Official Title: **A MULTICENTER, OPEN-LABEL, LONG-TERM SAFETY EXTENSION OF PHASE II STUDIES ABE4869g AND ABE4955g IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE**

NCT Number: NCT01723826

Document Date: Protocol Version 6: 22-November-2014

PROTOCOL

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PROTOCOL NUMBER:	GN28525
VERSION NUMBER:	6
EUDRACT NUMBER:	2012-003242-33
IND NUMBER:	IND 100,839
TEST PRODUCT:	Crenezumab (RO5490245)
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	Genentech, Inc.
DATE FINAL:	Version 1: 13 July 2012
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PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	22-Nov-2014 17:45:31

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A MULTICENTER, OPEN-LABEL, LONG-TERM SAFETY EXTENSION OF PHASE II STUDIES ABE4869g AND ABE4955g IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE**
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I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please return a copy of this form to the contract research organization's representative. Please retain the original for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A MULTICENTER, OPEN-LABEL, LONG-TERM SAFETY EXTENSION OF PHASE II STUDIES ABE4869g AND ABE4955g IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE**
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IND NUMBER:	IND 100,839
TEST PRODUCT:	Crenezumab (RO5490245)
PHASE:	II
INDICATION:	Alzheimer's Disease
SPONSOR:	Genentech, Inc.

Objectives

Primary Objective

The primary objective for this study is as follows:

- To assess the long-term safety and tolerability of crenezumab administered subcutaneously every 2 weeks (q2w) or intravenously every 4 weeks (q4w), in eligible patients with Alzheimer's disease who participated in Study ABE4869g or ABE4955g and completed the Week 73 study visit, including brain magnetic resonance imaging (MRI)

Efficacy Objectives

There are no efficacy objectives for this study, although select efficacy outcome measures will continue to be collected.

Safety Objectives

The safety objective for this study is as follows:

- To evaluate the safety and tolerability of crenezumab in patients with Alzheimer's disease focusing on treatment-emergent adverse events, vital signs, routine laboratory analysis, immunogenicity, and cerebral imaging abnormalities (assessed by MRI)

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To evaluate the long-term effect of crenezumab on disease progression using the Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog [12-item])
- To evaluate the long-term effect of crenezumab on disease progression using Clinical Dementia Rating, Sum of Boxes (CDR-SOB)
- To evaluate the long-term effect of crenezumab on patient functioning using the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL)
- To evaluate the long-term effect of crenezumab on disease progression using supplemental neurocognitive measures (i.e., Exploratory Neurocognitive Test Panel [ENTP]) selected to assess episodic memory performance, executive functions, verbal fluency, working memory, and psychomotor speed
- To evaluate the long-term effect of crenezumab on behavior using the Neuropsychiatric Inventory (NPI)

- To evaluate the long-term effects of crenezumab on the amount of assistance patients with dementia require in performing daily activities using the Dependence Scale
- To evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of crenezumab
- To evaluate the PK/PD relationship of crenezumab using exploratory PD biomarkers
- To evaluate changes in MRI biomarkers, such as global and regional brain volumes and functional connectivity

Study Design

Description of Study

Study GN28525 is a Phase II, open-label extension (OLE), multicenter study to evaluate the long-term safety and tolerability of crenezumab in patients with mild-to-moderate Alzheimer's disease who have participated in and completed the treatment period of the Phase II Study ABE4869g or ABE4955g. Patients from Studies ABE4869g and ABE4955g who discontinued from study treatment early but remained on study for safety evaluations, or discontinued prior to completion of the Week 73 study visit, are not eligible for this OLE study.

ABE4869g (ABBY) is a completed Phase II, multicenter, global, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the safety and efficacy of crenezumab in patients with mild-to-moderate Alzheimer's disease. Four hundred forty-six patients were randomized and 444 patients were dosed at approximately 100 sites in North America and Europe.

ABE4955g (BLAZE) is a completed Phase II, multicenter, global, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the effects of crenezumab on brain amyloid burden, as assessed by florbetapir- positron emission tomography (PET), and other biomarkers in patients with mild-to-moderate Alzheimer's disease. Ninety-one patients were randomized and 61 were dosed at approximately 30 sites in North America and Europe.

This OLE study includes patients who have been diagnosed with Alzheimer's disease and have a Mini-Mental State Examination (MMSE) score of 10 or more at the time of screening, which is lower than in Studies ABE4869g and ABE4955g (MMSE 18 – 26) to account for the disease progression in the course of these studies. An MMSE score of less than 10 at the beginning of the OLE study would substantially increase the risk that a patient would not be able to complete the study assessments and to comply with the protocol's requirements in the future.

Patients will undergo a neuroradiological evaluation using a standard MRI protocol and T2* gradient echo MRI to exclude any significant MRI abnormality and presence of cerebral superficial siderosis or more than eight cerebral microhemorrhages. Only patients with 4 or less cerebral microhemorrhages at screening are allowed to participate in Studies ABE4869g and ABE4955g and study drug will be discontinued in patients with an increase of six or more in the number of asymptomatic microhemorrhages in these studies since high numbers of cerebral microhemorrhages have been associated with future risk of ischemic and hemorrhagic strokes. The microhemorrhage threshold for entry in this study is intended to minimize potential safety risks associated with microhemorrhages, but would not preclude the majority of the patients from Study ABE4869g or ABE4955g from rolling over into this OLE study. However, this might exclude patients from participating in the OLE study due to the number of cerebral microhemorrhages that would not have led to treatment discontinuation in the Study ABE4869g or ABE4955g. Patients with medical or psychiatric contraindication or clinically significant abnormalities that, in the investigator's judgment, would substantially increase the risk associated with the patient's participation in the study or interfere with the evaluation of the patient's response will not be included in the study.

All patients enrolled in the OLE study were to receive active drug at the same dosing frequency, dose level, and route of administration they were assigned to after the Week 73 visit of Study ABE4869g or ABE4955g. Patients who received matching placebo in Study ABE4869g or ABE4955g were to receive active drug (i.e., crenezumab 300 mg subcutaneously [SC] q2w for patients who were randomized in the SC cohort [Part 1] or 15 mg/kg IV q4w for patients who were randomized in the intravenous [IV] cohort [Part 2]). However, evaluation of efficacy in ABE4869g and ABE4955g indicates that there was no consistent treatment effect in patients who received 300 mg q2w SC that would support continuation of this dose level. In contrast,

there appears to be a trend towards reduction in cognitive decline in patients who received 15 mg/kg q4w IV. Considering these efficacy results and the available safety information, all patients in the OLE study will be dosed at 15 mg/kg q4w IV. All patients who have been receiving active drug in the SC dosing arm will be transferred into the IV dosing arm.

The study consists of three periods: a screening period (up to 14 days), the window between the last dose in ABBY/BLAZE and the first dose in OLE may last 6 weeks, but may be prolonged on a case by case basis for relevant clinical, administrative, or operational reasons (these reasons must be discussed with the medical monitor in advance of screening; if necessary, some screening procedures may need to be repeated); period *of 144 weeks (Week 1 [Day 1] to Week 145*), and a*n 8-week safety* follow-up period (*Weeks 145 to 153*). The final safety analysis will be performed at *153* weeks. *The original GN28525 protocol included a treatment period of 92 weeks (Week 1 [Day 1] to Week 93). Version 6 of the GN28525 protocol expands this treatment period by 52 weeks (13 additional IV doses from Week 97 to Week 145). Patients who are still enrolled in Study GN28525 may enter the additional OLE treatment period (Week 97 to Week 145) if they have not discontinued treatment for safety reasons. Patients who have already completed or discontinued from Study GN28525 are not eligible to receive additional treatment from Week 97 to Week 145.*

The Week 73 assessment (including MRI) of Studies ABE4869g and ABE4955g will be used to determine the patient's eligibility in this OLE trial. Data from the Week 73 visit assessments in Studies ABE4869g and ABE4955g will be extracted and incorporated in the OLE screening datasets. Patients participating in this OLE study must be enrolled (i.e., Day 1 of the OLE treatment period) no later than 14 days after completion of the Week 73 assessments (including MRI) of Study ABE4869g or ABE4955g, except for individual exceptions, determined on a case by case basis, as mentioned above.

The first dose of crenezumab is administered on Day 1 of the treatment period, and the last dose of treatment is at Week *145*. After patients complete the *144-week* treatment period, they will enter the follow-up period. Patients who are prematurely discontinued from the OLE study treatment will also discontinue from the OLE study and will be followed for safety for *8* weeks after their last dose of crenezumab.

Patients will remain blinded to their assignment in Study ABE4869g or ABE4955g, and investigators are not permitted to provide treatment assignment in ABE4869g or ABE4955g until permitted by the Sponsor.

Number of Patients

This study is open to all patients who completed Study ABE4869g or ABE4955g and who met the eligibility criteria. Four hundred forty-six patients were randomized, and 444 patients were dosed in Study ABE4869g at approximately100 sites in North America and Europe. Ninety-one patients were randomized, and 61 were dosed in Study ABE4955g at approximately 30 sites in North America and Europe.

Target Population

Patients who completed the Week 73 visit of Study ABE4869g or ABE4955g are eligible to participate in this OLE study; patients discontinued from study treatment or discontinued from study prior to completion of the Week 73 visit, will not be eligible for this OLE study.

Patients must meet the following criteria for study entry:

- Ability to provide written informed consent by the patient or the patient's authorized representative under applicable local law
- Ability and willingness of the patient to comply with the protocol's requirements
- Previous participation in Study ABE4869g or ABE4955g and completion of the Week 73 visit
  - Patients who discontinued from study treatment or from the study prior to completion of the Week 73 visit are not eligible.
- Adequate visual and auditory acuity, in the investigator's judgment, to allow for neuropsychological testing
- Availability of a person ("caregiver") who can provide information on activities of daily living and behavior in order to complete the study-specific assessments

  - This caregiver must have sufficient cognitive capacity, in the judgment of the investigator, to accurately report upon the patient's function and behavior. In addition, the caregiver must spend sufficient time with the patient to be familiar with the overall function and behavior of the patient. As guidance, a caregiver would ordinarily need to spend an average of at least 8 hours per week with the patient in order for the caregiver to meet the requirements for this study.
- Diagnosis of probable Alzheimer's disease according to the National Institute on Neurological and Communication Disease and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria
- MMSE score of 10 or more at screening
- For male patients with partners with reproductive potential, agreement to use a reliable means of contraception (e.g., condoms) during the study *and for at least 8 weeks following the last dose of study drug*
- For female patients, a negative urine dipstick pregnancy test at screening (not required if patient has undergone documented surgical sterilization or have not experienced menstruation for at least 12 consecutive months)

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

General

- Early treatment and/or study discontinuation prior to completion of the Week 73 visit of Genentech Study ABE4869g or ABE4955g
- *Early discontinuation from the treatment schedule of a prior version of Study GN28525 for safety reasons. If treatment discontinuation occurred for safety reasons, patients may not re-start dosing on extended treatment schedules offered in amendments to Study GN28525.*
- Inability to tolerate MRI procedures or contraindication to MRI, including but not limited to pacemakers; implantable cardioverter defibrillators; cochlear implants; cerebral aneurysm clips; implanted infusion pumps; implanted nerve stimulators; metallic splinters in the eye; other magnetic, electronic, or mechanical implants; or any other clinical history or examination finding that, in the judgment of the investigator, would pose a potential hazard in combination with MRI
- Female patient with reproductive potential: Female patients must either have undergone documented surgical sterilization or have not experienced menstruation for at least 12 consecutive months.
- Severe or unstable medical condition that, in the opinion of the investigator or Sponsor, would interfere with the patient's ability to complete the study assessments or would require the equivalent of institutional or hospital care

Related to Medical History/Conditions

- History or presence of clinically evident vascular disease potentially affecting the brain (e.g., stroke, clinically significant carotid or vertebral stenosis or plaque, aortic aneurysm, intracranial aneurysm, cerebral hemorrhage, arteriovenous malformation)
- History of severe, clinically significant (persistent neurologic deficit or structural brain damage) central nervous system trauma (e.g., cerebral contusion)
- History or presence of clinically relevant intracranial tumor (e.g., meningioma, glioma)
- Presence of infections that affect the brain function or history of infections that resulted in neurologic sequelae (e.g., syphilis, neuroborreliosis, viral or bacterial meningitis/encephalitis, HIV encephalopathy)
- History or presence of systemic autoimmune disorders potentially causing progressive neurologic disease (e.g., multiple sclerosis, lupus erythematosus, anti-phospholipid antibody syndrome, Behçet disease)

- History or presence of a neurologic disease other than Alzheimer's disease that may affect cognition, including but not limited to Parkinson's disease, corticobasal degeneration, dementia with Lewy bodies, Creutzfeldt–Jakob disease, progressive supranuclear palsy, frontotemporal degeneration, Huntington's disease, normal pressure hydrocephalus, and hypoxia
- Patients with severe or unstable medical conditions (including Alzheimer's Disease) that, in the opinion of the investigator or Sponsor, would interfere with the patient's ability to complete the study assessments, pose an unacceptable risk, or would require the equivalent of institutional or hospital care
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins
- Evidence of malignancies (except squamous cell cancer or basal cell cancer of the skin), acute infections, renal failure that requires dialysis, or other unstable medical disease not related to Alzheimer's disease that, in the investigator's opinion, would preclude patient participation
  - Cancer that is not being actively treated with anti-cancer therapy or radiotherapy as well as cancers that are considered to have low probability of recurrence (with supporting documentation from the treating oncologist if possible) are allowed
- History or presence of atrial fibrillation that, in the investigator's judgment, poses a risk for future stroke
- Chronic kidney disease of Stage ≥ 4, according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines for chronic kidney disease (CKD)
- Impaired hepatic function, as indicated by transaminases > 2 times the upper limit of normal (ULN) or abnormalities in synthetic function tests judged by the investigator to be clinically significant
- Impaired coagulation (aPTT $> 1.2 \times$ ULN)
- Platelet count $< 100{,}000/\mu L$

Related to MRI Imaging

- Presence $at\ screening$ of superficial siderosis of central nervous system, more than eight cerebral microhemorrhages, or evidence of a prior cerebral macrohemorrhage as assessed by T2*-weighted gradient echo (GRE) MRI
- Presence $at\ screening$ of any other significant cerebral abnormalities, including amyloid-related imaging abnormalities (ARIA-E), as assessed by MRI

Related to Medication

- Treatment with anticoagulation medications (e.g., heparin, warfarin, thrombin inhibitors, Factor Xa inhibitors) within 2 weeks prior to enrollment
  - Clopidogrel, dipyridamole, and aspirin are permitted.
- Treatment with anticholinergic antidepressants, typical antipsychotics, or barbiturates, within 2 weeks prior to enrollment.
  - All other antidepressants and atypical antipsychotics are allowed with certain restrictions.
- Chronic use of opiates, opioids, or benzodiazepines
  - Intermittent short-term use is allowed except within 5 half-lives prior to any neurocognitive assessment.
- Any biologic therapy within 75 weeks prior to enrollment
  - Crenezumab and routinely recommended vaccinations are allowed.
- Any investigational agent (other than crenezumab) within 75 weeks prior to enrollment

- Treatment with anticholinergic antidepressants, typical antipsychotics, barbiturates, or narcotics within 5 half-lives or 3 months prior to screening, whichever is longer
  - All other antidepressants and atypical antipsychotics are allowed. Chronic use of benzodiazepines is not allowed; however, the intermittent use of benzodiazepines is allowed, except within 2 days prior to any neurocognitive assessment.

Length of Study

The study consists of three periods: a screening period (up to 14 days), the window between the last dose in ABBY/BLAZE and the first dose in OLE may last 6 weeks, but may be prolonged on a case by case basis for relevant clinical, administrative, or operational reasons (these reasons must be discussed with the medical monitor in advance of screening; if necessary, some screening procedures may need to be repeated); a treatment period *of 144 weeks (Week 1 [Day 1] to Week 145*), and a*n 8-week safety* follow-up period (*Weeks 145 to 153*). The final safety analysis will be performed at *153* weeks.

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date on which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. LPLV is expected to occur *153* weeks after the last patient is enrolled.

Efficacy Outcome Measures

There are no efficacy outcome measures for this study.

Primary Outcome Measures

Safety and tolerability will be assessed through regular neurologic and physical examinations and MRI assessments. In addition, the following information will be collected and analyzed:

- Frequency of adverse events during the treatment period
- Nature and severity of adverse events during the treatment period
- Changes in vital signs and physical and neurological findings
- Changes in clinical laboratory test results including routine hematology, chemistry, coagulation, and urinalysis
- Incidence of human anti-therapeutic antibody (ATA) formation
- Incidence of ARIA-E and amyloid-related imaging abnormalities-hemorrhage (ARIA-H)

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Change in ADAS-Cog (12-item) score from baseline to Week *153*
- Change in CDR-SOB score from baseline to Week *153*
- Change in Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) score from baseline to Week *153*
- Change in the following ENTP scores from baseline to Week *153*:
  - Free and Cued Selective Reminding Test (FCSRT)
  - Trail-Making Test (TMT)
  - Digit Span Test (DST)
  - Digit Symbol Substitution Test (DSST)
  - Letter Fluency Test (LFT)
  - Category Fluency Test (CFT)
- Change in NPI score from baseline to Week *153*
- Change in NPI Caregiver Distress Scale score from baseline to Week *153*
- Change in Dependence Scale total score from baseline to Week *153*

- Changes in MRI biomarkers, such as global and regional brain volume*s,* from baseline to Week *153*
- Serum crenezumab concentration at protocol-specified time points; PK parameters including trough serum concentrations at steady state ($C_{trough, ss}$) will be explored, as applicable
- Plasma Abeta1-40 and Abeta1-42 concentrations

Investigational Medicinal Products

Test Product

All patients enrolled in the OLE study will receive active drug at 15 mg/kg IV q4w. Patients who received placebo in Study ABE4869g or ABE4955g will also receive active drug (i.e., crenezumab 15 mg/kg IV q4w).

Comparator

Not applicable.

Statistical Methods

Primary Analysis

The safety analyses will include all enrolled patients who received at least one dose of study drug in this OLE study following their completion of Study ABE4869g or ABE4955g.

These patients will be grouped based on treatment assignment in the OLE study and Study ABE4869g or ABE4955g. Primary safety analysis will be performed after enrolled patients have completed Week *153* visit of the OLE study.

Safety will be assessed by monitoring adverse events, clinical laboratory evaluations, MRI evaluations, and immunogenicity as measured by ATAs. Patients will be analyzed according to actual treatment received.

Determination of Sample Size

This study is open to all patients who completed Study ABE4869g or ABE4955g and who met the eligibility criteria. Accordingly, the sample size for this study is not based on a formal sample size calculation.

Interim Analyses

No interim analysis is planned for this study.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
Abeta	accumulation of extracellular β-amyloid
AChE	acetylcholinesterase
ADAD	autosomal dominant Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale Cognitive Subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory
AESI	adverse event of special interest
ARIA-E	amyloid-related imaging abnormalities (vasogenic edema and sulcal effusions)
ATA	anti-therapeutic antibody
APP	amyloid precursor protein
aPTT	activated partial thromboplastin time
ARIA-E	amyloid-related imaging abnormalities-edema/effusions
ARIA-H	amyloid-related imaging abnormalities-hemorrhage
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	Beta human chorionic gonadotropin
BUN	blood urea nitrogen
CAA	cerebral amyloid angiopathy
CCQ	Caregiver Characterization Questionnaire
CDR	Clinical Dementia Rating
CDR-SOB	Clinical Dementia Rating, Sum of Boxes
CFT	Category Fluency Test
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
$C_{trough, ss}$	trough serum concentration at steady state
DSST	Digit Symbol Substitution Test
DST	Digit Span Test
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ENTP	Exploratory Neurocognitive Test Panel

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS (CONT'D)

Abbreviation	Definition
ePRO	electronic patient-reported outcome
FCSRT	Free and Cued Selective Reminding Test
FDA	Food and Drug Administration
FLAIR	fluid-attenuated inversion recovery
GRE	gradient echo
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug (application)
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous(ly)
IxRS	interactive voice or web-based response system
LFT	Letter Fluency Test
LPLV	last patient, last visit
LRTI	lower respiratory tract infection
MB	microbleeds
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NINCDS-ADRADA	National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association
NKF KDOQI	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
NPI	Neuropsychiatric Inventory
OLE	open-label extension
PD	pharmacodynamic
PET	positron emission tomography
PK	pharmacokinetic
PT	preferred term
q2w	every 2 weeks
q4w	every 4 weeks
RPCP	randomized placebo-controlled portion
RBC	red blood cell
SC	subcutaneous(ly)
SRI	safety run-in
TE	echo time
TLRTI	total lower respiratory tract infections

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS (CONT'D)

Abbreviation	Definition
TMT	Trail-Making Test
ULN	upper limit of normal
U.S.	United States
WBC	white blood cell

1. BACKGROUND

1.1 BACKGROUND ON ALZHEIMER'S DISEASE

Alzheimer's disease is the most common cause of dementia, affecting an estimated 4.5 million individuals in the United States and 26.6 million worldwide (Hebert et al. 2003; Brookmeyer et al. 2007). The disease is characterized pathologically by the accumulation of extracellular β-amyloid (Abeta) plaques and intracellular neurofibrillary tangles in the brain. Diagnosis is made through the clinical assessment of the neurologic and neuropsychiatric signs and symptoms of Alzheimer's disease and the exclusion of other causes of dementia. Alzheimer's disease is commonly classified into mild, moderate, and severe stages by a brief cognitive screening examination, the Mini-Mental State Examination (MMSE; Folstein et al. 1975). Approved medical therapies that inhibit acetylcholinesterase (AChE) activity or antagonize *N*-methyl-d-aspartate receptors in the brain may temporarily improve the symptoms of Alzheimer's disease in some patients but do not modify the progression of the disease (Cummings 2004).

Genetic factors in early- and late-onset familial Alzheimer's disease are now well documented. The *APOE4* allele is strongly associated with late-onset familial and sporadic Alzheimer's disease, with a reported allele frequency of 50%–65% in patients with Alzheimer's disease, which is approximately three times that in the general population and for other neurologic disorders (Saunders et al. 1993; Prekumar et al. 1996). In addition to Alzheimer's disease, the *APOE4* allele has been implicated in other amyloid-forming disorders, including cerebral amyloid angiopathy (CAA) (Prekumar et al.1996). Thus, patients who carry the *APOE4* allele may represent an etiologically distinct population of patients with Alzheimer's disease.

The deposition of extracellular amyloid plaques in the brain is a hallmark pathologic finding in Alzheimer's disease, first reported by Alois Alzheimer in 1906. These amyloid plaques are primarily composed of Abeta peptides (Haass and Selkoe 2007) generated by the sequential cleavage of amyloid precursor protein (APP) via β- and γ-secretase activity. Abeta, particularly in its oligomerized forms, is toxic to neurons and is believed to be causative in Alzheimer's disease. Therapies that reduce Abeta levels in the brain may alleviate cognitive dysfunction and block further synaptic loss, axon degeneration, and neuronal cell death.

Abeta can be transported actively across the blood–brain barrier (Deane et al. 2004). In murine models of Alzheimer's disease, systemic delivery of antibodies to Abeta increases Abeta levels in plasma while reducing levels in the central nervous system through several proposed mechanisms, including dissolution of brain Abeta plaque, phagocytic removal of opsonized Abeta, and finally via efflux of Abeta from the brain as a result of an equilibrium shift of Abeta resulting from circulating antibodies (Morgan 2005). Current anti-Abeta clinical therapeutic development approaches are largely based on these proposed mechanisms.

1.2 BACKGROUND ON CRENEZUMAB (MABT5102A)

Crenezumab (MABT5102A) is a fully humanized immunoglobulin (Ig) G4 (IgG4) monoclonal antibody to Abeta selected for its ability to bind both monomeric and oligomeric forms of Abeta in vitro. Crenezumab binds both Abeta1-40 and Abeta1-42, inhibits Abeta aggregation, and promotes Abeta disaggregation. Since crenezumab is a human IgG4 backbone antibody, it has reduced Fcγ receptor (FcγR) binding affinity compared with human IgG1 or IgG2, which is predictive of reduced immune effector response. These properties, combined with the ability to systemically deliver crenezumab to decrease Abeta levels in the central nervous system in a murine model of Alzheimer's disease, suggest that this anti-Abeta therapeutic approach may offer clinical efficacy while reducing the risk of toxicity, with the ultimate goal of modifying disease progression in patients with Alzheimer's disease with lower risk of cerebral vasogenic edema or hemorrhages.

See the crenezumab (MABT5102A) Investigator's Brochure for additional details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

This open-label extension (OLE) study will investigate the long-term safety and tolerability of crenezumab in patients with Alzheimer's disease. Currently, there are no approved treatments to prevent the progression of Alzheimer's disease; crenezumab is being studied as a potential treatment for this indication. Alzheimer's disease is a chronic disease that is anticipated to require continued treatment over many years, data from this study will help to define the long-term safety profile of crenezumab.

Nonclinical data collected to date have not revealed any body system- or organ-specific toxicities associated with crenezumab.

Two Phase II studies with crenezumab have recently completed dosing.
Study ABE4869g was a Phase II, randomized, double-blind, parallel-group, placebo-controlled study designed to evaluate the safety and efficacy of crenezumab in patients 50–80 years of age who have been diagnosed with mild-to-moderate Alzheimer's disease. The study enrolled 446 patients. Treatment duration was 68 weeks (the last dose was administered on the first day of Week 69), and final assessments for efficacy occurred at Week 73. Dosing was completed in October 2013, the study was unblinded in January 2014, and the study was completed in May 2014.
Study ABE4955g was a Phase II, randomized, double-blind, parallel-group, placebo-controlled study designed to evaluate the effects of crenezumab on brain amyloid burden as assessed by florbetapir-positron emission tomography (PET), and other biomarkers in patients 50–80 years of age who have been diagnosed with mild-to-moderate Alzheimer's disease. The study enrolled 91 patients. Treatment duration was 68 weeks (the last dose was administered on the first day of Week 69), and

final assessments for efficacy occurred at Week 73. Dosing was completed in January 2014, and the study was unblinded in February 2014.

An additional Phase II study is ongoing in an autosomal dominant Alzheimer's disease (ADAD) population. Study GN28352 is a Phase II, randomized, double-blind, parallel-group, placebo-controlled study designed to evaluate the safety and efficacy of crenezumab in participants 30–60 years of age who are carriers of the PSEN1 E280A mutation and who do not meet criteria for mild cognitive impairment because of Alzheimer's disease or dementia because of Alzheimer's disease. The first patient was enrolled in December 2013, and the study is currently ongoing. Safety data are limited.

1.3.1 Clinical Experience with Study ABE4869g (Completed)

Study ABE4869g was a Phase II, randomized, double-blind, parallel-group, placebo-controlled study designed to evaluate the safety and efficacy of 68 weeks of crenezumab treatment in patients 50–80 years of age who have been diagnosed with mild-to-moderate Alzheimer's disease. Four hundred forty-six patients were enrolled and 444 were dosed in the study: 184 in a subcutaneous (SC) cohort, 247 in an intravenous (IV) cohort, and 13 in a safety run-in cohort (see below). The first patient in ABE4869g was dosed in April 2011. Dosing was completed on 29 October 2013, and the study was unblinded on 28 January 2014. Initial unblinded safety information is detailed below (Section 1.3.3); full evaluation of safety, efficacy, and pharmacokinetics is ongoing.

In Study ABE4869g, the 72-week change from baseline in the Alzheimer Disease Assessment Scale Cognitive Subscale (ADAS-cog12) and Clinical Dementia Rating Scale Sum of Boxes Scores (CDR-SOB) served as co-primary endpoints. A trend towards reducing cognitive decline at 72 weeks post-baseline was observed in patients with an MMSE of 18 – 26 in the 15-mg/kg IV cohort (1.8 ADAS-cog12 points difference versus placebo; 80% Confidence Interval [CI]: 0.0, 3.5 points; 16.8% reduction in decline; $p = 0.19$). This ADAS-cog12 treatment effect was augmented with increasingly milder patients in the IV cohort, increasing to 2.2 points difference versus placebo (80% CI: 0.4, 4.1 points; 23.8%; $p = 0.13$) in patients with an MMSE of 20 – 26, and to 3.4 points (80% CI: 1.4, 5.5 points; 35.4%; $p = 0.04$) in patients with an MMSE of 22 – 26. No consistent treatment effect was seen in the CDR-SOB in the 15-mg/kg IV cohort at 72 weeks post-baseline, for patients with an MMSE of 18 – 26, 20 – 26, or 22 – 26.

A consistent treatment effect was not seen in the ADAS-cog12 or CDR-SOB in the SC cohort at 72 weeks post-baseline for patients in the 18 – 26, 20 – 26 or 22 – 26 range.

1.3.2 Clinical Experience with Study ABE4955g (Completed)

Study ABE4955g, a Phase II, randomized, double-blind, parallel-group, placebo-controlled study was designed to evaluate the effects of crenezumab on brain amyloid burden as assessed by florbetapir-PET and other biomarkers in patients 50–80 years of age who have been diagnosed with mild-to-moderate Alzheimer's disease. This

is a companion study to Study ABE4869g. Randomization was completed on 14 September 2012. Thirty-nine patients were enrolled and dosed in Part 1 (SC cohort) of the study, and 52 patients were enrolled and dosed in Part 2 (IV cohort). Patients were randomized to receive crenezumab or placebo in a 2:1 ratio. SC dosing was completed on 16 October 2013, and IV dosing was completed on 16 January 2014. The study was unblinded on 10 February 2014. Initial unblinded safety information is detailed below (Section 1.3.3); full evaluation of safety, efficacy, and pharmacokinetics is ongoing.

In the 15-mg/kg IV cohort of Study ABE4955g, a 0.7 point difference versus placebo (80% CI: −3.8, 5.2 points; 10.3%; p=0.84) was seen in the mild−to-moderate population (MMSE: 18−26) in the ADAS-cog12 at Week 73. This point difference versus placebo in the ADAS-cog12 increased to 3.0 points (80% CI: −0.7, 6.8 points; 52.0%; p=0.29) in patients with an MMSE of 20−26, although the sample size was small for this subset (n=12 for active, n=7 or placebo). In the IV cohort of Study ABE4955g, a 0.23 point difference versus placebo (80% CI: −1.2, 1.7 points; 7.4%; p=0.84) was seen in the mild−to-moderate population in the CDR-SOB at Week 73. This difference versus placebo in the CDR-SOB increased to 0.80 points (80% CI: −0.5, 2.1; 41.5%; p=0.44) in patients with an MMSE of 20−26.

In the SC cohort of Study ABE4955g, a consistent treatment effect was not observed in the mild-to-moderate population in the ADAS-Cog or the CDR-SOB at Week 73.

1.3.3 Safety Experience in the Phase II Program

Safety information from the Phase II program (ABE4869g, ABE4955g, GN28525) is summarized in this section. Unblinded safety data from the randomized placebo-controlled portion (RPCP) of ABE4869 and ABE4955g (as of 27 May 2014) are summarized, as are all known fatalities as of 27 May 2014 in all three studies (ABE4869g, ABE4955g, GN28525). There have been no fatalities in study GN28352.

During the RPCP of the Phase II program, 346 patients were treated with SC or IV crenezumab for up to 68 weeks, and 176 patients received placebo for up to 68 weeks (this includes the 2:1 randomized IV and SC cohorts of ABE4869g and ABE4955g, but not the safety run-in [SRI] cohort of ABE4869g).

1.3.3.1 Deaths

During the RPCP of the Phase II program, there were 5 deaths. All 5 deaths occurred in patients treated with crenezumab, and none were assessed as related to study drug by the investigator. This represents 1.4% of patients receiving crenezumab compared with 0% of patients receiving placebo. The rate of death in the crenezumab arm is within the expected rates of death in the Alzheimer's disease clinical trial population treated with placebo (0%− 1.9%) or with Abeta-directed passive immunotherapy (2.1%−2.4%) (Doody et al. 2014; Salloway et al. 2009; Salloway et al. 2014).

The causes of death were as follows: 1) Alzheimer's disease progression characterized by an inability to perform most tasks, including walking and talking (ABE4869g, SC); 2) central respiratory paralysis in the context of a rapidly progressive form of Alzheimer's disease (ABE4869g, SC); 3) community-acquired pneumonia, on a background of chronic obstructive pulmonary disease (COPD; ABE4869g, IV); 4) "sudden death" (ABE4955g, IV); 5) respiratory failure due to a right-sided pleural effusion of unknown etiology (differential diagnosis being pneumonia versus malignancy) (ABE4955g, IV).

Deaths were not related to serum crenezumab steady-state (AUC or C_{max}) in the RPCP of the Phase II Studies ABE4869g and ABE4955g.

In addition, as of 27 May 2014, four patients treated with crenezumab died outside of the RPCP of the Phase II program. All 4 deaths were assessed as not related to study drug by the investigator. Three of the 4 patients received crenezumab, and 1 patient received placebo during their participation in the RPCP of ABE4869g or ABE4955g. The causes of deaths were as follows: 1) pneumonia (occurred in a patient who withdrew from the study and occurred outside the reporting period, 6 months after the last dose of study drug) (ABE4869g, IV); 2) colon adenocarcinoma (ABE4869g roll-over to GN28525, SC); 3) acute delirium (ABE4869g roll-over to GN28525, SC); 4) Alzheimer's disease progression without further details, as the caregiver refused to be contacted (ABE4869g, placebo IV roll-over to GN28525 crenezumab IV). No patients died in the SRI cohort of ABE4869g.

1.3.3.2 Discontinuations

During the RPCP of the Phase II program, patients discontinued treatment due to an adverse event in 12 (3.5%) patients receiving crenezumab and in 10 (5.7%) patients receiving placebo. In the ABE4869g SC cohort, 2 (1.6%) patients receiving crenezumab and 3 (4.8%) patients receiving placebo discontinued treatment due to an adverse event. In the ABE4869g IV cohort, 8 (4.9%) patients receiving crenezumab and 3 (3.6%) patients receiving placebo discontinued treatment due to an adverse event. In the ABE4955g SC cohort, 1 patient (3.8%) receiving crenezumab and 0 (0%) patients receiving placebo discontinued treatment due to an adverse event. In the ABE4955g IV cohort, 1 patient (2.9%) receiving crenezumab and 4 (23.5%) patients receiving placebo discontinued treatment due to an adverse event.

1.3.3.3 Serious and Non-Serious Adverse Events

During the RPCP of the Phase II program, serious adverse events were reported in 57 (16.5%) patients receiving SC or IV crenezumab, and in 21 (11.9%) patients receiving SC or IV placebo. An imbalance in serious adverse events of total lower respiratory tract infections (TLRTI; including preferred terms [PT] of pneumonia, lower respiratory tract infection [LRTI] and bronchitis) driven by pneumonia was observed in the RPCP of the Phase II program, with 6 cases versus 2 cases (1.7% vs. 1.1%) of TLRTI and 6 cases versus 1 case (1.7% vs. 0.6%) of pneumonia observed in the crenezumab and placebo arms, respectively. An imbalance in non-serious adverse

events of TLRTI also driven by pneumonia was observed in the RPCP of the Phase II program, with 18 cases versus 6 cases (5.2% vs. 3.4%) of non-serious TLRTI, and 5 cases versus 0 cases (1.4% vs. 0%) of non-serious pneumonia observed in the crenezumab and placebo arms, respectively.

Adverse events (serious and non-serious) reported in > 5% of crenezumab or placebo patients in the RPCP of the Phase II program included urinary tract infection (11.6% vs. 11.4%, crenezumab vs. placebo, respectively), nasopharyngitis (11.3% vs. 11.9%), cerebral microhemorrhage (10.1% vs. 11.4%), fall (10.1% vs. 6.8%), upper respiratory tract infection (9.8% vs. 9.1%), headache (9.8% vs. 7.4%), anxiety (9.2% vs. 7.4%), diarrhea (8.1% vs. 9.1%), dizziness (7.5% vs. 10.2%), agitation (7.5% vs. 2.8%), arthralgia (7.2% vs. 5.1%), back pain (6.9% vs. 9.7%), nausea (6.9% vs. 6.8%), fatigue (6.4% vs. 6.3%), contusion (6.1% vs. 1.7%), depression (5.5% vs. 8.5%), cough (5.5% vs. 2.8%), and vomiting (5.2% vs. 5.1%).

Adverse events were not related to dose in the RPCP of the Phase II Studies ABE4869g and ABE4955g.

1.3.3.4 Adverse Events of Special Interest

1.3.3.4.1 Amyloid-Related Imaging Abnormalities (ARIA) and Macrohemorrhages

During the RPCP of the Phase II program, a single case of asymptomatic amyloid-related imaging abnormalities (ARIA-E; sulcal effusion in the [redacted] occipital, parietal and temporal region and in the [redacted] occipital region) was reported in a [redacted]-year-old [redacted] patient on IV crenezumab in ABE4869g in the Week 23 magnetic resonance imaging (MRI) assessment (after the sixth IV infusion). No events of ARIA-E were reported as assessed by brain MRI in ABE4955g.

This single case represents 0.2% of all patients enrolled in the RPCP of the Phase II program, 0.3% of all patients who received crenezumab in the RPCP of the Phase II program, and 0.5% of all patients who received IV crenezumab in the RPCP of the Phase II program. Safety data collected in the crenezumab Phase II program indicate that the risk of ARIA-E in crenezumab-treated patients is similar to the background rate of ARIA-E in the mild–to-moderate Alzheimer's disease population (0.2%–0.4%). The background incidence rate of ARIA-E in patients with mild–to-moderate Alzheimer's disease is based on results from placebo groups over 18 months in four large Phase III clinical studies (bapineuzumab and solanezumab)(Carlson et al. 2011; Eli Lilly August 2012 PRNewswire press release).

In the ABE4869g SC cohort, incident superficial siderosis was reported in 1 patient receiving placebo and in no patients receiving crenezumab. One patient in the ABE4869g SC cohort had superficial siderosis detected at screening, was incorrectly randomized, and received 6 biweekly doses of crenezumab before being discontinued. In the ABE4869g IV cohort, superficial siderosis was reported in 1 patient receiving

placebo and in no patients receiving crenezumab. One case of incident superficial siderosis was reported in a patient receiving placebo in the ABE4955g IV cohort; no other cases of superficial siderosis were reported in ABE4955g.

In the ABE4869g IV cohort, 1 macrohemorrhage was reported in 1 patient receiving crenezumab; this was a macrohemorrhage approximately [redacted] cm in length along the [redacted] hippocampus, most likely subependymal. It is not known if this macrohemorrhage was symptomatic or asymptomatic. No macrohemorrhages were reported in patients receiving placebo in the ABE4869g IV cohort, in patients in the ABE4869g SC cohort, or in patients in ABE4955g.

During the RPCP of the Phase II program, incident microhemorrhages were reported in 40 (11.6%) patients receiving crenezumab and in 22 (12.5%) patients receiving placebo. One microhemorrhage was reported to be symptomatic in an SC placebo patient. In the SC cohort of Study ABE4869g, the proportion of patients who experienced incident microhemorrhages was higher in patients receiving placebo (10 patients, 16.1%) than in patients receiving crenezumab (16 patients, 13.1%). In the IV cohort of Study ABE4869g, the proportion of patients who experienced incident microhemorrhages was higher in patients receiving placebo (11 patients, 13.1%) than in patients receiving crenezumab (15 patients, 9.2%). In the SC cohort of Study ABE4955g, the proportion of patients who experienced incident microhemorrhages was higher in patients receiving crenezumab (4 patients, 15.4%) than in patients receiving placebo (0 patients). In the IV cohort of Study ABE4955g, the proportion of patients who experienced incident microhemorrhages was higher in patients receiving crenezumab (5 patients, 14.3%) than placebo (1 patient, 5.9%). The imbalance in incident microhemorrhages between patients who received crenezumab and placebo in Study ABE4955g may be due to the small number of events.

Adverse events of special interest were not related to serum crenezumab steady-state AUC or C_{max} in the RPCP of Phase II.

1.3.3.4.2 Pneumonia and Other Lower Respiratory Tract Infections

In the RPCP of Phase II clinical trials in mild-to-moderate Alzheimer's disease (ABE4869g and ABE4955g), there was an imbalance in the overall rates of pneumonia *(including serious and non-serious)*, with 3.2% (11/346) of crenezumab-treated patients and 0.6% (1/176) of patients receiving placebo *experiencing* pneumonia. Of these 12 pneumonia cases, 7 were assessed as serious (*in* 4 *patients* receiving crenezumab IV, 2 *patients* receiving crenezumab SC, and 1 *patient* receiving placebo).

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 et al. 2008), but rates (both total and serious) are slightly higher in crenezumab-treated patients (3.2%) and slightly lower in placebo-treated patients (0.6%) than rates reported in the active and placebo arms of clinical trials in Alzheimer's disease (Doody et al. 2014; Henley et al.

2014; Salloway et al. 2014). There is no clinical evidence of immunosuppression (e.g., effects on white blood cells or neutrophils; or pattern of infection type, e.g., opportunistic infections). In addition, no evidence of immunosuppression or of a lung toxicity effect has been observed in preclinical studies. Based on the currently available data, a causal relationship between the drug and events of pneumonia cannot be established or ruled out. Pneumonia is considered a potential risk to be monitored closely, and is added to this protocol as an adverse event of special interest.

1.3.3.5 Additional Safety Information

In the ongoing OLE study (GN28525) as of 27 May 2014, three deaths occurred (additional details above). As of 27 May 2014, serious adverse events were reported in 15 SC patients (10.1%) and 18 IV patients (8.5%). Eight SC patients (5.4%) and 2 IV patients (0.9%) discontinued treatment due to an adverse event. Asymptomatic ARIA-E was reported in 1 IV patient (0.5%; the same patient with ARIA-E in ABE4869g) and no SC patients. Superficial siderosis was reported in one SC patient (0.7%) and no IV patients. No macrohemorrhages were reported in SC or IV patients. Incident asymptomatic microhemorrhages were reported in 6 SC patients (4.1%) and 3 IV patients (1.4%).

Additional safety information for the ABE4869g, ABE4955g, GN28525, and GN28352 studies are provided in the Investigator's Brochure.

Based on a review of Phase II safety data to date, while imbalances in deaths and pneumonia were observed in the RPCP, a drug-related causal relationship has not been established. New fatalities in the ongoing OLE study (GN28525) will be closely monitored, and exposure-adjusted fatality rates using the total-person time on crenezumab treatment will be compared to expected rates from published data.

1.3.4 Clinical Pharmacokinetics

The pharmacokinetics of crenezumab have been evaluated in two Phase I studies (ABE4427g and ABE4662g) and in the two Phase II studies (ABE4869g and ABE4955g) and will be further assessed upon completion of the ongoing, OLE study (GN28525) and the Phase II study (GN28352) in PSEN1 E280A mutation carriers. Overall, the observed clearance and volume of distribution in the Phase I studies are consistent with those for other humanized IgG monoclonal antibodies that exhibit kinetics in the linear concentration range (Mould and Sweeney 2007; Dirks and Meibohm 2010; Deng et al. 2011).

In Study ABE4427g, crenezumab was given either as a single (0.3–10 mg/kg) or weekly (0.5 –5 mg/kg) IV bolus to patients with mild-to-moderate Alzheimer's disease. Following single-dose administration, crenezumab pharmacokinetics were characterized by linear exposure across the dose range tested, slow clearance (2.5–3.3 mL/day/kg) and a long half-life (17–26 days). With weekly administration, there did not appear to be

any time-dependent change in crenezumab kinetics, as evidenced by similar terminal elimination half-life estimates (18–23 days) relative to the single-dose arm.

[redacted]

In the Phase II studies (Study ABE4869g and Study ABE4955g), serum crenezumab concentrations were measured in samples collected after bi-weekly SC (300 mg every 2 weeks [q2w]) or monthly IV (15 mg/kg every 4 weeks [q4w]) administration in patients with mild–to-moderate Alzheimer's disease. In general, serum pharmacokinetic (PK) concentrations were similar between the two Phase II studies. In Study ABE4869g, after 68 weeks of dosing with SC (q2w) or IV (q4w) crenezumab, mean (standard deviation; SD) steady state trough serum crenezumab levels were 69 (30) μg/mL and 118 (72) μg/mL, respectively. For patients in the IV and SC treatment groups, steady-state trough serum crenezumab levels appeared to have been attained between Week 13 and Week 25 (after 3 – 6 doses of IV or 6 – 12 doses of SC) in both studies. The trough crenezumab levels in cerebrospinal fluid (CSF) were measured in a subset of patients in ABE4869g and in all patients in ABE4955g at Week 69. In preliminary analysis of CSF crenezumab concentrations, penetration into CSF was similar between the two studies as well as between the SC and IV doses. In study ABE4869g, the mean (SD) CSF/serum ratio was 0.26% (0.16%) and 0.28% (0.17%) for IV and SC dosing, respectively. [redacted]

Additional PK information for Studies ABE4427g, ABE4662g, and ABE4869g are provided in the Investigator's Brochure.

1.3.5 Immunogenicity

In the Phase I studies anti-therapeutic antibodies (ATAs [directed against crenezumab]) were detected in 1 of 36 (Study ABE4427g) and 0 of 22 (Study ABE4662g) crenezumab-treated patients. The presence of a positive ATA response in the single patient (1.5-mg/kg dose level; multiple-dose phase) was associated with reduced serum crenezumab exposure (50% and 20% lower Day 22 predose and peak concentrations compared to the group median). In a preliminary analysis of ATAs in the Phase II studies, treatment-emergent ATAs were detected in 2 of 164 (1.2%) crenezumab-treated patients in the IV cohort (Study ABE4869g) and in 7 of 122 (5.7%) crenezumab-treated patients in the SC cohort (Study ABE4869g). No apparent impact of ATAs on pharmacokinetics or safety was observed in either the IV or SC cohorts in ABE4869g. Treatment-emergent ATAs were not detected in 61 crenezumab-treated patients in the IV and SC cohorts of Study ABE4955g.

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

1.3.6 Benefit-Risk Summary

The safety and tolerability of crenezumab in humans has been assessed in 540 patients exposed to crenezumab in six studies (two Phase I and four Phase II) that showed an acceptable safety profile. Details are provided above and in the crenezumab Investigator's Brochure.

Clinical experience to date has not identified any events considered to be adverse drug reactions (i.e., a drug causality link has not been established with any of the reported adverse events). Potential safety considerations associated with treatment include those inherent to recombinant protein therapeutics as well as those specific to the crenezumab molecule or pharmacology. These include pneumonia, the spectrum of potential immune-mediated responses (e.g., hypersensitivity reactions, anaphylaxis), immunogenicity (anti-drug antibody formation), cerebral vasogenic edema/sulcal effusion, cerebral micro-/macro-hemorrhages, and superficial siderosis. Given the imbalances observed in pneumonia reports between crenezumab and placebo during the RPCP of the Phase II program, pneumonia is now considered a new potential risk for crenezumab treatment.

Given the early stage of development, the long-term safety profile of crenezumab in humans has not yet been fully characterized. Therefore, not all of the potential adverse effects, and the likelihood of their occurrence, are known at this time. Patients will continue to be carefully monitored throughout the clinical development of crenezumab to collect additional safety information.

This OLE study will permit the evaluation of long-term safety and tolerability of crenezumab in patients who completed the Week 73 assessment in Study ABE4869g or ABE4955g. In addition, this OLE study will provide the opportunity for eligible patients treated with placebo in Studies ABE4869g and ABE4955g to continue into the OLE and receive crenezumab.

Clinical efficacy data from ABE4869g and ABE4955g suggest that there is a potential treatment effect with high-dose crenezumab (15 mg/kg IV q4w), but there is a lack of consistent benefit with low-dose crenezumab (300 mg SC q2w). The safety profile of crenezumab to date is acceptable. Furthermore, adverse events were not related to dose, and fatalities, serious adverse events, and adverse events of special interest were not related to steady-state serum crenezumab exposure (AUC and C_{max}). Therefore, the potential treatment benefit, in light of the safety characteristics of crenezumab, supports continuing dosing at 15 mg/kg IV q4w in Study GN28525.

Based on the safety profile and the potential clinical efficacy of crenezumab at 15 mg/kg IV q4w, all patients who entered GN28525 in the SC dosing arm will transition to the 15 mg/kg IV arm.

The safety of patients participating in this trial will be ensured through the use of stringent inclusion and exclusion criteria for study entry, and through close patient monitoring. Investigators will assess the occurrence of adverse events and serious adverse events at all patient evaluation time points 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. Patients will be carefully followed for adverse events during the study, including a safety follow-up period.

2. OBJECTIVES

The primary objective of this study is to assess the long-term safety and tolerability of crenezumab administered subcutaneously q2w or intravenously q4w, in eligible patients with Alzheimer's disease who participated in Study ABE4869g or ABE4955g and completed the Week 73 study visit, including brain MRI.

2.1 EFFICACY OBJECTIVES

There are no efficacy objectives for this study, although select efficacy outcome measures will continue to be collected.

2.2 SAFETY OBJECTIVE

The safety objective of this study is to evaluate the safety and tolerability of crenezumab in patients with Alzheimer's disease focusing on treatment-emergent adverse events, vital signs, routine laboratory analysis, immunogenicity, and cerebral imaging abnormalities (assessed by MRI).

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives of this study are as follows:

- To evaluate the long-term effect of crenezumab on disease progression using the ADAS-Cog (12-item)
- To evaluate the long-term effect of crenezumab on disease progression using CDR-SOB
- To evaluate the long-term effect of crenezumab on patient functioning using the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL)
- To evaluate the long-term effect of crenezumab on disease progression using supplemental neurocognitive measures (i.e., Exploratory Neurocognitive Test Panel [ENTP]) selected to assess episodic memory performance, executive functions, verbal fluency, working memory, and psychomotor speed
- To evaluate the long-term effect of crenezumab on behavior using the Neuropsychiatric Inventory (NPI)

- To evaluate the long-term effects of crenezumab on the amount of assistance patients with dementia require in performing daily activities using the Dependence Scale
- To evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of crenezumab
- To evaluate the PK/PD relationship of crenezumab using exploratory PD biomarkers
- To evaluate changes in MRI biomarkers, such as global and regional brain volumes and functional connectivity

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study Design

Study GN28525 is a Phase II, OLE, multicenter study to evaluate the long-term safety and tolerability of crenezumab in patients with Alzheimer's disease who have participated in and completed the treatment period of the Phase II Study ABE4869g or ABE4955g. Patients from Studies ABE4869g and ABE4955g who discontinued from study treatment early but remained on study for safety evaluations, or discontinued prior to completion of the Week 73 study visit, are not eligible for this OLE study.

ABE4869g (ABBY) is a completed Phase II, multicenter, global, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the safety and efficacy of crenezumab in patients with mild-to-moderate Alzheimer's disease. Four hundred forty-six patients were randomized and 444 patients were dosed at approximately 100 sites in North America and Europe.

ABE4955g (BLAZE) is a completed Phase II, multicenter, global, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the effects of crenezumab on brain amyloid burden, as assessed by florbetapir-PET, and other biomarkers in patients with mild-to-moderate Alzheimer's disease. Ninety-one patients were randomized and 61 were dosed at approximately 30 sites in North America and Europe.

This OLE study includes patients who have been diagnosed with Alzheimer's disease and have an MMSE score of 10 or more at the time of screening, which is lower than in Studies ABE4869g and ABE4955g (MMSE 18 – 26) to account for the disease progression in the course of these studies. An MMSE score of less than 10 at the beginning of the OLE study would substantially increase the risk that a patient would not be able to complete the study assessments and to comply with the protocol's requirements in the future.

Patients will undergo a neuroradiological evaluation using a standard MRI protocol and T2* gradient echo MRI to exclude any significant MRI abnormality and presence of cerebral superficial siderosis or more than eight cerebral microhemorrhages. Only

patients with 4 or less cerebral microhemorrhages at screening are allowed to participate in Studies ABE4869g and ABE4955g and study drug will be discontinued in patients with an increase of six or more in the number of asymptomatic microhemorrhages in these studies since high numbers of cerebral microhemorrhages have been associated with future risk of ischemic and hemorrhagic strokes (Greenberg et al. 2009). The microhemorrhage threshold for entry in this study, which is based on the natural incidence of cerebral microhemorrhages in this patient population, is intended to minimize potential safety risks associated with cerebral microhemorrhages, but would not preclude the majority of the patients from Study ABE4869g or ABE4955g from rolling over into this OLE study. However, this might exclude patients from participating in the OLE study due to the number of cerebral microhemorrhages that would not have led to treatment discontinuation in the Study ABE4869g or ABE4955g. Patients with medical or psychiatric contraindication or clinically significant abnormalities that, in the investigator's judgment, would substantially increase the risk associated with the patient's participation in the study or interfere with the evaluation of the patient's response will not be included in the study.

All patients enrolled in the OLE study were to receive active drug at the same dosing frequency, dose level, and route of administration they were assigned to after the Week 73 visit of Study ABE4869g or ABE4955g. Patients who received matching placebo in Study ABE4869g or ABE4955g were to receive active drug (i.e., crenezumab 300 mg SC q2w for patients who were randomized in the SC cohort [Part 1] or 15 mg/kg IV q4w for patients who were randomized in the IV cohort [Part 2]). However, evaluation of efficacy in ABE4869g and ABE4955g indicates that there was no consistent treatment effect in patients who received 300 mg q2w SC that would support continuation of this dose level. In contrast, there appears to be a trend towards reduction in cognitive decline in patients who received 15 mg/kg q4w IV. Considering these efficacy results and the available safety information, all patients in the OLE study will be dosed at 15 mg/kg q4w IV. All patients who have been receiving active drug in the SC dosing arm will be transferred into the IV dosing arm.

The study consists of three periods: a screening period (up to 14 days), the window between the last dose in ABBY/BLAZE and the first dose in OLE may last 6 weeks, but may be prolonged on a case by case basis for relevant clinical, administrative, or operational reasons (these reasons must be discussed with the medical monitor in advance of screening; if necessary, some screening procedures may need to be repeated); a treatment period *of 144 weeks (Week 1 [Day 1] to Week 145*), and a*n 8-week safety* follow-up period (*Weeks 145 to 153*). The final safety analysis will be performed at *153* weeks. *The original GN28525 protocol included a treatment period of 92 weeks (Week 1 [Day 1] to Week 93). Version 6 of the GN28525 protocol expands this treatment period by 52 weeks (13 additional IV doses from Week 97 to Week 145). Patients who are still enrolled in Study GN28525 may enter the additional OLE treatment period (Week 97 to Week 145) if they have not discontinued treatment for*

safety reasons. Patients who have already completed or discontinued from Study GN28525 are not eligible to receive additional treatment from Week 97 to Week 145.

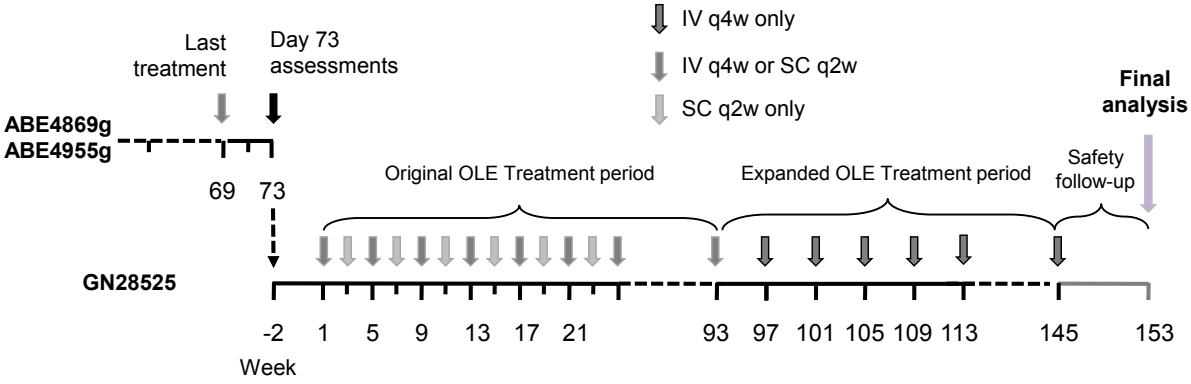
The Week 73 assessment (including MRI) of Studies ABE4869g and ABE4955g will be used to determine the patient's eligibility in this OLE trial. Data from the Week 73 visit assessments in Studies ABE4869g and ABE4955g will be extracted and incorporated in the OLE screening datasets. Patients participating in this OLE study must be enrolled (i.e., Day 1 of the OLE treatment period) no later than 14 days after completion of the Week 73 assessments (including MRI) of Study ABE4869g or ABE4955g, except for individual exceptions, determined on a case by case basis, as mentioned above.

The first dose of crenezumab is administered on Day 1 of the treatment period, and the last dose of treatment is at Week *145*. After patients complete the *144-week* treatment period, they will enter the follow-up period. Patients who are prematurely discontinued from the OLE study treatment will also discontinue from the OLE study and will be followed for safety for *8* weeks after their last dose of crenezumab.

Patients will remain blinded to their assignment in Study ABE4869g or ABE4955g, and investigators are not permitted to provide treatment assignment in ABE4869g or ABE4955g until permitted by the Sponsor.

The study timeline is presented in Figure 1. A schedule of assessments is provided in Appendix 1.

Figure 1 Study Timeline



IV =intravenous; OLE =open-label extension; q4w =every 4 weeks; SC =subcutaneous.

3.1.2 Internal Safety Monitoring Committee

The incidence and nature of adverse events, serious adverse events, and laboratory abnormalities will be assessed on a regular basis by an internal Safety Monitoring Committee, composed of a biostatistician, drug safety scientist, statistical programming analyst, and a clinical scientist, who may be members of the project team. The committee will continually monitor all serious adverse events. External experts may be

consulted. The incidence and distribution of non-serious adverse events will be reviewed frequently (e.g., every 12 weeks). The committee will recommend changes to the study conduct or study termination as required. The responsibilities and operation of the committee will be documented in the Safety Monitoring Committee charter. *The feeder studies ABE4869g and ABE4955g are completed and unblinded; therefore, the Internal Safety Monitoring Committee will be disbanded at an appropriate time, and periodic review of safety data will be conducted by the Sponsor project team.*

3.2 END OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date on which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later. LPLV is expected to occur *153* weeks after the last patient is enrolled.

3.3 RATIONALE FOR STUDY DESIGN

As Alzheimer's disease is a chronic disease that is anticipated to require continuous treatment over many years, data from this study will help to define the long-term safety profile of crenezumab. Study GN28525 is designed to assess the long-term safety and tolerability of crenezumab in Alzheimer's disease patients beyond the 69 weeks of dosing provided in Studies ABE4869g and ABE4955g. To capture this long-term safety and tolerability data, patients will be followed for an additional *144* weeks of dosing.

3.4 OUTCOME MEASURES

3.4.1 Primary Outcome Measures

Safety and tolerability will be assessed through regular neurologic and physical examinations and MRI assessments. In addition, the following information will be collected and analyzed:

- Frequency of adverse events during the treatment period
- Nature and severity of adverse events during the treatment period
- Changes in vital signs and physical and neurological findings
- Changes in clinical laboratory test results including routine hematology, chemistry, coagulation, and urinalysis
- Incidence of human anti-therapeutic antibody (ATA) formation
- Incidence of ARIA-E and amyloid-related imaging abnormalities-hemorrhage (ARIA-H)

3.4.2 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

– Change in ADAS-Cog (12-item) score from baseline to Week *153*

– Change in CDR-SOB score from baseline to Week *153*

– Change in ADCS-ADL score from baseline to Week *153*

- Change in the following ENTP scores from baseline to Week *153*:
  - Free and Cued Selective Reminding Test (FCSRT)
  - Trail-Making Test (TMT)
  - Digit Span Test (DST)
  - Digit Symbol Substitution Test (DSST)
  - Letter Fluency Test (LFT)
  - Category Fluency Test (CFT)
- Change in NPI score from baseline to Week *153*
- Change in NPI Caregiver Distress Scale score from baseline to Week *153*
- Change in Dependence Scale total score from baseline to Week *153*
- Changes in MRI biomarkers, such as global and regional brain volume*s,* from baseline to Week *153*
- Serum crenezumab concentration at protocol-specified time points; PK parameters including trough serum concentrations at steady state ($C_{trough, ss}$) will be explored, as applicable
- Plasma Abeta1-40 and Abeta1-42 concentrations

4. MATERIALS AND METHODS

4.1 PATIENTS

Patients who completed the Week 73 visit of Study ABE4869g or ABE4955g are eligible to participate in this OLE study; patients discontinued from study treatment or discontinued from study prior to completion of the Week 73 visit, will not be eligible for this OLE study.

Patients in this study are required to meet standard research criteria for probable Alzheimer's disease (the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorder Association [NINCDS–ADRDA] criteria) with an MMSE score of 10 or more points at screening. Patients will undergo a neuroradiological evaluation using a standard MRI protocol, including a T2-weighted FLAIR and T2* gradient echo sequence, to exclude any significant MRI abnormality and presence of ARIA-H or ARIA-E. Specifically, patients with more than eight cerebral microhemorrhages at screening will not be eligible for the study. This might exclude patients from participating in the OLE study due to the number of cerebral microhemorrhages that would not have led to treatment discontinuation in Study ABE4869g or ABE4955g. Patients with medical or psychiatric contraindications or clinically significant abnormalities that, in the investigator's judgment, will substantially increase the risk associated with the patient's participation in the study or interfere with the evaluation of the patient's response will not be included in the study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Ability to provide written informed consent by the patient or the patient's authorized representative under applicable local law
- Ability and willingness of the patient to comply with the protocol's requirements
- Previous participation in Study ABE4869g or ABE4955g and completion of the Week 73 visit
  - Patients who discontinued from study treatment or from the study prior to completion of the Week 73 visit are not eligible.
- Adequate visual and auditory acuity, in the investigator's judgment, to allow for neuropsychological testing
- Availability of a person ("caregiver") who can provide information on activities of daily living and behavior in order to complete the study-specific assessments
  - This caregiver must have sufficient cognitive capacity, in the judgment of the investigator, to accurately report upon the patient's function and behavior. In addition, the caregiver must spend sufficient time with the patient to be familiar with the overall function and behavior of the patient. As guidance, a caregiver would ordinarily need to spend an average of at least 8 hours per week with the patient in order for the caregiver to meet the requirements for this study.
- Diagnosis of probable Alzheimer's disease according to the National Institute on Neurological and Communication Disease and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al. 1984)
- MMSE score of 10 or more at screening (Folstein et al. 1975)
- For male patients with partners with reproductive potential, agreement to use a reliable means of contraception (e.g., condoms) during the study *and for at least 8 weeks following the last dose of study drug*
- For female patients, a negative urine dipstick pregnancy test at screening (not required if patient has undergone documented surgical sterilization or have not experienced menstruation for at least 12 consecutive months)

4.1.2 Exclusion Criteria

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

General

- Early treatment and/or study discontinuation prior to completion of the Week 73 visit of Genentech Study ABE4869g or ABE4955g
- *Early discontinuation from the treatment schedule of a prior version of Study GN28525 for safety reasons. If treatment discontinuation occurred for safety reasons, patients may not re-start dosing on extended treatment schedules offered in amendments to Study GN28525.*

- Inability to tolerate MRI procedures or contraindication to MRI, including but not limited to pacemakers; implantable cardioverter defibrillators; cochlear implants; cerebral aneurysm clips; implanted infusion pumps; implanted nerve stimulators; metallic splinters in the eye; other magnetic, electronic, or mechanical implants; or any other clinical history or examination finding that, in the judgment of the investigator, would pose a potential hazard in combination with MRI
- Female patient with reproductive potential: Female patients must either have undergone documented surgical sterilization or have not experienced menstruation for at least 12 consecutive months.
- Severe or unstable medical condition that, in the opinion of the investigator or Sponsor, would interfere with the patient's ability to complete the study assessments or would require the equivalent of institutional or hospital care

Related to Medical History/Conditions

- History or presence of clinically evident vascular disease potentially affecting the brain (e.g., stroke, clinically significant carotid or vertebral stenosis or plaque, aortic aneurysm, intracranial aneurysm, cerebral hemorrhage, arteriovenous malformation)
- History of severe, clinically significant (persistent neurologic deficit or structural brain damage) central nervous system trauma (e.g., cerebral contusion)
- History or presence of clinically relevant intracranial tumor (e.g., meningioma, glioma)
- Presence of infections that affect the brain function or history of infections that resulted in neurologic sequelae (e.g., syphilis, neuroborreliosis, viral or bacterial meningitis/encephalitis, HIV encephalopathy)
- History or presence of systemic autoimmune disorders potentially causing progressive neurologic disease (e.g., multiple sclerosis, lupus erythematosus, anti-phospholipid antibody syndrome, Behçet disease)
- History or presence of a neurologic disease other than Alzheimer’s disease that may affect cognition, including but not limited to Parkinson’s disease, corticobasal degeneration, dementia with Lewy bodies, Creutzfeldt–Jakob disease, progressive supranuclear palsy, frontotemporal degeneration, Huntington’s disease, normal pressure hydrocephalus, and hypoxia
- Patients with severe or unstable medical conditions (including Alzheimer’s Disease) that, in the opinion of the investigator or Sponsor, would interfere with the patient’s ability to complete the study assessments, pose an unacceptable risk, or would require the equivalent of institutional or hospital care
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins
- Evidence of malignancies (except squamous cell cancer or basal cell cancer of the skin), acute infections, renal failure that requires dialysis, or other unstable medical disease not related to Alzheimer’s disease that, in the investigator’s opinion, would preclude patient participation

  - Cancer that is not being actively treated with anti-cancer therapy or radiotherapy as well as cancers that are considered to have low probability of recurrence (with supporting documentation from the treating oncologist if possible) are allowed
- History or presence of atrial fibrillation that, in the investigator's judgment, poses a risk for future stroke
- Chronic kidney disease of Stage ≥ 4, according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines for chronic kidney disease (CKD)
- Impaired hepatic function, as indicated by transaminases > 2 times the upper limit of normal (ULN) or abnormalities in synthetic function tests judged by the investigator to be clinically significant
- Impaired coagulation (aPTT $> 1.2 \times$ ULN)
- Platelet count $< 100{,}000/\mu L$

Related to MRI Imaging

- Presence *at screening* of superficial siderosis of central nervous system, more than eight cerebral microhemorrhages, or evidence of a prior cerebral macrohemorrhage as assessed by T2*-weighted gradient echo (GRE) MRI
- Presence *at screening* of any other significant cerebral abnormalities, including ARIA-E, as assessed by MRI

Related to Medication

- Treatment with anticoagulation medications (e.g., heparin, warfarin, thrombin inhibitors, Factor Xa inhibitors) within 2 weeks prior to enrollment
  - Clopidogrel, dipyridamole, and aspirin are permitted.
- Treatment with anticholinergic antidepressants, typical antipsychotics, or barbiturates, within 2 weeks prior to enrollment.
  - All other antidepressants and atypical antipsychotics are allowed with certain restrictions (see Section 4.2.5).
- Chronic use of opiates, opioids, or benzodiazepines
  - Intermittent short-term use is allowed except within 5 half-lives prior to any neurocognitive assessment.
- Any biologic therapy within 75 weeks prior to enrollment
  - Crenezumab and routinely recommended vaccinations are allowed.
- Any investigational agent (other than crenezumab) within 75 weeks prior to enrollment
- Treatment with anticholinergic antidepressants, typical antipsychotics, barbiturates, or narcotics within 5 half-lives or 3 months prior to screening, whichever is longer
  - All other antidepressants and atypical antipsychotics are allowed. Chronic use of benzodiazepines is not allowed; however, the intermittent use of

benzodiazepines is allowed, except within 2 days prior to any neurocognitive assessment.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an OLE study. Patients in the OLE study will receive study drug at 15 mg/kg IV q4w. Patients who received active drug in Study ABE4869g or ABE4955g will continue to receive active drug. Patients who received placebo in Study ABE4869g or ABE4955g will also receive active drug (i.e., crenezumab 15 mg/kg IV q4w).

4.2.1 Formulation, Packaging, and Handling

4.2.1.1 Crenezumab (MABT5102A)

Crenezumab is produced using Chinese hamster ovary cells, purified, and formulated. Crenezumab is subjected to a series of quality-control tests to confirm its identity, purity, potency, quality, and sterility. The drug product is a sterile, preservative-free liquid intended for SC or IV administration.

*D*etails on crenezumab *and placebo* formulation, dosage, *configuration,* administration, and storage are provided in the crenezumab (MABT5102A) Investigator's Brochure and *the GN28525* pharmacy manual.

4.2.2 Crenezumab Dosage, Administration, and Compliance

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.

4.2.2.1 Subcutaneous Dosing

All patients previously enrolled in the SC cohort of Study ABE4869g, ABE4955g, or GN28525 will receive 15 mg/kg of crenezumab intravenously every 4 weeks as described below in Section 4.2.2.2. Missed treatments will not be made up.

4.2.2.2 Intravenous Dosing

Crenezumab will be given by IV infusion once every 4 weeks. Missed treatments will not be made up.

For IV use, the drug will be diluted as described in the *GN28525* pharmacy manual. The IV drug will be administered [redacted]. IV infusions will be administered by the site staff in a hospital, clinic, or practice environment. All patients will be followed for a minimum of 1 hour postdose and vital signs will be measured post-infusion and 60 minutes after the end of the infusion as described in the *GN28525* pharmacy manual.

For IV dose calculation in the OLE study, the screening weight refers to the patient's weight at Week 73. For patients who entered GN28525 immediately upon completion of

ABE4869g or ABE4955g, the IV dose will be calculated based on the patient's screening weight (reference weight) unless the patient's current weight changes (increases or decreases) ≥ 10% from the screening weight. For patients who will be transitioned from SC dosing to IV dosing during the conduct of GN28525, the IV dose will be calculated based on the patient's current weight at the time of transition (their reference weight). For all patients, whether originally in the IV cohort or transitioning from the SC cohort, if the current weight changes ≥ 10%, the current weight will become the new reference weight for subsequent dosing. If the patient's weight again changes by ≥ 10% from the reference weight, the IV dose will again be recalculated. Please refer to the *GN28525* pharmacy manual for further information.

If a patient experiences a mild infusion-related reaction, the infusion will be halted. Once the reaction has resolved, the infusion will be resumed at half of the most recently used rate [redacted]. Patients who experience a moderate infusion-related reaction (e.g., fever, chills) should have their 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 have their infusion stopped immediately and should receive aggressive symptomatic treatment, and they should not receive additional study drug.

4.2.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study will be provided by the Sponsor where required by local health authority regulations. The investigational site will acknowledge receipt of IMPs by returning the appropriate documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced.

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

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

4.2.4 Post-Trial Access to Crenezumab

The Sponsor does not intend to provide crenezumab or other study interventions to patients after conclusion of the study or any earlier patient withdrawal.

4.2.5 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from the day of study enrollment (Day 1) through study completion or early termination. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Except for excluded medications, patients who use other maintenance therapies may continue their use (see Section 4.1.2).

Patients are permitted to take approved Alzheimer's disease treatments (e.g., AChE inhibitors, and memantine). An approved Alzheimer's disease treatment may be initiated, stopped, or altered in dose or formulation up to, and including, the Week 13 visit. If an approved Alzheimer's disease treatment is no longer commercially available or no longer available through patients' insurance formulary, the treatment may be substituted with an equivalent dose of a comparable medication at any time during the trial. Stable doses of other maintenance medications will also be permitted. The intermittent use of opiates, opioids, soporifics, or benzodiazepines is allowed, except within 5 half-lives prior to any neurocognitive assessment (see Section 4.1.2).

Chronic treatment with benzodiazepines, opiates, or opioids is prohibited; however, intermittent, short-term treatment is allowed except within 5 half-lives prior to any neurocognitive assessment.

Non-excluded prescription and over-the-counter medications (see Section 4.1.2) that might affect cognitive function (e.g., non-anticholinergic antidepressants, atypical antipsychotics, non-benzodiazepine anxiolytics, soporifics, centrally acting anticholinergic antihistamines, centrally acting anticholinergic antispasmodics) are allowed a) if initiation or discontinuation of therapy or dose changes do not occur within 5 half-lives prior to cognitive assessment (however, initiation, discontinuation, or dose changes are discouraged), or b) administered intermittently and on a short-term basis, they are not used within 5 half-lives prior to neurocognitive assessment.

During the study, patients may receive any treatment deemed necessary by the investigator for the management of their disease. However, patients requiring commencement of prohibited therapies will be discontinued from the study.

4.2.6 Prohibited Therapy

Use of the following therapies is prohibited during the study, unless otherwise specified below:

- Anticholinergic antidepressants, typical antipsychotics, or barbiturates
  - All other antidepressants and atypical antipsychotics are allowed with certain limitations (see Section 4.2.5).

- Anticoagulation medications (e.g., heparin, warfarin, thrombin inhibitors, Factor Xa inhibitors)
  - Clopidogrel, dipyridamole, and aspirin are permitted.
- Any biologic therapy
  - Routinely recommended vaccinations are allowed.
- Any investigational agent

4.3 STUDY ASSESSMENTS

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

4.3.1 Informed Consent Forms and Screening Log

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

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. 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.

4.3.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient at the time of study enrollment on Day 1.

A complete medical history should include a negative or positive history for risk factors for pneumonia including asthma, COPD, heart disease, and smoking; and any other potential risk factor considered significant in the investigator's judgment.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.3.3 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, and gastrointestinal systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.3.4 Vital Signs

Vital signs will include measurements of heart rate, respiratory rate, temperature, and systolic and diastolic blood pressure after the patient has been supine for $\geq$3 minutes.

4.3.5 Neurologic Examination

A complete neurologic examination should include the evaluation of consciousness, cranial nerves, motor and sensory system, coordination and gait, and reflexes. Changes from baseline abnormalities should be recorded at each subsequent neurologic examination. New or worsened abnormalities should be recorded as adverse events on the Adverse Event eCRF if considered clinically significant in the investigator's judgment.

4.3.6 Magnetic Resonance Imaging Assessments

Neuroradiologic evaluation will be performed using a standard MRI protocol at screening and for routine safety assessments. The MRI protocol will include the following sequences: T1-weighted 3D GRE, dual-echo fast-spin-echo with T2 and proton density weighting (or separate T2-weighted and proton-density-weighted sequences on systems that will not accommodate dual-echo acquisition), T2*-weighted GRE, and T2-weighted FLAIR. The minimum requirements for T2*-weighted GRE scans are as follows: field strength of 1.5T or greater, slice thickness of 5 mm or less, and echo time (TE) of 20 ms or greater. Volumetric analysis of the T1-weighted 3D GRE scans is included as an exploratory evaluation of the effect of crenezumab on regional brain volume. All MRIs will be evaluated by a central imaging reader.

4.3.7 Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS) will be used for prospective suicidality assessment. The C-SSRS is a tool used to assess the lifetime suicidality of a patient and to track suicidal events through the treatment. The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual/potential lethality.

The scale will be administered by qualified site personnel. The C-SSRS "baseline" will be administered at Day 1, and the C-SSRS "since last visit" will be administered at subsequent visits. Patients who are suicidal based on C-SSRS will be referred for appropriate psychiatric evaluation and management as per local clinical practice.

Note: Assessing the risk of suicide is a difficult and complex task when applied to an individual patient. Certainly, no single clinical scale can replace a thorough medical examination and suicide risk assessment. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

4.3.8 Neurocognitive and Functional Assessments

In this trial, a number of neurocognitive and functional assessments will be administered, some to the patient and some to the caregiver. In addition, a Caregiver Characterization Questionnaire (CCQ) will be completed prior to the administration of the caregiver assessments at each visit. All neurocognitive and functional assessments are to be performed prior to dosing and any potentially stressful procedures (e.g., blood draws, imaging).

The following assessments will be administered to the patient:

- MMSE
- ADAS-Cog
- CDR (patient portion)
- FCSRT
- TMT
- DST
- DSST
- LFT
- CFT

The following assessments will be administered to the caregiver:

- CCQ
- CDR (caregiver portion)
- ADCS-ADL
- Dependence Scale
- NPI

See Appendix *6* for details regarding the neurocognitive and functional assessments.

4.3.9 Laboratory Assessments

Samples for the following laboratory tests will be sent to one or several central laboratories or to the Sponsor for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments.

- Hematology: hemoglobin, RBC count, WBC count, and platelets
- Serum chemistry: sodium, potassium, BUN, estimated glomerular filtration rate, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase, alkaline phosphatase, lactate dehydrogenase, total protein, glucose, cholesterol, triglycerides, and creatine phosphokinase.
- Urinalysis, including dipstick (i.e., pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (e.g., sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria)
- Coagulation: aPTT and INR

- Anti-therapeutic antibodies
- PK assessments: blood samples will be collected for measurement of serum crenezumab concentrations to confirm exposure. On dosing days, PK blood samples will be collected prior to study drug administration unless otherwise specified.
- PD assessments: blood samples will be collected from all patients at specified time points for the determination of total plasma Abeta levels as an exploratory measure of PD response to crenezumab treatment. Additional plasma, serum, and RNA samples will be collected from all patients at specified time points to enable exploratory analysis of biomarkers, their response to crenezumab, and their association with clinical efficacy. [redacted] On dosing days, PD blood samples will be collected prior to study drug administration, unless otherwise specified.

4.3.10 Electrocardiograms

Single ECG recordings will be obtained at each specified time point (see the schedule of assessments in Appendices 1 – 3). ECGs acquired on different days should be as closely time-matched as feasible. If possible, ECGs should be recorded on the same type of machine for each site involved in the study, and the same machine should be used for all ECGs for a specific patient.

Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

4.4 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.4.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. 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

- Patient non-compliance, specifically defined as follows:
  - Patient in the SC cohort misses more than two doses within 6 months
  - Patient in the IV cohort misses more than one dose within 6 months
  - Patients considered non-compliant may need to be withdrawn from the study treatment. Patients should then complete the early treatment discontinuation safety follow-up visit (ET FU Week 8).

Every effort should be made to obtain information on patients who withdraw from the study. Patients who discontinue from the treatment period prior to Week 145 will be asked to return to the clinic within 4 weeks after the last administration of study drug to undergo early termination assessments and should return for additional safety assessments 8 weeks after the early termination assessments. See Appendix 5. 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.

4.4.2 Study Treatment Discontinuation

Patients with a serious, life-threatening adverse event, superficial siderosis of central nervous system, one new cerebral macrohemorrhage, an increase by one or more in the number of symptomatic cerebral microhemorrhages compared with screening, or an increase by six or more in the number of asymptomatic cerebral microhemorrhages compared with screening, as assessed by T2*-weighted GRE MRI, must not receive additional doses of crenezumab, and must be discontinued from the study treatment.

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

4.4.3 Study and Site Discontinuation

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

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Study ABE4689g or ABE4955g is prematurely terminated or fails to demonstrate minimal safety, tolerability, or evidence of activity criteria following completion and evaluation of Study ABE4689g or ABE4955g.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

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:

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Crenezumab has not been approved for use by global health authorities and is currently in clinical development. Thus, the entire safety profile is not known at this time. Human experience is currently limited, and the following information is based on results from nonclinical and clinical studies as well as published data on similar molecules. The safety plan for this study is designed to ensure patient safety and will include specific eligibility criteria and monitoring assessments as detailed below.

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

The occurrence of imaging abnormalities believed to represent cerebral vasogenic edema has been reported in association with the investigational use of compounds that are intended to treat Alzheimer's disease by reducing Abeta in the brain.

These MRI signal hyperintensities seen in the parenchyma and leptomeninges are now more specifically named "amyloid-related imaging abnormalities – edema/effusion" (ARIA-E) to cover the MRI alterations seen in the FLAIR sequence thought to represent edema in the gray and white matter, and effusion or extravasated fluid in the sulcal space (Sperling et al. 2011). These FLAIR signal abnormalities have, in the majority of instances, been asymptomatic, and their presence has been detected by routine brain MRI. 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 (Sperling et al. 2012; Salloway et al. 2009). The mechanisms underlying ARIA-E observed in these trials are unclear but may at least in part be related to FcγR activity of these anti-Abeta antibodies.

When anti-Abeta antibodies bind to amyloid deposited around blood vessels, an FcγR-mediated immune response may be elicited, compromising vascular integrity and resulting in ARIA-E. The hypothesis that FcγR-mediated immune response may contribute to the occurrence of ARIA-E is supported by results from clinical studies that have shown that up to 17% of the patients treated with anti-Abeta antibodies with full effector function developed ARIA-E that was dependent on the dose level and related to

ApoE4 status (Sperling et al. 2012). In that study, the mean number of infusions before detection of ARIA-E was 2.4, and most cases of ARIA-E (69%) were identified after the first or second infusion (Sperling et al., 2012).

Crenezumab, a human IgG4, has reduced FcγR binding compared with IgG1/2 and thus has reduced effector function that theoretically might lower the risk of ARIA-E.

The potential for improved safety of crenezumab is supported by safety observed in both clinical and nonclinical studies. In the completed Phase I study (ABE4427g), no signs or symptoms of ARIA-E (clinical or radiological) were observed following a single dose of up to 10 mg/kg or four weekly doses of up to 5 mg/kg. In the completed Phase II Studies ABE4869g and ABE4955g, a single case of ARIA-E has been observed (see above), supporting the reduced risk of developing ARIA-E with crenezumab. The very low rate of ARIA-E in Studies ABE4869g and ABE4955g supports a reduced frequency of brain MRIs (every 6 months vs. 3 months) in this study. For additional details on clinical studies, see the Investigator's Brochure.

In this OLE study, the following safety monitoring plan has been designed to mitigate and monitor the potential risk of cerebral ARIA-E:

- Patients included in the study will regularly undergo neurologic examinations to evaluate for any neurologic signs or symptoms that are suggestive of the presence of ARIA-E (e.g., confusion, dizziness, vomiting, lethargy).
- Brain MRI (including FLAIR) will be performed at least every 6 months to detect non-symptomatic ARIA-E.
- All MRIs will be read in real time for the evaluation of ARIA-E by independent radiologists at a central contract imaging reader. Study drug will be held if MRI abnormalities consistent with ARIA-E appear.
- Patients who exhibit ARIA-E as assessed by FLAIR MRI will not receive additional study drug until the investigator has determined that ARIA-E has resolved (as assessed by short-interval MRI and clinical evaluation). Treatment with high-dose dexamethasone should be considered if symptoms of ARIA-E are severe.
- Regardless of severity, all events of ARIA-E that occur at any time after receiving study drug are considered to be adverse events of special interest and will be reported in an expedited manner (see Section 5.2.3).

5.1.2 Amyloid-Related Imaging Abnormalities–Hemorrhage (ARIA-H)

Cerebral microhemorrhages (microbleeds [MBs]) are radiologically defined as small dot-like foci of signal loss observed on MRI sequences sensitive for paramagnetic tissue properties (i.e., T2*-weighted or SWI) (Greenberg et al. 2009). This signal loss is caused by residual blood breakdown products, hemosiderin, or iron stored in macrophages in the brain parenchyma around damaged small vessels. The most common causes for this small vessel damage and subsequent leakage are hypertensive vasculopathy and CAA. CAA is believed to predominantly cause MBs in Alzheimer's disease (Cordonnier et al. 2011).

MBs in Alzheimer's disease have a point prevalence of 23% (Cordonnier et al. 2011). One longitudinal study found that in Alzheimer's disease patients the incidence of one or more MBs after a mean follow-up of 2 years was 12% (Goos et al. 2010). Recently, the occurrence of MBs has also been identified as an adverse event in anti-amyloid vaccination trials, and together with superficial siderosis, they have been termed "amyloid-related imaging abnormalities-hemorrhage (ARIA-H) (Sperling et al. 2011). Limited data on ARIA-H occurrence is available, but a recent retrospective analysis in Alzheimer's disease patients treated with anti-Abeta antibodies with full effector function reported that 24 out of 207 participants (11.6%) developed ARIA-H (Sperling et al. 2012). Acute occurrence of MBs is not considered clinically symptomatic (Greenberget al., 2009). In fact, study patients who received active drug and developed ARIA-H without ARIA-E were all clinically asymptomatic (Sperling et al. 2012).

In the *completed* Phase II studies ABE4869g and ABE4955g, patients underwent an MRI assessment at least every 3 months that included a T2*-weighted sequence; new MBs were detected in 11.6% of patients receiving crenezumab and 12.5% of patients receiving placebo. For additional details on clinical studies see the Investigator's Brochure.

In this OLE study, the following safety monitoring plan has been designed to mitigate and monitor the potential risk of cerebral ARIA-H:

- Patients with superficial siderosis of central nervous system, more than eight cerebral microhemorrhages, or evidence of a prior cerebral macrohemorrhage (as assessed by a central reader based on T2*-weighted GRE MRI) will be excluded from the trial.
- Brain MRIs (T2*-weighted GRE sequences) will be performed at least every 6 months to detect superficial siderosis of central nervous system, and cerebral micro- or macrohemorrhages.

- All MRIs will be read in real time for the evaluation of ARIA-H by independent radiologists at a central contract imaging reader. Study drug will be discontinued if patients who exhibit superficial siderosis of central nervous system, one new cerebral macrohemorrhage, an increase by one or more in the number of symptomatic cerebral microhemorrhages compared with screening, or an increase by six or more in the number of asymptomatic cerebral microhemorrhages compared with screening.
- Patients who exhibit new asymptomatic cerebral microhemorrhages, but do not qualify for treatment discontinuation as defined above, will be re-scanned within 8 weeks after the last MRI scan to evaluate their stability.
- Regardless of severity, all events of ARIA-E that occur at any time after receiving study drug are considered to be adverse events of special interest and will be reported in an expedited manner (see Section 5.2.3).

5.1.3 Pneumonia

As described in Section 1.3.3, in the RPCP of Phase II clinical trials in mild-to-moderate Alzheimer's disease (ABBY and BLAZE), there was an imbalance in the rates of pneumonia, with 3.2% (11/346) of crenezumab-treated patients and 0.6% (1/176) of patients on placebo having pneumonia. Of these 12 pneumonia cases, 7 were assessed as serious (4 on crenezumab IV, 2 on crenezumab SC, and 1 on placebo).

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 et al. 2008), but rates (both total and serious) are slightly higher in crenezumab-treated patients (3.2%) and slightly lower in placebo-treated patients (0.6%) than rates reported in the active and placebo arms of clinical trials in Alzheimer's disease (Doody et al. 2014; Henley et al. 2014; Salloway et al. 2014). There is no clinical evidence of immunosuppression (e.g., effects on white blood cells or neutrophils; or pattern of infection type, e.g., opportunistic infections). In addition, no evidence of immunosuppression or of a lung toxicity effect has been observed in preclinical studies. Based on the currently available data, a causal relationship between the drug and events of pneumonia cannot be established or ruled-out. Pneumonia is considered a potential risk and will be monitored closely.

Pneumonia is now considered an adverse event of special interest and should be reported in an expedited manner (see Section 5.2.3).

Patients with signs and/or symptoms suggestive of pneumonia (e.g., cough, fever, pleuritic chest pain) should undergo chest radiography for confirmation of diagnosis. Additional tests might be considered at the discretion of the treating physician. Patients should be treated as per the standard treatment of care, and any change to study drug should be considered within a benefit/risk assessment frame and be in agreement with the Medical Monitor.

5.1.4 Deaths

As described in Section 1.3.3, in the RPCP of the Phase II clinical trials in mild–to-moderate Alzheimer's disease (ABBY and BLAZE), there were 5 deaths. All 5 deaths occurred in patients treated with crenezumab, and none were assessed as related to study drug by the investigator. This represents 1.4% (5/346) of patients receiving crenezumab compared with 0.0% (0/176) of patients receiving placebo. The causes of death are in line with published literature showing no prevalent cause of death among Alzheimer's disease treatment trials (Henley et al. 2012; Henley et al. 2014; Doody et al. 2014).

A causal relationship between crenezumab and the fatal events cannot be established or ruled out. Fatal events will continue to be monitored closely for the identification of any potential pattern (e.g., a more frequent cause of death) or a particular population group at risk (e.g., gender, age group, particular comorbidity). Exposure-adjusted rates will be assessed and compared with published background rates from a similar study population (Henley et al. 2012; Henley et al. 2014).

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9
- 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:

- Fatal (i.e., the adverse event actually causes or leads to death)
- 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 5.3.5.10)
- 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)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- 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 (rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

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

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

Non-serious 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:

- Cerebral vascular edema (ARIA-E)

- Superficial siderosis of central nervous system (ARIA-H)
- Cerebral microhemorrhages (ARIA-H) or macrohemorrhages
- Occurrence of pneumonia regardless of severity/seriousness or relatedness with study drug. Diagnosis is to be verified by imaging (e.g., chest X-ray) (see Sections 3.4.3 and 5.1.3)
- Suspected transmission of an infectious agent by the investigational product, 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.
- 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 5.3.5.6)

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.

Adverse events occurring 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 (e.g., serious adverse events related to invasive procedures such as biopsies). No events during the screening period should be entered into the Adverse Event eCRF; they should be captured in the original study AE CRF (i.e., Abby or Blaze), if within the reported period for those.

Only adverse events and serious adverse events that are unresolved when the patient is randomized (on Day 1) in Study GN28525 should be carefully recorded over to the GN28525 eCRF Database.

After initiation of study drug, all adverse events and serious adverse events, regardless of relationship to study drug, will be reported until at least $8\ weeks$ after the last dose of study drug. After this period, investigators should report any deaths, serious adverse events, or other adverse events of special interest (see 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 time points. 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

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 2 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 1 Adverse Event Severity Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the NCI CTCAE (v4.0), which can be found at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions) per the definition of serious adverse event in 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 or not 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 (see Table 3):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering the effects of discontinuation of study drug, or reintroduction of study drug (where 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

Table 2 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug and, if applicable, reappears upon re-challenge.
NO	AEs will be considered related, unless they fulfill the criteria as specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

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 Diagnosis versus Signs and Symptoms

Adverse events that occur during or within 24 hours after study drug infusion should be captured as individual signs and symptoms rather than a diagnosis of allergic reaction or infusion reaction.

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.

Diagnoses for cerebral vasogenic edema (ARIA-E), superficial siderosis of central nervous system, cerebral microhemorrhage, and cerebral macrohemorrhage will be made based on MRI. It is suggested that the descriptions "cerebral vasogenic edema," "superficial siderosis of central nervous system," "cerebral microhemorrhage," and "cerebral hemorrhage," be used for AE and SAE reporting purposes.

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring 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. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events 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 a mild, non-serious infection, only neutropenia should be reported on the eCRF.
- If neutropenia is accompanied by a severe or serious 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.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution between patient evaluation time points. Such events should only be recorded once in the Adverse Event eCRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded as a separate event on the Adverse Event eCRF. The initial (less severe) adverse event report should be updated to indicate that the event resolved on the date just prior to the day the event became more severe. If a persistent adverse event becomes serious, it should be recorded as a separate event on the Adverse Event eCRF and 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 initial (non-serious) adverse event report should be updated to indicate that the event resolved on the date just prior to the day the event became serious.

A recurrent adverse event is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent adverse events should be recorded on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

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

- 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
- Clinically significant in the investigator's judgment

  For oncology trials, certain abnormal values may not qualify as adverse events.

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 times the upper limit of normal [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 if 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

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

- 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
- 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 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. 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 5.3.5.1) 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 a non-serious adverse event of special interest (see Section 5.4.2).

5.3.5.7 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 Alzheimer's disease.

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

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

5.3.5.8 Pre-Existing Medical Conditions

A pre-existing 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").

5.3.5.9 Worsening of Alzheimer's Disease

Medical occurrences or symptoms of deterioration that are anticipated as part of Alzheimer's disease should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of Alzheimer's disease on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated Alzheimer's disease")

5.3.5.10 Hospitalization or Prolonged Hospitalization

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

The following hospitalization scenarios are <u>not</u> considered to be adverse events:

- Hospitalization for respite care
- Planned hospitalization required by the protocol
- 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 suffered an adverse event
- Hospitalization due solely to progression of Alzheimer's disease

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- *Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available*

5.3.5.11 Adverse Events Associated with an Overdose

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 serious 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).

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

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

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

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Primary Medical Monitor Contact Information for sites in North America:

[redacted] Medical Monitor: [redacted], M.D.

24-Hour Emergency Telephone No.: [redacted]

Primary Medical Monitor Contact Information for sites in Europe:

[redacted] Medical Monitor: [redacted], M.D.

24-Hour Emergency Telephone No.: [redacted]

Alternate Medical Monitor Contact Information:

Medical Monitor: [redacted], M.D., Ph.D.

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

Alternate Telephone No.: (888) 835-2555

5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

For reports of serious adverse events and non-serious adverse events of special interest, investigators should record all case details that can be gathered immediately (i.e., within 24 hours) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to the Sponsor's Safety Risk Management department by the EDC system.

In the event that the EDC system is unavailable, a paper Serious Adverse Event/Non-Serious Adverse Event of Special Interest CRF and Fax Coversheet should be completed and faxed to Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), using the fax numbers provided below. Once the EDC system is available, all information will need to be entered and submitted via the EDC system. *Instructions for reporting post-study adverse events are provided in Section 5.6.*

For Sites in U.S. and Canada:

Fax No.: [redacted]

For Sites in France:

Fax No.: [redacted]

For Sites in Germany:

Fax No.: [redacted]

Alternate Fax No.: [redacted] (pause) [redacted]

For Sites in Spain:

Fax No.: [redacted]

For Sites in United Kingdom:

Fax No.: [redacted]

Relevant follow-up information should be submitted to Genentech's Drug Safety Department or its designee as soon as it becomes available and/or upon request.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within $8\ weeks$ after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Safety Risk Management. 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.

In the event that the EDC system is unavailable, a Pregnancy Report worksheet and Pregnancy Fax Coversheet should be completed and faxed to Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), using the fax numbers provided in Section 5.4.2.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within $8\ weeks$ after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her

pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. 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.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.

5.4.3.3 Abortions

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant events), 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. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information

(e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

At the time of study completion or study discontinuation, the investigator should instruct each patient to report to the investigator any subsequent adverse events that the patient's personal physician believes could be related to prior study drug treatment or study procedures.

The investigator should notify the Sponsor of any death, serious adverse event, or other adverse event of concern occurring at any time after a patient has discontinued study participation if the event is believed to be related to prior study drug treatment. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a female patient exposed to study drug or the female partner of a male patient exposed to study drug.

The investigator should report these events directly to Safety Risk Management via *fax machine using the Serious Adverse Event Reporting Form and fax cover sheet as follows:*

For Sites in U.S. and Canada:

Fax No.: [redacted]; *Alternative Fax No.:* [redacted]

For Sites in Germany:

Fax No.: [redacted]

For Sites in France:

Fax No.: [redacted]

For Sites in the U.K.:

Fax No.: [redacted]

For Sites in Spain:

Fax No.: [redacted]

For Sites in Canada:

Fax No.: [redacted]

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

The Sponsor will promptly evaluate all serious adverse events and non-serious 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

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

6.1 DETERMINATION OF SAMPLE SIZE

This study is open to all patients who completed Study ABE4869g or ABE4955g and who met the eligibility criteria. Accordingly, the sample size for this study is not based on a formal sample size calculation.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue (early discontinuation of treatment or early termination from the study), and complete the study (through Week *153*) will be tabulated by treatment group. Reasons for early discontinuation of treatment or early termination from the study will be listed and summarized by treatment group. Any eligibility criteria exceptions and other protocol deviations will also be summarized by treatment group

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics such as age, sex, race, *ApoE4* status, and baseline MMSE and group assignment in Study ABE4869g and ABE4955g will be summarized for all enrolled patients by use of descriptive statistics.

6.4 SAFETY ANALYSES

The safety analyses will include all enrolled patients who received at least one dose of study drug in this OLE study following their completion of Study ABE4869g or ABE4955g.

These patients will be grouped based on treatment assignment in the OLE study and Study ABE4869g or ABE4955g. Primary safety analysis will be performed after enrolled patients have completed Week *153* visit of the OLE study.

Safety will be assessed by monitoring adverse events, clinical laboratory evaluations, MRI evaluations, and immunogenicity as measured by ATAs. Patients will be analyzed according to actual treatment received.

6.4.1 Adverse Events

Adverse events will be recorded from the time informed consent is given until a patient completes the study or discontinues prematurely. Adverse events reported during the screening period, the *144*-week treatment period, and the *8*-week follow-up period will be summarized separately. Verbatim descriptions of adverse events will be coded and analyzed using appropriate thesaurus terms. A treatment-emergent adverse event is defined as any adverse event reported during or after the first dose of study drug.

6.4.2 Clinical Laboratory Evaluations

Clinical laboratory data (i.e., serum chemistry, hematology evaluations including CBC with differential and platelet counts, urinalysis values) will be summarized by descriptive statistics by treatment group at the end of the final follow-up visit (Week *153*).

6.4.3 MRI Evaluations

Neuroradiologic evaluation with respect to the occurrence of cerebral vasogenic edema, superficial siderosis of central nervous system, and cerebral micro- or macrohemorrhages will be performed during the *153*-week study period and will be summarized by treatment group using descriptive statistics.

6.4.4 Anti-Therapeutic Antibodies

The number and percentage of patients with confirmed positive ATA levels will be reported for each treatment group at the end of the final follow-up visit (Week *153*).

6.5 PHARMACODYNAMIC ANALYSES

Exploratory PD biomarkers will be evaluated in plasma samples collected at specified visits indicated in the study flowchart (see Appendices A1 and A2) and will consist of Abeta species as well as other plasma markers implicated in Alzheimer's disease progression. Individual and mean plasma total Abeta1-40 and Abeta1-42 concentrations versus time data will be tabulated and plotted by dose level.

6.6 PHARMACOKINETIC ANALYSES

Individual and mean serum crenezumab concentration versus time data will be tabulated by dose level, and $C_{trough,\ ss}$ will be reported. Parameters will be tabulated and summarized (e.g., mean, standard deviation, minimum, and maximum). Additional PK analyses may be conducted as appropriate.

6.7 EXPLORATORY ANALYSES

Refer to the Statistical Analysis Plan for analyses related to the exploratory objectives.

6.8 INTERIM ANALYSES

No interim analysis is planned for this study.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

A contract research organization (CRO) will be responsible for the data management of this study, including quality checking of the data. Data entered manually will be collected via electronic data capture (EDC) using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will perform oversight of the data management of this study, and produce an EDC Study Specification document that describes the quality checks to be performed on the data. Central laboratory data and central imaging data will be sent directly to Genentech, using Genentech'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 record 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 using a Sponsor-designated EDC system. 'Sites will receive training and a have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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

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

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

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 of 1996 (HIPAA). 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 9.4).

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

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

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 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.

9.3 ADMINISTRATIVE STRUCTURE

The study is sponsored by Genentech, Inc., a member of the Roche group; crenezumab is being developed by Genentech and AC Immune SA. This trial will be managed by a CRO. Approximately 390 patients will participate in this study at up to 100 centers in North America and Europe.

Patients will be registered in the study using a central IxRS vendor.

All laboratory tests of blood specimens will be performed by a central laboratory or the Sponsor, as appropriate.

A central imaging reader will determine the presence of cerebral vasogenic edema by FLAIR MRI, and the presence of superficial siderosis of central nervous system and cerebral micro- or macrohemorrhages by T2*-weighted GRE MRI scans.

9.4 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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