension study)* based on 1500 patients enrolled in both Phase III studies and an estimated reduction by 35% (i.e., withdrawals from double-blind treatment) and by a further 5% of completers who may not opt to enroll in this OLE study. Approximately *350* centers in approximately *40* countries worldwide will participate in this study.

Patients and all clinical site staff will remain blinded to the original treatment assignment in Studies BN29552 and BN29553 on entry into the OLE study and until a later time which will be determined by the Sponsor.

Following completion of the global enrollment phase of *Study BN29553*, additional patients *will continue to* be enrolled in a China extension phase (i.e., China extension to *the main Phase III study BN29553*) to ensure a total enrollment sufficient to support registration in the People's Republic of China. This China subpopulation may include patients enrolled at sites in China during both the global enrollment phase and the China extension phase *and could be included in this OLE, if applicable*.

3.2 STUDY DESIGN

All patients who are enrolled in the OLE study will receive crenezumab 60 mg/kg administered by IV infusion Q4W.

Data collected at Week 105 of the DBTP of Studies BN29552 and BN29553 and results from a coagulation blood test taken before the first OLE infusion will be used to assess patient eligibility for the OLE study. This Week 105 data will also be used as OLE baseline data.

Prior to administering the first infusion in the OLE, eligibility will be ensured by reviewing Week 105 assessment results *(including MRI results)*, *OLE screening* coagulation blood test results, and any other significant patient changes.

Once a patient is identified as eligible for the OLE study, the following will occur:

- Patients can receive the first infusion of crenezumab at any time on or up to *8* weeks after the Week 105 visit of the double-blind studies. Any extensions to this period must be approved by the Sponsor. Sites can arrange an infusion visit as soon as *eligibility assessment results* are available (including MRI results and results from the coagulation test) to assess OLE eligibility. Details of the visit schedule and associated assessments are given in Appendix 1.
- The day that the first dose of crenezumab is administered will be Visit 1, Week 1 of the OLE.
- On Visit 1, Week 1 of OLE (i.e., the first open-label infusion of crenezumab), safety assessments must be done as indicated in the schedule of activities (see Appendix 1).

For details on the schedule of activities, see Appendix 1. For details on the length of the study, see Section 3.3.

3.2.1 Independent 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, and laboratory abnormalities will be assessed on a regular basis by an iDMC. It is anticipated that these assessments will occur approximately every 3 months until Studies BN29552 and BN29553 are unblinded.

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

3.3 END OF STUDY AND LENGTH OF STUDY

The OLE study will continue until crenezumab is commercially available in the patient's country, as per local regulation, or should the Sponsor decide to terminate the program for *pAD* to *mAD*. *However, all patients will have the opportunity to complete approximately 2 years of treatment even if crenezumab is commercially available in the patient's country.* The study will not exceed approximately 2 years after the last patient *enrolled during the global enrollment phase (in Study BN29552 or BN29553)* enters the OLE study.

For United Kingdom only: The OLE study will not exceed approximately 2 years after the last patient *enrolled during the global enrollment phase in Study BN29552 or BN29553* enters the OLE study or until a decision to terminate the program for pAD to mAD is made by the Sponsor.

For the first patient entering the OLE study, the maximum duration would be approximately *4* years, depending on the date of commercialization or the date of the last patient enrolled in Study BN29553 (12 July 2018).

The 2-year duration of the OLE study serves to evaluate long-term safety, tolerability, and efficacy of crenezumab treatment in patients with AD and allows for all patients to reach the 2-year treatment duration in the OLE study for the efficacy analysis.

Patients who discontinue crenezumab treatment during Year 1 of the OLE study will be followed for 16 weeks after their last dose of crenezumab and will also be asked to complete the remaining scheduled efficacy assessments at Week 53 of the OLE as per the schedule of activities (see Appendix 1).

Patients who discontinue crenezumab treatment during Year 2 of the OLE study will be followed for 16 weeks after their last dose of crenezumab and will also be asked to complete the remaining scheduled efficacy assessments at Week 105 of the OLE as per the schedule of activities (see Appendix 1).

Patients who discontinue treatment after Year 2 (Week 105) of the OLE study will be followed up for safety for 16 weeks. Patients who complete the OLE study and continue treatment with crenezumab thereafter will not be followed up.

Patients and sites will remain blinded to their assignment in Study BN29552 or BN29553 until permitted by the Sponsor.

Every effort should be made to have the same caregiver participate throughout the duration of the OLE study who also participated in Study BN29552 or BN29553. If the caregiver cannot continue to participate in the OLE study and cannot be replaced, the patient can continue in the OLE as long as patient safety can be assured.

The end of this study is defined as the date when the last patient, last visit occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately 28 months after the last patient is enrolled.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately *4* years.

3.4 RATIONALE FOR STUDY DESIGN

This study is the OLE study of BN29552 (CREAD) and BN29553 (CREAD2), the Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies of the efficacy and safety of crenezumab in patients with a diagnosis of pAD to mAD.

3.4.1 Rationale for Treatment Duration

AD is a chronic condition with any efficacious therapy likely necessitating many years of treatment. Therefore, it is important to understand the long-term safety of any potential AD treatment beyond the 2-year DBTP in Studies BN29552 and BN29553.

See Section 3.3 for information about the end of the study.

3.4.2 Rationale for Long-Term Follow-Up

The primary objective of the study is to evaluate the long-term safety and tolerability of crenezumab. If a patient discontinues treatment early, or if a patient completes the study and does not continue treatment with crenezumab thereafter, assessments performed at 4 and 16 weeks after the last dose of treatment will evaluate the relevant safety parameters over an extended period when no study drug is administered.

Efficacy 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. If a patient discontinues treatment before Week 105, assessments performed at the next annual visit will inform the exploratory efficacy analysis (see Section 1.3.3). For details of the schedule of activities, see Appendix 1.

3.4.3 Rationale for Patient Population

The patient population for this OLE study will comprise patients who completed Week 105 in either Study BN29552 or BN29553 and who meet the inclusion criteria of this Study BN40031 protocol.

3.4.4 Rationale for Safety Outcome Measures

Adverse event data will be gathered in this OLE study, including adverse events related to MRIs (ARIA-E and ARIA-H) to allow collection of long-term safety data in patients who continue to receive crenezumab after completing the main study DBTPs. This data will allow evaluation of the long-term safety and tolerability of exposure to crenezumab in this population. After Week 105 of the OLE study, assessment frequency is reduced to minimize patient burden but to continue safety monitoring. For details of the schedule of activities, see Appendix 1.

3.4.5 Rationale for Exploratory Efficacy Outcome Measures

Efficacy assessments/scales in the OLE replicate those in Studies BN29552 and BN29553, allowing a full profile of efficacy data to be collected for all patients, including those who received placebo in Studies BN29552 and BN29553 but will receive crenezumab 60 mg/kg during the OLE. As with Studies BN29552 and BN29553, assessments in clinical trials for AD should be obtained across several domains of neurologic function, including cognition and functioning. After Week 105 of the OLE study, assessment frequency is reduced to minimize patient burden but continue efficacy monitoring. For details of the schedule of activities, see Appendix 1.

3.4.6 Rationale for Pharmacokinetic Sampling

A sparse sampling schedule for serum concentrations of crenezumab is being utilized to minimize patient burden and yet still provide an adequate assessment of crenezumab exposure.

The serum PK data will be needed for interpretation of the ADA impact of pharmacokinetics and may be compared with available data from other crenezumab studies as well as for the assessment of exposure-response relationships for relevant imaging, plasma PD biomarkers, ECG, and efficacy and safety outcomes in patients with pAD to mAD, as appropriate.

Crenezumab concentration in CSF will be measured at Week 53 *only* in patients who were in the CSF longitudinal substudy (see Section 3.4.7.1), *provided they* consent *to continue in the substudy during the OLE*. The CSF measurement will contribute to the longitudinal CSF substudy and the assessment of crenezumab partitioning into the CSF at 60-mg/kg Q4W dosing as well as of the exploratory exposure-response relationship between crenezumab concentration and CSF biomarkers.

3.4.7 Rationale for Biomarker, PET Assessments and MRI Assessments

The biomarker, PET, and MRI assessments described in Section 3.4.7.1 (CSF), Section 3.4.7.2 (PET imaging), and Section 3.4.7.3 (brain volumetry) will be used to investigate the effect of crenezumab on the underlying pathology of AD in the clinical trial population.

3.4.7.1 Cerebrospinal Fluid Biomarkers (for Patients Who Were in the *BN29552 or BN29553* CSF Longitudinal Substudy Only)

Amyloid plaque deposition, neurofibrillary tangle formation, and neuronal degeneration are known pathologic features of AD. Decreased CSF $A\beta_{1-42}$ and elevated CSF 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.

The planned additional CSF assessment at Week 53 of the OLE study will contribute to the CSF longitudinal data collected in the substudy associated with Protocols BN29552 and BN29553 (CSF Longitudinal Substudy) and will be taken for patients who have completed the following:

- The CSF Longitudinal Substudy in either Study BN29552 or BN29553
- *Consented to additional* CSF *s*ample*s* during the OLE study

3.4.7.2 Positron Emission Tomography Imaging Assessment

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

The planned additional PET imaging assessment will contribute to the substudies associated with Protocols BN29552 and BN29553, the Amyloid-PET Longitudinal Substudy and the Tau-PET Longitudinal Substudy and will be taken for patients who have completed the following:

- The Amyloid-PET Longitudinal Substudy and/or the Tau-PET Longitudinal Substudy for either Study BN29552 or BN29553
- *Consented to additional* PET *i*maging *a*ssessments during the OLE study

3.4.7.3 MRI Assessments for 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). On the basis of 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 reading facility.

4. MATERIALS AND METHODS

4.1 PATIENTS

Patients who completed the Week 105 study visit of Study BN29552 or BN29553 and meet the eligibility criteria are eligible to participate in this OLE study. Patients who discontinued the study prior to completion of the Week 105 visit will not be eligible for this OLE study.

Concomitant acute and chronic diseases (including significant laboratory abnormalities) should be monitored and treated towards treatment targets as per local guidance.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Previous participation in Study BN29552 or BN29553 and completion of the Week 105 visit.

  Patients who discontinued from one of these studies prior to completion of the Week 105 visit are not eligible. Temporary halting of study drug (e.g., because of an adverse event) in Study BN29552 or BN29553 is not exclusionary.

- *W*ritten *informed* 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 [EC] or Institutional Review Board [IRB]) or the patient's authorized representative under applicable local law

  In the course of the study, assessment of a subject's capacity to re-consent *should be done, and written informed re-consent signed by the patient* (co-signed by the patient's legally authorized representative if required by the local regulations, guidelines, or independent EC/IRB) or the patient's authorized representative should be *obtained,* as per applicable local law and requirements.

- *Every* effort *should be made* to have the same caregiver participate throughout the duration of the OLE study who also participated in Study BN29552 or BN29553.

  The caregiver, in the investigator's judgment, should fulfill the following:

  - Have frequent and sufficient contact with the patient to be able to provide accurate information regarding the patient's cognitive and functional abilities, agree to provide information at clinic visits (which require partner input for scale completion), sign the necessary consent form, and have sufficient cognitive capacity to accurately report upon the patient's behavior and cognitive and functional abilities.
  - Be 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.

- If the caregiver cannot continue to participate in the OLE study and cannot be replaced, the patient can continue in the OLE so long as patient safety can be assured.

- Willingness and ability to complete all aspects of the study (including MRI, lumbar puncture [if applicable], 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 measures, and agreement to refrain from donating eggs, as defined below:*

  Women must remain abstinent 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 *final* dose of study drug. *Women must refrain from donating eggs during this same period.*

  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). *The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.*

  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 *a* female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for at least 8 weeks after the *final* 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 *preventing drug exposure*.

4.1.2 Exclusion Criteria

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

- Patients who discontinued treatment permanently in Study BN29552 or BN29553 for safety reasons
- *Impaired coagulation (screening PT >1.2 ×the upper limit of normal (ULN) that remains abnormal on retest)*
- Evidence of more than 10 *ARIA-H (*microbleeds and/or *leptomeningeal hemosiderin deposits)* at the Study BN29552 or BN29553 Week 105 visit, as assessed by central review of MRI
- Diagnosed with three recurrent, symptomatic ARIA-E events or exacerbations of previous events
- Presence of intracranial lesion that could potentially increase the risk of CNS bleeding (e.g., intracranial aneurysm; arteriovenous malformation)
- 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 Version 5 criteria) within the past 2 years and during the study

  Nicotine use is allowed.

  Marijuana use is not allowed within the past 2 years.
- 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
- Pregnant or lactating, or intending to become pregnant during the study
- 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, or interfere with the patient's ability to complete the study assessments
- Chronic use of anticoagulants or participation in any other investigational drug treatment trial

  See Section 4.4 for further details and other concomitant medication restrictions.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

All patients who meet the eligibility criteria will receive 60 mg/kg of crenezumab IV Q4W.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is crenezumab. *According to E.U. guidance, the PET ligands used in the context of this study have been designated as non-IMPs. In some regions, according to local regulations, these PET tracers may be considered as IMPs.*

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Crenezumab

Crenezumab 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.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimen is summarized in Section 3.1.

4.3.2.1 Crenezumab

Crenezumab will be administered via IV infusion to all patients at a dose of 60 mg/kg Q4W until the end of the study (see Section 3.3).

All IV infusions of crenezumab will be administered by appropriately trained staff in the clinic or other agreed environment (e.g., the patient's home if that option becomes available at a later time). The first four infusions of study drug must be administered at the clinic for all patients as a minimum.

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. 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 weight at Week 105 of Study BN29552 or BN29553 (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 or severe hypersensitivity reactions, a blood sample will be collected at the time of the event for analyses of antibodies to crenezumab and/or other components of the drug product, and crenezumab serum concentration. In addition, for any patient suspected of developing anaphylaxis, or anaphylactoid or serious or severe hypersensitivity reactions warranting discontinuation of dosing, a washout ADA sample (16 weeks postdose) and concurrent PK sample must be collected.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (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 and once that option is available (please see Section 4.5 for details).

4.3.2.2 Non-Investigational Medicinal Products

All patients who are assessed by PET imaging *(as described in Section 3.4.7.2) will be assessed* using an appropriate PET ligand.

According to E.U. guidance, the PET ligands used in the context of this study 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, please refer to Section 5.7.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (crenezumab) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the interactive voice or web-based response system (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 be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied

IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied 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.

4.3.4 Continued Access to Crenezumab

The Sponsor will offer post-trial access to the Roche IMP (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 Roche IMP (crenezumab) 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 Roche IMP 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 him or her.

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

- The Roche IMP 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 would not otherwise create a financial hardship for the patient).
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for AD.
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for AD.
- Provision of Roche IMP 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

4.4 CONCOMITANT THERAPY

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

Adding a new medication or changing the dose of a medication should occur only for the treatment of an adverse event.

For the entire OLE period, the following medications are prohibited:

- Anti-coagulation medications

  Anti-platelet treatments (e.g. aspirin, clopidogrel, dipyridamole) are permitted.

  Under certain circumstances, anti-coagulation 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).
- Any other investigational drug treatment throughout participation in the trial

For the first year of the OLE study, the following medications are prohibited. After Year 1 of the OLE study, initiation of new therapy should be proactively discussed with the Sponsor:

- Any other therapeutic that targets Aβ or tau
- Stimulant medications (amphetamine, methylphenidate preparations, or modafinil)
- Typical antipsychotic and/or neuroleptic medication except as brief treatment for a non-psychiatric indication (e.g., emesis)
- Tricyclic antidepressants (amtriptyline, imipramine, timipramine, doxepin)

  Secondary amines (e.g., desipramine, nortriplyline) may be permitted for use in treatment of chronic pain.
- Chronic and/or daily use of opiates or opioids (including long-acting opioid medication)
- Chronic and/or daily use of benzodiazepines

The following medications are permitted under certain conditions:

- Atypical anti-psychotics are permitted if assessed as not clinically affecting the patient's cognitive symptoms.
- 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. Individual cases of concomitant intermittent barbiturate use should be discussed with the Sponsor.
- Dose of benzodiazepine for pre-surgical and pre-imaging sedation at appropriate visits is permitted if allowed by the EC or IRB

Concomitant and excluded therapies for determination of patient eligibility are described in Sections 4.1.1 and 4.1.2.

4.5 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 4.5.11 and as specified in the schedule of activities (see Appendix 1).

At a time to be determined by the Sponsor, at applicable sites, study infusions and associated 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 relevant assessments to be performed by the HN professional. At the time the Sponsor initiates HN visits, specific visits and assessments that may be performed by an HN professional will be described in a HN manual.

Rescue medications and equipment to treat anaphylactic and anaphylactoid reactions must be available for HN visits. Patients or 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.

4.5.1 Informed Consent Forms and Screening Log

All patients, caregivers, and others as specified on the ICFs 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.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history and demographic data was collected as part of the main study protocols (BN29552 or BN29553).

4.5.3 Physical and Neurologic Examinations

In the OLE, *complete physical and neurologic examinations will be performed as per the schedule of activities and should be conducted in the same manner on each occasion to ensure comparability to previous examinations. The scheduled examinations should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Neurologic examinations should include assessment of mental status, level of consciousness, cranial nerve function (including fundoscopic examination), motor function, sensory function, reflexes, coordination, and assessment of gait. Other examination components or systems may be assessed as clinically indicated. Symptom-directed physical and neurologic examinations may be done at any other visit as needed to assess the safety of the participant. Any significant c*hanges *from prior examinations* 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 activities indicates when weight should be recorded as part of the vital sign assessments (see Appendix 1).

4.5.4 Vital Signs

Vital signs, including systolic and diastolic blood pressure, pulse rate, body temperature, respiratory rate, and oxygen saturation will be measured according to the schedule of activities (see Appendix 1). Vital signs should be measured per clinic standard operating

procedures as long as the patient is supine, at rest, and at least 15 minutes have passed since a blood draw.

4.5.5 Cognitive Assessments

Cognition will be assessed using the Alzheimer's Disease Assessment Scale—Cognition 13 (ADAS-Cog13), Free and Cued Selective Reminding Test (FCSRT), Clinical Dementia Rating (CDR), MMSE, and those instruments listed below.

The cognitive assessments described in this section *are recommended* in the order specified in Section 4.5.11 and in the schedule of activities (see Appendix 1).

The scales and assessments for this study will be provided unless otherwise specified. *Consistency of* rater*s* and caregiver*s* for each patient throughout the duration of the DBTP in Study BN29552 or BN29553 and the OLE study *is important for collecting high-quality cognitive and functional outcomes. Every effort should be made to have the same CDR rater and caregiver participate throughout the duration of the OLE study who also participated in Study BN29552 or BN29553.*

New potential raters *must complete training and be approved* by the rating scale contract research organization (CRO) prior to administer*ing* any cognitive assessments or rating scales in the study.

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).

4.5.5.1 Clinical Dementia Rating Scale

Washington University's CDR is a global assessment instrument that yields a global score (i.e., CDR-Global Score [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 (Morris 1993; Lynch et al. 2006; 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 web site: 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, Alzheimer's Disease Cooperative Study—Activities of Daily Living Inventory

(ADCS-ADL)*, or Functional Activities Questionnaire (FAQ)*. 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.

4.5.5.2 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 (Rosen et al. 1984; Connor and Sabbagh 2008; Cano et al. 2010; Ihl et al. 2012). The modified version will be used; it has 13 items and includes the addition of delayed word recall and number cancellation and the 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 12-item version of ADAS-Cog (without number cancellation) will be also be analyzed for comparison with Phase II data.

4.5.5.3 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 activities of daily living (ADL) (e.g., eating and toileting) and more complex ADL or instrumental ADL (iADL; e.g., using the telephone, managing finances, preparing a meal).

4.5.5.4 Mini Mental State Examination

The MMSE (Version 9.8, including serial 7s) is a set of standardized questions used to evaluate possible cognitive impairment and help stage the severity level of this impairment (Folstein et al. 1975). The questions target six areas: orientation, registration, attention, short-term recall, language, and constructional praxis/visuospatial abilities.

4.5.5.5 Free and Cued Selective Reminding Test–Immediate Recall

The FCSRT–Immediate Recall (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 epidemiologic studies (Grober and Buschke 1987; Sarazin et al. 2007).

Free*, cued,* and total recall are the measures from this assessment. *T*he cueing index can be calculated from these scores. Lower scores imply poorer performance on all aspects of the test.

4.5.5.6 Functional Activities Questionnaire

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

The FAQ is an informant-based assessment that presents a forced choice of four levels of functioning for 10 *i*ADLs. The FAQ total score is calculated by adding together the scores of each item; higher scores indicate worse function (Pfeffer et al. 1982).

4.5.5.7 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 caregiver's distress is rated on a 6-point scale (no distress, minimal, mild, moderate, severe, or extreme or very severe).

4.5.5.8 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 any new instances of suicidality *since the last visit*. The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual or potential lethality. *The* C-SSRS will be collected as indicated in the schedule of activities (see 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.

4.5.5.9 Zarit Caregiver Interview for Alzheimer's Disease

The Zarit Caregiver Interview for Alzheimer's Disease (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 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.

4.5.5.10 Quality of Life–Alzheimer's Disease

The Quality of Life-Alzheimer's Disease (QoL-AD) was developed to assess quality of life (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.

4.5.5.11 EuroQOL 5-Dimension Questionnaire

The EuroQOL 5-Dimension questionnaire (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 5-Level (EQ-5D-5L) proxy Version 1, reported on behalf of the patient, and the EQ-5D-5L patient version provided to caregivers to assess caregiver health status.

4.5.6 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, C-SSRS, *EQ-5D-5L,* FAQ, FCSRT, MMSE, NPI-Q, QoL-AD, and ZCI-AD.

4.5.7 Laboratory, Biomarker, PK and Other Biologic Samples

4.5.7.1 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, ALP, total protein, total bilirubin, serum albumin, CPK, sodium, potassium, calcium, BUN or urea, and serum creatinine (and creatinine clearance calculated by the central laboratory)

- Hematology: hemoglobin, hematocrit, RBC (with morphology), WBC counts, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC (other total counts)
- Coagulation: PT (pre-first infusion)
- Immunophenotyping, including CD4, CD8, CD3, CD19, CD16+56
- Urinalysis will be performed at the site by dipstick for blood, protein, glucose, and pH. Microscopic examination will be 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.

4.5.7.2 Cerebrospinal Fluid Sampling

This section applies for patients who took part in the substudy associated with Study BN29552 or BN29553 and have opted to allow a further CSF sample to be taken during the OLE study. CSF samples will be collected *in the OLE study* at Week 53 *or at the early termination visit if prior to Week 53 and at least 6 months have elapsed since the previous lumbar puncture* (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 from patients.

The samples will be used to study the effect of crenezumab on biomarkers associated with AD; for research purposes to identify biomarkers that may be predictive of response to treatment with crenezumab; to better understand the pathogenesis, course, and outcome of AD and related diseases; and to support the development of biomarker assays for diagnostic use.

CSF samples (i.e., 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). For patients who consent to the optional Research Biosample Repository (RBR), residual biomarker samples may be kept longer for future biomarker research (see Section 4.5.10).

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

4.5.7.3 Plasma Biomarker Sampling

Plasma sampling will be conducted at Week 53 of the OLE study *or at the early termination visit if prior to Week 53* only as detailed in the schedule of activities (see Appendix 1). One whole blood sample will be obtained for plasma extraction from all patients.

This sample will be used to evaluate plasma Aβ levels in peripheral blood as PD markers and to evaluate other exploratory AD biomarkers.

Plasma samples (i.e., 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). For patients who consent to the optional RBR samples, residual biomarker samples may be kept longer for future biomarker research (see Section 4.5.10).

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

4.5.7.4 Amyloid- and Tau-PET Assessments

This section applies for patients who took part in either the amyloid- and/or tau-PET substudies associated with Study BN29552 or BN29553 and have opted to have a further amyloid- and/or tau-PET assessment during the OLE study.

The amyloid- and tau-PET assessments will allow longitudinal evaluation of the effect of crenezumab on cerebral fibrillar amyloid deposition as measured by florbetapir *F 18*-PET in this study population and tau burden as measured by [^{18}F]GTP1 (an investigational radioligand for in vivo imaging of tau protein aggregates).

The PET data collected are expected to help in understanding the effects of crenezumab on amyloid and tau pathology over time as well as the relationship between change in florbetapir *F 18*/[^{18}F]GTP1-PET and change in other endpoints in the Phase III studies and OLE study.

PET Imaging Procedures: For Amyloid-PET and Tau-PET Assessments

The Sponsor in conjunction with the CRO will prepare and distribute a detailed Imaging Manual for image acquisition and reconstruction procedures and parameters for each center prior to the start of the study. All imaging data will be transferred to the imaging CRO for quality control and image analysis as documented in the PET Imaging Charter.

Amyloid-PET Assessments

One further amyloid-PET scan is included in this OLE study. This assessment will be done at Week 53 of the OLE study or at the early termination visit *if prior to Week 53 and* at least 6 months have elapsed since the previous amyloid-PET scan (see Appendix 1) and annual radiation exposure limits as per local guidelines are not exceeded.

The selective amyloid-PET radioligand florbetapir *F 18* must be used for this assessment.

During the DBTP in Study BN29552 or BN29553, substudy patients will have had screening, treatment, and post-treatment imaging studies. With the addition of the amyloid scan during the OLE study, each patient may have received florbetapir *F 18* on four occasions over the course of 3 years (or less in case of early termination).

Detailed methodology, including scanning procedures, is included in the Imaging Manual.

Source of Production of Florbetapir *F 18*

Florbetapir *F 18* will be provided in accordance with approved national and/or local standards.

Warnings and Precautions Associated with Florbetapir *F 18* (AMYVID)

The most commonly reported adverse reactions after injection of florbetapir *F 18* are headache (2%), musculoskeletal pain (1%), fatigue (1%), and nausea (1%).

For more information, see the Amyvid (Florbetapir F 18 Injection) for Intravenous Use U.S. Package Insert or Amyvid Summary of Product Characteristics.

Tau-PET Assessments

The selective tau-PET radioligand [^{18}F]GTP1 will be used in this OLE study as an additional PET assessment to be done at Week 53 or the early termination visit if *prior to Week 53 and* at least 6 months have elapsed since the previous tau-PET scan (see Appendix 1), and annual radiation exposure limits as per local guidelines are not exceeded.

During the DBTPs of Study BN29552 and BN29553, patients received [^{18}F]GTP1 and had tau-PET scans on up to three occasions (at baseline, Week 53, and Week 105 or the early termination visit). With the addition of the tau scan during the OLE study, each patient may have received [^{18}F]GTP1 on four occasions over the course of 3 years (or less in case of early termination).

If occurring in the same visit, [^{18}F]GTP1 PET scans will be performed after administration of clinical scales. [^{18}F]GTP1 PET scans should not be performed on the same day as other PET scans.

Source of Production of [^{18}F]GTP1

[^{18}F]GTP1will be provided under contract with a tau-PET imaging CRO in accordance with approved national and/or local standards.

Warnings and Precautions Associated with [^{18}F]GTP1

[^{18}F]GTP1 is not approved by any health authority, and clinical development is ongoing. The safety plan for participants in this study is based on clinical experience with [^{18}F]GTP1 in *three* completed and *three* ongoing studies, and the safety experience to date is detailed in the [^{18}F]GTP1 Investigator's Brochure.

As of the most recent Investigator's Brochure (Version *5* dated *April* 201*8*) for [^{18}F]GTP1, *23* healthy volunteers*, 96* patients with AD*, and 3 patients with progressive supranuclear palsy have* been exposed to at least one dose of [^{18}F]GTP1, *with* a total of *251 doses across all studies. Two of the patients with AD were enrolled in more than one study.* Available safety data from *ongoing and completed clinical studies* with [^{18}F]GTP1 show that exposure to [^{18}F]GTP1 and imaging procedures *are* generally well tolerated. *As of 1 February 2018, t*here have been no deaths, no adverse events of special interest, *and* no hypersensitivity reactions. *One serious adverse event was reported in Study GN30009: a Grade 3 urinary tract infection, reported in a* [redacted]*-year-old* [redacted] *patient with moderate AD. The serious adverse event was assessed as not related to study drug. One* [redacted]*-year-old* [redacted] *patient with pAD discontinued the study due to a non-serious moderate headache and non-serious cervical neck pain 4 days after a baseline [*^{18}*F]GTP1 PET scan; both events were assessed as not related to study drug.*

More details are provided in the [^{18}F]GTP1 Investigator's Brochure.

Radiation Risk: For Amyloid-PET and Tau-PET

Radioligands, similar to other radiopharmaceuticals, contribute to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk of cancer. Safe handling of radioligands should be ensured to protect patients and health care workers from unintentional radiation exposure.

Radiation exposure for [^{18}F]GTP1 doses can be found in the [^{18}F]GTP1 Investigator's Brochure. For florbetapir *F 18*, see the Amyvid (Florbetapir F 18 Injection) for Intravenous Use U.S. Package Insert or Amyvid Summary of Product Characteristics.

Refer to local guidelines for recommended annual radiation exposure.

4.5.7.5 Immunogenicity Sampling

Blood samples will be collected to assess the possible development of ADAs in all patients as noted in the schedule of activities (see Appendix 1). In addition, in case of anaphylaxis, anaphylactoid, or serious or severe hypersensitivity reactions, an ADA

sample with a concurrent serum PK sample should be collected at the time of the event and at washout (16 weeks) in the case of discontinuation for anaphylaxis. Serum samples will be analyzed for antibodies to crenezumab using a validated 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.

4.5.7.6 Pharmacokinetic Sampling

Serum Crenezumab

Blood samples will be collected to evaluate the pharmacokinetics of crenezumab in serum as noted in the schedule of activities (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 or severe hypersensitivity reactions and at washout (16 weeks) in the case of discontinuation for anaphylaxis.

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

4.5.8 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 activities (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., *weight, pulse rate, systolic and diastolic blood pressure, respiratory rate, oxygen saturation, and body temperature*). 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, respiratory rate interval, QRS interval, pulse rate duration, uncorrected QT interval, and QT interval corrected through use of 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.

4.5.9 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 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 have a CSF sample taken at Week 53 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.

4.5.10 Optional Samples for Research Biosample Repository

4.5.10.1 Overview of the Research Biosample Repository

The RBR is a centrally administered group of facilities used for the long-term storage of human biologic*al* specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR *samples* 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, *for those patients who have previously consented to the RBR in the parent studies BN29552 and BN29553 and consent to RBR in Study BN40031,* all specimens for the RBR will come from retaining the residual sample remaining after the protocol-specified analysis has been performed on protocol-specified mandatory samples. These residual samples will be retained from patients who give specific consent to participate in this optional research.

RBR *samples* 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

4.5.10.2 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 4.5.10) will not be applicable at that site.

4.5.10.3 Sample Collection

In the OLE study, two types of residual sample will be retained by the RBR for identification of dynamic (non-inherited) biomarkers: CSF and plasma.

- 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.

RBR *samples* 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.

4.5.10.4 Confidentiality

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

Patient medical information associated with RBR *samples* 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 *or legally authorized representative*, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses, data derived from RBR *samples* 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 *samples* must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.10.5 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 *consent* will be required to document a patient's agreement to provide optional RBR *samples*. 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 participants who lack the capacity to consent, the patient's legally authorized representative may provide consent, per local requirements.*

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

4.5.10.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR *samples* have the right to withdraw their *consent* at any time for any reason. However, if RBR *samples* have been tested prior to withd*r*awal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her *RBR samples during the study*, the investigator must inform the Medical Monitor in writing of the

patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. *If a* patient *wishes* to withdraw consent *to the testing of his or her RBR samples* after *closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:*

global_rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.10.7 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.

4.5.11 Timing of Visits and Study Assessments

Written informed consent for participation in the OLE study must be obtained before performing any OLE study–specific tests or evaluations *by the patient or legally authorized representative, per local requirements*. 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 assessments as per the schedule of activities (see Appendix 1).

Following *completion of the parent studies* BN29552 or BN29553 *Week 105 assessments* and *review of the* Week 105 MRI results *and OLE screening coagulation blood test results*, the patient*'s eligibility for OLE* can be assessed.

If needed (e.g., for completion of Week 105 visit assessments and/or the OLE study screening coagulation blood test), an unscheduled visit can be done *after consent* and before Week 1, Visit 1 of the OLE study.

If assessed as eligible, patients may receive the first crenezumab infusion on or up to 8 weeks after the parent study Week 105 visit. Visit 1 of the OLE safety assessments

must be done on the day of infusion as indicated on the schedule of activities (see Appendix 1).

4.5.11.1 Study Assessments

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; and blood draws for clinical laboratory assessments, pharmacokinetics, ADA 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 during treatment and at the early termination visit is described in Table 2.

Table 2 Order of Clinical Assessment and Rating Scale Collection

Patient	Caregiver
1. ADAS-Cog13	1. CDR (caregiver input)
2. CDR (patient interview)	2. ADCS-ADL
3. MMSE	3. FAQ
4. FCSRT [a]	4. *EQ-5D-5L*
5. QoL-AD	5. ZCI-AD
6. C-SSRS	6. QoL-AD
	7. NPI-Q

ADAS-Cog-13 = Alzheimer's Disease Activity Scale-Cognition 13; ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living; CDR = Clinical Dementia Rating; C-SSRS = Columbia-Suicide Severity Rating Scale; EQ-5D-*5L*=EuroQoL 5-Dimension*, 5-Level* questionnaire; 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 for Alzheimer's Disease.

[a] *If appropriate per schedule of activities.*

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

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Pregnancy

- Evidence of more than 15 *ARIA-H (*microbleeds and/or areas of leptomeningeal hemosiderosis*)* 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.

All patients who discontinue from the study treatment early will be asked to return at 4 and 16 weeks from the time of the last dose of study treatment for safety assessments. Patients that discontinue before Week 105 will also be asked to return for their next scheduled annual assessment (Week 53 or Week 105). If the next annual follow-up visit (Week 53 or *Week* 105) is expected within 3 months of the 4-week safety visit, the annual and 4-week safety visits can be combined.

4.6.2 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. 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.

4.6.3 Study 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.

4.6.4 Site Discontinuation

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 Council for 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. 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 *16* weeks after the last dose of study drug.

An iDMC will review unblinded safety and efficacy data at regular intervals (see Section 3.2.1 and the iDMC Charter for further details).

5.1.1 ARIA-E and ARIA-H

The occurrence of imaging abnormalities believed to represent ARIA-E has been reported in association with the investigational use of compounds that are intended to treat AD through the reduction of Aβ in the brain. These imaging abnormalities have, in the majority of instances, been asymptomatic, and their presence has been detected by brain MRI (Salloway et al. 2009; Sperling et al. 2011). These MRI signal hyperintensities seen in the parenchyma and leptomeninges are named ARIA-E to cover the MRI 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 mHs in AD have a point prevalence of 23% (Vernooij et al. 2008). One longitudinal study found that in patients with AD the incidence of ≥1 mH after a mean follow-up of 2 years was 12% (Goos et al. 2010). Recently, the occurrence of mH has also been identified as an adverse event in anti-amyloid vaccination trials, and together with superficial siderosis, these events have been termed ARIA-H deposition (Sperling et al. 2011).

Limited data on ARIA-H deposition occurrence are available, but a retrospective analysis in patients with AD who were treated with anti-Aβ antibodies with full effector function reported that 24 of 207 patients (11.6%) developed ARIA-H deposition (Sperling et al. 2012). Acute occurrence of cerebral mH is not always considered clinically significant (Greenberg et al. 2009). Study patients who received bapineuzamab and developed ARIA-H deposition without ARIA-E were clinically asymptomatic (Sperling et al. 2012). However, the clinical significance of cerebral mH is not yet fully understood.

Recent population-based studies have shown that cerebral mHs 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 mHs (Cordonnier and van der Flier 2011) and high numbers of cerebral mHs 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 mHs (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 APOE4 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-Aβ antibodies bind to amyloid deposited around blood vessels, an FcγR–mediated immune response may be elicited. This compromises vascular integrity and results in ARIA-E or ARIA-H deposition. The hypothesis that FcγR–mediated immune response may contribute to the occurrence of ARIA-E and/or ARIA-H deposition is supported by results from clinical studies that have shown that patients with AD who were treated with anti-Aβ antibodies with full effector function developed ARIA-E (symptomatic and asymptomatic) that were dependent on the dose level and related to APOE4 status.

Crenezumab, a human IgG4, has reduced FcγR binding compared with IgG1/IgG2 and, thus, has reduced effector function that theoretically might lower the risk of ARIA-E. 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 ARIA-E has been observed as of 27 May 2016 (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 ARIA-E effusion during the corresponding OLE study.

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

In this Phase III OLE study, a safety monitoring plan has been designed to monitor the potential risk of ARIA-E and ARIA-H deposition. This plan consists of the following key elements:

- Exclusion criteria:

  Evidence of >10 *ARIA-H (*microbleeds and/or areas of leptomeningeal hemosiderosis*)* as assessed by central review of T2* gradient–recalled echo MRI (see Magnetic Resonance Imaging Charter for further details)

- Prior to all MRI evaluations, the patient or 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 MRI (including fluid–attenuated inversion recovery sequence and T2*-weighted gradient-recalled echo sequences) will be performed *at Weeks 13, 25, 53, 105, and yearly thereafter* to detect ARIA-E and ARIA-H deposition.

- All MRI scans will be read in a timely fashion and will evaluate ARIA-E and ARIA-H deposition as well as other abnormalities. Assessments will be made by independent blinded radiologists at a central contract imaging vendor.
- Patients who exhibit new ARIA-E (but do not qualify for treatment discontinuation as defined below) will be rescanned within approximately 4 weeks after the last MRI scan to evaluate the evolution of the findings.

ARIA-E or ARIA-H deposition findings that lead to dose modification or treatment discontinuation and study drug discontinuation rules in specific cases are detailed in Section 5.1.2.

5.1.2 ARIA-Related Dose Adjustments

The following dose adjustments and discontinuation rules for MRI–related findings will apply.

5.1.2.1 ARIA-E

Asymptomatic ARIA-E 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 ARIA-E is stable or decreased, continue study drug and monthly MRI monitoring until event resolves. Once ARIA-E completely resolves, conduct MRI monitoring as per Section 4.5.9.

  If ARIA-E increases (Barkhof Grand Total Score ≥ 4) or symptoms develop, refer to the rule below.

Symptomatic ARIA-E (any size) or ARIA-E with Barkhof Grand Total Score ≥ 4:

- Temporarily interrupt study drug and implement monthly MRI monitoring
- Once symptoms and ARIA-E resolve, reintroduce study drug at the same dose (i.e., 60 mg/kg crenezumab) and perform an MRI after 4 weeks of dosing. If no new ARIA-E is detected, MRI monitoring as per Section 4.5.9.

Any new onset of ARIA-E: Treat the same as the first event on the basis of symptoms and Barkhof Grand Total Score. However, **in the case where a patient is diagnosed with three recurrent, symptomatic ARIA-E events or exacerbations of previous events, permanently discontinue the study drug.** Implement monthly MRI monitoring until resolution of both symptoms and ARIA-E. As per the protocol, maintain the patient in the study until study end and perform assessments as per the schedule of activities.

5.1.2.2 ARIA-H

Dose reduction: Patients who develop >10 ARIA-H cumulatively will receive a lower dose of the study drug. Of note, patients who received a reduced dose of blinded study drug can start the OLE phase with the full dose of 60 mg/kg crenezumab.

Study drug discontinuation: Patients who develop > 15 ARIA-H cumulatively will be permanently discontinued from the study drug.

Cumulative ARIA-H is the sum of ARIA-H at baseline (of Study BN29552 or BN29553) and newly detected ARIA-H during the studies.

The rules in Sections 4.1.2 and 5.1, coupled with frequent MRI monitoring and collection of CNS symptoms, are put in place by the Sponsor to ensure safety while maximizing benefit for patients.

5.1.3 Management of Patients Who Experience Specific Adverse Events

5.1.3.1 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.

5.1.3.2 Amyloid-Related Imaging Abnormalities

To date, there has been limited clinical experience ARIAs with crenezumab; however, data from studies on other MAb treatments reveal that ARIA events tend to occur early after treatment initiation, are dose dependent and APOE4 dependent, are manageable with MRI monitoring, and do not lead to significant adverse outcomes.

All clinical trials with crenezumab include APOE4 genotyping, MRI safety monitoring, and an ARIA-based dose-intervention algorithm.

5.1.4 Additional Safety Monitoring

Laboratory tests, including hematology and chemistry, will be performed throughout the OLE study. ECGs will be recorded regularly (see Section 4.5.8). *Complete* examinations will be performed as required *per the schedule of activities* to assess physical and neurologic events that are not consistent with normal disease progression. *Symptom-directed physical and neurologic examinations may be done at any other visit as needed to assess the safety of the participant.* The C-SSRS will be used for prospective suicidality assessment. Pregnancy testing will be performed at each visit in women of childbearing potential. Samples to assess immunogenicity will be collected throughout the OLE study.

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 Sections 5.2.2 and 5.2.3.

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; see Sections 5.3.5.9 and 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; see Table 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.

5.2.4 Selected Adverse Events

To further elucidate potential clinical implications of ARIA findings, patients will be asked if they experience CNS adverse events up to 1 week before each MRI 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 MRI scans will be collected for the following selected adverse events:

- ARIA-E: ARIAs suggestive of vasogenic edema and sulcal effusions
- ARIA-H deposition: ARIAs suggestive of mH and hemosiderin deposits

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).

After initiation of study drug, all adverse events will be reported until 4 elimination half-lives after the last dose of study drug and collected on the occasion of the safety follow-up visit (16 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 3 provides guidance for assessing adverse event severity.

Table 3 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. Details regarding any increases or decreases in severity will be captured on the Adverse Event Intensity or Grade Changes 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., ALP 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. 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. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed to progression of AD, "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., National Institute on Aging and Alzheimer's Association [NIAAA] New Diagnostic Criteria and Guidelines for AD). 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.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- 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.

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

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-Centered or Observer-Reported Outcome Data

Adverse event reports will not be derived from patient-centered outcome (or observed-reported outcome) data by the Sponsor, and safety analyses will not be performed using patient-centered outcome (or observed-reported outcome) data. Although sites are not expected to review the patient-centered outcome (or observed-reported outcome) data, it is possible that an investigator could become aware of patient-centered outcome (or observed-reported outcome) data that may be indicative of an adverse event. Under these circumstances, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

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 (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

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., M.A.S. (Primary)

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 and Adverse Events of Special Interest

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, only serious adverse events caused by a protocol-mandated intervention should be reported. Investigators should report to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event).

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 paper Clinical Trial 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 *final* dose of study drug. A paper 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 *final* dose of study drug. A paper 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. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should 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, email, 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 16 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 paper Clinical Trial 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
- *PET Ligand Investigator's Brochures*

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 safety analysis population will include all patients who consented to the OLE study, including those who enrolled in the OLE but did not receive open-label treatment. The intent-to-treat (ITT) population includes all patients who consented to the OLE study and received at least one dose of open-label treatment.

Safety will be assessed by monitoring adverse events, clinical laboratory evaluations, clinical assessments such as ECG and vital signs measurements, MRI evaluations and immunogenicity as measured by ADAs. Patients will be analyzed according to actual treatment received. All safety data will be summarized using descriptive statistics.

6.1 DETERMINATION OF SAMPLE SIZE

This study is open to all patients who completed Study BN29552 or BN29553 and who meet the eligibility criteria. Accordingly, the sample size for this study is not based on a formal sample size calculation. The planned number of patients for this OLE study is not expected to exceed 1500 (approximately 750 randomized to crenezumab 60 mg/kg IV and 750 randomized to placebo, that is, the total planned number of patients in *the parent s*tudies BN29552 and BN29553, not including patients from the China extension study). An estimate for the actual number of patients in this OLE study is approximately 925 patients *(not including patients from the China extension study)* based on 1500 patients enrolled in both Phase III studies and an estimated reduction by 35% (i.e., withdrawals from double-blind treatment) and by a further 5% of completers who may not opt to enroll in this OLE study.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, patient disposition, and incidence of protocol deviations will be summarized descriptively for the ITT population.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (such as age, sex, race, disease severity, APOE4 status, and use and non-use of background therapy for AD) will be summarized descriptively for the ITT population.

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 exploratory analyses will include all randomized patients, with patients grouped according to the treatment assigned at randomization until the OLE study.

6.4 SAFETY ANALYSES

The safety analysis population will include all patients who completed the DBTP and received at least one dose of study drug in either Study BN29552 or BN29553 and entered the OLE study. Patients will be grouped according to the treatment actually received until the first visit of the OLE study.

- Incidence, nature, and severity of adverse events
- Incidence, nature, and severity of serious adverse events
- Incidence of adverse events of special interest
- Incidence and nature of MRI safety findings: ARIA-E and ARIA-H
- 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
- 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.

6.5 EFFICACY ANALYSES

All efficacy data during the open-label study will be summarized using descriptive statistics for the ITT population. Observed values and change from the OLE baseline values at each scheduled visit will be summarized.

For all continuous safety parameters, efficacy parameters, and biomarkers, *descriptive statistics for the change from baseline will be generated using* the baseline value for the

OLE study *(*defined as the last value recorded during the DBTP*). Descriptive statistics may also be generated for the change from the DBTP baseline.*

All efforts will be made to minimize missing data. Descriptive summaries of the number of patients with missing data and the timing and reasons for discontinuation from study will also be provided. Additional details will be documented in the SAP.

6.5.1 Exploratory Efficacy Endpoints

The absolute change from baseline in the continuous exploratory 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 summarized using descriptive statistics. Additional exploratory analysis of selected endpoints may also be performed using an MMRM analysis model similar to that described *in the following section* for the *change from baseline in CDR-SB*.

For time-to-event endpoints, the Kaplan-Meier method will be used to estimate the median time to event for each treatment arm. The Cox proportional hazard model stratified by the randomization stratification factors will be used to estimate the hazard ratio and its 95% CI.

6.5.2 Exploratory Efficacy Analyses

An analysis of the change from baseline in CDR-SB values recorded during the DBTP in Studies BN29552 and BN29553 and at specified timepoints of the OLE study will be performed. In this case, a mixed-effect model for repeated measures (MMRM) will be used to compare the change from the double-blind baseline at OLE timepoints, relative to the change from the double-blind baseline to the end of double-blind treatment. This analysis will compare the patients randomized to placebo during the DBTP (delayed start patients) with those randomized to crenezumab during the DBTP (early start patients). This analysis will be performed using all data from the ITT populations of Studies BN29552 and BN29553 as well as the ITT population from the OLE study. Details of this analysis will be specified in the SAP.

The effect of randomization stratification factors (dementia status [pAD vs. mAD], patient APOE4 status [presence or absence of ε4 allele], background medication at baseline [present, absent], and geographic region) may be explored by adding each of these covariates to *this* MMRM model.

Subgroup analysis of efficacy results will also be performed for subgroups defined by age, sex, race, dementia status (pAD vs. mAD), APOE4 status, geographic region, use and non-use of background therapies for AD, and other clinically relevant factors at baseline.

6.5.3 Exploratory 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 concentration data for crenezumab and the ratio between CSF and serum crenezumab will be tabulated and summarized as appropriate for the patients who participated in the CSF substudy.

Additional PK analyses will be conducted as appropriate.

6.5.4 Exploratory Biomarker Analyses

An analysis will be performed to explore association of the treatment effect with patient genotypes to assess the influence of the APOE4 status, [redacted] on the crenezumab treatment effect, the primary efficacy variable, and selected safety parameters and summarized by each of the genotypes.

Exploratory analyses of the relationship between crenezumab exposure and biomarker (imaging, plasma pharmacodynamics, or CSF pharmacodynamics), efficacy, or safety measures will be performed as appropriate. The results of these analyses may be reported separately from the Clinical Study Report.

6.6 CHINA SUBPOPULATION ANALYSIS

Following completion of the global enrollment phase *of Study BN29553*, additional patients *will continue to* be enrolled in a China extension phase *(i.e., China extension to the main Phase III study BN29553)* to ensure *a total enrollment sufficient to support registration in the People's Republic of China. This* China subpopulation *may* include patients enrolled at sites in China during both the global enrollment phase and the China extension phase *and could be included in this OLE, if applicable*.

The objective of the China extension phase and the China subpopulation analyses is to assess the long-term treatment effects of crenezumab in a population of patients in the People's Republic of China and to investigate the consistency in treatment effects between the China subpopulation and the global population for the purpose of registration in the People's Republic of 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.

6.7 INTERIM ANALYSIS

No formal interim analysis of the efficacy results is planned for the OLE study. In the event that an interim efficacy analysis is performed prior to the primary analysis, it will be described in the SAP and will include specifications for adjustment of the Type I error level at the time of the primary analysis.

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 that must be kept with the study records. Acknowledgement of receipt of the *data* is required.

7.3 ELECTRONIC PATIENT AND CLINICIAN REPORTED OUTCOME DATA

An electronic device *will be used* to capture PRO and clinically reported outcome data. 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 data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure method. Only identified and trained users may view the data, and their actions will 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.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review 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 7.6.

To facilitate source data verification and review, 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.

7.5 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.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper 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.

Roche will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

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 Application (IND) 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 Home Nursing Informed Consent Form) 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 *or legally authorized representative*, 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 exploratory biomarker analyses, data derived from these analyses 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 (see definition of end of study in Section 3.3).

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, ICFs, 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. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' 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 4.3.3). 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:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.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).

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Appendix 1
Schedule of Activities: Open-Label Extension Study

Assessment/ Procedure		Open-Label Extension							Follow-Up for Pts Discontinuing OLE Treatment			Follow-Up for Pts Completing OLE Treatment [a]	
	OLE Scrn. [b]	Visit 1 OLE Wk 1 [c]	OLE Wk 5 and Every 4 Wks thereafter (±7 days) [c]	Visit 4 OLE Wk 13 (±7 days) [c,d]	OLE Wk 25 (±7 days) [c,d]	OLE Wk 53 (±7 days) [c,d]	OLE Wk 77 (±7 days) [c,d]	OLE Wk 105 and Every 52 Wks thereafter (±7 days) [c,d]	Last Dose in OLE +4 Wks (or ET)	Last Dose in OLE +16 Wks	Final Annual Visit for OLE Discon. before Wk 53/105 [e]	Last Dose in OLE +4 Wks	Last Dose in OLE +16 Wks
Informed consent for OLE	x												
Review of OLE eligibility criteria	x												
Coagulation blood test	x [f]												
Vital signs [g]		x	x	x	x	x	x	x	x	x	x	x	x
Urinalysis [h]					x	x	x	x	x	x		x	x
Urine pregnancy test [i]		x	x	x	x	x	x	x	x			x	
PK serum sample [j]		x		*x* [k]	x [k]	x		x	x	x		x	x
Immunogenicity sample [l]		x		*x*	x	x		x	x	x		x	x
Amyloid-PET/tau-PET/CSF [m, n]						x [n]			*x* [n]				
PD plasma sample [j, n]						x [n]			*x* [n]				
12-Lead ECG [o]					x	x		x	x			x	

Appendix 1
Schedule of Activities: Open-Label Extension Study (cont.)

Assessment/ Procedure		Open-Label Extension							Follow-Up for Pts Discontinuing OLE Treatment			Follow-Up for Pts Completing OLE Treatment [a]	
	OLE Scrn. [b]	Visit 1 OLE Wk 1 [c]	OLE Wk 5 and Every 4 Wks thereafter (±7 days) [c]	Visit 4 OLE Wk 13 (±7 days) [c,d]	OLE Wk 25 (±7 days) [c,d]	OLE Wk 53 (±7 days) [c,d]	OLE Wk 77 (±7 days) [c,d]	OLE Wk 105 and Every 52 Wks thereafter (±7 days) [c,d]	Last Dose in OLE +4 Wks (or ET)	Last Dose in OLE +16 Wks	Final Annual Visit for OLE Discon. before Wk 53/105 [e]	Last Dose in OLE +4 Wks	Last Dose in OLE +16 Wks
Physical and neurologic exams [p]						x		x	x			x	
Serum chemistry and hematology [q, r]					x	x	x	x	x			x	
MRI [s]				x	x	x		x	x			x	
CDR					x	x	x	x	x		x	x	
ADAS-Cog-13					x	x	x	x	x		x	x	
ADCS-ADL/FAQ [t]					x	x	x	x	x		x	x	
MMSE					x	x	x	x	x		x	x	
NPI-Q					x	x	x	x	x		x	x	
FCSRT-IR						x		x	x		x	x	
EQ-5D-5L					x	x	x	x	x		x	x	
QoL-AD					x	x	x	x	x		x	x	
ZCI-AD					x	x	x	x	x		x	x	
C-SSRS SLV					x	x	x	x	x			x	

Appendix 1
Schedule of Activities: Open-Label Extension Study (cont.)

Assessment/ Procedure		Open-Label Extension							Follow-Up for Pts Discontinuing OLE Treatment			Follow-Up for Pts Completing OLE Treatment [a]	
	OLE Scrn. [b]	Visit 1 OLE Wk 1 [c]	OLE Wk 5 and Every 4 Wks thereafter (±7 days) [c]	Visit 4 OLE Wk 13 (±7 days) [c,d]	OLE Wk 25 (±7 days) [c,d]	OLE Wk 53 (±7 days) [c,d]	OLE Wk 77 (±7 days) [c,d]	OLE Wk 105 and Every 52 Wks thereafter (±7 days) [c,d]	Last Dose in OLE +4 Wks (or ET)	Last Dose in OLE +16 Wks	Final Annual Visit for OLE Discon. before Wk 53/105 [e]	Last Dose in OLE +4 Wks	Last Dose in OLE +16 Wks
Concomitant medications		x	x	x	x	x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x	x	x [u]	x	x
Study drug administration [c]		x	x	x	x	x	x	x					

ADA=anti-drug antibody; ADAS-Cog13=Alzheimer's Disease Activity Scale Cognition 13; ADCS-ADL=Alzheimer's Disease Cooperative Study–Activities of Daily Living; CDR=Clinical Dementia Rating; CSF=cerebrospinal fluid; C-SSRS=Columbia Suicide Severity Rating Scale; DBTP=Double-Blind Treatment Period; *Discon.=Discontinuation;* eCRF=electronic Case Report Form; EQ-5D-*5L*= EuroQOL 5-Dimension*, 5-Level* questionnaire; 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; PD=pharmacodynamic; PET=positron emission tomography; PK=pharmacokinetic; Pts=patients; QOL-AD=Quality of Life–Alzheimer's Disease; *Scrn. =screening;* 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. For patients who terminate early, assessments listed in the visit "Last Dose in OLE +4 weeks [or ET visit]" should be completed.

[a] Patients who continue treatment with crenezumab after completing of the study will not have any follow-up visits.

[b] Assessments performed at Week 105 of *the parent studies* BN29552 and BN29553 will be used as screening assessments for the OLE study *as well as* an OLE protocol-specific pre-infusion coagulation assessment *(which can be done any time after consent)*. If needed to complete assessments for OLE eligibility, an extra unscheduled visit can be done after *consent and* before Week 1, Visit 1 of the OLE.

[c] Study drug administration should be performed only after all assessments/rating scales have been completed (unless indicated otherwise). Study drug will be administered to patients by infusion (full details in the pharmacy manual). Patients must 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. There should be a telephone call to the patient following the first infusion.

[d] 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.

[e] A final annual assessment (Week 53 or Week 105) will be obtained for patients who discontinue study treatment prior to Week 105. If the next annual visit (Week 53 or Week 105) is expected within 3 months of the discontinuation, the final annual visit may be combined with the 4-week postdose safety visit.

[f] The coagulation test can be done *as soon as* the OLE main Informed Consent Form has been signed.

[g] 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. Pulse 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 vital signs should be recorded in the eCRF.

[h] Urinalysis will be performed at the site by dipstick for blood, protein, glucose, and pH. Microscopic examination should be 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.

[i] 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.

[j] Predose PK samples and plasma pharmacodynamics should be obtained prior to study drug administration on the same day of dosing. Accurate recording of the time of study drug administration and pharmacokinetics is critical. Unscheduled PK samples should be taken in the event of anaphylaxis, anaphylactoid, or serious or severe hypersensitivity reactions. For any patient suspected of developing anaphylaxis, or anaphylactoid or serious or severe hypersensitivity reactions warranting discontinuation of dosing, collect a wash-out ADA sample (16 weeks postdose) and concurrent PK sample.

[k] An additional PK sample should be collected 60–90 minutes after end of infusion.

[l] Immunogenicity samples should be obtained prior to study drug administration on the same day of dosing; samples should be 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 or severe hypersensitivity reactions at the time of the event. For any patient suspected of developing anaphylaxis, or anaphylactoid or serious or severe hypersensitivity reactions warranting discontinuation of dosing, collect a wash-out ADA sample (16 weeks postdose) and concurrent PK sample.

[m] CSF PK and biomarker samples, amyloid-PET, and tau-PET should be taken for patients who were in the respective longitudinal substudies of Studies BN29552 or BN29553 and have *consented to additional sampling in the OLE*. Florbetapir *F 18* must be used for the amyloid-PET assessment. The same scanner should be used as used in the substudy associated with Study BN29552 or BN29553. Any scanner changes must be approved by the Sponsor. See Section 4.5.7 for details of sampling. CSF samples should be collected prior to dosing at the same day of dosing or the day prior to dosing. It is critical that the actual date and the time of sample collection is recorded.

[n] *Plasma PD, CSF, and/or PET assessment to be performed at Week 53.* In the event that a patient terminates participation in the study *prior to the Week 53 visit, the* assessment should be *performed at the early termination visit. CSF and/or PET assessments will not be performed at early termination if less than 6 months have elapsed since the previous CSF and/or PET assessment.*

[o] 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 *other assessments (e.g., weight, pulse rate, systolic and diastolic blood pressure, respiratory rate, oxygen saturation, and body temperature).*

[p] *Complete physical and neurologic examinations should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Neurologic examinations should include assessment of mental status, level of consciousness, cranial nerve function (including fundoscopic examination), motor function, sensory function, reflexes, coordination, and assessment of gait. Other examination components or systems may be assessed as clinically indicated. Symptom-directed physical and neurologic examinations may be done at any other visit as needed to assess the safety of the participant.*

[q] Serum chemistry includes AST, ALT, ALP, total protein, total bilirubin, serum albumin, CPK, sodium, potassium, calcium, BUN or urea, and serum creatinine (and creatinine clearance calculated by the central laboratory).

[r] Hematology includes hemoglobin, hematocrit, RBC (with morphology), WBC counts, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC (other total counts). In the event *of* pneumonia, immunophenotyping analysis of peripheral blood cells should be done.

[s] MRI*s* should be done at Weeks 13, 25, 53*, 105, and yearly thereafter*. MRI central read results must be available for review by site staff before dosing can proceed. The patient will be called in advance of the MRI to check for any CNS-*related* symptoms.

[t] FAQ for *caregivers of* patients from Study BN29553.

[u] Only study-related serious adverse events will be collected (see also Section 5.6).