PROTOCOL

TITLE:	**AN OPEN-LABEL, MULTICENTER, ROLLOVER STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF LONG-TERM ADMINISTRATION OF GANTENERUMAB IN PARTICIPANTS WITH ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	WN41874
VERSION NUMBER:	2
EUDRACT NUMBER:	2019-004431-23
IND NUMBER:	102,266
NCT NUMBER	NCT04339413
TEST PRODUCT:	Gantenerumab (RO4909832)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL DATE:	See electronic date stamp below

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
27-Jan-2022 17:14:28	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
2	See electronic date stamp on title page
1	27 November 2019

PROTOCOL AMENDMENT, VERSION 2:
RATIONALE

Protocol WN41874 has been amended to allow participants who complete dosing visit (Week 104) to continue participation in the study for an additional 2 years. Changes to the protocol, along with a rationale for each change, are summarized below:

- The study has been accordingly divided in to two parts. Part 1 reflects the initial study period of 2 years and Part 2 reflects the study period of additional 2 years beyond the initial 2 years because the safety profile combined with the potential benefit indicates that a longer period of treatment is justified. The protocol body has been updated accordingly to clarify Part 1 from Part 2. Text from Part 1 has also been updated from present to past tense to reflect the completion of Part 1, where applicable.
- To reflect the recent study status in alignment with the Gantenerumab Investigator's Brochure v17, Sections 1.2.1, 1.2.1.4 and 1.2.2 have been updated accordingly.
- Benefit-risk assessment on concomitant administration of severe acute respiratory syndrome coronavirus 2 vaccines with gantenerumab has been added to address a Health Authority request. Section 1.3.3 has been updated accordingly.
- The sample size for Part 1 of the study was not available at the time of writing the protocol, as it was going to be determined by the number of participants who complete OLE part of Studies WN25203 and WN28745. As this number has now been determined. Section 3 has been updated accordingly.
- Sections 4.4.1 have been revised to clarify the Medical Monitor's responsibility to review and support participant cohort management and other protocol activities. Any reference to approval by the Medical Monitor with regards to medical decisions following enrollment has been removed from the protocol. This means that the Principal Investigator (PI) may consult with the Medical Monitor/Sponsor for advice or clarification and may share risk factor information pertinent to the participant, but the medical decisions for the study participants are the responsibility of the PI.
- Section 4.1.1 (Inclusion Criteria) has been updated to:
  - Include the requirement to agree not to donate blood or blood products during the study and for one year after final dose
  - Include the requirement for a caregiver during the study.
- Language has been added to clarify that adverse events associated with a special situation that also qualify as adverse events of special interest should be reported within 24 hours. Section 5.3.5.13 has been updated accordingly.
- Language has been added to indicate that the Informed Consent Form will instruct female participants to inform the investigator if they become pregnant. Section 5.4.3.1 has been updated accordingly.
- The name of a Roche policy on data sharing has been corrected. Section 9.6 has been updated accordingly.

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

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PROTOCOL ACCEPTANCE FORM

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MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor to the contact provided below.

Name
Address

PROTOCOL SYNOPSIS

TITLE:	**AN OPEN-LABEL, MULTICENTER, ROLLOVER STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF LONG-TERM ADMINISTRATION OF GANTENERUMAB IN PARTICIPANTS WITH ALZHEIMER'S DISEASE**
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EUDRACT NUMBER:	2019-004431-23
IND NUMBER:	102,266
TEST PRODUCT:	Gantenerumab (RO4909832)
PHASE:	III
INDICATION:	Alzheimer's disease
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

The main objective of this study *(Part 1 and Part 2)* is to continue to collect long-term safety and tolerability data in participants with Alzheimer's disease (AD) treated with gantenerumab. Specific objectives and corresponding endpoints for the study are outlined below.

Objectives and Corresponding Endpoints

Safety Objective	Corresponding Endpoints
• To evaluate the long-term safety and tolerability of continued treatment with SC gantenerumab at target dose in participants with AD who received gantenerumab in OLEs of Studies WN25203 or WN28745	• Nature, frequency, severity, and timing of AEs and SAEs • Physical examinations (including neurological systems), vital signs, blood tests, ECGs, and C-SSRS • Nature, frequency, severity, and timing of MRI findings: ARIA-E and ARIA-H • Nature, frequency, severity, and timing of injection-site reactions • Immunogenicity of long-term treatment with gantenerumab through the measurements of ADAs • Incidence of treatment discontinuations for AEs • Incidence of AEs of special interest
Exploratory Efficacy Objective	**Corresponding Endpoint**
• To assess the long-term clinical effect in participants with AD	• MMSE total score will be used to assess AD progression
Exploratory Pharmacodynamic Biomarker Objective	**Corresponding Endpoints**
• To evaluate the long-term effect of gantenerumab in participants with AD	• MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, in all participants • Plasma pharmacodynamic biomarkers over time

AD = Alzheimer's disease; ADA = anti-drug antibody; AE = adverse event; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities – hemosiderin deposition; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; MMSE = Mini Mental State Examination; MRI = magnetic resonance imaging; OLE = open-label extension; SAE = serious adverse event; SC = subcutaneous.

Study Design

Description of Study

All participants who had completed the open-label extension (OLE) of Studies WN25203 or WN28745 (i.e., not discontinued from study drug) were eligible for this study.

Participants will receive open-label gantenerumab by subcutaneous (SC) injection every 4 weeks (Q4W) for up to an additional 2 years beyond the initial 2 years of the OLE, followed by a safety and Mini Mental State Examination (MMSE) assessment 4 weeks following the last dose (follow-up visit; see Schedule of Activities). The first dose of open-label gantenerumab will be administered after the participant has signed the Informed Consent Form for this study.

Participants who discontinue study drug at any time during this study will be asked to complete follow-up visits at 4 weeks from their last dose.

Target Population

Inclusion Criteria

All participants who completed the OLEs of Studies WN25203 or WN28745 (i.e., latest version of protocol in their countries, and did not discontinue study drug early) were eligible to participate in Part 1 of the study.

For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 16 weeks after the last dose of study drug.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other

than menopause), and has not undergone surgical sterilization (removal of ovaries, fallopian tubes, and/or uterus).

Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

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

Eligible participants provide written consent signed by them or by the participant's legally authorized representative before his or her participation in the study (in accordance with applicable laws and Institutional Review Board/Ethics Committee policy).

Agreement to not donate blood or blood products for transfusion for the duration of the study and for 1 year after final dose of study drug will be needed for all participants.

Availability of a person (referred to as the "caregiver" throughout this protocol) who in the investigator's judgement, has frequent and sufficient contact with the participant.

Exclusion Criteria

Participants who met any of the following criteria will not be eligible:

- Prematurely discontinued from the OLEs of Studies WN25203 or WN28745 or from study drug for any reason
- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment
- If the participant is unlikely to benefit from gantenerumab therapy, based on disease progression or other factors, or if study participation is otherwise not in the participant's best interest, by determination of the investigator or Sponsor
- Any investigational treatment other than gantenerumab during or since completion of the OLEs of Studies WN25203 or WN28745
- Pregnancy
- Evidence of disseminated leptomeningeal hemosiderosis (i.e., more than three focal leptomeningeal hemosiderosis)
- Evidence of intracerebral macrohemorrhage

Eligibility in Part 2

- *All participants who have completed Week 104 visit in Part 1 of the study and have not been discontinued from Part 1 of the study can continue to participate in Part 2 of the study*
- *The criteria mentioned in Inclusion Criteria and Exclusion Criteria will also be applicable to Part 2 of the study*

End of Study

The end of study is defined as the date when the last participant, last visit (LPLV) occurs or the date on which the last data point required for safety follow-up is received from the last participant in the study*, whichever is later.*

Length of Study

The study will consist of open-label treatment for *2 years beyond the initial* 2 years, with a 4 week post-treatment follow-up period.

Investigational Medicinal Products

*For Part 1, a*ll participants will receive the same dose of gantenerumab SC Q4W as the last dose received in the qualifying studies, either 1200 mg or 900 mg.

For Part 2, all participants will continue to receive the same dose of gantenerumab SC Q4W as the last dose received in Part 1 of the study.

At applicable sites, study drug may be administered by a trained nursing professional at the participant's home or another suitable location, if the participant has given written informed consent to participate in *mobile* nursing visits.

Non-Investigational Medicinal Products

Participants will be permitted to receive any treatment deemed necessary by the investigator for the management of their disease, with the exception of any other disease-modifying drug for AD.

Statistical Methods

Participant disposition (including withdrawals from treatment), protocol deviations, demographic and baseline characteristics (such as age, sex, race, disease stage, and APOE ε4 status) will be summarized descriptively for all participants in the safety population who receive at least one dose of treatment in this study.

To monitor AD progression, MMSE will be summarized using mean, SD, median, inter-quartile range, and minimum and maximum. No hypothesis testing will be performed.

Safety Analyses

The safety analysis population will include all participants who received at least one dose of study drug. The following safety outcome measures will be summarized using descriptive statistics:

- Incidence, nature, severity, and timing of adverse events
- Incidence, nature, severity, and timing of serious adverse events
- Changes from baseline of this study in vital signs, blood tests, ECGs, and Columbia-Suicide Severity Rating Scale (C-SSRS)
- Incidence, nature, severity, and timing of magnetic resonance imaging (MRI) safety findings: amyloid related imaging abnormalities-edema/effusion (ARIA-E) and amyloid-related imaging abnormalities-hemosiderin deposition (ARIA-H)
- Incidence, nature, severity, and timing of injection-site reactions (ISRs)
- Number and proportion of anti-drug antibody (ADA)-positive and ADA-negative participants during both the treatment and follow-up periods
- Incidence of treatment discontinuations for adverse events
- Incidence of adverse events of special interest

Determination of Sample Size

For Part 1, the sample size *was* determined by the number of participants who complete the OLE part of Studies WN25203 or WN28745 and subsequently enroll*ed* in this study. *There were 116 participants that participated in Part 1 of the study.*

For Part 2, the sample size is expected to be no more than 116 participants.

Interim Analyses

No interim analyses *will be* planned *for this study.*

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
Aβ	amyloid-β
AD	Alzheimer's disease
ADA	anti-drug antibody
APOE	apolipoprotein E
ARIA	amyloid-related imaging abnormality
ARIA-E	amyloid-related imaging abnormality–edema/effusion
ARIA-H	amyloid-related imaging abnormality–hemosiderin depositions
BP	blood pressure
COVID-19	coronavirus disease 2019
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
DIAN-TU	Dominantly Inherited Alzheimer Network Trial
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
GCP	Good Clinical Practice
GRE	gradient recalled echo
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Forms
ICH	International Conference for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
ISR	injection-site reaction
IxRS	interactive voice/web response system
IV	Intravenous
LAR	legally authorized representative
LPLV	last participant, last visit
MAD	multiple-ascending dose
MMSE	Mini Mental State Examination
MN	mobile nursing

Abbreviation	Definition
MRI	magnetic resonance imaging
OLE	open-label extension
PD	Pharmacodynamics
PET	positron emission tomography
PI	Principal Investigator
PK	Pharmacokinetic
PK-PD	pharmacokinetic-pharmacodynamic
Q4W	every 4 weeks
RBR	Research Biosample Repository
SC	Subcutaneous
SUVr	standardized uptake value ratio
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ON ALZHEIMER'S DISEASE

The WHO estimates that approximately 50 million people worldwide are living with dementia and that 10 million new cases are diagnosed every year. The total number of people with dementia is estimated to reach 82 million in 2030 and will almost triple to 152 million by 2050. Alzheimer's disease (AD) is the most common form of dementia, accounting for 60%–70% of cases (WHO 2017). The prevalence of AD increases with age, with a global prevalence of 5%–8% in people aged 60 years or over.

AD is clinically characterized by a progressive impairment in cognitive and executive abilities, which results in decreased function and gradual loss of independence (Mesterton et al. 2010). There is great inter-individual variability in AD progression with survival dependent on many factors, including age at onset. In general, the clinical picture evolves from "predementia" or "prodromal AD" to mild, moderate, and then severe AD. At the early stage of AD, a slight impairment of memory, language, and visuospatial function can be observed. As AD advances, patients become progressively impaired and the burden on caregivers significantly increases. The median survival time following a diagnosis of AD depends on the patient's age at diagnosis and ranges from 8.3 years for persons diagnosed with AD at 65 years old to 3.4 years for those 90 years old (Brookmeyer et al. 2002). On average, individuals live 6 years after diagnosis (Helzner et al. 2008).

Pathologically, AD is characterized by the presence of cerebral amyloid-β (Aβ) plaques, neurofibrillary tangles, and a loss of neurons. Aβ is a peptide derived from proteolytic processing of the amyloid precursor protein. This peptide exists in two major forms: $A\beta_{1-40}$ and $A\beta_{1-42}$ (Citron 2004). Although the etiology of AD is not completely understood, current research suggests that Aβ processing and deposition play a critical role in the cascade of biological events involved in the pathogenesis of the disease. Consequently, therapies targeting this process have the potential to significantly alter the progression of the disease.

Because of ADs increasing prevalence, long duration, and high cost of care, it is expected to continue to represent a major public health problem for decades to come.

1.2 BACKGROUND ON GANTENERUMAB

Gantenerumab (or RO4909832) is a fully human anti–Aβ peptide antibody developed by in vitro selection utilizing aggregated Aβ and in vitro maturation within a complete human Igγ, subclass-1 framework (immunoglobulin G1). Gantenerumab recognizes a conformational epitope of Aβ present in aggregated Aβ and that is demonstrated for both major species of Aβ;that is, $A\beta_{1-40}$ and $A\beta_{1-42}$. Gantenerumab has a molecular mass of 146.3 kDa. In vitro, gantenerumab recognizes synthetic aggregated Aβ fibrils and Aβ oligomers with high nanomolar affinity (K_D, ~0.6–1.2 nM). Based on additional in vitro studies and studies in animal models, the pharmacologic profile suggests that in humans,

gantenerumab may prevent, inhibit, and reduce accumulation of Aβ, which is believed to play an important role in the pathogenesis of AD.

Gantenerumab is manufactured by cell culture of a recombinant Chinese hamster ovary–K1 mammalian cell line and subsequent purification of the antibody. The gantenerumab drug substance manufacturing was optimized during development, leading to several manufacturing processes (G1, G2, G3, and G4). In this study, G3 material will be used. Gantenerumab is in clinical development for participants with early (prodromal to mild) AD and is also being investigated in carriers of familial AD mutations (Dominantly Inherited Alzheimer Network Trial [DIAN-TU]) (Bateman et al. 2017).

Refer to the Gantenerumab Investigator's Brochure (IB; version 15, July 2019) for details on nonclinical and clinical studies.

1.2.1 Clinical Studies

Gantenerumab has been investigated in 10 completed Phase I clinical studies: three single-ascending dose studies (BN18726, JP22474, and BP30042) of healthy volunteers and participants with mild to moderate AD, two multiple-ascending dose (MAD) studies (NN19866 and JP22431) of participants with mild to moderate AD, and four bioavailability studies of healthy subjects (one comparing the intravenous [IV] and subcutaneous [SC] formulations of gantenerumab [Study WP22461], two comparing lyophilized and high-concentration liquid formulations of gantenerumab [Studies WP27951 and BP29113], and one comparing G3 and G4 material [Study WP40052]). In addition, a tolerability study comparing the pain between faster and slower SC administrations of gantenerumab has been completed (Study WP39322).

Gantenerumab has also been investigated in two Phase III studies that have been converted to open-label extension (OLE) studies: WN25203 and WN28745. Two additional Phase III studies (WN29922 and WN39658) investigating the effect of gantenerumab in prodromal to mild AD are ongoing.

A total of 543 participants have participated in the Phase I studies; of these, 406 healthy volunteers and 101 participants with AD have received gantenerumab.

In addition, gantenerumab is being investigated in *Dominantly-Inherited Alzheimer's Network Trials Unit (*DIAN-TU-001), a Phase II/III study sponsored by Washington University School of Medicine. *The double-blind, placebo-controlled part of a Phase II/III study, the DIAN-TU-001 concluded (last participant, last visit [LPLV]: 6 March 2020). The DIAN-TU-001 was designed to test the effects of gantenerumab, solanezumab, or JNJ-54861911 versus placebo in individuals at risk for early-onset AD caused by a genetic mutation (i.e., Dominantly-Inherited Alzheimer's disease). The objective of the study was to assess the safety, tolerability, biomarker, and cognitive efficacy of the treatments after 4 years of treatment. The OLE portion of the study, which includes only gantenerumab treatment, is ongoing.*

Results of relevant studies are summarized below. Refer to the gantenerumab IB for further information.

1.2.1.1 Study NN19866

In the MAD study (NN19866), a total of 60 participants (34 males and 26 females) diagnosed with mild to moderate probable AD received multiple IV doses of gantenerumab (doses ranging from 6 mg, 20 mg, 60 mg, and 200 mg) or placebo every 4 weeks (Q4W) for up to 7 months. Owing to amyloid-related imaging abnormalities (ARIAs), or ARIAs of "vasogenic edema" (ARIA-E) and of "hemosiderosis or microbleeds" (ARIA-H), on brain magnetic resonance imaging (MRI) scans that occurred in some participants after two to four doses of 200 mg of gantenerumab in Cohort 4 (200 mg IV Q4W gantenerumab [equivalent to 330 mg SC Q4W] or placebo), it was decided to terminate dosing for all participants on 9 June 2008. The findings resolved spontaneously within 1–4 months after discontinuation of gantenerumab and no participant required treatment.

1.2.1.1.1 Study NN19866: Pharmacodynamic Results in the NN19866 PET-Substudy

In a positron emission tomography (PET) substudy of Study NN19866 (NN19866-PET), the effects of gantenerumab on amyloid load in the brain (defined as standardized uptake value ratio [SUVr] of a cortical composite volume of interest over mean cerebellum gray and using ^{11}C-PiB PET) were evaluated in 18 participants (4 in the placebo group, 8 in the 60-mg IV gantenerumab dose group, and 6 in the 200-mg IV gantenerumab dose group) after 6 months. A mean decrease of 14.9% from baseline was observed in the 200-mg gantenerumab dose group, whereas an increase was seen in the placebo group (mean, 20.9%), with relative stability compared with baseline in the 60-mg group (mean, 5.3%) (Ostrowitzki et al. 2012).

1.2.1.2 Study WN25203

Based on the results from Study NN19866 and a relative bioavailability study WP27951, the doses of 105 mg SC Q4W (equivalent to 60 mg IV Q4W) and 225 mg SC Q4W (equivalent to 130 mg IV Q4W) were selected for Study WN25203. Study WN25203 was designed as a Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of 105 mg and 225 mg of gantenerumab administered subcutaneously Q4W in prodromal AD after two years of treatment. Randomization was based on apolipoprotein E (APOE ε4), allele ε4 status. Selection of gantenerumab doses was largely driven by the objective of reducing risk of MRI findings (in the context of the clinical understanding of ARIAs at the time of study design) and by pharmacodynamic (PD) results in the MAD Study NN19866. Study WN25203 enrolled 799 participants, and 797 participants were treated (the safety-evaluable population).

The results of the preplanned futility analysis of data from approximately 300 participants in Study WN25203 revealed the low likelihood for study success with the original doses

studied. Though no significant differences were observed on clinical outcome measures, additional post-hoc analyses strongly suggested that the doses studied in Study WN25203 (105 and 225 mg) were subtherapeutic and that a higher gantenerumab dose may have a clinically relevant effect (Ostrowitzki et al. 2017).

These post-hoc analyses supported the rationale of converting the study into an OLE with higher doses.

1.2.1.3 Study WN28745

Study WN28745 was initially designed as a Phase III, 2-year, double-blind, placebo-controlled, efficacy, and safety study of gantenerumab in approximately 1000 participants with mild AD. Participants randomized to receive gantenerumab were to follow a slow titration scheme independent of APOE-ε4 genotype, starting at 105 mg of SC gantenerumab Q4W for the first 24 weeks, with progression to 225 mg, based on acceptable results of the control MRI scan. The study enrolled 389 participants, and 387 participants were treated. There were 108 participants also enrolled in a PET substudy of brain amyloid imaging (Study WN28745-PET). Following the Study WN25203 futility analysis, study recruitment was stopped and the study was converted to an OLE study, evaluating the safety and tolerability of gantenerumab at higher doses (up to 1200 mg).

1.2.1.4 OLE Studies WN25203 and WN28745

Both the WN25203 and WN28745 studies were converted to OLE studies to evaluate the long-term safety of higher dose administration of gantenerumab. Doses up to 1200 mg SC Q4W of gantenerumab were tested, using titration regimens designed to minimize the risk of ARIA and taking into account the APOE genotype and the previous double-blind treatment and dose.

The PET substudy also continued in the OLE Studies WN25203 and WN28745 to evaluate target engagement of the higher dose of gantenerumab. The study showed higher reductions of amyloid plaque over a shorter time period with the 1200 mg dosing regimen of gantenerumab compared with 105 or 225 mg dosing. Results from this study confirm the amyloid plaque removal component of the gantenerumab mechanism of action, which is more prominent with high dose administration. Following two years of treatment, approximately 50% of subjects achieved below threshold PET SUVr signals based on quantitative measures, and 74% of subjects were below threshold after three years of treatment. Refer to the gantenerumab IB for further details.

Both of the double blind and OLE studies of WN25203 and WN28745 have been closed.
A total of 385 participants had been enrolled in the OLE Studies WN25203 and WN28745, with 363 participants exposed to G3 gantenerumab doses higher than 225 mg (i.e., more than the highest repeat dose previously tested in participants with AD) and 255 participants having reached the OLE target 1200 mg dose. Injection-site reactions (ISRs) and ARIAs remain the identified risks for gantenerumab. Safety data

and MRI findings have been monitored by Internal Monitoring Committee, which has not identified any new safety signal in these studies.

Refer to the gantenerumab IB for details on nonclinical and clinical studies.

1.2.2 Safety Overview

Nonclinical characterization of gantenerumab did not show any relevant safety findings. To date, ARIAs and ISRs are the identified risks for gantenerumab. No differences between active and placebo groups have been observed in laboratory parameters, physical and neurological examinations, vital signs, or ECG parameters.

Gantenerumab has been generally safe and well-tolerated in healthy volunteers and participants with AD.

The identified risks of gantenerumab treatment are ARIA-E and of ARIA-H, and ISRs.

Both of the double blind and OLE studies of WN25203 and WN28745 have been closed and data monitoring for these studies has been completed. Safety data and MRI findings from the OLEs of Studies WN25203 and WN28745 *were* continuously monitored and no new safety signals *were* identified in these studies where gantenerumab has been administered in doses of up to 1200 mg SC Q4W.

A summary of safety data with gantenerumab SC in participants with AD from Studies WN25203 and WN28745, up to the cutoff date of 1 May 2019, is presented below.

Data from Study JP22431 is presented in Section 5.5.2.1 of the IB, and data from healthy volunteer studies with gantenerumab SC and studies with gantenerumab IV is presented in Section 5.5.1 of the gantenerumab IB.

Overview of Adverse Events

In the double-blind part of Study WN25203, gantenerumab, in doses of 105 mg or 225 mg SC Q4W for up to 3.9 years was safe and well-tolerated by participants with prodromal AD. Adverse events were reported for 94.0%, 88.9%, and 92.3% of participants in the placebo, gantenerumab 105 mg, and gantenerumab 225 mg groups, respectively. Similarly, in Study WN28745, gantenerumab at a dose of 105 mg SC Q4W for 6 months followed by 225 mg SC Q4W for up to 24 months was safe and well-tolerated by participants with mild AD. Adverse events were reported in 80.5% and 82.8% of participants in the placebo and gantenerumab groups, respectively.

In the OLE of Studies WN25203 and WN28745 *(snapshot* date*–11 January 2021),* gantenerumab, in doses of up to 1200 mg SC Q4W for up to approximately 156 weeks (~3 years), was safe and well-tolerated by participants with AD. *In the OLE phase* of *Study WN25203, 1750* adverse events were reported in 14*6* of 154 participants (*94.8*%),

and 2113 adverse events were reported in 209 of 225 participants (92.9%) in Study WN28745.

MRI Findings of Amyloid-Related Imaging Abnormalities

In the double-blind part of Study WN25203, ARIA events were dependent on time (duration of treatment), dose, and APOE ε4 allele status. The frequency of ARIA-E MRI findings was 0.8%, 6.6%, and 13.5% and the frequency of ARIA-H was 13.2%, 22.9%, and 16.2% in the placebo, 105-mg gantenerumab, and 225-mg gantenerumab groups, respectively.

Generally, ARIA events were asymptomatic and resolved spontaneously; discontinuation due to protocol-mandated rules for ARIA-E or ARIA-H occurred in less than 5% of participants.

In the double-blind part of Study WN28745, the frequency of new ARIA-E was 1.5% and 11.5% and the frequency of ARIA-H was 11.8% and 15.1% in the placebo and gantenerumab groups, respectively. Most ARIAs were asymptomatic and did not lead to clinically significant consequences. One participant (0.5%) in the placebo and gantenerumab groups each reported symptoms related to ARIA, which were mild to moderate and non-serious. Discontinuation due to protocol-mandated rules for ARIA-E or ARIA-H occurred in approximately 3.4% of participants.

In the OLE part of Study WN25203, all 154 participants dosed with gantenerumab *in the OLE* had *at least one* post-*OLE* baseline MRI scan. *Of these,* 47 participants (30.5%) had new ARIA-E and *51 participants (33.*1%) had new ARIA-H. *Additionally, 31 participants (20.1%) had new ARIA-*E *and new ARIA-H at any point during the OLE. The* CNS adverse events *temporally associated ARIA-E MRI findings* were mostly *non-serious,* mild to moderate in intensity, *and resolved spontaneously with protocol-defined ARIA management rules. None of these adverse events led to* permanent *discontinuation* of study treatment.

In OLE *part* of *the* Study WN28745 *and up to snapshot date of 11 January 2021*, 219 of 225 participants dosed with gantenerumab *in the OLE phase* had a post-baseline MRI scan. *Of these,* 71 participants (32.4%) had new ARIA-E and *75 participants (34.*24%) had *new ARIA-H. Additionally, 49 participants (22.37%) had new ARIA-E and* ARIA-H *at any point during the OLE.* The CNS adverse events were mostly mild to moderate in intensity, non-serious, did not require permanent cessation of study treatment, and resolved spontaneously with protocol-defined ARIA management rules. *None of these adverse events led to permanent discontinuation of study treatment.*

To minimize ARIA occurrence, the highest dose level is reached with a gradual up-titration; ARIA-E incidence observed in the OLEs has been in the expected range and in alignment with the ARIA-E pharmacokinetic-pharmacodynamic (PK-PD) model

(see Section 5.1 of the Gantenerumab IB). ARIA-*E events* are clinically manageable by protocol-defined MRI monitoring and dose intervention algorithms.

Injection-Site Reactions

In the double-blind part of Study WN25203, the incidence of ISRs was 4.5%, 18.8%, and 23.1% in the placebo, 105-mg gantenerumab, and 225-mg gantenerumab group, respectively. In the double-blind part of Study WN28745, the incidence of ISRs was 1.0% and 9.4% in the placebo and gantenerumab groups, respectively. The most common ISR was erythema.

In the OLE *phase* of Studies WN25203 and WN28745 *(snapshot date–11 January 2021),* ISRs have been reported in 36.4% of participants (56 of 154) in Study WN25203, and *40.0*% of participants *(90* of 225) in Study WN28745. Overall, 5.4% of participants (3 of 56) in the OLE of Study WN25203 and *11.1% of participants (*10 of *90*) in the OLE of Study WN28745 who had ISR received treatment, which included topical steroids and antihistamines.

In both studies, across phases, all ISRs were non-serious, most were of mild intensity and resolved without requiring treatment. The most common ISR was erythema, both in the double-blind phase and the OLE phase of Studies WN25203 and WN28745.

Refer to the gantenerumab IB for safety data from all studies.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Currently, approved therapies for AD focus on symptomatic approaches that target synaptic function and cognitive enhancement (Cummings 2004). However, the amyloid hypothesis suggests that overproduction of Aβ or failure to effectively clear this peptide contributes to AD (Selkoe and Hardy 2016) and that accumulation of Aβ peptides is one factor contributing to AD progression (Sun et al. 2015). Thus, the targeting of Aβ and subsequent displacement of Aβ from the brain is a rational approach to modify AD progression.

Despite compelling results in AD animal models (Wisniewski and Goñi 2014), clinical success with passive immunization targeting brain amyloid in global Phase III studies remains an unachieved goal. It has been suggested that lack of sufficient target engagement of anti-amyloid antibodies has been a factor in the failure of these Phase III studies (Cummings et al. 2016). An important advancement for therapies targeting aggregated amyloid was provided based on data from the Phase Ib PRIME study of aducanumab (Biogen) (Sevigny et al. 2016).

Accumulating clinical evidence also supports that monoclonal Aβ antibodies can bind Aβ and promote its clearance (Salloway et al. 2009; Ostrowitzki et al. 2012; Sevigny et al. 2016; Klein et al. 2017), reduce deposition of Aβ aggregates, and reduce

markers of neurodegeneration in the cerebral spinal fluid (Ostrowitzki et al. 2017). A Phase I study of aducanumab (Sevigny et al. 2016) and a Phase II study of BAN2401 (Swanson et al. 2018) suggested that reduction of deposited amyloid, as seen on brain amyloid PET imaging was associated with a dose-related slowing of cognitive decline.

1.3.1 Study Rationale

The rationale of this study is to continue to collect long-term safety and tolerability data in participants with AD treated with gantenerumab.

The rationale of continuous administration of gantenerumab is supported by data from the PET substudy in the OLE Studies WN25203 and WN28745 that showed continuous reduction of the amyloid plaque component beyond two years of treatment.

1.3.2 Rationale for Dosing Strategy

Rationale for the Dosing Strategy in Part 1

All participants received the same dose of gantenerumab SC Q4W as the last dose received in the qualifying studies, either 1200 mg or 900 mg. Participants who had a dose gap between the last visit from the WN25203/WN28745 OLE and this study, depending on the actual duration of the dosing gap and their ARIA history, may be asked to start with a lower dose, as detailed in Appendix 3 and then be up-titrated to the target dose.

Rationale for the Dosing Strategy in Part 2

All participants will continue to receive the same dose of gantenerumab SC Q4W as the last dose received in Part 1 of the study.

1.3.3 Overall Benefit–Risk Summary

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

- Gantenerumab has shown evidence of reducing amyloid plaques (i.e., observed evidence of brain amyloid reduction, see Section 1.2.1.4) and, thus, shows potential benefit in slowing the progression of AD.
- Findings from the WN25203 and BAN2401 studies (Swanson et al. 2018) provide additional support for the hypothesis that anti-amyloid treatment may be associated with a beneficial clinical effect.
- Results from the double-blind part of Studies WN25203 and WN28745, as well as from the OLEs of Studies WN25203 and WN28745, showed that ARIA-E findings are mostly asymptomatic, non-serious, of mild severity, and do not require permanent cessation of treatment. ARIAs are manageable with MRI monitoring and dose intervention algorithms, as detailed in Section 5.1.2.
- No new safety signal has been identified in data from the OLEs of Studies WN25203 and WN28745 with doses of up to 1200 mg Q4W. These data support the continued administration of gantenerumab at doses up to 1200 mg Q4W in both APOE ε4 carriers and non-carriers in this study.

- *Based on its mechanism of action, there is no reason to believe that gantenerumab administration would compromise the immunologic reaction of the body. This is supported by the nonclinical and clinical data collected through the development program of gantenerumab, where there has been no indication that gantenerumab administration compromised immune system or made individuals more susceptible to infections. Thus, there are no data or biological rationale suggesting that gantenerumab administration could increase the risk of infection by severe acute respiratory syndrome coronavirus 2 or more severe coronavirus disease 2019 (COVID-19) outcomes. Whereas people with AD, because of advanced age, may be in a higher-risk group for COVID-19, participation in Study WN41874 is not expected to increase that risk.*
- *Based on the available information, no interactions between gantenerumab and the COVID-19 vaccines are expected to occur, and no other safety concerns have been identified that would prohibit the vaccination of participants enrolled in the studies where gantenerumab is being investigated for the treatment of AD. Just as with other vaccinations (e.g., influenza), the administration of COVID-19 vaccines will be considered as a concomitant medication in this study.*

Overall, the benefit–risk profile of gantenerumab *supports open-label gantenerumab treatment* in *Study WN41874* for participants who completed the OLE *part*s of Stud*y* WN25203 *or* WN28745.

2. OBJECTIVES AND ENDPOINTS

The main objective of this study *(Part 1 and Part 2)* is to continue to collect long-term safety and tolerability data in participants with AD treated with gantenerumab. Specific objectives and corresponding endpoints for the study are outlined in Table 1.

Table 1 Objectives and Corresponding Endpoints

Safety Objective	Corresponding Endpoints
• To evaluate the long-term safety and tolerability of continued treatment with SC gantenerumab at target dose in participants with AD who received gantenerumab in OLEs of Studies WN25203 or WN28745	• Nature, frequency, severity, and timing of AEs and SAEs • Physical examinations (including neurological systems), vital signs, blood tests, ECGs, and C-SSRS • Nature, frequency, severity, and timing of MRI findings: ARIA-E and ARIA-H • Nature, frequency, severity, and timing of injection-site reactions • Immunogenicity of long-term treatment with gantenerumab through the measurements of ADAs • Incidence of treatment discontinuations for AEs • Incidence of AEs of special interest
Exploratory Efficacy Objective	**Corresponding Endpoint**
• To assess the long-term clinical effect in participants with AD	• MMSE total score will be used to assess AD progression

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Pharmacodynamic Biomarker Objective	Corresponding Endpoints
• To evaluate the long-term effect of gantenerumab in participants with AD	• MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, in all participants • Plasma pharmacodynamic biomarkers over time

AD = Alzheimer's disease; ADA = anti-drug antibodies; AE = adverse event; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; MMSE = Mini Mental State Examination; MRI = magnetic resonance imaging; OLE = open-label extension; SAE = serious adverse event; SC = subcutaneous

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design *in Part 1*

This is an open-label, multicenter, rollover study to evaluate the safety and tolerability of long-term administration of gantenerumab in participants with AD.

All participants who had completed the OLEs of Studies WN25203 or WN28745 were eligible to participate in this study. Participants, who discontinued early from study treatment during Study WN25203 or WN28745, regardless of the reason, were not eligible for this study.

Informed consent was obtained by participants while they were active in the qualifying study. In the case of protocol approval delays, informed consent could be obtained at a later timepoint, but before any study procedures in this study are performed.

The first administration of gantenerumab in this part of the study will be considered the baseline visit and, whenever possible, should coincide with the first post-treatment follow-up visit of OLEs of Studies WN25203 or WN28745. The data of the follow-up assessments will be used as baseline data for this study if they take place on the same day or within a period of 4 weeks. Magnetic resonance imaging, Mini Mental State Examination (MMSE), and Columbia-Suicide Severity Rating Scale (C-SSRS) do not need to be repeated if the baseline occurs in less than 6 months from the final follow-up visit in the previous parent study. MRI and urine pregnancy test results should be available before dosing.

In this study, participants will continue receiving open-label gantenerumab by SC injection Q4W at the same dose as administered in the parent Studies WN25203 or WN28745. There is a ± 7 day window for all visits. However, the minimal time between doses is 21 days, and the target day for each Q4W visit is timed with respect to baseline, not to the prior visit.

Participants who had a dose gap between the last visit from the WN25203/WN28745 OLE and this study *(Part 1),* depending on the actual duration of the dosing gap and their ARIA history, may be asked to start with a lower dose, as detailed in Appendix 3.

In the case that a participant had at the baseline visit an ARIA-E that was ongoing since the parental study, there was a continuity of ARIA management between the two studies, and ARIA management rules as described in Appendix 2 will apply.

Participants will be treated for 2 years, followed by a safety and MMSE assessment 4 weeks following the last dose (follow-up visit; see Schedule of Activities).

Participants who discontinue study drug at any time during this study will be asked to complete an early termination visit 4 weeks after their last dose (early termination visit; see Appendix 1).

3.1.2 *Overview of the Study Design in Part 2*

All participants who are actively enrolled in Part 1 of Study WN41874 (i.e., have completed Week 104 visit in Part 1 and have not discontinued from study drug per Section 4.6.1) will be invited to participate in Part 2 of the study.

Informed consent should be obtained by participants while they are active in the Part 1 of the study.

In Part 2 of the study, participants who have previously completed the Week 104 visit, (i.e., without having to perform a follow up visit post Week 104 in Part 1) can continue receiving open-label gantenerumab for additional 2 years. Additionally, participants might also have an option of participating in another open label extension study while completing the Part 2 of the study.

Gantenerumab will be administered by SC injection Q4W at the same dose as administered in the Part 1 of the study. There is a ±7 day window for all visits. However, the minimal time between doses is 21 days, and the target day for each Q4W visit is timed with respect to baseline, not to the prior visit.

Participants will be treated for an additional 2 years, followed by a safety and MMSE assessment 4 weeks following the last dose (follow-up visit; see Appendix 1). Participants will undergo tests of safety, efficacy as per the schedule of assessments.

The end of the study will be considered as the follow-up visit 4 weeks after the last dose for the last participant *that enrolled over to Part 2.*

All participants have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason.

Participants who discontinue study drug at any time during this study will be asked to complete a follow-up visit at 4 weeks after their last dose (*early termination visit; see Appendix 1*).

Participants who do not want to participate in Part 2 of the study will be discontinued from the study and will be asked to complete follow up visit *4 weeks after the last dose as per the Schedule of Assessments (follow up visit; see Appendix 1*).

3.1.3 Internal Monitoring Committee

For Part 1 and Part 2

During the study, the nature, frequency, severity, and timing of adverse events, serious adverse events, ARIA-E and ARIA-H findings, ISRs, and laboratory and other test abnormalities will be assessed on a regular basis by an IMC.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study is defined as the date when the LPLV occurs or the date on which the last data point required for safety follow-up is received from the last participant in the study*, whichever is later*.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Gantenerumab Dose and Schedule *Part 1*

All participants will receive the same dose of gantenerumab SC Q4W as the last dose received in the qualifying studies, either 1200 mg or 900 mg.

Participants who ha*d* a dose gap between the last visit from the OLEs of Studies WN25203/WN28745 and *Part 1 of the* study due to unforeseen circumstances, depending on the actual duration of the dosing gap and their ARIA history, may be asked to start with a lower dose, as detailed in Appendix 3. Before up-titration to the target dose, three administrations of a lower dose have to take place.

Rationale for Gantenerumab Dose and Schedule Part 2

All participants will continue to receive the same dose of gantenerumab SC Q4W as the last dose received in Part 1 of the study.

3.3.2 Rationale for Pa*rticipant* Population

In Part 1, participants with AD who ha*d* completed the OLEs of Studies WN25203 or WN28745 *were* eligible to participate in *Part 1 of the* study, to evaluate long-term safety and tolerability of gantenerumab. Thus, per eligibility criteria for this study, all participants who ha*d* completed the OLEs of Studies WN25203 or WN28745 and meet all the eligibility criteria, *were* able to participate in the study.

In Part 2, participants with AD who have completed the Week 104 visit in Part 1 and have not discontinued from study drug per Section 4.6.1, will be given the option to

continue to participate in Part 2 of the study, to evaluate long-term safety and tolerability of gantenerumab

3.3.3 Rationale for Key Endpoints *(Part 1 and Part 2)*

The primary objective of this study is to collect long-term safety and tolerability data for gantenerumab.

3.3.4 Rationale for Study Treatment Duration

This study will continue providing gantenerumab to the participants who completed the OLEs of Studies WN25203 or WN28745*, and Part 1 of Study WN41874 for an additional 2 years beyond the initial 2* years to collect long-term safety and tolerability data for gantenerumab.

3.3.5 Rationale for Biomarker Assessments

Biomarker assessments will be used to investigate, in an exploratory fashion, the effect of gantenerumab on the underlying pathology of AD in the clinical study population.

3.3.5.1 Blood Biomarkers

Blood samples will be obtained from all participants and will be used for research purposes to identify dynamic biomarkers that may help to understand the response to treatment with gantenerumab (in terms of dose, safety, and tolerability) and will help to better understand the pathogenesis, course, and outcome of AD and related diseases.

Roche may keep information about test results, medical history, and demographic information for all participants for future development of diagnostic tests related to Aβ, APOE genotype, and AD, as well as additional analyses.

3.3.5.2 Brain Volumetry

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

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

4. MATERIALS AND METHODS

4.1 PARTICIPANTS

In Part 1, participants who completed the OLEs of Studies WN25203 or WN28745 *were* eligible to participate. Participants who discontinued early from study treatment during OLEs of Studies WN25203 or WN28745 (for any reason) *were* not be eligible *in Part 1 of the* study.

In Part 2, participants with AD who have completed the Week 104 visit in Part 1 and have not discontinued from study drug per Section 4.6.1, will be given the option to continue to participate in Part 2 of the study.

4.1.1 Inclusion Criteria

All participants who completed the OLEs of Studies WN25203 or WN28745 (i.e., latest version of protocol in their countries, and did not discontinue study drug early) *we*re eligible to participate in *Part 1 of the* study.

For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 16 weeks after the last dose of study drug.

A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries, fallopian tubes, and/or uterus).

Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

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

Eligible participants provide written consent signed by them or by the participant's legally authorized representative (LAR) before his or her participation in the study (in accordance with applicable laws and Institutional Review Board [IRB]/Ethics Committee [EC] policy).

Agreement to not donate blood or blood products for transfusion for the duration of the study and for 1 year after final dose of study drug will be needed for all participants.

Availability of a person (referred to as the "caregiver" throughout this protocol) who in the investigator's judgement, has frequent and sufficient contact with the participant.

4.1.2 Exclusion Criteria

Participants who met any of the following criteria *will* not be eligible:

- Prematurely discontinued from the OLEs of Studies WN25203 or WN28745 or from study drug for any reason
- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment
- If the participant is unlikely to benefit from gantenerumab therapy, based on disease progression or other factors, or if study participation is otherwise not in the participant's best interest, by determination of the investigator or Sponsor
- Any investigational treatment other than gantenerumab during or since completion of the OLEs of Studies WN25203 or WN28745
- Pregnancy
- Evidence of disseminated leptomeningeal hemosiderosis (i.e., more than three focal leptomeningeal hemosiderosis)
- Evidence of intracerebral macrohemorrhage

4.1.3 Eligibility in Part 2

- *All participants who have completed Week 104 visit in Part 1 of the study and have not been discontinued from Part 1 of the study can continue to participate in Part 2 of the study*
- *The criteria mentioned in Sections 4.1.1 and 4.1.2 will also be applicable to Part 2 of the study*

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This study is an open-label study, and each participant enrolled will be administered the same dose of gantenerumab that was received at the final dosing visit.

For Part 1, participants who ha*d* a dose gap between the last visit from the WN25203/WN28745 OLE and this study, depending on the actual duration of the dosing gap and their ARIA-E history, may be asked to start with a lower dose, as detailed in Appendix 3.

An interactive (voice/web) response system (IxRS) will be used to manage participant, enrollment and drug supply. The participant number will be allocated *in* IxRS and will be used in the clinical database and for recording data in the electronic Case Report Form (eCRF). The enrollment call to the IxRS should occur on Day 1 after the participant's eligibility (i.e., eligibility criteria) has been confirmed.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

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

At applicable sites, study drug may be administered by a trained nursing professional at the participant's home or another suitable location, if the participant has given written informed consent to participate in *mobile* nursing (*MN*) visits.

4.3.1 Formulation, Packaging, and Handling

Gantenerumab is available in the following drug product formulation: 2 mL vials (300 mg/vial) from which drug product needs to be withdrawn via a disposable syringe. The study drug can be delivered SC either using multiple syringes, or using a syringe pump. Syringe pumps offer a significant advantage over manual administration because they allow delivering higher volumes of the study drug at a defined injection rate.

All formulations should be stored at 2°C–8ºC and protected from light. All drug product solutions should be brought to room temperature prior to administration to minimize discomfort during the injection.

Liquid vials: Gantenerumab must be prepared for dosing under appropriate aseptic conditions as it does not contain antimicrobial preservatives. The dose solution should be used immediately. If not used immediately, the total storage time of the dose solution prior to administration should not exceed 24 hours to limit the risk of microbiological growth in case of accidental contamination. The recommended storage condition for the dose solution is 2°C–8°C, but dose solutions may be stored at room temperature for up to a maximum of 4 hours.

Packaging of the study drug will be overseen by the Roche Clinical Trial Supplies Department and will bear a label with the identification required by local law, the protocol number, study drug identification, and dose. The packaging and labeling will be in accordance with Roche standard and local regulations. Upon receipt of the investigational products at the site, site personnel should check the product for damage and verify the proper identity, quantity, and integrity of the study drug. Site personnel should report any deviations or product complaints to the monitor upon discovery. *For further details, please* refer to the Gantenerumab Investigator's Brochure.

For information on the formulation and handling of gantenerumab, see the pharmacy manual and Gantenerumab Investigator's Brochure.

Refer to the pharmacy manual and other applicable manuals for detailed instructions on drug preparation, storage, and administration.

4.3.1.1 Non-Investigational Medicinal Products

Not applicable.

4.3.1.2 Compliance

Participants who are non-compliant with the study and/or study procedures, defined as missing more than three consecutive dose administrations or more than half of the dosing visits in a calendar year, because of non-safety-related reasons, may be allowed to continue in this study *after consulting with* the Medical Monitor.

4.3.2 Investigational Medicinal Product Accountability

All IMPs required for completion of this study will be provided by the Sponsor *where required by local regulations.* The *study site (i.e., investigator or other authorized personnel [e.g., pharmacist or mobile nurse]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, IMP distribution to each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received and ensuring that participants are provided with doses specified by the protocol.*

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs *supplied by the Sponsor*, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. *The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received at the site and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs shipped to the site must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.*

Only participants enrolled in the study may receive the IMP, and only authorized staff may supply the IMP, and only authorized staff may administer the IMP.

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

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the *drug accountability log*.

Refer to the pharmacy manual and/or the home administration manual and Gantenerumab Investigator's Brochure for information on IMP handling, including preparation, storage, and accountability.

4.3.3 *Continued* Access to Gantenerumab

The Sponsor will *offer continued access* to *Sponsor study drug (*gantenerumab*) free of charge* to *eligible* participants *in accordance with the Roche Global Policy* on *Continued Access to Investigational Medicinal Product, as outlined below.*

A participant will be eligible to receive Sponsor study drug (gantenerumab) after completing the *study if all* of *the following conditions are met:*

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

A participant will not be eligible to receive Sponsor study drug (gantenerumab) after completing the study if any of the following conditions are met:

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

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

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

Eligible participants may qualify for continued access or ongoing extension studies *as outlined above.*

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the counter drugs, *vaccines,* herbal/homeopathic remedies, nutritional supplements) used by a participant 6 months prior to baseline (Day 1) to the study completion visit. All *such* concomitant medications *(including name, dose, administration schedule, start and end dates)* should be reported to the investigator and recorded on the Concomitant Medications Case Report Form (CRF).

4.4.1 Permitted *and Prohibited* Therapy

Participants will be permitted to receive any treatment deemed necessary by the investigator for the management of their disease, with the exception of any other disease-modifying drug for AD. For anticoagulant medications, short-term, perioperative use of anticoagulant medications will not result in permanent discontinuation from the study; however, any such use *it is recommended to* prospectively *seek advice from* the Medical Monitor and temporary study drug interruption *may be required*.

4.5 STUDY ASSESSMENTS

The study assessments are detailed in the following sections. Please see Appendix 1 for the Schedule of Activities.

At applicable sites, certain study assessments may be performed by a *MN* professional at the participant's home or nursing center to improve access and convenience for participants participating in the study. *Mobile nursing can be provided for the visits where attendance at the study site is not considered necessary (i.e., at visits except for Week 24, Week 52, Week 76, Week 104, Week 128, Week 156, Week 180, and Week 208).* The Sponsor will select a healthcare company that will be responsible for providing HN services for participating sites (the *M*N vendor). The *MN* vendor is responsible for ensuring that all *MN* professionals are licensed, qualified, and in good standing, per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that *M*N services are appropriate for a participant and the participant gives written informed consent to participate in *M*N visits, the *M*N network will communicate with the participant and the participant's site. *Mobile nursing* visits will be scheduled on specified visit days to allow relevant assessments to be performed by the *M*N professional.

4.5.1 Informed Consent Forms and Screening Log

The Sponsor's sample Informed Consent Form (ICF) (and ancillary sample ICFs such as *M*N ICF, 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 ICFs 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.

All participants and caregivers must review, sign, and date the most current IRB/EC-approved written ICF(s) before any study-specific assessments or procedures are performed.

Where approved as per local regulations, the participant's LAR may sign/co-sign the ICF if the participant is no longer able to provide consent. However, participants will need to

provide assent that should be documented at the site level. Participants who do not sign the ICF will be discontinued from the study.

An optional substudy may be introduced to obtain post-mortem brain tissue from participants for evaluation of the effect of long-term gantenerumab therapy on the brain. The opportunity to donate post-mortem brain tissue may be discussed with participants, and interested participants would be provided with additional details. Any further procedures, with respect to this optional substudy, will be governed by a separate Consent Form and separate protocol document.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history and *demographic data* collected in the OLEs of Studies WN25203 and WN28745 will be used in this study and should include clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), *reproductive status* smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs*, vaccines*, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the participant within 6 months prior to the baseline visit (Day 1). Demographic data will include age, sex, and self-reported race/ethnicity. Adverse events, resolved or ongoing, reported in the OLEs of Studies WN25203 and WN28745, will be considered as medical history in this study. *Medical history and demographic data will be automatically transferred to the Study WN41874 eCRF.*

4.5.3 Physical Examinations

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

At subsequent visits *(for Part 1 and Part 2),* per the Schedule of Activities (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Change from baseline abnormalities should be recorded in the participant's notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the adverse event eCRF.

In Part 1 of the study, the baseline physical examination results for the participants of this study will be the same as in the post-treatment follow-up visit in Studies WN25203 and WN28745 if they occur on the same day or within 4 weeks. The information will be recorded in the eCRF at the baseline (Day 1) visit. If the two visits occur more than 4 weeks apart, the physical examination has to be repeated.

4.5.4 Vital Signs

Vital signs (systolic and diastolic blood pressure [BP], heart rate, and temperature) will be measured as per the Schedule of Activities. Blood pressure and heart rate should *be taken when the participant is at rest and should* not be measured unless 15 minutes have elapsed since the last blood draw. The same arm should be used for all BP measurements.

In Part 1 of the study, the vital signs assessments for the participants in this study at baseline will be the same as in the post-treatment follow-up visit in Studies WN25203 and WN28745 if they occur on the same day or within 4 weeks. If the two visits occur more than 4 weeks apart, then the assessment will need to be repeated and the information will be recorded in the eCRF at the baseline (Day 1) visit.

Vital sign measurements may be performed by a MN professional.

4.5.5 Cognitive Assessments

The cognitive assessment is the MMSE and will be collected as specified in the Schedule of Activities (see Appendix 1).

The MMSE will be provided as a paper scale and will be entered in designated eCRF.

The MMSE is a set of standardized questions used to evaluate possible cognitive impairment and help stage the severity level of this impairment. The questions target six areas: orientation, registration, attention, short-term recall, language, and constructional praxis/visuospatial abilities. *The assessment will be completed only by a certified MMSE rater.*

In Part 1 *of the study, the baseline (Day 1)* MMSE for the participants will be the same as in the post-treatment follow-up visit in Studies WN25203 and WN28745. If the last MMSE assessment is completed more than 6 months from the baseline visit, the assessment has to be repeated*, and will be recorded in the eCRF at the baseline (Day 1) visit.*

4.5.6 Laboratory Assessments

Samples for the following laboratory tests will be sent to a central laboratory for analysis. The baseline laboratory assessment *(Part 1 of the study)* results for the participants participating in this study will be the same as in the post-treatment follow-up visit in Studies WN25203 and WN28745 if they occur on the same day or within 4 weeks. If the two visits occur more than 4 weeks apart, the laboratory assessments have to be repeated.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

- **Serum Chemistry**: AST/SGOT, ALT/SGPT, alkaline phosphatase, total protein, total bilirubin, serum albumin, CPK, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory)
- **Hematology**: Hemoglobin, hematocrit, RBC (with morphology), WBC, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC–other total counts
- **Coagulation**: Prothrombin time
- **Urine for Pregnancy**: Urine pregnancy testing will be performed at each dosing *visit (prior to dose administration) and at follow up/early termination/unscheduled* visit for women of childbearing potential (including those who have had a tubal ligation), and at the site for any other female participants if required by local regulations. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory.
- **Anti-Drug Antibody Sampling:** Plasma samples will be collected to assess the possible development of anti-drug antibodies (ADAs) in all participants as noted in the Schedule of Activities (see Appendix 1). Unused sample material may also be used for the purposes of current ADA assay improvement.
- **PK samples**: Collection of a PK plasma sample at the time of the ADA sample collection is required for the ADA assessment. Plasma samples will be collected to evaluate the plasma levels of gantenerumab for ADA assessment as per Schedule of Activities.
- **Biomarker Samples**: Plasma samples will be collected at baseline (Day 1) before dosing, once yearly, at the end of the study, *and at early termination visit* (for details see Schedule of Activities [Appendix 1]) for exploratory research on biomarkers and biomarker assay development

Biomarker research may include, but will not be limited to amyloid assessments.

Unless the participant gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.10), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- PK and ADA samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Biomarker plasma samples collected for biomarker research and biomarker assay development will be destroyed no later than 5 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the IRB/EC-approved ICF and applicable laws (e.g., health authority requirements).

When a participant withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the participant specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

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

4.5.7 Electrocardiograms

After 5 minutes in a supine position, a single 12-lead ECG read will be performed at baseline and any time during the study if deemed necessary by the investigator. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

All ECGs will be performed using a local ECG device. ECGs for each participant should be only obtained from the same machine, where possible. On visits where ECGs and other laboratory assessments are performed, ECGs should be performed prior to any blood draws, and brain MRI scans. ECG characteristics, including heart rate, QRS duration, and RR, PR, and QT intervals, will be evaluated by the Principal Investigator (PI) and ensure there are no clear alerts for quality or clinical issues and then sign and date the outputs.

Paper copies of ECG tracings will be kept as part of the participant's permanent study file at the site.

4.5.8 Columbia-Suicide Severity Rating Scale

The C-SSRS (http://www.cssrs.columbia.edu) is an assessment tool used to assess any new instances of suicidality (C-SSRS >6 months since last visit). The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual or potential lethality. The C-SSRS since the last visit will be collected at visits as indicated in the Schedule of Activities (see Appendix 1). The assessment will be completed by a certified C-SSRS rater after he or she interviews the participant and the participant's caregiver during the study visit.

The baseline (Day 1) C-SSRS for the participants participating in this study will be the same as in the post- treatment follow-up visit in Studies WN25203 and WN28745. If the last C-SSRS assessment was completed more than 6 months from the baseline visit, the assessment has to be repeated*, this* will be recorded in the eCRF *at the baseline (Day 1) visit.*

4.5.9 Brain Magnetic Resonance Imaging

The MRI should be performed using 1.5-T or 3.0-T scanners, and the same scanner is strongly preferred for an individual participant for the full duration of the study. Only scanners approved for use in the study should be used. MRI will be conducted at baseline for safety monitoring prior to dosing and for structural brain volumes measures. Magnetic resonance imaging will be used during the study to help assess safety such as the occurrence of microbleeds or signs potentially indicative of inflammation or ARIA-E. Additional unscheduled MRI scans may be utilized to better understand relevant CNS related-adverse events (such as increased confusion) or to follow a sign that emerges at a scheduled scan; contrast agent may be used in such a case of follow-up if administration of contrast agent is considered safe for the participant according to local standards.

MRI scans will include the following sequences:

- 3D T_1-weighted gradient recalled echo (GRE) scans
- T_2*-weighted GRE scans
- T_2-weighted fluid-attenuated inversion recovery (FLAIR) scans

The MRI will take approximately 30 minutes to complete.

The MRI scans will be reviewed by a central MRI core laboratory, which will perform the diagnostic reads and assessment of MRI outcome measures. Magnetic resonance imaging scans should preferably be transferred to the central MRI core laboratory electronically. Data transfer from individual study sites to the central MRI core laboratory may take up to 7−10 days, if not done electronically. Upon receipt of the MRI scans from the study sites, the central MRI core laboratory will provide the diagnostic reads. MRI results must be made available to investigators prior to the next dosing $visit$.

The MRI facility qualification and scan quality control will be performed by the central MRI core laboratory.

The MRI scan performed for the follow-up visit in Studies WN25203 and WN28745 will be used as baseline scan in this study, where possible. In case there might be a gap between follow-up visit from OLEs of WN25203/WN28745 and the first dose in this study of more than six months MRI has to be repeated.

Additional instructions regarding the procedures for MRI facility qualification and MRI scan acquisition and transmittal to the central reading facility can be found in the MRI Manual.

4.5.9.1 Healthy Volunteer Magnetic Resonance Imaging Scans for Site Qualification

Investigational sites that have not experienced a discontinuation in MRI scheduling from the previous OLE Studies WN25203 and WN28745 may not require MRI scan requalification. This will be determined by the MRI vendor on a case by case basis.

If deemed necessary, as part of site qualification, one to two healthy volunteers (preferably two) at each site should be recruited and scanned using the same machine and the same sequences to be used for site qualification before any participant is scanned in this study. The choice of healthy volunteers is at the discretion of the Principal Investigator and/or the imaging center, and the volunteer must provide written consent to take part in the scanning calibration. Volunteers must not have any contraindications for MRI scanning (evaluation as per local procedures at the imaging site), and they will not be enrolled in the study or undergo any other assessments as part of the study. If volunteer scans are acquired, then they will be reviewed for suitable image quality and used for qualitative comparison with additional scans with the same volunteer acquired after certain events as follows: at the time of a major upgrade to the site's scanner, or any other event deemed significant enough to affect image quality. This procedure will help ensure consistency in scanning quality over the duration of the study. Two volunteers are ideal in case one volunteer is no longer readily available for test scanning.

4.5.10 Optional Samples for Research Biosample Repository

4.5.10.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for participants in the future. Specimens for the RBR will be collected from retaining the residual samples remaining after the protocol-specified analysis has been performed on protocol-specified mandatory biomarker samples. Research Biosample Repository samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.10.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the ICF by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.10) will not be applicable at that site.

4.5.10.3 Sample Collection

Leftover plasma biomarker samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to gantenerumab, diseases, or drug safety.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

See the laboratory manual for sampling procedures, storage conditions, and shipment instructions.

Research Biosample Repository samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved ICF and applicable laws (e.g., health authority requirements).

4.5.10.4 Confidentiality

Research Biosample Repository samples and associated data will be labeled with a unique participant identification number.

Participant medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

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

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

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

4.5.10.5 Consent to Participate in the Research Biosample Repository

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

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

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

4.5.10.6 Withdrawal from the Research Biosample Repository

Participants who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the participant. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a participant wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the participant's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a participant wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and participant number to the following email address:

global_rcr-withdrawal@roche.com

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

4.5.10.7 Monitoring and Oversight

Research Biosample Repository samples will be tracked in a manner consistent with Good Clinical Practice (GCP) by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this

protocol and in the ICF. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to participant participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.5.11 Unscheduled Assessments

Assessments at unscheduled visits should be determined by the investigator based on clinical relevance and appropriateness to the cause of the unscheduled visit. The Schedule of Activities in Appendix 1 allows for all assessments to be performed at unscheduled visits.

4.6 TREATMENT, *PARTICIPANT*, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant
- Pregnancy
- Upon evidence of any disseminated leptomeningeal hemosiderosis (i.e., more than three focal leptomeningeal hemosiderosis)
- Upon evidence of intracerebral macrohemorrhage

All participants who withdraw from treatment will be asked to return 4 weeks after last dose to complete the early termination visit assessments.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

4.6.2 *Participant* Discontinuation

Participants 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 participant from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

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

All participants who discontinue from the study early will be asked to return 4 weeks after last dose to complete the early termination visit.

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

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

4.6.3 Study Discontinuation

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

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to participants
- Participant enrollment is unsatisfactory
- Sponsor determines it is the best interest of the participants

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

4.6.4 Site Discontinuation

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

- High drop-out rate
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline for GCP
- No study activity (i.e., all participants have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Gantenerumab is not yet approved, and clinical development is ongoing. The safety plan for participants in this study is based on clinical experience with gantenerumab in completed and ongoing studies. The identified risks for gantenerumab are outlined below. Please refer to the gantenerumab IB for a complete summary of safety information.

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

Participants should be observed for a minimum one-hour post IMP administration. Rescue medications to treat anaphylactic and anaphylactoid reactions must be available at the site or at the dosing location for MN visits. Participants and their study partners will be alerted to watch for signs of anaphylactic and anaphylactoid reactions and to contact the study center as soon as possible if any such signs are noted (refer to the pharmacy manual).

5.1.1 Risks Associated with Gantenerumab

5.1.1.1 Amyloid-Related Imaging Abnormalities

Amyloid-related imaging abnormality is the most significant adverse event reported with therapies against aggregated forms of Aβ. These findings are dose-, time-, and APOE ε4 allele-dependent (Piazza and Winblad 2016).

The mechanism underlying the development of ARIA-E and ARIA-H during anti-amyloid treatment is unknown. Because antibodies target removal of Aβ from both the parenchyma and cerebral vasculature, vessels with preexisting amyloid vascular pathology might become transiently more susceptible to leakage of vascular contents. This pathology results in ARIA-E if the leakage consists of proteinaceous fluid and in ARIA-H if the leakage consists of blood products (Sperling et al. 2012).

Thus, an anti-Aβ therapy that effectively maintains vascular β-amyloid clearance would allow vascular remodeling and may, with time, decrease the risk of such extravasation events (Sperling et al. 2012). This is consistent with experience in previous and ongoing studies and with reported data from the long-term extension study of aducanumab treatment (Viglietta et al. 2016).

In this study, an MRI scan documenting the absence of disseminated leptomeningeal hemosiderosis will be required prior to first gantenerumab dose. If ARIA findings occur, more intense MRI monitoring, dose adjustments, temporary dose holding, or permanent discontinuation will be implemented according to an ARIA-related dose-adjustment plan, described in Section 5.1.2. Safety findings (including individual participant and aggregate data) will be reviewed on a regular basis by the Roche Internal Monitoring Committee (IMC).

To date, clinical experience with gantenerumab has shown that ARIA events are time, dose, and APOE ε4 dependent. ARIA events are manageable with MRI monitoring and

dose intervention algorithms. In addition, in case of clinical symptoms associated with ARIA-E, the use of IV glucocorticosteroids may be considered.

Rules for management of participants who develop ARIA-E or ARIA-H are provided in Appendix 2.

5.1.1.2 Injection-Site Reactions

Gantenerumab may cause a reaction when given as an SC injection. In studies with gantenerumab, the most common adverse events occurring more frequently with gantenerumab than with placebo were local ISRs, such as injection-site erythema. The majority of events were of mild intensity and resolved without treatment.

Detailed information on the characteristic signs and symptoms of ISRs (e.g., erythema, pruritus) will be recorded on the dedicated eCRF page.

5.1.1.3 Immunogenicity

As with administration of any exogenous protein, a potential exists for the development of ADAs which can be neutralizing and/or sensitizing, producing the potential for febrile or allergic reactions, including anaphylaxis. The immunogenic risk of gantenerumab is considered low given it is a fully human antibody.

Anti-drug antibodies against gantenerumab were assessed in Studies BP29113, BP30042, WP39322, WP22461, WP27951, WP40052, NN19866, JP22431, WN25203, and WN28745 using a validated two-step bridging ELISA.

Of the 1*312* clinical *trial participants* who ha*ve* received gantenerumab at any of the doses investigated in these studies and had a post-baseline ADA assay result, *68 participants* (5.2%) showed treatment-emergent (induced or enhanced) ADA to gantenerumab. The percent of *participants* with treatment-induced ADAs was *4.8*% in the gantenerumab-treated group. A total of 478 *participants* received placebo and had a post-baseline ADA assay result of which 21 *participants* (4.4%) showed treatment-emergent ADA. Overall, 2.3% in the placebo group had treatment-induced ADAs. The majority of positive ADA results were below a titer (sample dilution factor) of 100.

In general, gantenerumab plasma concentration levels were similar between ADA-negative and ADA-positive participants. A correlation between ADA response and decreased gantenerumab plasma concentrations was only reported in two ADA-positive participants in the Japanese MAD Study JP22431.

There are no clinical findings indicative of an immunogenic response to gantenerumab.

5.1.2 Management of *Participants* Who Experience Selected Adverse Events

For Part 1 of the study, each participant continue*d* to receive SC gantenerumab Q4W at the dose they received in the qualifying study (OLE part of Studies WN25203 or WN28745) and will undergo a brain MRI examination as per Schedule of Activities, with the following exception: Participants who experience*d* a dosing gap of more than 16 weeks for any reason between the last gantenerumab dose in the qualifying study and first gantenerumab dose in this study may, depending upon whether they previously experienced an ARIA-E event, start dosing at a lower dose and undergo an up-titration step (see Appendix 3). A brain MRI examination will be required prior to the dose increase (pre-up-titration MRI scan) and then according to the Schedule of Activities once the target dose is reached. The pre-up-titration MRI scan will determine eligibility for the next dose, as described in Appendix 2.

In the case that a participant has at the baseline *(Day 1)* visit an ARIA-E that is ongoing since the qualifying study, there will be a continuity of ARIA management between the two studies, and ARIA management rules as described in Appendix 2 will apply

For ARIA MRI findings detected during the study (Part 1 and Part 2), the dose adjustment and discontinuation rules described in Appendix 2 *will apply.*

The IMC will review the nature, incidence, severity, and timing of ARIA findings and may recommend adjustment of dosing regimen and/or ARIA management for the overall study population or for a specific APOE ε4 genotype.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

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

- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.11
- 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

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the participant 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 5.3.5.12)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the participant's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe; the event itself may be of relatively minor medical significance such as severe headache without any further findings).

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

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

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

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

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, without evidence of another liver or biliary disorder as defined by Hay's Law (see Section 5.3.5.8)
- Suspected transmission of an infectious agent by the study drug, as defined below:
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

5.2.4 Selected Adverse Events

Data on associated symptoms and safety MRI scans will be collected for the following selected adverse events:

- ARIA-E: ARIAs suggestive of vasogenic edema and sulcal effusions
- ARIA-H: ARIAs suggestive of microhemorrhages and/or hemosiderin deposits

Please refer also to Section 5.3.5.1 for further details how to report ARIA events.

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. The investigator is also responsible for reporting medical device complaints (see Section 5.4.4)

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 participant contact. All adverse events, whether reported by the participant/caregiver or noted by study personnel, will be recorded in the participant's medical record and on the adverse event eCRF.

After informed consent has been obtained but prior to the first administration of study drug in this study, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After the first dose of study drug in this study, all adverse events will be reported until the participant's last visit (including long-term follow-up visit).

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

5.3.2 Eliciting Adverse Event Information

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

- "How have you felt since your last clinic visit?"
- "Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

Table 2 provides guidance for assessing adverse event severity.

Table 2 Adverse Event Severity Grading Scale

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

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

5.3.4 Assessment of Causality of Adverse Events

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

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

- Presence of risk factors in the participant or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Amyloid-related Imaging Abnormality Findings

Not every ARIA finding in MRI qualifies as an adverse event. An ARIA finding must be reported as an adverse event if it meets any of the following criteria:

- ARIA-E which is symptomatic (i.e., accompanied by CNS symptoms), and/or
- ARIA that results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation), and/or
- Is otherwise clinically significant in the investigator's judgment

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

It is the investigator's responsibility to review all ARIA findings.

Observations of the same clinically significant ARIA finding should only be recorded once on the adverse event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.2 Injection Reactions

Injection reactions (local and systemic) are defined as adverse events that occur during or within 24 hours after study drug administration and that are judged to be related to the study drug injection.

For local reactions, the diagnosis of ISR should be captured on the adverse event eCRF and associated signs and symptoms (e.g., erythema at injection site) should be recorded on the dedicated injection-site reaction eCRF.

Systemic reactions should be recorded as a single diagnosis on the adverse event eCRF (e.g., anaphylactic reaction). If possible, avoid ambiguous terms such as "systemic reaction."

5.3.5.3 Diagnosis vs. Signs and Symptoms

A diagnosis (if known) should be recorded on the adverse event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than

jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the adverse event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.4 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.5 Persistent or Recurrent Adverse Events

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

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

5.3.5.6 Abnormal Laboratory Values

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

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

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × 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 whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia".

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the adverse event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.7 Abnormal Vital Sign Values

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

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

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the adverse event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.8 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the adverse event eCRF (see Section 5.3.5.6) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.9 Deaths

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

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the adverse event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the adverse event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression of AD, "Alzheimer's disease progression" should be recorded on the adverse event eCRF.

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

5.3.5.10 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the Day 1 visit for this study. Adverse events, resolved or ongoing, reported in the OLEs of Studies WN25203 and WN28745 should be considered as medical history in 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").

5.3.5.11 Lack of Efficacy or Worsening of Alzheimer's Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse event. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.12 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  - The participant has not experienced an adverse event

5.3.5.13 Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations") are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the adverse event eCRF. If the associated adverse event fulfills seriousness criteria *or qualifies as an adverse event of special interest*, 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). For gantenerumab, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and “Medication error” boxes.

In addition, all special situations associated with gantenerumab, regardless of whether they result in an adverse event, should be recorded on the adverse event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box
- Medication error that qualifies as an overdose: Enter the drug name and "Accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the adverse event eCRF, one entry to report the accidental overdose and one

entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

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 study. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)
- Medical device complaints (see Section 5.4.4 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information 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

Medical Monitor: [redacted], M.D. (Primary)

Mobile Telephone No.: [redacted]

Medical Monitor: [redacted] *MBBS, MA (Cantab), Ph.D.* (Secondary)

Mobile Telephone No.: [redacted]

To ensure the safety of study participants, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls,

provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported.

The paper Clinical Trial *A*dverse *E*vent/Special *Situations* Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until the participant's last visit (including long-term follow-up visits). Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the adverse event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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

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

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female *Participants*

Female participants of childbearing potential will be instructed *through the Informed Consent Form* to immediately inform the investigator if they become pregnant during the study or within 16 weeks after the last dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy),

either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the adverse event eCRF. The investigator should discontinue study drug and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy. Any serious adverse event associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the adverse event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

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

If a therapeutic or elective abortion was performed because of an underlying maternal or embryo-fetal toxicity, the toxicity 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). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryo-fetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female participant 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).

5.4.4 Reporting Requirements for Medical Device Complaints

The investigator must report all medical device complaints (e.g., devices for study drug administration) to the Sponsor. The investigator should document as much information as possible on the IMP Deviation Form, including the product batch number, and forward the form to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) (refer to the pharmacy manual for further details). If the medical device results in an adverse event to the study participant, the event must be reported on the adverse event eCRF and submitted through the EDC system. If the event is serious, the adverse event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2.

5.5 FOLLOW-UP OF *PARTICIPANTS* 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 participant is lost to follow-up, or the participant withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or study-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 participant's medical record to facilitate source data verification.

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

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

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

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

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the document listed below:

Drug	Document
Gantenerumab	Gantenerumab 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

The purpose of this study is to assess the long-term safety and tolerability of gantenerumab in participants who complete the OLEs of Studies WN25203 or WN28745. The sample size will include all eligible participants who consent to this study.

Therefore, *in Part 1 of the study,* the sample size *was* driven by the number of participants who complete the OLE part of Studies WN25203 or WN28745 and subsequently enroll*ed* in this study. *There were 116 participants that participated in Part 1 of the study.*

For Part 2, the sample size is expected to be no more than 116 participants.

6.2 SUMMARIES OF CONDUCT OF STUDY

Participant disposition (including withdrawals from treatment) and protocol deviations will be summarized descriptively for all participants in the safety population who receive at least one dose of treatment in this study.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (such as age, sex, race, disease stage, and APOE ε4 status) will be summarized descriptively for all participants enrolled in the safety population.

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

6.4 EFFICACY ANALYSES

There will be no formal confirmatory efficacy analyses for this study.

6.4.1 Exploratory Efficacy Endpoints

To monitor AD progression, MMSE will be summarized using mean, SD, median, inter-quartile range and minimum and maximum. No hypothesis testing will be performed.

6.4.2 Secondary Efficacy Endpoints

Not applicable.

6.5 SAFETY ANALYSES

The safety analysis population will include all participants in the safety population who received at least one dose of study drug. The following safety outcome measures will be summarized using descriptive statistics:

- Incidence, nature, severity, and timing of adverse events
- Incidence, nature, severity, and timing of serious adverse events
- Changes from baseline of this study in vital signs, blood tests, ECGs, and C-SSRS
- Incidence, nature, severity, and timing of MRI safety findings: ARIA-E and ARIA-H
- Incidence, nature, severity, and timing of ISRs
- Number and proportion of ADA-positive and ADA-negative participants during both the treatment and follow-up periods
- Incidence of treatment discontinuations for adverse events
- Incidence of adverse events of special interest

Statistical methods, endpoint definitions and analyses of the safety endpoints will be described in the Statistical Analysis Plan.

6.6 PHARMACOKINETIC ANALYSES

No dedicated pharmacokinetic (PK) analysis will be performed for this study. Gantenerumab plasma concentration results obtained for ADA assessment may be pooled with results from other studies for the population PK analysis.

6.7 BIOMARKER ANALYSES

Exploratory biomarker analyses will include MRI volumetric changes.

6.8 INTERIM ANALYSIS

No interim analyses will be planned for this study.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

7.2 ELECTRONIC CASE REPORT FORMS

Electronic Case Report Forms are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. Electronic Case Report Forms 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. Electronic Case Report Forms should be reviewed and electronically signed and dated by the investigator or a designee.

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

7.3 ELECTRONIC DATA

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

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification 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 participant 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, participant-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, participant files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical study.

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

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

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

7.5 USE OF COMPUTERIZED SYSTEMS

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

7.6 RETENTION OF RECORDS

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

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

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for GCP 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. Food and Drug Administration regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample ICF (and ancillary sample ICFs such as HN ICF, 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 ICFs or any alternate Consent Forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

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

The Consent Forms must be signed and dated by the participant or the participant's LAR before his or her participation in the study. The case history or clinical records for each participant 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 participant to participate in the study. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a participant is participating in the study, the participant or a LAR must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each participant 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 participant or the participant's LAR. All signed and dated Consent Forms must remain in each participant'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 participant authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for participant 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 ICFs, any information to be given to the participant, 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 participant 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 9.7).

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 participant enrolled in the study through assignment of a unique participant identification number. This means

that participant names are not included in data sets that are transmitted to any Sponsor location.

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

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or participants unless required by law (with the exception of the report from Foundation Medicine). The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

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

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

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 one year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol

amendments, ICFs, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the participant data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on participant safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of GCP guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring participant safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical study processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

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

9.5 ADMINISTRATIVE STRUCTURE

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

Approximately *6*0 sites globally *have participated* to enroll up to *116* participants *in Part 1 of the study.* Enrollment *has taken place* through an IxRS. Study drug distribution may occur through an IxRS (see Section 4.2). Central facilities may be used for study assessments (i.e., ECG, lumbar puncture, specified laboratory tests, pharmacokinetics, rating scales, and MRI and PET imaging, as applicable).

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on the study to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical *Study Information* at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

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

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

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

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

9.7 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 participants or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1 Schedule of Activities *(Part 1)*

Weeks (± 7 days)		Day 1[a]	Treatment *Period* W4-20	W24	W24*8*-48	W52	W5*6*-72	W76	W80–100	W104	Follow-Up/Early Termination	UV [k]
Informed consent(s) [b]	x [b]											
Study Drug Administration		x	x	x	x	x	x	x	x	x		
MRI [c]		x [d]		x		x [d]		x		x [d]	x [l]	x
Vital signs [e]		x	x	x	x	x	x	x	x	x	x	x
ECG [f]		x										x
Serum chemistry, hematology [g]		x				x				x	x	x
Coagulation (prothrombin time) [g]		*x*				*x*				*x*	*x*	*x*
PK plasma sample [h]		x				x				x	x	
Biomarker plasma sample [h]		x				x				x	x	
ADA plasma sample [h]		x				x				x	x	
Urine pregnancy test [i]		x	x	x	x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x	x	x	x
Concomitant meds		x	x	x	x	x	x	x	x	x	x	x
MMSE		x		x		x		x		x	x	x
C-SSRS [j]		x		x		x		x		x	x	x
Physical examination		x				x				x	x	x

Appendix 1 Schedule of Activities (*Part 2*)

Weeks (± 7 days)		W104	Treatment Period								Follow-Up/Early Termination	UV [k]
			W108–124	W128	W132–152	W156	W160–176	W180	W184–204	W208		
Informed consent(s) [b]	x [b]											
Study Drug Administration		x	x	x	x	x	x	x	x	x		
MRI [c]		x [d]		x		x [d]		x		x [d]	x [l]	x
Vital signs [e]		x	x	x	x	x	x	x	x	x	x	x
ECG [f]												x
Serum chemistry,' and hematology [g]		x				x				x	x	x
Coagulation (prothrombin time)		x				x				x	x	x
PK plasma sample [h]		x				x				x	x	
Biomarker plasma sample [h]		x				x				x	x	
ADA plasma sample [h]		x				x				x	x	
Urine pregnancy test [i]		x	x	x	x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x	x	x	x
Concomitant meds		x	x	x	x	x	x	x	x	x	x	x
MMSE		x		x		x		x		x	x	x
C-SSRS [j]		x		x		x		x		x	x	x
Physical examination		x				x				x	x	x

Appendix 1 Schedule of Activities (Part 1 and Part 2)

ADA = anti-drug antibody; ALT/SGPT = alanine aminotransferase/serum glutamicpyruvic transaminase; ARIA = amyloid-related imaging abnormality; ARIA-E = amyloid-related imaging abnormality-edema/effusion; ARIA-H = amyloid-related imaging abnormality–hemosiderin deposition; AST/SGOT = aspartate aminotransferase/serum glutamicoxaloacetic transaminase; BP = blood pressure; BUN = blood urea nitrogen; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; F1 = follow-up 1; HR = heart rate; ICF = Informed Consent Form; IMP = investigational medicinal product; MMSE = Mini Mental State Examination; MRI = magnetic resonance imaging; PI = Principal Investigator; PK = pharmacokinetic; Q4W = every 4 weeks; UV = Unscheduled Visit; WBC = white blood cell.

Notes: There is a ±7 day window for all visits. However, the minimal time between doses is 21 days, and the target day for each Q4W visit is timed with respect to baseline, not to the prior visit.

Participants who will undergo an up-titration step, due to a dose gap of more than 16 weeks (see Appendix 3), will follow the same Schedule of Activities, except that an additional MRI will be performed before up-titration (further details in Appendix 3). Also, participants who have their dosing modified due to an ARIA-E event will follow the same Schedule of Activities, with the exception of any additional safety MRI scans that might be required (see Appendix 2).

[a] Day 1 visit is the baseline visit and the visit of the first IMP administration for this study. Day 1 visit should take place on the same day as the follow-up visit (4 weeks after last dose) of the qualifying studies whenever possible.

The Day 1 vital signs, serum chemistry and hematology, urine pregnancy test, and physical examination results will be the same as in the post-treatment follow-up visit in Studies WN25203 and WN28745 if they occur on the same day or within 4 weeks.

The Day 1 MRI, MMSE, and C-SSRS will be the same as in the post-treatment follow-up visit in Studies WN25203 and WN28745 if they occur on the same day or within 6 months.

[b] Informed consent should be obtained by the participants before any study procedures are performed, and may be obtained while they are active in the qualifying study; however, enrollment in this study is contingent upon completion of the qualifying study, and any premature discontinuation of study participation or study drug in the qualifying study, or failure to meet any other eligibility criterion (see Section 4.1.1), precludes enrollment in this study.

[c] MRI results should be available before dosing on Day 1. At subsequent visits indicated in the schedule, MRI scans must be performed within 20 days after dose administration and results made available and reviewed before the next scheduled dose. Participants will be asked if they experience CNS adverse events up to one week before each MRI is performed.

[d] Includes volumetric outcome measures.

[e] Vital signs include HR, BP, and *temperature*. The same arm should be used for all blood pressure measurements. HR and BP should not be measured unless 15 minutes have passed since the last blood draw. Weight will be recorded yearly at the time of physical examination.

[f] Perform after the participant has been in a supine position for 5 minutes. ECGs for each participant should be obtained at baseline and any time during the study if deemed necessary by the investigator from the same machine whenever possible and performed prior to any blood draws, brain MRI scans.

[g] Serum chemistry includes AST/SGOT, ALT/SGPT, alkaline phosphatase, total protein, total bilirubin, serum albumin, CPK, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory).

Hematology includes hemoglobin, hematocrit, red blood cell (with morphology), WBCs, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC–other total counts.

[h] At all visits where biomarker plasma, PK, and ADA samples are needed, the samples should be obtained before administration of gantenerumab if applicable. Accurate recording of the time of study drug administration and PK sampling is critical.

[i] Female *participants* of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory.

[j] C-SSRS (since last visit) should be obtained every 6 months *and additionally* at any time deemed necessary by the investigator.

[k] *Only the* relevant assessments will be *performed,* determined per *the investigator's* clinical judgment*, and do* not necessar*ily* includ*e* all *those* listed above.

[l:] *MRI must be performed within 20 days after dose administration and results made available and reviewed before the final follow-up or drop-out visit to allow review before the final visit. Participants will be asked if they experience CNS adverse events up to one week before each MRI is performed.*

Appendix 2 Management Rules for Amyloid-Related Imaging Abnormalities

Event	Characteristics	Action to be Taken
ARIA-E	Asymptomatic ARIA-E ≥1 and <4 BGTS	Participants who had MRI on target dose: • Continue study drug at the same dose level and perform MRI scans at 4-week intervals until ARIA-E resolves, then resume the standard MRI schedule (Appendix 1) Participants who had MRI prior to up-titration to target dose: • Continue study drug and do not up-titrate. Repeat MRI scan 4 weeks later • As long as BGTS is <4 and ≥1, continue study drug at the same dose level and continue MRI monitoring at 4-week interval • Once ARIA-E resolves, complete up-titration to target dose and resume the standard MRI schedule (Appendix 1)
	Symptomatic ARIA-E (of any size) or asymptomatic ARIA-E and BGTS ≥4	Participants who had MRI on target dose: • Temporarily interrupt study drug and perform MRI scans at 4-week intervals until symptoms and ARIA-E resolve • When symptoms and ARIA-E resolve, reintroduce study drug at target dose and resume the standard MRI schedule (Appendix 1) Participants who had MRI prior to up-titration to target dose: • Temporarily interrupt study drug and perform MRI scans at 4-week intervals until symptoms and ARIA-E resolve • When symptoms and ARIA-E resolve, reintroduce study drug at the dose level given at the time the event was detected • After one dose at the dose level given at the time the event was detected, but before the next scheduled dose, perform a subsequent MRI scan • If no new ARIA-E is detected, then complete up-titration to target dose and resume the standard MRI schedule (Appendix 1)
	Any recurrence of ARIA-E	• Treat as above (based on symptoms and BGTS)
ARIA-H	Any disseminated LH (more than 3 focal LH)	Permanently discontinue study drug Note: In the absence of disseminated LH, study drug can be continued, including up-titration to target dose

Appendix 2 Management Rules for Amyloid-Related Imaging Abnormalities (continued)

ARIA-E = amyloid-related imaging abnormality–edema/effusion; ARIA-H = amyloid-related imaging abnormality–hemosiderin deposition; BGTS = Barkhof grand total score; CNS = central nervous system; LH = leptomeningeal hemosiderosis; MRI = magnetic resonance imaging; Q4W = every 4 weeks.

Notes:

- Symptomatic ARIA-E is defined as onset or worsening of CNS symptom(s) that is/are temporally associated with ARIA-E MRI findings.
- In exceptional cases of (1) an ARIA-E that is asymptomatic with BGTS <4 and considered stable over consecutive MRI images by the Sponsor and investigator; or (2) symptomatic ARIA-E for which the imaging evidence of ARIA-E has resolved but the CNS symptoms continue, gantenerumab can be either reintroduced or up-titrated, as applicable, and Q4W MRI monitoring may no longer be necessary, as determined by the Sponsor and investigator.
- Investigators may choose to perform additional MRI monitoring for ARIA at any time.
- In this study, "up-titration to target dose" applies to participants who may have started with lower dose level due to the length of dosing gap and their ARIA-E history (see Appendix 3) and need to return to the dose that they were receiving in the qualifying study (e.g., 1200 mg or 900 mg Q4W).

Appendix 3 Gantenerumab Dosing Schedule for the Study
(only for Part 1)

Duration of treatment gap from last dose in parental study to first dose in this study	Gantenerumab dosing schedule
≤16 weeks	Re-start at the last dose administered in the parent study
>16 weeks	No ARIA-E in the double-blind or OLE part (including post-treatment follow-up) of WN25203/WN28745: Re-start at the target dose of the parent study ARIA-E in the double-blind or OLE part of WN25203/WN28745: Re-start at one dose lower on the titration schedule: • For participants on 1200 mg: 900 mg • For participants on 900 mg: 450 mg • After 3 consecutive Q4W doses of the corresponding lower dose (900 or 450 mg, as above), perform an MRI scan within 20 days after the last dose administration, with results made available and reviewed before the next scheduled dose • If the MRI scan reveals no ARIA-E, then up-titrate to the target dose (the last dose administered in the parent study)

ARIA-E = amyloid-related imaging abnormality–edema/effusion; MRI = magnetic resonance imaging; OLE = open-label extension; PET = positron emission tomography; Q4W = every 4 weeks.