Official Title: A Phase III, Multicenter, Randomized, Parallel-Group, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Gantenerumab in Participants at Risk for or at the Earliest Stages of Alzheimer's Disease

NCT Number: NCT05256134

Document Dates: Protocol Version 2: 02-November-2021

PROTOCOL

PROTOCOL TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, PARALLEL-GROUP, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF GANTENERUMAB IN PARTICIPANTS AT RISK FOR OR AT THE EARLIEST STAGES OF ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	WN42444
STUDY NAME	SKYLINE
VERSION NUMBER:	2
TEST COMPOUND:	Gantenerumab (RO4909832)
STUDY PHASE:	III
EUDRACT NUMBER:	2021-001184-25
IND NUMBER:	102,266
NCT NUMBER:	To be determined
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL DATE:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
02-Nov-2021 18:07:57	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
2	See electronic date stamp on title page
1	24 September 2021

PROTOCOL AMENDMENT, VERSION 2
RATIONALE

Protocol WN42444 has been amended to address a health authority (HA) requirement to include a coronavirus disease 2019 (COVID-19) vaccination risk assessment, clarify magnetic resonance imaging (MRI) monitoring requirements, the requirements for starting the post-progression dose escalation period, the assessment schedule related to the post-progression escalation period, the process of rescreening, and to add plasma samples as specified below. Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- Sections 2.3 and 6.8.1 have been updated to address a HA requirement to include a COVID-19 vaccination risk assessment
- Section 8.2.7 has been updated to clarify the MRI safety monitoring schedule for each study period (initial dose escalation, maintenance dosing, and post-progression dose escalation periods) and dosing schedule (every week [Q1W], every 2 weeks [Q2W], every 4 weeks [Q4W])
- Table A3-1 has been updated to clarify timing of MRIs related to amyloid-related imaging abnormality (ARIA) management for each study period and dosing schedule
- Footnotes have been added to Tables 2, 3, 5 and 6 to clarify the assessment schedule during and following the post-progression dose escalation
- Text has been updated to clarify that, before a participant enters the post-progression dose escalation period based on having clinically progressed, they need to be on target dose; it has also been clarified that, in order to conclude on clinical progression, the change in diagnostic classification must be confirmed on a second visit, approximately 6 months later so that the diagnosis can be considered stable
- Pharmacokinetic samples at Week 131 and Week 183 have been added in Table 2 and Table 5 because they are needed for the valid assessment of anti-drug antibodies (ADAs) at these timepoints
- Tables 1–6 and A24-1 have been updated to clarify prothrombin time collection timepoints
- The process for rescreening has been clarified

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.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, PARALLEL-GROUP, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF GANTENERUMAB IN PARTICIPANTS AT RISK FOR OR AT THE EARLIEST STAGES OF ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	WN42444
STUDY NAME:	SKYLINE
VERSION NUMBER:	2
TEST COMPOUND:	Gantenerumab (RO4909832)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR'S NAME:	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.

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE: **A PHASE III, MULTICENTER, RANDOMIZED, PARALLEL-GROUP, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF GANTENERUMAB IN PARTICIPANTS AT RISK FOR OR AT THE EARLIEST STAGES OF ALZHEIMER'S DISEASE**

Study Rationale

The primary purpose of this secondary prevention study is to evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of gantenerumab, an anti-amyloid β antibody, in amyloid-positive, cognitively unimpaired participants at risk for or at the earliest stages of Alzheimer's disease (AD).

Alzheimer's disease, a debilitating and progressive neurodegenerative disease, represents a significant unmet medical need with no fully approved therapeutics to halt, slow, or prevent the onset of symptoms. The currently available treatment options primarily include symptomatic medications and are only approved for the overtly symptomatic stages of AD.

The amyloid hypothesis postulates that amyloid may be an early, key driver of AD pathophysiology. If this hypothesis is true, then early intervention at the amyloid-positive, cognitively unimpaired stage (i.e., at-risk stage of disease), may result in a high efficacy potential for an anti-amyloid β antibody (i.e., gantenerumab), to slow the disease process and preserve the cognitive and functional abilities of affected individuals. This is the main hypothesis Study WN42444 (SKYLINE) aims to test.

Objectives and Endpoints and Estimands

Study WN42444 will evaluate the efficacy and pharmacodynamics of gantenerumab treatment compared with control treatment as well as the safety and pharmacokinetics of gantenerumab treatment compared with placebo in cognitively unimpaired participants, aged 60–80 years, at risk for or at the earliest stages of AD who are amyloid-positive based on evaluations of either cerebrospinal fluid (CSF) sampling or amyloid positron emission tomography (PET) imaging.

Study WN42444 is a randomized, double-blind, placebo-controlled study. Eligible participants will be randomized in a 1:1 ratio to receive either gantenerumab or placebo. If, in the course of the study, a participant progresses to a clinical diagnosis of mild cognitive impairment (MCI) or dementia due to AD, a 'post-progression dose escalation' period will commence. During the post-progression dose escalation period, participants who were randomized to placebo will switch to gantenerumab in a double-blinded manner. Participants who were randomized to gantenerumab will continue with gantenerumab (255 mg SC every 1 week [Q1W] or 510 mg SC every 2 weeks [Q2W]). All participants who progress to a clinical diagnosis of MCI or dementia due to AD must comply with all aspects of the post-progression dose escalation schedules of activities.

The study treatment duration is 211 weeks regardless of the dosing regimen (i.e., Q1W or Q2W) or whether a participant progresses to a clinical diagnosis of MCI or dementia due to AD.

The primary comparison for efficacy will be between the following arms:

- **Experimental arm**: participants randomized to gantenerumab at the beginning of the study
- **Control arm**: participants randomized to placebo at the beginning of the study, irrespective of whether they progressed during the study and thus, started gantenerumab

The primary objective of this study is to evaluate the difference between the experimental and control arms in the change from baseline to Year 4 in cognition, as measured by the Preclinical Alzheimer's Cognitive Composite-5 (PACC-5) score.

For pharmacodynamic measures, the primary comparison will be between gantenerumab and control. For safety measures, the primary comparison will be between gantenerumab and placebo.

Primary Objective	Corresponding Endpoint
• To evaluate the efficacy of gantenerumab compared with control on cognition	• Change from baseline to Year 4 in the Preclinical Alzheimer's Cognitive Composite-5 score
Secondary Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab compared with control on clinical progression	• Time from randomization to clinical progression to mild cognitive impairment or dementia due to Alzheimer's disease based on the diagnosis of the independent Clinical Adjudication Committee
• To evaluate the efficacy of gantenerumab compared with control on clinical progression	• Time to onset of confirmed clinical progression, defined as the time from randomization to the first occurrence of two consecutive visits (approximately 6 months apart) with a Clinical Dementia Rating Global Score $>$ 0
• To evaluate the efficacy of gantenerumab compared with control on cognition and/or function	• Change from baseline to Year 4 in the Amsterdam Instrumental Activities of Daily Living Questionnaire Short Version and the Cognitive Function Instrument acute • Change from baseline to Year 4 in the Clinical Dementia Rating Sum of Boxes
• To evaluate the safety of gantenerumab compared with placebo	• Nature, frequency, severity, and timing of adverse events, serious adverse events, and adverse events of special interest • Physical examinations (including neurological systems), vital signs, blood tests, ECGs, and Columbia-Suicide Severity Rating Scale • Nature, frequency, severity, and timing of magnetic resonance imaging (MRI) findings: amyloid-related imaging abnormalities–edema/effusion and amyloid-related imaging abnormalities–hemosiderin deposition • Nature, frequency, severity, and timing of injection-site reactions • Presence of anti-drug antibodies (ADAs) during the study relative to the presence of ADAs at baseline
Pharmacodynamic Biomarker Objective	**Corresponding Endpoints**
• To evaluate biomarkers of pharmacodynamics of gantenerumab compared with control	• Change in brain amyloid load over time, as measured by amyloid positron emission tomography (PET) in a subset of participants • Change in brain tau load over time, as measured by tau PET in a subset of participants

Pharmacodynamic Biomarker Objective	Corresponding Endpoint
	• Change in cerebrospinal fluid (CSF) biomarkers, including, but not limited to, $A\beta_{1-42}$, $A\beta_{1-40}$, neurofilament light (NfL), pTau, and tTau in a subset of participants • Change in blood-based biomarkers, including, but not limited to, $A\beta_{1-42}$, $A\beta_{1-40}$, NfL, and pTau in all participants • Change in MRI-derived measurements over time, including, but not limited to, volumetric changes in whole-brain, ventricles, hippocampus, or other structures in all participants
Exploratory Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab compared with control on (1) depressive symptoms, (2) clinician-rated, participant-rated, and study partner-rated global impression of overall disease severity, and (3) health-related quality of life	• (1) Change from baseline to Year 4 in the Geriatric Depression Scale-30 • (2) Change from baseline to Year 4 in the AD Clinical Global Impression of Cognitive Function, AD Participant Global Impression of Cognitive Function, and AD Study Partner Global Impression of Cognitive Function scales • (3) Change from baseline to Year 4 in the EuroQoL 5-Dimension, 5-Level Questionnaire index-based and visual analogue scores
• To evaluate the efficacy of gantenerumab compared with control on clinical progression	• Time from randomization to clinical progression to MCI or dementia based on the site clinician's diagnostic classification
• To characterize the pharmacokinetic (PK) profile of gantenerumab	• Trough plasma concentrations of gantenerumab at specified timepoints • PK parameters estimated with population PK modeling
• To evaluate the potential relationships between drug exposure and the efficacy and safety of gantenerumab	• Relationship between plasma concentration or PK parameters of gantenerumab and pharmacodynamics (PD) as well as efficacy endpoints • Relationship between CSF concentration or PK parameters of gantenerumab and safety endpoints
• To evaluate the effect of ADAs	• Relationship between ADA status and efficacy, safety, PD, as well as PK endpoints

Exploratory Objective	Corresponding Endpoints
• To identify biomarkers that are: (1) predictive of response to gantenerumab (i.e., predictive biomarkers), (2) early surrogates of efficacy, (3) associated with progression to a more severe disease state (i.e., prognostic biomarkers), (4) associated with acquired resistance to gantenerumab, (5) associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers) (6) able to increase the knowledge and understanding of disease biology and drug safety	• Relationship between biomarkers in blood and CSF and efficacy, safety, PK, immunogenicity, or other biomarker endpoints • Relationship between biomarkers (such as MRI, PET, CSF and blood mentioned in secondary objectives) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

Overall Design

Study WN42444 is a 4-year and 9-month, Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of gantenerumab in amyloid-positive, cognitively unimpaired participants at risk for or at the earliest stages of AD.

The planned number of participants for the study is approximately 1200 participants randomized in a 1:1 ratio to receive either gantenerumab or placebo (600 participants randomized to gantenerumab and 600 participants randomized to placebo).

Participants will be selected based on (1) evidence of underlying cerebral Aβ pathology as indicated by amyloid PET or by the $pTau_{181}/A\beta_{1-42}$ ratio in the CSF, and (2) having both unimpaired cognitive and functional status as evidenced by a Clinical Dementia Rating (CDR) Global Score (CDR-GS = 0), and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Delayed Memory Index (DMI; ≥ 80). Eligible participants will be 60–80 years of age, inclusive, must not meet the clinical diagnostic criteria for MCI due to AD or dementia due to AD, and must meet all the eligibility criteria.

If, in the course of the study, participants*, who have reached target dose,* progress to a clinical diagnosis of MCI or dementia due to AD (as determined by the independent clinical adjudication committee [iCAC]), a post-progression dose escalation period will commence. During the post-progression dose escalation period, participants who were randomized to placebo will switch to gantenerumab in a double-blinded manner, unless the ongoing Phase III studies of gantenerumab in early AD do not demonstrate efficacy. For study purposes, clinical progression to MCI or dementia due to AD is determined by the iCAC. *In order to conclude on clinical progression, the diagnostic classification change must be confirmed on the next cognitive assessment visit, approximately 6 months later.* Evaluation by the iCAC will be triggered by pre-specified trigger criteria. Details of the trigger and diagnostic criteria for MCI and dementia due to AD will be provided in the iCAC Charter.

The study treatment period for each participant is 211 weeks (i.e., baseline to Week 211, inclusive) which constitutes the primary efficacy analysis dataset.

Number of Participants

Study WN42444 will enroll approximately 1200 participants aged 60–80, who are cognitively unimpaired or at risk for or are at the earliest stages of AD during the global enrollment phase of this study.

Study Treatment

The active study drug under investigation for this study is gantenerumab.

Gantenerumab

Gantenerumab will be administered by SC injections to all participants.

Participants who choose the Q1W dosing regimen at the target dose, and are randomized to the active treatment arm will receive a dose of gantenerumab 120 mg SC every 4 weeks (Q4W) three times, 255 mg SC Q4W three times, and 255 mg SC Q2W six times, regardless of apolipoprotein E (*APOE* ε4) status, prior to reaching the target dose of 255 mg Q1W (i.e., 1020 mg per month).

Participants who choose the Q2W dosing regimen at the target dose, and are randomized to the active treatment arm will receive a dose of gantenerumab 120 mg SC Q4W three times, 255 mg SC Q4W three times, and 510 mg SC Q4W three times, regardless of *APOE* ε4 status, prior to reaching the target dose of 510 mg Q2W (i.e., 1020 mg per month).

> Note: the minimum number of study drug doses, as outlined above, must be administered during each titration step prior to dose escalation.

Following the initial dose escalation period, study drug will be administered at a Q1W or Q2W dosing regimen. Participants will use their selected dosing regimen throughout the maintenance dosing phase of the study.

For Q4W injections, a visit window of ± 7 days is allowed for dosing visits. Once study drug is administered Q1W or Q2W, the visit window for dosing visits is ± 3 days. It is recommended not to administer more than 1020 mg (i.e., 4×255 mg Q1W or 2×510 mg for Q2W) within 28 days. Always return to the initial planned dosing regimen for subsequent visits. If administration is not possible on the scheduled dosing day, the study drug should be administered as soon as possible within the time window from the scheduled dosing date. If the study drug cannot be administered within the time window, the dose should be skipped, and the participant should receive the next dose at the next scheduled time with the study drug dosing resumed in accordance with the original dosing schedule.

During the initial dose escalation, the maintenance dosing periods, and the post-progression dose escalation period (if applicable), injections will be administered SC into the abdomen as a single injection, 2 or 3 injections as any combination of the following:

- 0.8 mL injection for the 120 mg dose or placebo
- 1.7 mL injection for the 255 mg dose or placebo

Participants on the Q1W dosing regimen will receive 1 SC study drug injection per dosing visit during the initial dose escalation and maintenance dosing periods. However, participants on the Q1W dosing regimen will receive 2 SC study drug injections per dosing visit at Week 1P, Week 5P, and Week 9P, and 1 SC study drug injection per dosing visit at all other dosing visits during the post-progression dose escalation period.

Participants on the Q2W dosing regimen will receive 1 SC study drug injection per dosing visit until Week 25 during the initial dose escalation period. Starting at Week 25, participants will receive 2 SC study drug injections per dosing visit during the initial dose escalation, maintenance dosing, and post-progression dose escalation periods with the exception of dosing at Week 1P, Week 5P, and Week 9P when they will receive 3 SC study drug injections per dosing visit.

During pre-specified visits, the study drug may be administered by the participant or their study partner (non-professional caregiver) at the participant's home or another suitable location depending on the individual participant's/study partner's preference, if appropriately trained and certified by the investigator or delegate, and allowed by local regulations.

During the initial dose escalation period, participants will receive SC injections of study drug by the investigator or an appointed qualified study staff for the first 3 doses at the clinic. If the participant or their study partner is willing and determined capable of administering SC injections by the investigator or delegate, this participant or study partner will receive observer and dose administration training at the first 3 dosing visits (i.e., Weeks 1, 5, 9). At the next 4 visits (i.e., Weeks 13, 17, 21, and 25) the injections will be administered by the participant or study partner under the site staff's supervision. Following the supervised dosing visits at the clinic, subsequent dosing may be administered by the participant or study partner at home except for doses that coincide with a clinic visit, in which case the participant or study

partner should administer the injection in the clinic, under investigator/study staff supervision. Study staff will document the outcome of the supervised administrations. Training and supportive materials will be provided to the site and the participant and/or their study partner. Following the in-person instructional training and supervised administrations at the site, adequate supply of study drug will be provided. Participants should be observed for at least 2 hours after dosing for the first 4 administrations of study drug (corresponding to the injections at Week 1, Week 5, Week 9 and Week 13); the observation time may be reduced to *at least* 1 hour following all other administrations. However, participants must be observed for a minimum of 1 hour after each injection by their study partner or another suitably trained individual (i.e., "postdose observer") even if they are self-administering the study drug. Study partners and postdose observers will be trained by the site staff to recognize signs and symptoms of allergic reactions and the appropriate actions to be taken if the participant were to develop those signs and symptoms. Postdose observers must also sign the Postdose Observer Informed Consent Form prior to the initiation of the training.

At subsequent visits, the investigator or appointed qualified study staff will determine if the participant or study partner continues to be qualified to perform home administrations. If at any time the investigator, participant, or study partner determines that home administration by the participant or study partner is unqualified, then the study drug must be administered at home or in the clinic by an alternative trained study drug administrator.

Starting from the fifth dose, at applicable sites, study drug may also be administered by a trained healthcare professional (mobile nurse) at the participant's home or another suitable location, if the participant has given written informed consent.

During the post-progression dose escalation period, participants must be observed for at least 2 hours after the first 4 'definitely active doses' (i.e., dosing at Week 1P, Week 5P, Week 9P and Week 13P). The observation time may be reduced to at least 1 hour following all other administrations. Participant or study partner administration is prohibited during the post-progression dose escalation period. The study drug administration by the participant or their study partner may resume after Week 37P following assessment and adequate training, if necessary, by the site. Sites must verify participant/study partner readiness for study drug administration.

A vial adapter will be available in countries where it has been approved to withdraw the medication from the vial into a disposable syringe (this device will be optional for health care professionals and for participants and study partners [non-professional caregivers]).

For study drug administration days that include efficacy assessments, study drug must be administered at the clinical site by the site staff or the participants/study partner. Study personnel preparing and administering study drug must not be involved with any efficacy or safety assessments.

Placebo

A placebo of identical composition (except gantenerumab) and volume to gantenerumab will be administered by SC injection to the abdomen. The dosing schedule of the placebo and gantenerumab will also be identical throughout the duration of the study.

Duration of Participation

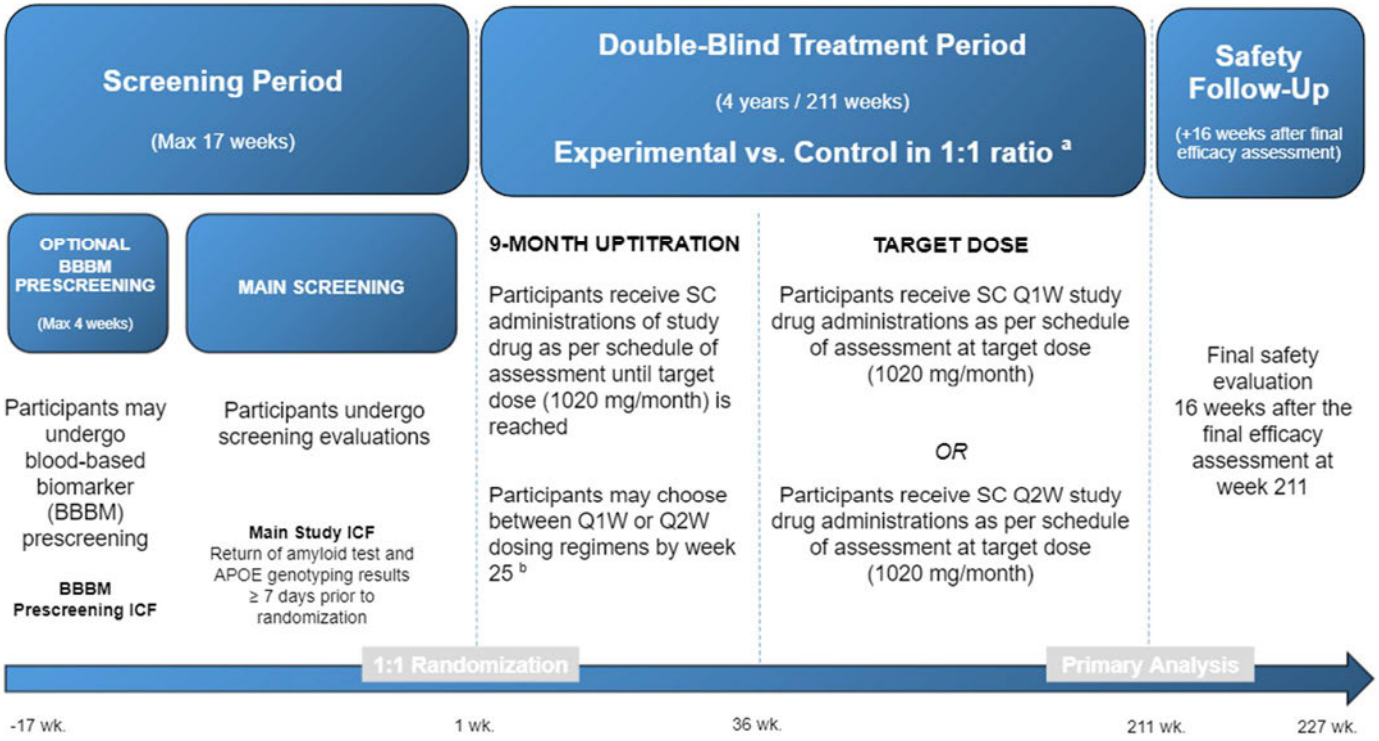
The total duration of study participation for each participant is expected to be 244 weeks, which includes the screening period (up to 17 weeks), the double-blind treatment period (211 weeks), and the subsequent safety follow-up visit 16 weeks after the final safety and efficacy assessment at Week 211.

Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) is being used.

1.2 STUDY DESIGN

Figure 1 Study Design Schematic



AD = Alzheimer's disease; *APOE* = apolipoprotein E; BBBM = blood-based biomarker; ICF = Informed Consent Form; Max = maximum; MCI = mild cognitive impairment; Q1W = every 1 week; Q2W = every 2 weeks; wk = week.

[a] This is a randomized, double-blind, placebo-controlled study. Eligible participants will be randomized in a 1:1 ratio to receive either gantenerumab or placebo. If, in the course of the study, participants *who are on target dose* progress to a clinical diagnosis of MCI or dementia due to AD, a blinded, post-progression dose escalation period will commence, with participants who were randomized to placebo switching to gantenerumab.

[b] The default dosing regimen is Q2W.

1.3 SCHEDULE OF ACTIVITIES

Table 1 Schedule of Activities: Week –17 to Week 37; Dose Escalation to Target Dose of 255 mg Q1W

	Screening Period		Baseline	Dose Escalation Period												Early Term Visit (2 weeks after last study drug dose)	Unsch Visit [b]
	Optional BBBM Prescreening [a] (Max. 4 weeks)	Main Screening															
Assessment/ Procedure	Week – 17 to – 1		Wk 1	Wk 5	Wk 9	Wk 13	Wk 17	Wk 21	Wk 25	Wk 27	Wk 29	Wk 31	Wk 33	Wk 35	Wk 37		
Dose Number			1	2	3	4	5	6	7	8	9	10	11	12	13		
Dose Level (mg)			120	120	120	255	255	255	255	255	255	255	255	255	255		
Study drug administration			C	C	C	C/ CS	C/ CS/ *MN*	C/ CS/ *MN*	C/ CS	C/ CS/ H/ *MN*	C/ CS/ H/ *MN*	C/ CS/ H/ *MN*	C/ CS/ H/ *MN*	C/ CS/ H/ *MN*	C/ CS		
Informed Consent(s)	x	x															
Plasma sample for BBBM prescreening (optional)	x																
Review of inclusion and exclusion criteria		x	x [B]														
Clinical genotyping samples		x															
Return of amyloid test (CSF or PET) and *APOE* genotyping results [c]		x															
Medical history, personal status, and demographics		x															
Weight		x	x [B]						x [B]							x	x

Table 1 Schedule of Activities: Week –17 to Week 37; Dose Escalation to Target Dose of 255 mg Q1W (cont.)

	Screening Period		Baseline	Dose Escalation Period												Early Term Visit (2 weeks after last study drug dose)	Unsch Visit [b]
	Optional BBBM Prescreening [a] (Max. 4 weeks)	Main Screening															
Assessment/ Procedure	Week – 17 to – 1		Wk 1	Wk 5	Wk 9	Wk 13	Wk 17	Wk 21	Wk 25	Wk 27	Wk 29	Wk 31	Wk 33	Wk 35	Wk 37		
Dose Number			1	2	3	4	5	6	7	8	9	10	11	12	13		
Dose Level (mg)			120	120	120	255	255	255	255	255	255	255	255	255	255		
Height		x															
12-lead ECG		x	x [B]			x [B]			x [B]							x	x
Urinalysis		x															
Urine pregnancy test		x	x [B]													x	x
Urine sample for drugs of abuse		x															
PK plasma sample [d]			x [B]			x [B]			x [B]						x [B]	x	x
Plasma biomarker sample [d, e]		x	x [B]						x [B]							x	x
ADA plasma sample [d]			x [B]			x [B]			x [B]						x [B]	x	x
Serum chemistry and hematology		x	x [B]						x [B]							x	x
Metabolic tests, CRP, *and PT* [f]		x														*x*	*x*

Table 1 Schedule of Activities: Week –17 to Week 37; Dose Escalation to Target Dose of 255 mg Q1W (cont.)

	Screening Period		Baseline	Dose Escalation Period												Early Term Visit (2 weeks after last study drug dose)	Unsch Visit [b]
	Optional BBBM Prescreening [a] (Max. 4 weeks)	Main Screening															
Assessment/ Procedure	Week – 17 to – 1		Wk 1	Wk 5	Wk 9	Wk 13	Wk 17	Wk 21	Wk 25	Wk 27	Wk 29	Wk 31	Wk 33	Wk 35	Wk 37		
Dose Number			1	2	3	4	5	6	7	8	9	10	11	12	13		
Dose Level (mg)			120	120	120	255	255	255	255	255	255	255	255	255	255		
Viral serology: HIV, HBV, HCV		x															
Complete physical examination (Includes neurological systems)		x	x [B]													x	x
Limited physical examination									x [B]								x
MRI scan		x							x [B]						x [B]	x	x
Amyloid PET scan [g]		x														x	
Tau PET Scan [g, h]			x													x	
CSF sampling [i]		x														x	
Vital signs		x	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]						x [B]	x	x
Concomitant medications [j]		x	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]		x [B]		x [B]		x [B]	x	x
Adverse events [j]	x	x	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]		x [B]		x [B]		x [B]	x	x

Table 1 Schedule of Activities: Week –17 to Week 37; Dose Escalation to Target Dose of 255 mg Q1W (cont.)

	Screening Period			Dose Escalation Period												Early Term Visit (2 weeks after last study drug dose)	Unsch Visit [b]
	Optional BBBM Prescreening [a] (Max. 4 weeks)	Main Screening	Baseline														
Assessment/ Procedure	Week – 17 to – 1		Wk 1	Wk 5	Wk 9	Wk 13	Wk 17	Wk 21	Wk 25	Wk 27	Wk 29	Wk 31	Wk 33	Wk 35	Wk 37		
Dose Number			1	2	3	4	5	6	7	8	9	10	11	12	13		
Dose Level (mg)			120	120	120	255	255	255	255	255	255	255	255	255	255		
RBANS		x															
PACC-5		x	x [B]						x [B]							x	x
CDR		x							x [B]							x	x
CFIa			x [B]						x [B]							x	x
A-IADL-Q-SV			x [B]													x	x
AD-SPGI-S			x [B]													x	x
AD-PGI-S			x [B]													x	x
AD-CGI-S		x							x							x	x
EQ-5D-5L			x [B]													x	x
GDS-30			x [B]						x [B]							x	x
C-SSRS			x [B]						x [B]							x	x
DCF			x [B]						x							x	x

Table 1 Schedule of Activities: Week –17 to Week 37; Dose Escalation to Target Dose of 255 mg Q1W (cont.)

ADA = anti-drug antibody; AD-CGI-S = Clinician Global Impression of Cognitive Function; AD-PGI-S = Participant Global Impression of Cognitive Function; AD-SPGI-S = Study Partner Global Impression of Cognitive Function; A-IADL-Q-SV = Amsterdam Instrumental Activities of Daily Living Questionnaire Short Version; *APOE* = apolipoprotein E; ARIA-E = amyloid-related imaging abnormalities – edema/effusion; ARIA-H = amyloid-related imaging abnormalities – hemosiderin deposition; BBBM = blood-based biomarker; C = in-clinic administration by study staff; CDR = Clinical Dementia Rating; CFIa = Cognitive Function Instrument acute; CRP = C-reactive protein; C-SSRS = Columbia-Suicide Severity Rating Scale; CS = supervised in-clinic administration, where applicable; CSF = cerebrospinal fluid; DCF = Diagnostic Classification Form; Early Term = Early Termination; EQ-5D-5L = EuroQol 5-Dimension 5-Level Questionnaire; GDS-30 = Geriatric Depression Scale; H = visit appropriate for home administration by participant or study partner, where applicable; HBV = hepatitis B virus; HCV = hepatitis C virus; CF = Informed Consent Form; Max. = maximum; *MN = visit appropriate for home administration by mobile nursing professional, where applicable;* MRI = magnetic resonance imaging; PACC-5 = Preclinical Alzheimer's Cognitive Composite-5; PET = positron emission tomography; PK = pharmacokinetic; Q1W = every 1 week; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; Unsch = unscheduled; Wk = week.

x [B] = before study drug administration; visits may be split over 2 consecutive days.

The baseline visit (Week 1) may be split over 5 consecutive business days. All cognitive and functional assessments must be completed first, and before study drug administration. All safety assessments (e.g., vitals, blood tests, and ECGs) must be completed on the day of dosing and before study drug administration. Study drug administration should be the last baseline visit activity, marking the end of Week 1.

Participants should be observed for at least 2 hours after dosing for the first 4 administrations of study drug (corresponding to the injections at Week 1, Week 5, Week 9 and Week 13); the observation time may be reduced to at least 1 hour following all other administrations.

[a] Not applicable for sites where BBBM prescreening is not approved. Participation in the optional BBBM prescreening requires signing of the separate BBBM prescreening ICF.

[b] Scope of the unscheduled visit should include all efficacy assessments if they were missed at the preceding, regularly scheduled efficacy assessment visit. Safety assessments, including physical examinations, must also be included if they were missed at the preceding, regularly scheduled safety assessment visit or as clinically indicated. Unscheduled visits related to the occurrence of ARIA-E or ARIA-H are to follow the PK and plasma biomarker sampling rules as detailed below.

[c] Return of amyloid test and *APOE* genotyping results must take place at least 7 days prior to the randomization visit. Follow-up over disclosures should occur within 1 week of the provision of results.

[d] Visits, including PK, ADA and plasma biomarker sampling must take place in-clinic.

A PK sample is to be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following an MRI scan showing new occurrence or worsening of ARIA-E or ARIA-H that meets the discontinuation criteria.

An additional plasma exploratory biomarkers sample is to be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E).

[e] Plasma biomarker sample during the main screening period should only be collected if the BBBM prescreening was not completed for the participant.

[f] *Metabolic tests include hemoglobin A_{1C}, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, folic acid, vitamin B-12, methylmalonic acid, total thyroxine, free thyroxine, and thyroid-stimulating hormone levels. These tests should be collected as fasting samples (i.e., at least 4 hours after meals).*

[g] Tau and amyloid PET scheduling window is ± 14 days. In an exceptional case of tau or amyloid PET scheduling issue the Sponsor must be notified and the scans may be performed up to 3 months after the scheduled assessment. For Early Termination visits, tau and amyloid PET scans should only be obtained if the last scan was > 6 months earlier.

Table 1 Schedule of Activities: Week –17 to Week 37; Dose Escalation to Target Dose of 255 mg Q1W (cont.)

[h] Baseline tau PET should be obtained prior to first dose of study drug. However, in an exceptional case, and with the notification of the Sponsor, the baseline tau PET may be obtained within 3 months of randomization.

[i] Cerebrospinal fluid collection must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing. For Early Termination visits, CSF sampling should only be obtained if the last CSF sampling was > 6 months earlier.

[j] Every 4 weeks, except when there is an in-clinic visit, the investigator or an appointed qualified study staff member will have a telephone conversation with the participant and study partner to elicit, in a non-leading way, information on medication errors, adverse events, and changes to concomitant medications that may have occurred in the home setting. Therefore, there will be contact between the study staff and the participant/study partner at least every 4 weeks. The study staff is encouraged to have more frequent calls with a particular participant/study partner if considered appropriate by the investigator. In addition, the participant and study partner must be instructed to contact the investigator and seek approval for continued study drug dosing in the home setting in case of onset of any new symptoms or symptom worsening, new or changed concomitant medications, or medication errors.

Table 2 Schedule of Activities: Week 38 to End of Study; 255 mg Q1W

	Maintenance Dosing from Week 38 to Week 210													Final Safety and Efficacy Assessment	Follow-up Safety Assessment	Early Term Visit (2 weeks after last study drug dose)	Unsch Visit [a]
Assessment/ Procedure (week)	38 to 52	**53**	54 to 78	79	80 to 104	**105**	106 to 130	131	132 to 156	**157**	158 to 182	183	184 to 210	**Week 211**	Week 227 or 15 weeks after Early Term Visit		
Dose number	14 to 28	29	30 to 54	55	56 to 80	81	82 to 106	107	108 to 132	133	134 to 158	159	160 to 186				
Dose level (mg)	255	255	255	255	255	255	255	255	255	255	255	255	255				
Study Drug Administration	C/ CS/ H/ *MN*	C/ CS	C/ CS/ H/ *MN*	C/ CS	C/ CS/ H/ *MN*	C/ CS	C/ CS/ H/ *MN*	C/ CS	C/ CS/ H/ *MN*	C/ CS	C/ CS/ H/ *MN*	C/ CS	C/ CS/ H/ *MN*				
12-lead ECG		x [B]		x [B]		x [B]		x [B]		x [B]		x [B]		x	x	x	x
PK plasma sample [b]		x [B]		x [B]		x [B]		*x* [B]		x [B]		*x* [B]		x		x	x
Plasma biomarker sample [b]		x [B]		x [B]		x [B]				x [B]				x	x	x	x
ADA plasma sample [b]		x [B]		x [B]		x [B]		x [B]		x [B]		x [B]		x		x	x
Serum chemistry and hematology		x [B]		x [B]		x [B]		x [B]		x [B]		x [B]		x	x	x	x
Metabolic tests, CRP, *and PT* [c]		*x* [B]				*x* [B]				*x* [B]				*x*	*x*	*x*	*x*
Complete physical examination (Includes neurologic systems)		x [B]				x [B]				x [B]				x	x	x	x
Limited physical examination				x [B]				x [B]				x [B]					x
Weight		x [B]		x [B]		x [B]				x [B]				x	x	x	x
Vital signs		x [B]		x [B]		x [B]		x [B]		x [B]		x [B]		x	x	x	x
Concomitant medications [d]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x	x	x	x
Adverse events [d]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x	x	x	x
Urine pregnancy test						x [B]				x [B]				x	x	x	x
MRI scan		x [B]		x [B]		x [B]				x [B]					x (4 wks after last dose)	x	x

Table 2 Schedule of Activities: Week 38 to End of Study; 255 mg Q1W (cont.)

	Maintenance Dosing from Week 38 to Week 210													Final Safety and Efficacy Assessment	Follow-up Safety Assessment	Early Term Visit (2 weeks after last study drug dose)	Unsch Visit [a]
Assessment/ Procedure (week)	38 to 52	**53**	54 to 78	79	80 to 104	**105**	106 to 130	131	132 to 156	**157**	158 to 182	183	184 to 210	**Week 211**	Week 227 or 15 weeks after Early Term Visit		
Dose number	14 to 28	29	30 to 54	55	56 to 80	81	82 to 106	107	108 to 132	133	134 to 158	159	160 to 186				
Dose level (mg)	255	255	255	255	255	255	255	255	255	255	255	255	255				
Amyloid PET scan [e, f]						x				x				x		x	
Tau PET scan [e, f]						x				x				x		x	
CSF sampling [g]						x [B]				x [B]				x		x	
PACC-5		x[B]		x[B]		x[B]		x[B]		x[B]		x[B]		x		x	x
CDR		x[B]		x[B]		x[B]		x[B]		x[B]		x[B]		x		x	x
CFIa		x[B]		x[B]		x[B]		x[B]		x[B]		x[B]		x		x	x
A-IADL-Q-SV						x[B]								x		x	x
AD-SPGI-S						x								x		x	x
AD-PGI-S						x[B]								x		x	x
AD-CGI-S		x		x		x		x		x		x		x		x	x
EQ-5D-5L		x[B]				x[B]				x[B]				x		x	x
GDS-30		x[B]		x[B]		x[B]		x[B]		x[B]		x[B]		x		x	x
C-SSRS		x [B]		x [B]		x [B]		x [B]		x [B]		x [B]		x	x	x	x
DCF		x		x		x		x		x		x		x		x	x

ADA = anti-drug antibody; AD-CGI-S = Clinician Global Impression of Cognitive Function; AD-PGI-S = Participant Global Impression of Cognitive Function; AD-SPGI-S = Study Partner Global Impression of Cognitive Function; A-IADL-Q-SV = Amsterdam Instrumental Activities of Daily Living Questionnaire Short Version; ARIA-E = amyloid-related imaging abnormalities – edema/effusion; ARIA-H = amyloid-related imaging abnormalities – hemosiderin deposition; C = in-clinic administration by study staff; CDR = Clinical Dementia Rating; CFIa = Cognitive Function Instrument acute; CRP = C-reactive protein; C-SSRS = Columbia-Suicide Severity Rating Scale; CS = supervised in-clinic administration, where applicable; CSF = cerebrospinal fluid; DCF = Diagnostic Classification Form; Early Term = Early Termination; EQ-5D-5L = EuroQol 5-Dimension 5-Level Questionnaire; GDS-30 = Geriatric Depression Scale; H = visit appropriate for home administration by participant or

Table 2 Schedule of Activities: Week 38 to End of Study; 255 mg Q1W (cont.)

study partner, where applicable; *MN* = visit appropriate for home administration by *mobile* nursing professional, where applicable; MRI = magnetic resonance imaging; PACC-5 = Preclinical Alzheimer's Cognitive Composite-5; PET = positron emission tomography; PK = pharmacokinetic; Q1W = every 1 week; Unsch = unscheduled; Wk = week.

x [B] = before study drug administration; visits may be split over 2 consecutive days.

As per Table 1, participants reach the target dose at Week 37 after which they will continue with the Q1W dosing frequency. Subsequently, the next dose after Week 37 is given at Week 38, and last dose is given at Week 210 during maintenance dosing.

Participants should be observed for at least 2 hours after dosing at Week 1, Week 5, Week 9 and Week 13; the observation time may be reduced to at least 1 hour following all other administrations.

[a] Scope of the unscheduled visit should include all efficacy assessments if they were missed at the preceding, regularly scheduled efficacy assessments visit. Safety assessments, including physical examinations, must also be included if they were missed at the preceding, regularly scheduled safety assessments visit or as clinically indicated. Unscheduled visits related to the occurrence of ARIA-E or ARIA-H are to follow the PK and plasma biomarker sampling rules as detailed below.

[b] Visits, that include PK, ADA and plasma biomarker sampling must take place in-clinic.
A PK sample is to be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following an MRI scan showing new occurrence or worsening of ARIA-E or ARIA-H that meets the discontinuation criteria. An additional plasma exploratory biomarkers sample is to be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E).

[c] *Metabolic tests include hemoglobin A1C, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, folic acid, vitamin B-12, methylmalonic acid, total thyroxine, free thyroxine, and thyroid-stimulating hormone levels. These tests should be collected as fasting samples (i.e., at least 4 hours after meals).*

[d] Every 4 weeks, except when there is an in-person clinic visit, the investigator or an appointed qualified study staff will have a telephone conversation with the participant and study partner to elicit, in a non-leading way, information on medication errors, adverse events, and changes to concomitant medications that may have occurred in the home setting. Therefore, there will be contact between the study staff and the participant/study partner at least every 4 weeks. The study staff is encouraged to have more frequent calls with a particular participant/study partner if considered appropriate by the investigator. Following the first 2 years of study treatment, the frequency of this telephone surveillance may be reduced to occur at least once, at midtime, between the 6-month in-person clinic visits. *However, for participants who enter the post-progression dose escalation period, there will be contact between the study staff and the participant/study partner at least every 4 weeks for 2 years after entering the post-progression dose escalation period (Table 3). Following this 2-year period, the frequency of this telephone surveillance can be reduced again as outlined above.* In addition, the participant and study partner must be instructed to contact the investigator and seek approval for continued study drug dosing in the home setting in case of onset of any new symptoms or symptom worsening, new or changed concomitant medications, or medication errors.

[e] Optional post-baseline amyloid and tau PET scans will be administered until the target number of scans is reached.

[f] Tau and amyloid PET scheduling window is ± 14 days. In an exceptional case of tau or amyloid PET scheduling issues the Sponsor must be notified and the scans may be performed up to 3 months after the scheduled assessment. For Early Termination visits, tau and amyloid PET scans should only be obtained if the last scan was > 6 months earlier.

[g] Optional post-baseline CSF samples will be collected until the target number of samples is reached. Cerebrospinal fluid collection must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing. For Early Termination visits, CSF sampling should only be obtained if the last CSF sampling was > 6 months earlier.

Table 3 Schedule of Activities: Post-Progression Dose Escalation with Q1W Study Drug Administration Frequency; Dosing Weeks 1P–37P

Neuropsychological efficacy assessments (i.e., Preclinical Alzheimer's Cognitive Composite-5 [PACC-5], Cognitive Function Instrument acute [CFIa], Amsterdam Instrumental Activities of Daily Living Questionnaire Short Version [A-AIDL-Q-SV], Clinical Dementia Rating [CDR], Alzheimer's disease Clinician Global Impression of Cognitive Function [AD-CGI-S], Alzheimer's disease Participant Global Impression of Cognitive Function [AD-PGI-S], Alzheimer's disease Study Partner Global Impression of Cognitive Function [AD-SPGI-S], EuroQol 5-Dimension, 5-Level Questionnaire [EQ-5D-5L], Geriatric Depression Scale-30 [GDS-30]), and the Diagnostic Classification Form (DCF), should continue as per the original schedule of activities (i.e., Table 2).

Participants originally randomized to active treatment will continue with gantenerumab 255 mg SC every 1 week (Q1W).

Table 3 Schedule of Activities: Post-Progression Dose Escalation with Q1W Study Drug Administration Frequency; Dosing Weeks 1P–37P (cont.)

Assessment/ Procedure	Dose Escalation Period [a, b]																								Unsch Visit [c]
	Wk 1P	Wk 2P–4P	Wk 5P	Wk 6P–8P	Wk 9P	Wk 10P –12 P	Wk 13P	Wk 14P –16P	Wk 17P	Wk 18P –20P	Wk 21P	Wk 22P –24P	Wk 25P	Wk 26P	Wk 27P	Wk 28P	Wk 29P	Wk 30P	Wk 31P	Wk 32P	Wk 33P	Wk 34P	Wk 35P	Wk 36P	Wk 37P	
Dose Number	1	2–4	5	6–8	9	10–12	13	14–16	17	18–20	21	22–24	25	26	27	28	29	30	31	32	33	34	35	36	37	
Participants previously on placebo: Dose Level (mg)	120	pcb	120	pcb	120	pcb	255	pcb	255	pcb	255	pcb	255	pcb	255	pcb	255	pcb	255	pcb	255	pcb	255	pcb	255	
Participants previously on placebo: Injections (mL)	1 × 0.8A + 1 × 1.7 pcb	1 × 1,7 pcb	1 × 0.8A + 1 × 1.7 pcb	1 × 1,7 pcb	1 × 0.8A + 1 × 1.7 pcb	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	
Participants previously on active treatment: Dose Level (mg)	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	
Participants previously on active treatment: Injections (mL)	1 × 0.8 pcb + 1 × 1.7 A	1 × 1,7 A	1 × 0.8 pcb + 1 × 1.7 A	1 × 1,7 A	1 × 0.8 pcb + 1 × 1.7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	
Study drug administration [d]	C	C/ MN	C	C/ MN	C	C/ MN	C	C/ MN	C/ MN	C/ MN	C/ MN	C/ MN	C	C/ MN	C/ MN	C/ MN	C/ MN	C/ MN	C/ MN	C/ MN	C/ MN	C/ MN	C/ MN	C/ MN	C	
12-lead ECG [e]	x [B]						x [B]						x [B]													x
PK plasma sample [f]	x [B]						x [B]						x [B]												x [B]	x
Plasma Biomarker Sample [f]	x [B]												x [B]													x
ADA Plasma Sample [f]	x [B]						x [B]						x [B]												x [B]	x
Serum chemistry and hematology [e]	x [B]												x [B]													x
Metabolic tests, CRP *and PT* [g, h]	x [B]																									x

Table 3 Schedule of Activities: Post-Progression Dose Escalation with Q1W Study Drug Administration Frequency; Dosing Weeks 1P–37P (cont.)

	Dose Escalation Period [a, b]																								
Assessment/ Procedure	Wk 1P	Wk 2P–4P	Wk 5P	Wk 6P–8P	Wk 9P	Wk 10P –12 P	Wk 13P	Wk 14P –16P	Wk 17P	Wk 18P –20P	Wk 21P	Wk 22P –24P	Wk 25P	Wk 26P	Wk 27P	Wk 28P	Wk 29P	Wk 30P	Wk 31P	Wk 32P	Wk 33P	Wk 34P	Wk 35P	Wk 36P	Wk 37P	
Dose Number	1	2–4	5	6–8	9	10–12	13	14–16	17	18–20	21	22–24	25	26	27	28	29	30	31	32	33	34	35	36	37	
Participants previously on placebo: Dose Level (mg)	120	pcb	120	pcb	120	pcb	255	pcb	255	pcb	255	pcb	255	pcb	255	pcb	255	pcb	255	pcb	255	pcb	255	pcb	255	
Participants previously on placebo: Injections (mL)	1 × 0.8A + 1 × 1.7 pcb	1 × 1,7 pcb	1 × 0.8A + 1 × 1.7 pcb	1 × 1,7 pcb	1 × 0.8A + 1 × 1.7 pcb	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	
Participants previously on active treatment: Dose Level (mg)	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	
Participants previously on active treatment: Injections (mL)	1 × 0.8 pcb + 1 × 1.7 A	1 × 1,7 A	1 × 0.8 pcb + 1 × 1.7 A	1 × 1,7 A	1 × 0.8 pcb + 1 × 1.7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	Unsch Visit [c]
Complete physical examination (Includes neurological systems)	x [B]																									x
Limited physical examination													x [B]													x
Weight	x [B]												x [B]													x
Vital signs	x [B]		x [B]		x [B]		x [B]		x [B]		x [B]		x [B]												x [B]	x
Concomitant medications [i]	x [B]		x [B]		x [B]		x [B]		x [B]		x [B]		x [B]				x [B]				x [B]				x [B]	x
Adverse events [i]	x [B]		x [B]		x [B]		x [B]		x [B]		x [B]		x [B]				x [B]				x [B]				x [B]	x

Table 3 Schedule of Activities: Post-Progression Dose Escalation with Q1W Study Drug Administration Frequency; Dosing Weeks 1P–37P (cont.)

Assessment/ Procedure	Dose Escalation Period [a, b]																								
	Wk 1P	Wk 2P–4P	Wk 5P	Wk 6P–8P	Wk 9P	Wk 10P –12P	Wk 13P	Wk 14P –16P	Wk 17P	Wk 18P –20P	Wk 21P	Wk 22P –24P	Wk 25P	Wk 26P	Wk 27P	Wk 28P	Wk 29P	Wk 30P	Wk 31P	Wk 32P	Wk 33P	Wk 34P	Wk 35P	Wk 36P	Wk 37P	
Dose Number	1	2–4	5	6–8	9	10–12	13	14–16	17	18–20	21	22–24	25	26	27	28	29	30	31	32	33	34	35	36	37	
Participants previously on placebo: Dose Level (mg)	120	pcb	120	pcb	120	pcb	255	pcb	255	pcb	255	pcb	255	pcb	255	pcb	255	pcb	255	pcb	255	pcb	255	pcb	255	
Participants previously on placebo: Injections (mL)	1 × 0.8A + 1 × 1.7 pcb	1 × 1,7 pcb	1 × 0.8A + 1 × 1.7 pcb	1 × 1,7 pcb	1 × 0.8A + 1 × 1.7 pcb	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	1 × 1,7 pcb	1 × 1,7 A	
Participants previously on active treatment: Dose Level (mg)	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	255	
Participants previously on active treatment: Injections (mL)	1 × 0.8 pcb + 1 × 1.7 A	1 × 1,7 A	1 × 0.8 pcb + 1 × 1.7 A	1 × 1,7 A	1 × 0.8 pcb + 1 × 1.7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	1 × 1,7 A	Unsch Visit [c]
Urine pregnancy test	x [B]																									x
MRI scan [e, f]	x [B]												x [B]												x [B]	x
Amyloid PET scan [j, k, l]	x																									
Tau PET scan [j, k, l]	x																									
CSF sampling [l, m]	x [B]																									
C-SSRS	x [B]												x [B]													x

ADA = anti-drug antibody; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities– hemosiderin deposition; C = in-clinic administration by study staff; CSF = cerebrospinal fluid; C-SSRS = Columbia-Suicide Severity Rating Scale; *MN* = visit appropriate for home administration by *mobile* nursing professional, where applicable; MRI = magnetic resonance imaging; pcb = placebo; PET = positron emission tomography; PK = pharmacokinetic; Q1W = every 1 week; Unsch = unscheduled; Wk = week.

x [B] = before study drug administration; visits may be split over 2 consecutive days.

During the post-progression dose escalation period, all assessments, with the exception of the neuropsychological efficacy assessments, should be performed following the schedule of activities in Table 3 considering the related footnotes (a–m). Following Week 37P, assessments should be continued as per Table 2, *with the exception of MRI monitoring*, taking into account the time spent on the post-progression dose escalation (i.e., Table 3). For example, if a participant moved from Table 2 at Week 100, and completed the activities of Week 37P (Table 3), then activities of Table 2 should be resumed starting at Week 138. Early Termination visits should be conducted as detailed in Table 2.

Table 3 Schedule of Activities: Post-Progression Dose Escalation with Q1W Study Drug Administration Frequency; Dosing Weeks 1P–37P (cont.)

[a] Visit weeks and dose numbers only refer to the 'post-progression dose escalation' period. Visit weeks are labeled 'P' (i.e., post-progression).

[b] *Visits at Weeks 1P, 5P, 9P, 13P, 17P, 21P, 25P, 27P, 29P, 31P, 33P, 35P, and 37P are defined as 'definitely active dosing' visits when both participant previously on placebo and active treatment receive an active dose of study drug.*

[c] Scope of the unscheduled visit should include all efficacy assessments if they were missed at the preceding, regularly scheduled efficacy assessments visit. Safety assessments, including physical examinations, must also be included if they were missed at the preceding, regularly scheduled safety assessments visit or as clinically indicated. Unscheduled visits related to the occurrence of ARIA-E or ARIA-H are to follow the PK, ADA and plasma biomarker sampling rules as detailed below.

[d] Participants should be observed for at least 2 hours after the first 4 'definitely active doses' (i.e., dosing at Week 1P, Week 5P, Week 9P and Week 13P). The observation time may be reduced to at least 1 hour following all other administrations. Participant or study partner administration is prohibited during the 'post-progression dose escalation' period. Study drug administration by the participant or their study partner may resume after Week 37P following assessment and adequate training, if necessary, by the site. Sites must verify participant/study partner readiness for study drug administration.

[e] If MRI, 12-lead ECG, *metabolic tests, CRP, PT* serum chemistry and hematology were obtained within 4-weeks of Week 1P, these assessments do not need to be repeated during the Week 1P visit.

[f] Visits, including PK, ADA and plasma biomarker sampling must take place in-clinic. A PK sample is to be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following an MRI scan showing new occurrence or worsening of ARIA-E or ARIA-H that meets the discontinuation criteria. An additional plasma exploratory biomarkers sample is to be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E).

[g] *During the post-progression dose escalation period, MRIs must be obtained -at minimum- before the first post-progression dose (Week 1P), after the second (Week 25P) and third (Week 37P) dose-escalation steps as detailed in Table 3. Once participants have reached target dose, MRIs must be obtained 4 months, then 10 months, then 16 months after the first target dose, after which annual MRI monitoring frequency can be initiated.*

[h] *Metabolic tests include hemoglobin A1C, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, folic acid, vitamin B-12, methylmalonic acid, total thyroxine, free thyroxine, and thyroid-stimulating hormone levels. These tests should be collected as fasting samples (i.e., at least 4 hours after meals).*

[i] Every 4 weeks, except when there is an in-clinic visit, the investigator or an appointed qualified study staff member will have a telephone conversation with the participant and study partner to elicit, in a non-leading way, information on medication errors, adverse events, and changes to concomitant medications that may have occurred in the home setting. Therefore, there will be contact between the study staff and the participant/study partner at least every 4 weeks. The study staff is encouraged to have more frequent calls with a particular participant/study partner if considered appropriate by the investigator. In addition, the participant and study partner must be instructed to contact the investigator and seek approval for continued study drug dosing in the home setting in case of onset of any new symptoms or symptom worsening, new or changed concomitant medications, or medication errors.

[j] Optional post-baseline amyloid and tau PET scans will be administered until the target number of scans is reached.

[k] Tau and amyloid PET scheduling window is ± 14 days. In an exceptional case of tau or amyloid PET scheduling issue the Sponsor must be notified and the scans may be performed up to 3 months after the scheduled assessment.
For Early Termination visits, tau and amyloid PET scans should only be obtained if the last scan was > 6 months earlier.

[l] CSF sampling, amyloid and tau PET scans must be repeated prior to the first 'post-progression dose escalation' dose administration if the last such assessment occurred > 6 months earlier. This repeat assessment will then replace the next originally scheduled Year 2, Year 3 or Year 4 assessment if this assessment is due in < 6 months.
If the last CSF sampling, amyloid and tau PET scan took place ≤ 6 months of the first 'post-progression dose escalation' dose administration, assessments should be continued as per the original schedule of activities (i.e., Table 2).

[m] Optional post-baseline CSF sampling will be continued until the target number of samples is reached. Cerebrospinal fluid collection must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing.

Table 4 Schedule of Activities: Week –17 to Week 37; Dose Escalation to Target Dose of 510 mg Q2W

	Screening Period		Baseline	Dose Escalation Period									Early Term Visit (2 weeks after last study drug dose)	Unsch Visit [b]
	Optional BBBM Prescreening [a] (Max. 4 weeks)	Main Screening												
Assessment / Procedure	Week −17 to −1		Wk 1	Wk 5	Wk 9	Wk 13	Wk 17	Wk 21	Wk 25	Wk 29	Wk 33	Wk 37		
Dose Number			1	2	3	4	5	6	7	8	9	10		
Dose Level (mg)			120	120	120	255	255	255	510	510	510	510		
Study drug administration			C	C	C	C/ CS	C/ CS/ *MN*	C/ CS/ *MN*	C/ CS/	C/ CS/ H/ *MN*	C/ CS/ H/ *MN*	C/ CS		
Informed Consent(s)	x	x												
Plasma sample for BBBM prescreening (optional)	x													
Review of inclusion and exclusion criteria		x	x [B]											
Clinical genotyping samples		x												
Return of amyloid test (CSF or PET) and *APOE* genotyping results [c]		x												
Medical history, personal status, and demographics		x												
Weight		x	x [B]						x [B]				x	x
Height		x												
12-lead ECG		x	x [B]			x [B]			x [B]				x	x

Table 4 Schedule of Activities: Week –17 to Week 37; Dose Escalation to Target Dose of 510 mg Q2W (cont.)

	Screening Period		Baseline	Dose Escalation Period									Early Term Visit (2 weeks after last study drug dose)	Unsch Visit [b]
	Optional BBBM Prescreening [a] (Max. 4 weeks)	Main Screening												
Assessment / Procedure	Week −17 to −1		Wk 1	Wk 5	Wk 9	Wk 13	Wk 17	Wk 21	Wk 25	Wk 29	Wk 33	Wk 37		
Dose Number			1	2	3	4	5	6	7	8	9	10		
Dose Level (mg)			120	120	120	255	255	255	510	510	510	510		
Urinalysis		x												
Urine pregnancy test		x	x [B]										x	x
Urine sample for drugs of abuse		x												
PK plasma sample [d]			x [B]			x [B]			x [B]			x [B]	x	x
Plasma biomarker sample [d, e]		x	x [B]						x [B]				x	x
ADA plasma sample [d]			x [B]			x [B]			x [B]			x [B]	x	x
Serum chemistry and hematology		x	x [B]						x [B]				x	x
Metabolic tests, CRP *and PT* [f]		*x*											*x*	*x*
Viral serology: HIV, HBV, HCV		x												
Complete physical examination (Includes neurological systems)		x	x [B]										x	x
Limited physical examination									x [B]					x
MRI scan		x							x [B]			x [B]	x	x
Amyloid PET scan [g]		x											x	
Tau PET scan [g, h]			x										x	
CSF sampling [i]		x											x	

Table 4 Schedule of Activities: Week –17 to Week 37; Dose Escalation to Target Dose of 510 mg Q2W (cont.)

	Screening Period		Baseline	Dose Escalation Period									Early Term Visit (2 weeks after last study drug dose)	Unsch Visit [b]
	Optional BBBM Prescreening [a] (Max. 4 weeks)	Main Screening												
Assessment / Procedure	Week −17 to −1		Wk 1	Wk 5	Wk 9	Wk 13	Wk 17	Wk 21	Wk 25	Wk 29	Wk 33	Wk 37		
Dose Number			1	2	3	4	5	6	7	8	9	10		
Dose Level (mg)			120	120	120	255	255	255	510	510	510	510		
Vital signs		x	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]			x [B]	x	x
Concomitant medications [j]		x	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x	x
Adverse events [j]	x	x	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x	x
RBANS		x												
PACC-5		x	x [B]						x [B]				x	x
CDR		x							x [B]				x	x
CFIa			x [B]						x [B]				x	x
A-IADL-Q-SV			x [B]										x	x
AD-SPGI-S			x [B]										x	x
AD-PGI-S			x [B]										x	x
AD-CGI-S		x							x				x	x
EQ-5D-5L			x [B]										x	x
GDS-30			x [B]						x [B]				x	x
C-SSRS			x [B]						x [B]				x	x
DCF			x [B]						x				x	x

Table 4 Schedule of Activities: Week –17 to Week 37; Dose Escalation to Target Dose of 510 mg Q2W (cont.)

ADA = anti-drug antibody; AD-CGI-S = Clinician Global Impression of Cognitive Function; AD-PGI-S = Participant Global Impression of Cognitive Function; AD-SPGI-S = Study Partner Global Impression of Cognitive Function; A-IADL-Q-SV = Amsterdam Instrumental Activities of Daily Living Questionnaire Short Version; *APOE* = apolipoprotein E; ARIA-E = amyloid-related imaging abnormalities – edema/effusion; ARIA-H = amyloid-related imaging abnormalities – hemosiderin deposition; BBBM = blood-based biomarker; C = in-clinic administration by study staff; CDR = Clinical Dementia Rating; CFIa = Cognitive Function Instrument acute; CRP = C-reactive protein; C-SSRS = Columbia-Suicide Severity Rating Scale; CS = supervised in-clinic administration, where applicable; CSF = cerebrospinal fluid; DCF = Diagnostic Classification Form; Early Term = Early Termination; EQ-5D-5L = EuroQol 5-Dimension 5-Level Questionnaire; GDS-30 = Geriatric Depression Scale; H = visit appropriate for home administration by participant or study partner, where applicable; HBV = hepatitis B virus; HCV = hepatitis C virus; ICF = Informed Consent Form; Max. = maximum; *MN = visit appropriate for home administration by mobile nursing professional, where applicable;* MRI = magnetic resonance imaging; PACC-5 = Preclinical Alzheimer's Cognitive Composite-5; PET = positron emission tomography; PK = pharmacokinetic; Q2W = every 2 weeks; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; Unsch = unscheduled; Wk = week.

x [B] = before study drug administration; visits may be split over 2 consecutive days.

The baseline visit (Week 1) may be split over 5 consecutive business days. All cognitive and functional assessments must be completed first, and before study drug administration. All safety assessments (e.g., vitals, blood tests, and ECGs) must be completed on the day of dosing and before study drug administration. Study drug administration should be the last baseline visit activity, marking the end of Week 1.

Participants should be observed for at least 2 hours after dosing for the first 4 administrations of study drug (corresponding to the injections at Week 1, Week 5, Week 9 and Week 13); the observation time may be reduced to at least 1 hour following all other administrations.

[a] Not applicable for sites where BBBM prescreening is not approved. Participation in the optional BBBM prescreening requires signing of the separate BBBM prescreening ICF.

[b] Scope of the unscheduled visit should include all efficacy assessments if they were missed at the preceding, regularly scheduled efficacy assessments visit. Safety assessments, including physical examinations, must also be included if they were missed at the preceding, regularly scheduled safety assessments visit or as clinically indicated. Unscheduled visits related to the occurrence of ARIA-E or ARIA-H are to follow the PK and plasma biomarker sampling rules as detailed below.

[c] Return of amyloid test and *APOE* genotyping results must take place at least 7 days prior to the randomization visit. Follow-up over disclosures should occur within 1 week of the provision of results.

[d] Visits, including PK, ADA and plasma biomarker sampling must take place in-clinic.
A PK sample is to be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following an MRI scan showing new occurrence or worsening of ARIA-E or ARIA-H that meets the discontinuation criteria. An additional plasma exploratory biomarkers sample is to be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E).

[e] Plasma biomarker sample during the main screening period should only be collected if the BBBM prescreening was not completed for the participant.

[f] *Metabolic tests include hemoglobin A1C, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, folic acid, vitamin B-12, methylmalonic acid, total thyroxine, free thyroxine, and thyroid-stimulating hormone levels. These tests should be collected as fasting samples (i.e., at least 4 hours after meals).*

[g] Tau and amyloid PET scheduling window is ± 14 days. In an exceptional case of tau or amyloid PET scheduling issue the Sponsor must be notified and the scans may be performed up to 3 months after the scheduled assessment. For Early Termination visits, tau and amyloid PET scans should only be obtained if the last scan was > 6 months earlier.

Table 4 Schedule of Activities: Week –17 to Week 37; Dose Escalation to Target Dose of 510 mg Q2W (cont.)

[h] Baseline tau PET should be obtained prior to first dose of study drug. However, in an exceptional case, and with the notification of the Sponsor, the baseline tau PET may be obtained within 3 months of randomization.

[i] Cerebrospinal fluid collection must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing. For Early Termination visits, CSF sampling should only be obtained if the last CSF sampling was $>$ 6 months earlier.

[j] Every 4 weeks, except when there is an in-clinic visit, the investigator or an appointed qualified study staff member will have a telephone conversation with the participant and study partner to elicit, in a non-leading way, information on medication errors, adverse events, and changes to concomitant medications that may have occurred in the home setting. Therefore, there will be contact between the study staff and the participant/study partner at least every 4 weeks. The study staff is encouraged to have more frequent calls with a particular participant/study partner if considered appropriate by the investigator. In addition, the participant and study partner must be instructed to contact the investigator and seek approval for continued study drug dosing in the home setting in case of onset of any new symptoms or symptom worsening, new or changed concomitant medications, or medication errors.

Table 5 Schedule of Activities: Week 38 to End of Study; 510 mg Q2W

	Maintenance Dosing from Week 38 to Week 210													Final Safety and Efficacy Assessment	Follow-Up Safety Assessment	Early Term Visit (2 weeks after last dose of study drug)	Unsh Visit [a]
Assessment/ Procedure (week)	39 to 51	**53**	55 to 77	79	81 to 103	**105**	107 to 129	131	133 to 155	**157**	159 to 181	183	185 to 209	**Week 211**	Week 227 or 15 weeks after Early Term Visit		
Dose number	11 to 17	18	19 to 30	31	32 to 43	44	45 to 56	57	58 to 69	70	71 to 82	83	84 to 96				
Dose level (mg)	510	510	510	510	510	510	510	510	510	510	510	510	510				
Study drug administration	C/ CS/ H/ *MN*	C/ CS	C/ CS/ H/ *MN*	C/ CS	C/ CS/ H/ *MN*	C/ CS	C/ CS/ H/ *MN*	C/ CS	C/ CS/ H/ *MN*	C/ CS	C/ CS/ H/ *MN*	C/ CS	C/ CS/ H/ *MN*				
12-lead ECG		x [B]		x [B]		x [B]		x [B]		x [B]		x [B]		x	x	x	x
PK plasma sample [b]		x [B]		x [B]		x [B]		*x* [B]		x [B]		*x* [B]		x		x	x
Plasma biomarker sample [b]		x [B]		x [B]		x [B]				x [B]				x	x	x	x
ADA plasma sample [b]		x [B]		x [B]		x [B]		x [B]		x [B]		x [B]		x		x	x
Serum chemistry and hematology		x [B]		x [B]		x [B]		x [B]		x [B]		x [B]		x	x	x	x
Metabolic tests, *CRP, PT* [c]		*x* [B]				*x* [B]				*x* [B]				*x*	*x*	*x*	*x*
Complete physical examination		x [B]				x [B]				x [B]				x	x	x	x
Limited physical examination				x [B]				x [B]				x [B]					x
Weight		x [B]		x [B]		x [B]				x [B]				x	x	x	x
Vital signs		x [B]		x [B]		x [B]		x [B]		x [B]		x [B]		x	x	x	x
Concomitant medications [d]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x	x	x	x
Adverse events [d]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x [B]	x	x	x	x
Urine pregnancy test						x [B]				x [B]				x	x	x	x
MRI scan		x [B]		x [B]		x [B]				x [B]					x (4 wks after last dose)	x	x

Table 5 Schedule of Activities: Week 38 to End of Treatment Period (Week 211); 510 mg Q2W (cont.)

	Maintenance Dosing from Week 38 to Week 210 [a]													Final Safety and Efficacy Assessment	Follow-Up Safety Assessment	Early Term Visit (2 weeks after last dose of study drug)	Unsh Visit [b]
Assessment/ Procedure (week)	39 to 51	**53**	55 to 77	79	81 to 103	**105**	107 to 129	131	133 to 155	**157**	159 to 181	183	185 to 209	**Week 211**	Week 227 or 15 weeks after Early Term Visit		
Dose number	11 to 17	18	19 to 30	31	32 to 43	44	45 to 56	57	58 to 69	70	71 to 82	83	84 to 96				
Dose level (mg)	510	510	510	510	510	510	510	510	510	510	510	510	510				
Amyloid PET scan [e, f]						x				x				x		x	
Tau PET scan [e, f]						x				x				x		x	
CSF sampling [g]						x [B]				x [B]				x		x	
PACC-5		x[B]		x[B]		x[B]		x[B]		x[B]		x[B]		x		x	x
CDR		x[B]		x[B]		x[B]		x[B]		x[B]		x[B]		x		x	x
CFIa		x[B]		x[B]		x[B]		x[B]		x[B]		x[B]		x		x	x
A-IADL-Q-SV						x[B]								x		x	x
AD-SPGI-S						x								x		x	x
AD-PGI-S						x[B]								x		x	x
AD-CGI-S		x		x		x		x		x		x		x		x	x
EQ-5D-5L		x[B]				x[B]				x[B]				x		x	x
GDS-30		x[B]		x[B]		x[B]		x[B]		x[B]		x[B]		x		x	x
C-SSRS		x[B]		x[B]		x[B]		x[B]		x[B]		x[B]		x	x	x	x
DCF		x		x		x		x		x		x		x		x	x

ADA = anti-drug antibody; AD-CGI-S = Clinician Global Impression of Cognitive Function; AD-PGI-S = Participant Global Impression of Cognitive Function; AD-SPGI-S = Study Partner Global Impression of Cognitive Function; A-IADL-Q-SV = Amsterdam Instrumental Activities of Daily Living Questionnaire Short Version; ARIA-E = amyloid-related imaging abnormalities – edema/effusion; ARIA-H = amyloid-related imaging abnormalities – hemosiderin deposition; C = in-clinic administration by study staff; CDR = Clinical Dementia Rating; CFIa = Cognitive Function Instrument acute; C-SSRS = Columbia-Suicide Severity Rating Scale; CS = supervised in-clinic administration, where applicable; CSF = cerebrospinal fluid; DCF = Diagnostic Classification Form; Early Term = Early Termination; EQ-5D-5L = EuroQol 5-Dimension 5-Level Questionnaire; GDS-30 = Geriatric Depression Scale; H = visit appropriate for home administration by participant or study partner, where applicable; *M*N = visit appropriate for home administration by *mobile* nursing professional, where applicable; MRI = magnetic resonance imaging; PACC-5 = Preclinical Alzheimer's Cognitive Composite-5; PET = positron emission tomography; PK = pharmacokinetic; Q2W = every 2 weeks; Unsch = unscheduled; Wk = week.

Table 5 Schedule of Activities: Week 38 to End of Treatment Period (Week 211); 510 mg Q2W (cont.)

x [B] = before study drug administration; visits may be split over 2 consecutive days.

As per Table 4, participants reach the target dose at Week 37 after which they continue with the Q2W dosing frequency. Subsequently, the next dose after Week 37 is given at Week 39, and last dose is given at Week 209 during maintenance dosing.

Participants should be observed for at least 2 hours after dosing at Week 1, Week 5, Week 9 and Week 13; the observation time may be reduced to at least 1 hour following all other administrations.

[a] Scope of the unscheduled visit should include all efficacy assessments if they were missed at the preceding, regularly scheduled efficacy assessments visit. Safety assessments, including physical examinations, must also be included if they were missed at the preceding, regularly scheduled safety assessments visit or as clinically indicated. Unscheduled visits related to the occurrence of ARIA-E or ARIA-H are to follow the PK and plasma biomarker sampling rules as detailed below.

[b] Visits, including PK, ADA and plasma biomarker sampling must take place in-clinic.
A PK sample is to be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following an MRI scan showing new occurrence or worsening of ARIA-E or ARIA-H that meets the discontinuation criteria. An additional plasma exploratory biomarkers sample is to be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E).

[c] *Metabolic tests include hemoglobin A1C, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, folic acid, vitamin B-12, methylmalonic acid, total thyroxine, free thyroxine, and thyroid-stimulating hormone levels. These tests should be collected as fasting samples (i.e., at least 4 hours after meals).*

[d] Every 4 weeks, except when there is an in-clinic visit, the investigator or an appointed qualified study staff member will have a telephone conversation with the participant and study partner to elicit, in a non-leading way, information on medication errors, adverse events, and changes to concomitant medications that may have occurred in the home setting. Therefore, there will be contact between the study staff and the participant/study partner at least every 4 weeks. The study staff is encouraged to have more frequent calls with a particular participant/study partner if considered appropriate by the investigator. Following the first 2 years of study treatment, the frequency of this telephone surveillance may be reduced to occur at least once, at midtime, between the 6-month in-clinic visits. *However, for participants who enter the post-progression dose escalation period, there will be contact between the study staff and the participant/study partner at least every 4 weeks for 2 years after entering the post-progression dose escalation period (Table 6), after which the frequency of this telephone surveillance can be reduced again as outlined above.* In addition, the participant and study partner must be instructed to contact the investigator and seek approval for continued study drug dosing in the home setting in case of onset of any new symptoms or symptom worsening, new or changed concomitant medications, or medication errors.

[e] Tau and amyloid PET scheduling window is $\pm$ 14 days. In an exceptional case of tau or amyloid PET scheduling issue the Sponsor must be notified and the scans may be performed up to 3 months after the scheduled assessment. For Early Termination visits, tau and amyloid PET scans should only be obtained if the last scan was $>$ 6 months earlier.

f Optional post-baseline CSF samples will be collected until the target number of samples is reached. Cerebrospinal fluid collection must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing. For Early Termination visits, CSF sampling should only be obtained if the last CSF sampling was $>$ 6 months earlier.

g Optional post-baseline amyloid and tau PET scans will be administered until the target number of scans is reached.

Table 6 Schedule of Activities: Post-Progression Dose Escalation with Q2W Study Drug Administration Frequency; Dosing Weeks 1P–37P

Neuropsychological efficacy assessments, i.e., PACC-5, CFIa, A-AIDL-Q-SV, CDR, AD-CGI-S, AD-PGI-S, AD-SPGI-S, EQ-5D-5L, GDS-30, and the DCF, should continue as per the original schedule of activities (i.e., Table 5).

Participants originally randomized to active treatment will continue with gantenerumab 510 mg SC every 2 weeks (Q2W).

Assessment / Procedure	Dose Escalation Period [a, b]																		
	Wk 1P	Wk 3P	Wk 5P	Wk 7P	Wk 9P	Wk 11P	Wk 13P	Wk15P	Wk 17P	Wk19P	Wk 21P	Wk 23P	Wk 25P	Wk 27P	Wk 29P	Wk 31P	Wk 33P	Wk 35P	Wk 37P	
Dose Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	
Participants previously on placebo: Dose Level (mg)	120	pcb	120	pcb	120	pcb	255	pcb	255	pcb	255	pcb	510	pcb	510	pcb	510	pcb	510	
Participants previously on placebo: Injections (mL)	1 × 0.8 A + 2 × 1.7 pcb	2 × 1.7 pcb	1 × 0.8 A + 2 × 1.7 pcb	2 × 1.7 pcb	1 × 0.8 A + 2 × 1.7 pcb	2 × 1.7 pcb	1 ×1.7 A + 1 × 1.7 pcb	2 × 1.7 pcb	1 ×1.7 A + 1 × 1.7 pcb	2 × 1.7 pcb	1 ×1.7 A + 1 × 1.7 pcb	2 × 1.7 pcb	2 × 1.7 A	2 × 1.7 pcb	2 × 1.7 A	2 × 1.7 pcb	2 × 1.7 A	2 × 1.7 pcb	2 × 1.7 A	
Participants previously on active treatment: Dose Level (mg)	510	510	510	510	510	510	510	510	510	510	510	510	510	510	510	510	510	510	510	
Participants previously on active treatment: Injections (mL)	1 × 0.8 pcb + 2 × 1.7 A	2 × 1.7 A	1 × 0.8 pcb + 2 × 1.7 A	2 × 1.7 A	1 × 0.8 pcb + 2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	Unsch Visit [c]
Study drug administration [d]	C	C/ *MN*	C	C/ *MN*	C	C/ *MN*	C	C/ *MN*	C/ *MN*	C/ *MN*	C/ *MN*	C/ *MN*	C	C/ *MN*	C/ *MN*	C/ *MN*	C/ *MN*	C/ *MN*	C	
12-lead ECG [e]	x [B]						x [B]						x [B]							x
PK plasma sample [f]	x [B]						x [B]						x [B]						x [B]	x
Plasma biomarker sample [f]	x [B]												x [B]							x

Table 6 Schedule of Activities: Post-Progression Dose Escalation with Q2W Study Drug Administration Frequency; Dosing Weeks 1P–37P (cont.)

Assessment / Procedure	Dose Escalation Period [a, b]																		
	Wk 1P	Wk 3P	Wk 5P	Wk 7P	Wk 9P	Wk 11P	Wk 13P	Wk15P	Wk 17P	Wk19P	Wk 21P	Wk 23P	Wk 25P	Wk 27P	Wk 29P	Wk 31P	Wk 33P	Wk 35P	Wk 37P	
Dose Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	
Participants previously on placebo: Dose Level (mg)	120	pcb	120	pcb	120	pcb	255	pcb	255	pcb	255	pcb	510	pcb	510	pcb	510	pcb	510	
Participants previously on placebo: Injections (mL)	1 × 0.8 A + 2 × 1.7 pcb	2 × 1.7 pcb	1 × 0.8 A + 2 × 1.7 pcb	2 × 1.7 pcb	1 × 0.8 A + 2 × 1.7 pcb	2 × 1.7 pcb	1 ×1.7 A + 1 × 1.7 pcb	2 × 1.7 pcb	1 ×1.7 A + 1 × 1.7 pcb	2 × 1.7 pcb	1 ×1.7 A + 1 × 1.7 pcb	2 × 1.7 pcb	2 × 1.7 A	2 × 1.7 pcb	2 × 1.7 A	2 × 1.7 pcb	2 × 1.7 A	2 × 1.7 pcb	2 × 1.7 A	
Participants previously on active treatment: Dose Level (mg)	510	510	510	510	510	510	510	510	510	510	510	510	510	510	510	510	510	510	510	
Participants previously on active treatment: Injections (mL)	1 × 0.8 pcb + 2 × 1.7 A	2 × 1.7 A	1 × 0.8 pcb + 2 × 1.7 A	2 × 1.7 A	1 × 0.8 pcb + 2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	Unsch Visit [c]
ADA plasma sample [f]	x [B]						x [B]						x [B]						x [B]	x
Serum chemistry and hematology [e]	x [B]												x [B]							x
Metabolic tests, CRP, PT [e, g, h]	x [B]																			x
Complete physical examination (Includes neurological systems)	x [B]																			x

Table 6 Schedule of Activities: Post-Progression Dose Escalation with Q2W Study Drug Administration Frequency; Dosing Weeks 1P–37P (cont.)

Assessment / Procedure	Dose Escalation Period [a, b]																		
	Wk 1P	Wk 3P	Wk 5P	Wk 7P	Wk 9P	Wk 11P	Wk 13P	Wk15P	Wk 17P	Wk19P	Wk 21P	Wk 23P	Wk 25P	Wk 27P	Wk 29P	Wk 31P	Wk 33P	Wk 35P	Wk 37P	
Dose Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	
Participants previously on placebo: Dose Level (mg)	120	pcb	120	pcb	120	pcb	255	pcb	255	pcb	255	pcb	510	pcb	510	pcb	510	pcb	510	
Participants previously on placebo: Injections (mL)	1 × 0.8 A + 2 × 1.7 pcb	2 × 1.7 pcb	1 × 0.8 A + 2 × 1.7 pcb	2 × 1.7 pcb	1 × 0.8 A + 2 × 1.7 pcb	2 × 1.7 pcb	1 ×1.7 A + 1 × 1.7 pcb	2 × 1.7 pcb	1 ×1.7 A + 1 × 1.7 pcb	2 × 1.7 pcb	1 ×1.7 A + 1 × 1.7 pcb	2 × 1.7 pcb	2 × 1.7 A	2 × 1.7 pcb	2 × 1.7 A	2 × 1.7 pcb	2 × 1.7 A	2 × 1.7 pcb	2 × 1.7 A	
Participants previously on active treatment: Dose Level (mg)	510	510	510	510	510	510	510	510	510	510	510	510	510	510	510	510	510	510	510	
Participants previously on active treatment: Injections (mL)	1 × 0.8 pcb + 2 × 1.7 A	2 × 1.7 A	1 × 0.8 pcb + 2 × 1.7 A	2 × 1.7 A	1 × 0.8 pcb + 2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	Unsch Visit [c]
Limited physical examination													x [B]							x
Weight	x [B]												x [B]							x
Vital signs	x [B]		x [B]		x [B]		x [B]		x [B]		x [B]		x [B]						x [B]	x
Concomitant medications [i]	x [B]		x [B]		x [B]		x [B]		x [B]		x [B]		x [B]		x [B]		x [B]		x [B]	x
Adverse events [i]	x [B]		x [B]		x [B]		x [B]		x [B]		x [B]		x [B]		x [B]		x [B]		x [B]	x
Urine pregnancy test	x [B]																			x
MRI scan [e, f]	x [B]												x [B]						x [B]	x
Amyloid PET scan [j, k, l]	x																			

Table 6 Schedule of Activities: Post-Progression Dose Escalation with Q2W Study Drug Administration Frequency; Dosing Weeks 1P–37P (cont.)

Assessment / Procedure	Dose Escalation Period [a, l]																		
	Wk 1P	Wk 3P	Wk 5P	Wk 7P	Wk 9P	Wk 11P	Wk 13P	Wk15P	Wk 17P	Wk19P	Wk 21P	Wk 23P	Wk 25P	Wk 27P	Wk 29P	Wk 31P	Wk 33P	Wk 35P	Wk 37P	
Dose Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	
Participants previously on placebo: Dose Level (mg)	120	pcb	120	pcb	120	pcb	255	pcb	255	pcb	255	pcb	510	pcb	510	pcb	510	pcb	510	
Participants previously on placebo: Injections (mL)	1 × 0.8 A + 2 × 1.7 pcb	2 × 1.7 pcb	1 × 0.8 A + 2 × 1.7 pcb	2 × 1.7 pcb	1 × 0.8 A + 2 × 1.7 pcb	2 × 1.7 pcb	1 ×1.7 A + 1 × 1.7 pcb	2 × 1.7 pcb	1 ×1.7 A + 1 × 1.7 pcb	2 × 1.7 pcb	1 ×1.7 A + 1 × 1.7 pcb	2 × 1.7 pcb	2 × 1.7 A	2 × 1.7 pcb	2 × 1.7 A	2 × 1.7 pcb	2 × 1.7 A	2 × 1.7 pcb	2 × 1.7 A	
Participants previously on active treatment: Dose Level (mg)	510	510	510	510	510	510	510	510	510	510	510	510	510	510	510	510	510	510	510	
Participants previously on active treatment: Injections (mL)	1 × 0.8 pcb + 2 × 1.7 A	2 × 1.7 A	1 × 0.8 pcb + 2 × 1.7 A	2 × 1.7 A	1 × 0.8 pcb + 2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	2 × 1.7 A	Unsch Visit [b]
Tau PET scan [j, k, l]	x																			
CSF sampling [l, m]	x [B]																			
C-SSRS	x [B]												x [B]							x

ADA = anti-drug antibody; ARIA-E = amyloid-related imaging abnormalities – edema/effusion; ARIA-H = amyloid-related imaging abnormalities – hemosiderin deposition; C = in-clinic administration by study staff; CSF = cerebrospinal fluid; CRP = C-reactive protein; C-SSRS = Columbia-Suicide Severity Rating Scale; *MN* = visit appropriate for home administration by *mobile* nursing professional, where applicable; MRI = magnetic resonance imaging; pcb = placebo; PET = positron emission tomography; PK = pharmacokinetic; Q2W = every 2 weeks; Unsch = unscheduled; Wk = week.

x [B] = before study drug administration; visits may be split over 2 consecutive days.

During the post-progression dose escalation period, all assessments, with the exception of the neuropsychological efficacy assessments, should be performed following the schedule of activities in Table 6 considering the related footnotes (a–m). Following Week 37P, assessments should be continued as per Table 5, *with the exception of MRI monitoring*, taking into account the time spent on the post-progression dose escalation (i.e., Table 6). For example, if a participant moved from Table 5 at Week 100, and completed the activities of *Week 37P (Table 6)*, then activities of Table 5 should be resumed starting at Week 138. Early Termination visits should be conducted as detailed in Table 5.

Table 6 Schedule of Activities: Post-Progression Dose Escalation with Q2W Study Drug Administration Frequency; Dosing Weeks 1P–37P (cont.)

[a] Visit weeks and dose numbers only refer to the 'post-progression dose escalation' period. Visit weeks are labeled 'P' (i.e., post-progression).

[b] *Visits at Weeks 1P, 5P, 9P, 13P, 17P, 21P, 25P, 29P, 33P, and 37P are defined as 'definitely active dosing' visits when both participant previously on placebo and active treatment receive an active dose of study drug.*

[c] Scope of the unscheduled visit should include all efficacy assessments if they were missed at the preceding, regularly scheduled efficacy assessments visit. Safety assessments, including physical examinations, must also be included if they were missed at the preceding, regularly scheduled safety assessments visit or as clinically indicated. Unscheduled visits related to the occurrence of ARIA-E or ARIA-H are to follow the PK, ADA and plasma biomarker sampling rules as detailed below.

[d] Participants should be observed for at least 2 hours after after the first 4' definitvely active doses' (i.e., at Week 1P, Week 5P, Week 9P and Week 13P); the observation time may be reduced to at least 1 hour following all other administrations. Participant or study partner administration is prohibited during the 'post-progression dose escalation' period. Study drug administration by the participant or their study partner may resume after Week 37P following assessment and adequate training, if necessary, by the site. Sites must verify participant/study partner readiness for study drug administration.

[e] If MRI, 12-lead ECG, metabolic tests, CRP, *PT* serum chemistry and hematology were obtained within 4-weeks of Week 1P, these assessments do not need to be repeated during the Week 1P visit.

[f] Visits, including PK, ADA and plasma biomarker sampling must take place in-clinic.
A PK sample is to be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following an MRI scan showing new occurrence or worsening of ARIA-E or ARIA-H that meets the discontinuation criteria. An additional plasma exploratory biomarkers sample is to be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E).

[g] *During the post-progression dose escalation period, MRIs must be obtained -at minimum- before the first post-progression dose (Week 1P), after the second (Week 25P) and third (Week 37P) dose-escalation steps as detailed in Table 6. Once participants have reached target dose, MRIs must be obtained 4 months, then 10 months, then 16 months after the first target dose, after which annual MRI monitoring frequency can be initiated.*

[h] *Metabolic tests include hemoglobin A1C, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, folic acid, vitamin B-12, methylmalonic acid, total thyroxine, free thyroxine, and thyroid-stimulating hormone levels. These tests should be collected as fasting samples (i.e., at least 4 hours after meals).*

[i] Every 4 weeks, except when there is an in-clinic visit, the investigator or an appointed qualified study staff member will have a telephone conversation with the participant and study partner to elicit, in a non-leading way, information on medication errors, adverse events, and changes to concomitant medications that may have occurred in the home setting. Therefore, there will be contact between the study staff and the participant/study partner at least every 4 weeks. The study staff is encouraged to have more frequent calls with a particular participant/study partner if considered appropriate by the investigator. In addition, the participant and study partner must be instructed to contact the investigator and seek approval for continued study drug dosing in the home setting in case of onset of any new symptoms or symptom worsening, new or changed concomitant medications, or medication errors.

[j] Optional post-baseline amyloid and tau PET scans will be administered until the target number of scans is reached.

[k] Tau and amyloid PET scheduling window is $\pm$ 14 days. In an exceptional case of tau or amyloid PET scheduling issue the Sponsor must be notified and the scans may be performed up to 3 months after the scheduled assessment. For Early Termination visits, tau and amyloid PET scans should only be obtained if the last scan was $>$ 6 months earlier.

Table 6 Schedule of Activities: Post-Progression Dose Escalation with Q2W Study Drug Administration Frequency; Dosing Weeks 1P–37P (cont.)

[l] CSF sampling, amyloid and tau PET scans must be repeated prior to the first 'post-progression dose escalation dose administration if the last such assessment occurred > 6 months earlier. This repeat assessment will then replace the next originally scheduled Year 2, Year 3, or Year 4 assessment if this assessment is due in < 6 months.
If the last CSF sampling, amyloid and tau PET scan took place ≤ 6 months of the first 'post-progression dose escalation' dose administration, assessments should be continued as per the original schedule of activities (i.e., Table 5).

[m] Optional post-baseline CSF sampling will be continued until the target number of samples is reached. Cerebrospinal fluid collection must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing.

2. INTRODUCTION

2.1 STUDY RATIONALE

The primary purpose of this secondary prevention study is to evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of gantenerumab, an anti-amyloid β antibody, in amyloid-positive, cognitively unimpaired participants at risk for or at the earliest stages of Alzheimer's disease (AD).

Alzheimer's disease, a debilitating and progressive neurodegenerative disease, represents a significant unmet medical need with no fully approved therapeutics to halt, slow, or prevent the onset of symptoms. The currently available treatment options primarily include symptomatic medications and are only approved for the overtly symptomatic stages of AD.

The amyloid hypothesis postulates that amyloid may be an early, key driver of AD pathophysiology. If this hypothesis is true, then early intervention at the amyloid-positive, cognitively unimpaired stage (i.e., at-risk stage of disease), may result in a high efficacy potential for an anti-amyloid β antibody (i.e., gantenerumab), to slow the disease process and preserve the cognitive and functional abilities of affected individuals. This is the main hypothesis Study WN42444 (SKYLINE) aims to test.

2.2 BACKGROUND

The neuropathological hallmarks of AD are extracellular amyloid plaques built of insoluble amyloid β (Aβ) peptide and intraneuronal neurofibrillary tangles consisting of hyperphosphorylated tau filaments (Bloom 2014). Recent efforts have focused on targeting amyloid as a compelling therapeutic target (Bachurin et al. 2017; Graham et al. 2017). These investigational treatments are based on the amyloid hypothesis, which postulates that Aβ accumulation is a key factor driving AD pathogenesis (Selkoe 1991; Hardy and Selkoe 2002; Selkoe and Hardy 2016). Accumulation of cerebral Aβ may begin up to 20 years prior to the emergence of clinical symptoms (Bateman et al. 2012) and cause a series of downstream events leading to synaptic dysfunction, inflammation, neurodegeneration, and eventually clinical symptoms (Jack et. al. 2013).

Growing clinical evidence supports that monoclonal antibodies against amyloid can bind aggregated Aβ, promote its clearance (Salloway et al. 2009; Ostrowitzki et. al. 2012; Sevigny et al. 2016; Klein et al. 2019), and reduce markers of neurodegeneration in the cerebrospinal fluid (CSF; Ostrowitzki et al. 2017). In a Phase I study of aducanumab, reduction of amyloid plaques, as seen on brain amyloid positron emission tomography (PET) imaging, was suggested to be associated with a time- and dose-dependent slowing of cognitive decline (Sevigny et al. 2016). Reduction of Aβ plaques was also observed in the subsequent Phase III studies, leading to the accelerated approval of aducanumab by the U.S. Food and Drug Administration (FDA) in 2021. Evidence of

amyloid reduction and slowing of cognitive decline has also been reported for other monoclonal anti-Aβ antibodies (Eisai Co, Ltd 2018; Mintun et al. 2021).

The ability of gantenerumab to reduce aggregated cerebral Aβ has been confirmed in 2 PET sub-studies in participants with mild cognitive impairment (MCI) due to AD (Study WN25203 open-label extension [OLE]) or mild AD dementia (Study WN28745 OLE). Starting from a mean baseline level of 76 centiloids, a mean reduction of 39 centiloids by the first year and 59 centiloids by the second year was achieved at doses titrated up to 1200 mg. Moreover, at Years 1 and 2, 37% and 51% of participants, respectively, had cerebral Aβ levels below the PET amyloid positivity threshold (Klein et al. 2019). Continued monthly dosing for a third year resulted in 80% of participants reaching amyloid levels near centiloid zero, which is considered to be the mean amyloid PET value for young healthy individuals (Klein et al. 2021).

Gantenerumab is currently being investigated in a number of other studies in early AD and in familial AD. However, Study WN42444 is the first to investigate the effects of gantenerumab treatment in cognitively unimpaired older participants at risk for or at the earliest stages of AD.

On the basis of a meta-analysis that included participants who were at risk for or at the earliest stages of AD, it was estimated that the risk of progression to a clinical diagnosis of MCI or dementia due to AD is 20% (95% CI: 10%–34%) for individuals with Stage 1 preclinical AD and 38% (95% CI: 21%–59%) for those with Stage 2 preclinical AD as defined by the 2011 NIA-AA criteria (Sperling at al. 2011) during a maximum mean follow-up of 10.4 years (Parnetti et al. 2019).

However, not all cognitively unimpaired, amyloid-positive individuals will progress to clinically symptomatic stages of AD within the 4-year study period (Hansson et al. 2018), and the exact proportion of individuals who will progress to a clinically symptomatic stage at any time remains uncertain.

Analyses conducted in 3 observational cohorts (Harvard Aging Brain Study [HABS], Australian Imaging, Biomarker and Lifestyle [AIBL] Study of Aging, and Alzheimer's Disease Neuroimaging Initiative [ADNI]) with participants of similar age, cognitive status, and increased amyloid burden to the target population in Study WN42444, showed that subtle cognitive decline on the PACC-5 (between -0.14 and -0.26 standard deviations/year) was associated with an approximately 5–fold greater risk of subsequent clinical disease progression (i.e., MCI diagnosis or CDR-Global score [CDR-GS] >0; Papp et al. 2020) over a period of 3 years.

Detailed information on gantenerumab is provided in the Gantenerumab Investigator's Brochure.

2.3 BENEFIT–RISK ASSESSMENT

Currently, there are no approved disease-modifying therapies for cognitively unimpaired participants at risk for or at the earliest stages of AD. Study WN42444 will test the hypothesis that gantenerumab administration at the target dose of 1020 mg monthly (administered as either 510 mg SC Q2W or 255 mg SC Q1W) to cognitively unimpaired, amyloid-positive individuals, 60–80 years of age, reduces brain amyloid load and slows or delays clinical disease progression.

The key benefit–risk considerations for Study WN42444 are summarized below:

- According to the amyloid hypothesis of AD, Aβ aggregation and deposition play an important role in the pathophysiology of this disease, in particular, possibly early in the disease course. Gantenerumab has shown evidence of amyloid plaque reduction as measured by PET in prior studies, and thus, may have the potential to slow the progression of AD from the pre-symptomatic to the symptomatic stages of the disease.
- The target dose of gantenerumab in Study WN42444 is derived from a large body of amyloid PET and safety data from the ongoing clinical development program, including the ongoing Phase III studies, in early AD. Furthermore, the brain amyloid load of participants eligible for Study WN42444 is expected to be similar to the baseline cerebral amyloid load of participants of the ongoing studies. Therefore, a similar reduction of amyloid plaque is expected in Study WN42444 and similar amyloid-related imaging abnormalities (ARIA) risk mitigation measures are considered appropriate.
- Nonclinical and clinical studies suggest that target engagement, as shown by PET standard uptake value reference region amyloid reduction, is not driven by the maximum observed concentration (C_{max}) but rather depends on average exposure. Therefore, it is expected that the two offered dose regimens (i.e., 510 mg Q2W and 255 mg Q1W) can also be administered in Study WN42444 without altering the treatment effect.
- Gantenerumab has been generally safe and well-tolerated in healthy volunteers and participants with AD. The identified risks of gantenerumab treatment are ARIAs of edema/effusion (ARIA-E) and of microhemorrhage/hemosiderin deposition (ARIA-H), as well as injection-site reactions (ISRs) associated with SC administration. Both of these risks (i.e., ARIA and ISR) have been well-characterized and are clinically manageable with the implemented mitigation measures.
- Results from the double-blind portions, as well as from the OLEs of Studies WN25203 and WN28745, showed that ARIA findings are mostly asymptomatic, non-serious, of mild severity, do not require permanent cessation of treatment, and are manageable with MRI monitoring and dose intervention algorithms. Injection-site reactions are non-serious, largely mild to moderate in severity, and self-resolving.

- Potential risks of gantenerumab treatment include hypersensitivity, systemic injection reaction, and immunogenicity. There have been no reports of serious hypersensitivity or serious systemic injection reaction, or clinical findings indicative of an immunogenic response to gantenerumab in approximately 2500 participants that have been exposed.
- No new safety signals have emerged in the ongoing, blinded pivotal Studies WN29922 and WN39658 which are overseen by an independent Data Monitoring Committee (iDMC).
- Offering 2 different dosing frequency regimens (Q1W and Q2W dosing) and home administration by participants or their study partners (non-professional caregivers), is considered to represent a low risk to the overall safety, data integrity, and the benefit-risk profile of Study WN42444. Both regimens are expected to result in a comparable ARIA risk as they will provide the same gantenerumab exposure.
- Robust mitigation measures will be put in place to ensure and closely monitor the safe and correct administration of the study drug by the participant or study partner throughout the study in the home setting. These measures include participant and/or study partner training and approval for home administrations by the investigator or delegate (including training on the recognition of and action required for serious hypersensitivity reactions), an at least 1-hour postdose observation period, as well as regular telephone contact between the participant, study partner, and the clinical site. The benefit is to provide participants and their study partners appropriate opportunities to reduce the burden of study participation.
- Overall, a substantial body of evidence exists for the safety of administration of gantenerumab up-titrated to the target dose of 1020 mg monthly in amyloid-positive individuals, 60–80 years of age. An iDMC will evaluate safety data on a regular basis from Study WN42444 in an unblinded fashion, including the incidence, severity, and nature of adverse events, serious adverse events, ARIA-E and ARIA-H, ISRs, adverse events of special interest, ECGs, laboratory abnormalities, and the Mini Mental State Examination (MMSE).
- Based on its mechanism of action, there is no reason to believe that gantenerumab administration would compromise the immune function of the body. This notion 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 the immune system or made individuals more susceptible to infections. Thus, there are no data or biological rationales suggesting that gantenerumab administration could increase the risk of infection by severe acute respiratory syndrome coronavirus 2 (SARS–CoV-2) or the more severe coronavirus disease 2019 (COVID-19) outcomes. Whereas people of advanced age, including those with AD, may be at higher risk for COVID-19, participation in Study WN42444 is not expected to further increase this risk. Moreover, the Sponsor will implement COVID-19 mitigation measures as appropriate and feasible.
- *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 Alzheimer's disease. Just as with other vaccinations (e.g., influenza), the administration of COVID-19 vaccines will be considered as a concomitant medication in this study. Please see Section 6.8.1.1 for additional information.

- Overall, the anticipated benefit–risk profile of the target doses of gantenerumab of 1020 mg monthly (administered as either 510 mg SC Q2W or 255 mg SC Q1W) supports a clinical trial with these dosing regimens in cognitively unimpaired, amyloid-positive participants, aged 60–80 who are at risk for or at the earliest stages of AD.

See Appendix 3 for information on risks for gantenerumab and risk mitigation measures implemented, including guidelines for managing adverse events associated with gantenerumab.

More detailed information about the identified and potential risks of gantenerumab treatment may be found in the Gantenerumab Investigator's Brochure.

3. OBJECTIVES AND ENDPOINTS AND ESTIMANDS

Study WN42444 will evaluate the efficacy and pharmacodynamics of gantenerumab treatment compared with control treatment as well as the safety and pharmacokinetics of gantenerumab treatment compared with placebo in cognitively unimpaired participants, aged 60–80 years, at risk for or at the earliest stages of AD who are amyloid-positive based on evaluations of either CSF sampling or amyloid PET imaging.

Study WN42444 is a randomized, double-blind, placebo-controlled study.
Eligible participants will be randomized in a 1:1 ratio to receive either gantenerumab or placebo. If, in the course of the study, a participant *who has reached target dose* progresses to a clinical diagnosis of MCI or dementia due to AD, a 'post-progression dose escalation' period (Table 3 and Table 6) will commence. During the post-progression dose escalation period, participants who were randomized to placebo will switch to gantenerumab in a double-blinded manner. Participants who were randomized to gantenerumab will continue with gantenerumab (255 mg SC Q1W or 510 mg SC Q2W). All participants who progress to a clinical diagnosis of MCI or dementia due to AD must comply with all aspects of the post-progression dose escalation schedules of activities (i.e., Table 3 and Table 6).

The study treatment duration is 211 weeks regardless of the dosing regimen (i.e., Q1W or Q2W) or whether a participant progresses to a clinical diagnosis of MCI or dementia due to AD. See Section 4 for a more detailed description of the study design.

The primary comparison for efficacy will be between the following arms:

- **Experimental arm**: participants randomized to gantenerumab at the beginning of the study

- **Control arm**: participants randomized to placebo at the beginning of the study, irrespective of whether they progressed during the study and thus, started gantenerumab

The primary objective of this study is to evaluate the difference between the experimental and control arms in the change from baseline to Year 4 in cognition, as measured by the PACC-5 score.

For pharmacodynamic measures, the primary comparison will be between gantenerumab and control. For safety measures, the primary comparison will be between gantenerumab and placebo. Specific objectives and corresponding endpoints for the study are outlined in Table 7.

See Section 9.4.2 for a description of the elements of the primary estimand as per the estimand framework introduced in the International Council for Harmonisation (ICH)-E9 (R1) addendum (ICH 2019).

Table 7 Objectives and Endpoints

Primary Objective	Corresponding Endpoint
• To evaluate the efficacy of gantenerumab compared with control on cognition	• Change from baseline to Year 4 in the PACC-5 score
Secondary Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab compared with control on clinical progression	• Time from randomization to clinical progression to MCI or dementia due to AD based on the diagnosis of the iCAC
• To evaluate the efficacy of gantenerumab compared with control on clinical progression	• Time to onset of confirmed clinical progression, defined as the time from randomization to the first occurrence of two consecutive visits (approximately 6 months apart) with a CDR-GS > 0
• To evaluate the efficacy of gantenerumab compared with control on cognition and/or function	• Change from baseline to Year 4 in the A-IADL-Q-SV and the CFIa • Change from baseline to Year 4 in the CDR-SB
• To evaluate the safety of gantenerumab compared with placebo	• Nature, frequency, severity, and timing of adverse events, serious adverse events, and adverse events of special interest • 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 ISRs

Table 7 Objectives and Endpoints (cont.)

Secondary Objectives	Corresponding Endpoints
	• Presence of ADAs during the study relative to the presence of ADAs at baseline
Pharmacodynamic Biomarker Objectives	**Corresponding Endpoints**
• To evaluate biomarkers of pharmacodynamics of gantenerumab compared with control	• Change in brain amyloid load over time, as measured by amyloid PET in a subset of participants • Change in brain tau load over time, as measured by tau PET in a subset of participants • Change in CSF biomarkers, including, but not limited to, $A\beta_{1-42}$, $A\beta_{1-40}$, NfL, pTau, and tTau in a subset of participants • Change in blood-based biomarkers, including, but not limited to, $A\beta_{1-42}$, $A\beta_{1-40}$, NfL, and pTau in all participants • Change in MRI-derived measurements over time, including, but not limited to, volumetric changes in whole-brain, ventricles, hippocampus, or other structures in all participants
Exploratory Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab compared with control on (1) depressive symptoms, (2) clinician-rated, participant-rated, and study partner-rated global impression of overall disease severity, and (3) health-related quality of life	• (1) Change from baseline to Year 4 in the GDS-30 • (2) Change from baseline to Year 4 in the AD-CGI-S, AD-PGI-S, and AD-SPGI-S scales • (3) Change from baseline to Year 4 in the EQ-5D-5L index-based and VAS scores
• To evaluate the efficacy of gantenerumab compared with control on clinical progression	• Time from randomization to clinical progression to MCI or dementia based on the site clinician's diagnostic classification
• To characterize the PK profile of gantenerumab	• Trough plasma concentrations of gantenerumab at specified timepoints • PK parameters estimated with population PK modeling
• To evaluate the potential relationships between drug exposure and the efficacy and safety of gantenerumab	• Relationship between plasma concentration or PK parameters of gantenerumab and PD as well as efficacy endpoints • Relationship between CSF concentration or PK parameters of gantenerumab and safety endpoints

Table 7 Objectives and Endpoints (cont.)

Exploratory Objectives	Corresponding Endpoints
• To evaluate the effect of ADAs	• Relationship between ADA status and efficacy, safety, PD, as well as PK endpoints
• To identify biomarkers that are: (1) predictive of response to gantenerumab (i.e., predictive biomarkers), (2) early surrogates of efficacy, (3) associated with progression to a more severe disease state (i.e., prognostic biomarkers), (4) associated with acquired resistance to gantenerumab, (5) associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers) (6) able to increase the knowledge and understanding of disease biology and drug safety	• Relationship between biomarkers in blood (Section 8.5.1) and CSF (Section 8.11.4) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints • Relationship between biomarkers (such as MRI, PET, CSF and blood mentioned in secondary objectives) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

AD = Alzheimer's disease; ADA = anti-drug antibody; AD-CGI-S = Alzheimer's disease Clinician Global Impression of Cognitive Function; AD-PGI-S = Alzheimer's disease Participant Global Impression of Cognitive Function; AD-SPGI-S = Alzheimer's disease Study Partner Global Impression of Cognitive Function; A-IADL-Q-SV = Amsterdam Instrumental Activities of Daily Living Questionnaire Short Version; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; C-SSRS = Columbia-Suicide Severity Rating Scale; CDR-SB = Clinical Dementia Rating Sum of Boxes; CDR-GS = Clinical Dementia Rating Global Score; CFIa = Cognitive Function Instrument acute; EQ-5D-5L = EuroQol 5-Dimension, 5-Level Questionnaire; GDS-30 = Geriatric Depression Scale 30-items; CSF = cerebrospinal fluid; iCAC = independent Clinical Adjudication Committee; ISR = injection-site reaction; MCI = mild cognitive impairment; MRI = magnetic resonance imaging; NfL = neurofilament light; PACC-5 = Preclinical Alzheimer's Cognitive Composite-5; PD = pharmacodynamic; PET = positron emission tomography; PK = pharmacokinetic; VAS = visual analogue scale.

4. STUDY DESIGN

4.1 OVERALL DESIGN

Study WN42444 is a 4-year and 9-month, Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of gantenerumab in amyloid-positive, cognitively unimpaired participants at risk for or at the earliest stages of AD.

The planned number of participants for the study is approximately 1200 participants randomized in a 1:1 ratio to receive either gantenerumab or placebo (600 participants randomized to gantenerumab and 600 participants randomized to placebo).

Participants will be selected based on (1) evidence of underlying cerebral Aβ pathology as indicated by amyloid PET or by the $pTau_{181}/A\beta_{1-42}$ ratio in the CSF, and (2) having both unimpaired cognitive and functional status as evidenced by a CDR-GS = 0 (Morris 1993; 1997), and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Delayed Memory Index (DMI; ≥ 80 ; Randolph et al. 1998; Karantzoulis et al. 2013). Eligible participants will be 60–80 years of age, inclusive, must not meet the clinical diagnostic criteria for MCI due to AD (Albert et al. 2011) or dementia due to AD (McKhann et al. 2011), and must meet all the eligibility criteria outlined in Section 5.

If, in the course of the study, participants *who have reached target dose* progress to a clinical diagnosis of MCI or dementia due to AD (as determined by the independent clinical adjudication committee [iCAC]), a post-progression dose escalation period will commence. During the post-progression dose escalation period, participants who were randomized to placebo will switch to gantenerumab in a double-blinded manner, unless the ongoing Phase III studies of gantenerumab in early AD do not demonstrate efficacy (see Section 4.1.2). For study purposes, clinical progression to MCI or dementia due to AD is determined by the iCAC. *In order to conclude on clinical progression, the diagnostic classification change must be confirmed on the next cognitive assessment visit, approximately 6 months later.* Evaluation by the iCAC will be triggered by pre-specified criteria. Details of the trigger and diagnostic criteria for MCI and dementia due to AD will be provided in the iCAC Charter.

The study treatment period for each participant is 211 weeks (i.e., baseline to Week 211, inclusive) which constitutes the primary efficacy analysis dataset.

A schematic of the study design is provided in Section 1.2 (see Figure 1). A schedule of activities is provided in Section 1.3 (see Table 1, Table 2, and Table 3 for the Q1W dosing regimen and Table 4, Table 5, and Table 6 for the Q2W dosing regimen).

4.1.1 Screening Period

4.1.1.1 Optional Blood-Based Biomarker Prescreening

The overall screening period of Study WN42444 is 17 weeks. Within this 17-week period, participating sites will have the option to prescreen individuals aged 60–80 years, who do not have a known history of cognitive impairment or dementia, with the use of an optional blood-based biomarker (BBBM) test. This exploratory BBBM test will assess whether an individual is more likely or less likely to have sufficiently elevated cerebral amyloid levels to be eligible for Study WN42444. The prescreening period for BBBM testing may last up to 4 weeks for each eligible participant. Sites are encouraged to complete the optional BBBM prescreening process expeditiously to allow participants to complete the overall screening process within the protocol-defined 17-week period. Participants must sign a separate Blood-Based Biomarker Prescreening Informed Consent Form (ICF) to participate in the BBBM prescreening. Participation in the BBBM prescreening is, while encouraged where available, optional, and not a

prerequisite to screen for Study WN42444. However, for participants of the BBBM prescreening, main screening activities, including signing of the main study participant or study partner ICFs, may not be initiated until it is determined whether the participant may or may not move on to the main screening.

Based on information from epidemiological studies, it is estimated that only approximately 1 of 6 study candidates will meet the CSF or PET imaging amyloid-based inclusion criteria for Study WN42444. The optional BBBM prescreening estimates how likely (i.e., more or less likely) an individual is to meet the amyloid-based inclusion criteria. Therefore, the optional BBBM prescreening may reduce the probability of undergoing the extensive screening process unnecessarily for those who are considered unlikely to meet the CSF or PET imaging amyloid inclusion criteria. It is an exploratory test and should not be considered as a definitive test for cerebral amyloid. Only the subsequent CSF or PET results will be used to determine study eligibility.

Due to the experimental nature of the assay, results the BBBM prescreening test will not be returned to the participants or the sites. To further mask the results of the experimental BBBM prescreening test, approximately 10% of participants who are identified to be less likely to meet the amyloid-based inclusion criteria for Study WN42444, will also be invited to continue with the main study screening procedures.

Collection and submission of the prescreening blood samples for biomarker testing is contingent upon the review and approval by each site's Institutional Review Board (IRB) or Ethics Committee (EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval to use the BBBM prescreening, this part of the protocol will not be applicable at that site.

4.1.1.2 Main Screening

The overall study screening period, including the optional BBBM prescreening period, may last up to 17 weeks. Participants and their study partners must sign the main study ICF before the initiation of the main study screening procedures. Details of the inclusion and exclusion criteria are provided in Section 5. Participants who do not meet the cognition- or amyloid-based inclusion criteria for participation in this study (i.e., screen failure) cannot be rescreened. The investigator will record reasons for screen failure in the screening log and interactive voice or Web-based response system (IxRS).

Screening biomarker samples, including those collected from individuals who do not enroll in the study, may be used for future research and/or development of disease-related tests or tools as detailed in Section 8.11.5.

At the end of the screening period, but no later than 7 days prior to the scheduled randomization visit, results from the brain amyloid test (i.e., whether or not brain amyloid eligibility criteria are met) and apolipoprotein E (*APOE)* genotyping will be returned to

participants by the investigator or their qualified designee if allowed by local regulations and it is safe to do so. Participant's readiness to receive these results will be determined by the investigator or their qualified designee based on their clinical judgment. Sites will follow-up with every participant within approximately 1 week after the return of results conversation.

Amyloid-related imaging abnormalities are known to occur in an *APOE4* genotype-dependent fashion. Therefore, *APOE4* genotyping results are returned so that participants may make an optimally informed decision on further study participation. By default, *APOE* genotyping results are shared with individuals who qualify to participate in Study WN42444. However, these individuals may opt out from learning their *APOE* genotyping results. Participants who do not fulfill inclusion criteria will have their results returned upon request. The discussion between the investigator or their qualified designee and the participant pertinent to the return of results must be documented in the site's source documents.

Participants may be rescreened if recruitment for the study is still ongoing. In this case, all screening assessments must be repeated with the exception of lumbar puncture and PET scan, if they were performed within the previous 12 months for this study and were within eligible ranges. In case participant amyloid-based eligibility was established by an off-protocol PET scan, the same scan can be used as long as it has been performed within 12 months of starting rescreening. Given that APOE status will not change over time, there is no need to repeat clinical genotyping in case of rescreening.

4.1.2 Maintenance Treatment Period

After screening, participants who meet all eligibility criteria will be randomly assigned to one of two treatment arms in a 1:1 ratio. The duration of the double-blind treatment period will last 211 weeks for each enrolled participant.

Participants in the experimental arm will be administered active gantenerumab for the entire duration of the study. Participants randomized to receive placebo constitute the control arm. If, in the course of the study, participants *who have reached target dose* progress to a clinical diagnosis of MCI or dementia due to AD (as determined by the iCAC), a post-progression dose escalation period will commence. During the post-progression dose escalation period, participants who were randomized to receive placebo will switch to gantenerumab in a double-blinded manner, unless the ongoing Phase III studies with gantenerumab in early AD do not demonstrate efficacy. As a result, the control arm will contain both: (1) participants who do not meet the clinical progression criteria and remain on placebo throughout the duration of the study, and (2) participants who meet the clinical progression criteria and thus, initiate active gantenerumab treatment during the double-blind treatment period. Once the post-progression dose escalation is initiated, neither the participant, the investigators, nor the Sponsor will be blinded to current treatment (i.e., gantenerumab). They will,

however, remain blinded to the original treatment assigned at randomization (i.e., gantenerumab vs placebo).

During the double-blind treatment period, all participants will undergo assessments for cognition, function, and quality-of-life (QoL) status as detailed in Section 1.3 (see Table 1, Table 2, and Table 3 for the Q1W dosing regimen and Table 4, Table 5, and Table 6 for the Q2W dosing regimen), as well as standard tests to monitor safety (e.g., blood tests and ECGs), and potential suicidality (Columbia-Suicide Severity Rating scale [C-SSRS]) as detailed in in Section 1.3 (see Table 1, Table 2, and Table 3 for the Q1W dosing regimen and Table 4, Table 5, and Table 6 for the Q2W dosing regimen).

All participants will undergo longitudinal brain magnetic resonance imaging (MRI) examinations to monitor safety as well as structural and functional (where available) changes. A central MRI reader will evaluate MRI scans in addition to the local safety readings that will be performed in accordance with local standards and procedures.

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

Blood samples for the assessment of pharmacokinetic (PK), pharmacodynamic (PD) biomarkers, biomarker discovery, and anti-drug antibodies (ADAs) will also be obtained from all participants as detailed in Section 1.3 (see Table 1, Table 2, and Table 3 for the Q1W dosing regimen and Table 4, Table 5, and Table 6 for the Q2W dosing regimen).

4.1.3 Dosing in the Double-Blind Treatment Period

Participants will be given the opportunity to choose one of the following two dosing frequency options:

- 1 SC injection Q1W (Table 1, Table 2, Table 3) or
- 2 SC injections Q2W (Table 4, Table 5, Table 6)

Participants must decide between the two dosing regimen options by Week 25. Participants who do not make a decision by Week 25 will continue with the Q2W dosing regimen. The Q2W dosing regimen is the default dosing regimen for the study.

Following the baseline assessments, participants will undergo a 9-month 'initial dose escalation' period (Table 1 and Table 4) until the target dose (1020 mg monthly) is reached. Following the initial dose escalation period, participants will enter the maintenance dosing period (Table 2 and Table 5).

Participants who are randomized to placebo, but meet the clinical progression criteria (according to the iCAC's determination) during the double-blind treatment period, will be switched to gantenerumab. A 9-month, 'post-progression dose escalation' period will

follow as detailed in Table 3 (for the Q1W dosing frequency) or Table 6 (for the Q2W dosing regimen) followed by maintenance dosing at target dose. In order to keep the blind to the original treatment assignment, the 'post-progression dose escalation' will follow the respective Q1W or Q2W dosing regimen for all participants who have met clinical progression criteria (Table 3 or Table 6). Additionally, during the 'post-progression dose escalation' period, all participants will be asked to comply with all aspects of the post-progression dose escalation schedule of activities (Table 3 and Table 6), including increased frequency of in-clinic visits, increased number of SC injections at select visits, and safety MRI monitoring.

4.1.4 Follow-Up Period

When participants have completed the 211-week, double-blind treatment period, all participants who do not continue gantenerumab treatment via a post-trial access mechanism or another study, will be asked to return for a final safety follow-up visit at Week 227.

Participants, who prematurely discontinue treatment with the study drug in the double-blind treatment period but remain in the study, will be asked to follow the schedule of activities to the extent possible, unless their consent is withdrawn.

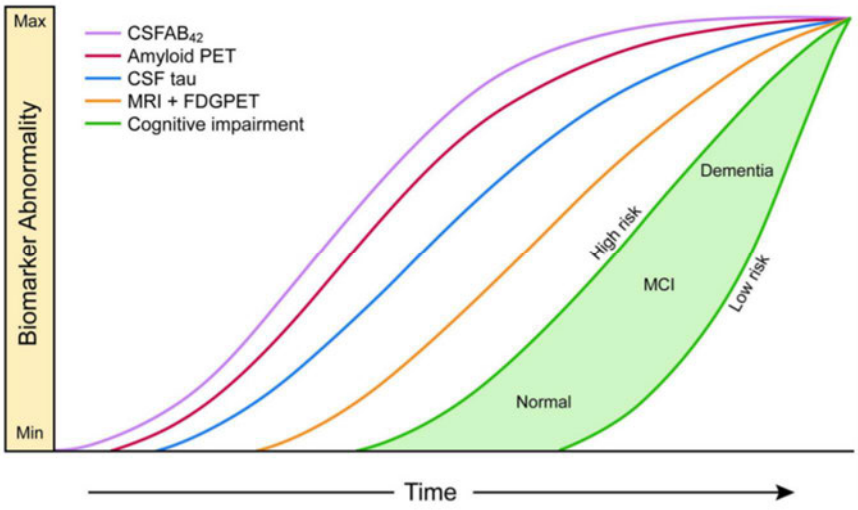
Participants who discontinue from Study WN42444 early will also be asked to return for a final safety follow-up visit 17 weeks after the last dose unless their consent is withdrawn.

4.2 RATIONALE FOR STUDY DESIGN

4.2.1 Rationale for Study Population

There is evidence from observational cohorts and clinicopathological correlation studies, indicating that neuropathological and in vivo biomarker changes typical of AD begin many years before the emergence of clinical symptoms. Moreover, changes in AD biomarkers have been suggested to occur in a temporally ordered manner (Ingelsson et al. 2004; Mormino et al. 2009, Jack et al. 2013) with Aβ abnormalities (measured by CSF $A\beta_{1-42}$ or amyloid PET) among the first to appear (see Figure 2). Recently, emerging biomarkers like plasma neurofilament light (NfL) and plasma pTau have also been found to become abnormal in the course of AD (Mattsson et al. 2019; Barthélemy et al. 2020).

Figure 2 Biomarker Abnormalities Detected Over Time



Source: Jack et al. 2013.

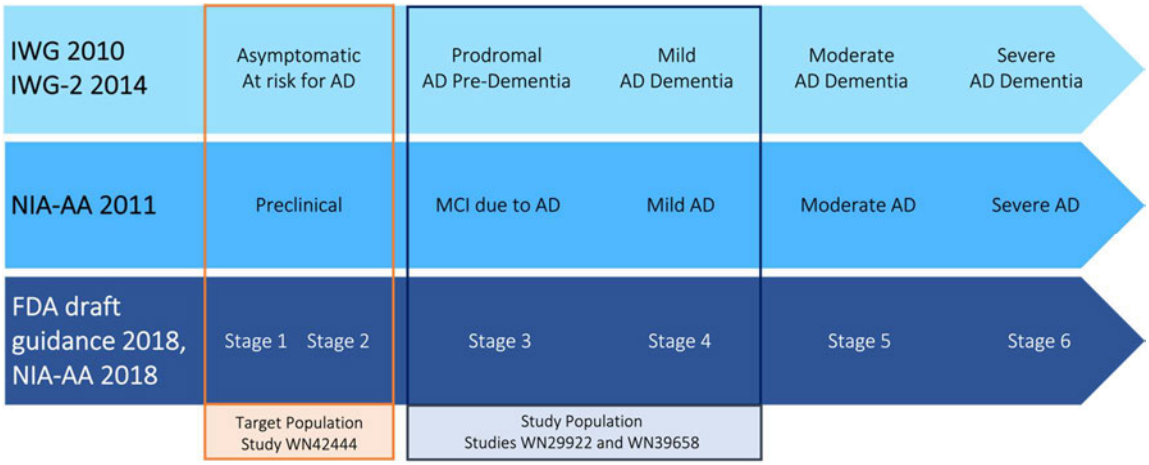
$A\beta_{42}$ = amyloid beta 42; CSF = cerebrospinal fluid; FDG = fluorodeoxyglucose; MCI = mild cognitive impairment; Min = minimum; Max = maximum; MRI = magnetic resonance imaging; PET = positron emission tomography.

Amyloid is identified by CSF $A\beta_{42}$ (purple) or PET amyloid imaging (red). Changes in tau are demonstrated by elevation in CSF tau (blue). Neurodegeneration is measured by FDG PET and structural MRI, respectively, which are drawn concordantly (orange). By definition, all curves converge at the top right-hand corner of the plot, the point of maximum abnormality.
The horizontal axis of disease progression is expressed as time. Cognitive response is illustrated as a zone (green filled area) with low- and high-risk borders.

The early emergence of biomarker changes allows the identification of participants at risk for or at the earliest stages of AD. During this stage, individuals can be characterized by the presence of abnormal biomarkers and the absence of overt clinical signs or symptoms of AD. Accordingly, eligibility to participate in Study WN42444 requires evidence of elevated cerebral Aβ pathology as indicated by either amyloid PET visual readings or the $pTau_{181}/A\beta_{1-42}$ ratio in the CSF. The PET and CSF-based amyloid thresholds used to establish eligibility for Study WN42444 may be beyond what would be required to determine amyloid positivity in standard clinical settings and may differ from other gantenerumab studies. These threshold values were chosen in an effort to enable the detection of gantenerumab's efficacy within the planned study duration.

Consensus is forming that AD represents a disease continuum spanning from asymptomatic stages to stages of overt dementia. The nomenclature that reflects the growing understanding of the overall disease span, has also evolved over time as detailed in Figure 3.

Figure 3 Evolution of the Nomenclature of Alzheimer's Disease Staging Since 2010



Source: Dubois et al. 2010; Albert et al. 2011; McKhann et al. 2011; Sperling et al. 2011; Dubois et al. 2014; FDA 2018a; Jack et al. 2018.
AD = Alzheimer's disease; FDA = U.S. Food and Drug Administration; IWG = International Working Group; NIA-AA = National Institute of Aging and the Alzheimer's Association.

As eligible participants will exhibit abnormal biomarkers but only very subtle or no cognitive impairment, they are considered to be either at the earliest stages of AD (i.e., Stage 1 and Stage 2 of AD as per the 2018 guidance by the FDA [FDA 2018a]) or preclinical AD in accordance with NIAA-AA criteria, or asymptomatic and at risk for AD in accordance with the 2014 IWG classification (Figure 3). However, overt cognitive difficulties (FDA Stage 3 and beyond) and subtle (FDA Stage 3) or overt (FDA Stage 4 and beyond) impairment in functional activities of daily living due to cognitive difficulties will be exclusionary, as participants with such impairments would meet the diagnostic criteria for MCI (Petersen et al. 1997), MCI due to AD/prodromal AD (Dubois et al. 2010; Albert et al. 2011), or dementia due to AD (McKhann et al. 2011) at screening.

It is expected that among cognitively unimpaired adults aged 60–80 years, approximately 15%–30% will have evidence of cerebral Aβ deposition based on amyloid PET imaging or CSF $A\beta_{42}$ concentrations (Jansen et al. 2015).
Moreover, amyloid-positive, cognitively unimpaired participants have been shown to exhibit subtle detectable cognitive decline on the PACC-5 (−0.14 to −0.26 standard deviations/year; Papp et al. 2020).

4.2.2 Rationale for Control Group

There are currently no approved disease-modifying compounds for participants who are at risk for or at the earliest stages of AD that could serve as an active control.

In order to assess the efficacy and safety of gantenerumab in the target population, eligible participants in Study WN42444 are randomized 1:1 to either gantenerumab or placebo.

Participants who are randomized to placebo but are diagnosed with early AD (i.e., MCI or dementia due to AD) during the double-blind treatment period, will switch to treatment with gantenerumab. The intent of this approach is provide access to active treatment for study participants who would benefit from gantenerumab treatment, in the event that it has proven to be efficacious in the ongoing Studies WN29922 and WN39658 in early AD.

4.2.3 Rationale for Biomarker Assessments

Alzheimer's disease is a heterogeneous disease, and the abundance of amyloid and tau pathology has been shown to vary among patients (Blennow et al. 2006). Given expected differences in baseline amyloid and tau burden, it is hypothesized that participants may not be equally likely to benefit from treatment with gantenerumab. Biomarker data will be collected prior to dosing in an effort to identify which participants are most likely to benefit. Pharmacodynamic biomarkers will be assessed to demonstrate evidence of biological activity of gantenerumab and the impact on Alzheimer's pathologies, to support the selection of a recommended dose and dosing regimen. As these biomarkers may also have prognostic value, their potential association with disease progression will also be explored.

4.2.3.1 Rationale for PET-, CSF- and Blood-Based Biomarker Assessments

Amyloid PET, tau PET and CSF, will be assessed at several longitudinal timepoints in a subset of participants who provide additional consent.

Amyloid PET imaging is of particular interest as it may provide evidence of a decrease in brain amyloid burden and; therefore, prove target engagement of the investigational treatment (Vandenberghe et al. 2013; Sevigny et al. 2016; Vandenberghe et al. 2016). The results of the amyloid PET assessments are expected to help in understanding the pharmacodynamic effect of gantenerumab on brain amyloid load, as well as the relationship between changes in amyloid load and changes in other endpoints of the study.

Tau PET imaging is a promising tool for monitoring the spatial and temporal changes of tau load, and has been reported to be a good predictor of short-term cognitive decline (Ossenkoppele et al. 2021). The results of the tau PET assessments are expected to help in understanding the relationship between treatment with gantenerumab and changes in tau load.

Decreased CSF $A\beta_{1-42}$ and elevated CSF tTau and pTau are considered a biochemical signature of AD and may be observed in individuals who are at risk for or at the earliest

stages of AD. Accumulating evidence suggests that low CSF $A\beta_{1-42}$ reflects underlying amyloid plaque pathology, whereas increased tTau and pTau levels may be reflective of neurodegeneration and/or tau pathology. Moreover, amyloid deposition may be the initiating event in the cascade of pathologic processes underlying AD, while tau pathology appears to be a subsequent event associated with neurodegeneration. Therefore, tTau and pTau may be studied as downstream biomarkers of the primary target of anti-amyloid therapies such as gantenerumab.

Several clinical trials with anti-amyloid antibodies, including gantenerumab, have shown treatment-related changes in both amyloid and tau biomarkers (Farlow et al. 2012; Salloway et al. 2014; Ostrowitzki et al. 2017). On the basis of these data and on the proposed mechanism of action of gantenerumab, levels of CSF tTau and pTau, and additional exploratory biomarkers reflecting other pathologies, neurodegeneration and neuroinflammation will be assessed at baseline and at several longitudinal timepoints. Because gantenerumab is also expected to clear amyloid from the brain, levels of CSF $A\beta_{1-42}$ and other $A\beta$ isoforms will also be measured.

More recently, technical advances have made it possible to also measure brain-derived proteins like amyloid, tau, and NfL in the blood (Mielke et al. 2017; Ovod et al. 2017). Interestingly, plasma NfL and plasma pTau have been shown to become abnormal in individuals that are cognitively normal but amyloid-positive (Mattsson et al. 2019; Grothe et al. 2021). Therefore, BBBMs for amyloid and tau, as well as additional exploratory biomarkers reflecting other pathologies, neurodegeneration, and neuroinflammation, will be assessed at baseline and several longitudinal timepoints.

4.2.3.2 Rationale for MRI-Based Biomarker Assessments

Several MRI techniques have demonstrated sensitivity to detect structural and functional cerebral abnormalities in individuals with AD, including preclinical AD. Previous studies reported changes in, among others, whole-brain and hippocampal and ventricular volumes (Fox et al. 2000; Fox et al. 2005; Jack et al. 2010). It was also found that the rate of volumetric changes correlated closely with changes in cognitive performance (Li and Wahlund 2011). Additionally, others reported measurable volumetric change and brain atrophy even in the preclinical stage of AD (Zhang et al. 2016; Ossenkoppele et al. 2019; Younes et al. 2019). To quantify the effects of gantenerumab on neurodegeneration, whole-brain, regional brain, hippocampal and ventricular volumes, changes will be assessed at screening and during study treatment.

Advanced anatomical and functional MRI measures, including diffusion MRI (dMRI), resting-state functional MRI (rs-fMRI) and arterial spin-labeling MRI (ASL-MRI) will be acquired and analyzed in all participants who are at sites where the required software and hardware are available.

Resting-state functional MRI studies generated evidence for the association between elevated cerebral amyloid load and functional connectivity alterations, reduced

resting-state functional connectivity of various brain networks, as well as impairment in clinical and cognitive measures in individuals with AD (Sheline et al. 2010; Binnewijzend et al. 2012; Brier et al. 2012; Sheline and Raichle 2013). In addition, therapeutic interventions, such as memantine (Lorenzi et al. 2011) or donepezil (Goveas et al. 2011; Solé-Padullés et al. 2013), were found to have an impact on the decreased brain functional connectivity of individuals with AD. Lastly, compromised resting-state functional connectivity in persons with preclinical AD was shown to foreshadow neurodegeneration and predict tau accumulation (Franzmeier et al. 2020; Hampton et al. 2020).

Diffusion-tensor imaging (DTI) MRI provides imaging metrics of the cellular organization by measuring water diffusion properties under the influence or restriction of biological barriers. Widespread group differences in the degree of fractional anisotropy were reported between participants with AD and healthy volunteers (Jack et al. 2013; Nir et al. 2013). White matter degeneration can be measured via DTI years before symptom onset (Ly et al. 2014; Hoy et al. 2017).

Potential changes in cerebral blood flow (CBF) due to gantenerumab treatment will be measured with use of MRI-based ASL. Persons with AD were shown to have regionally reduced CBF compared with age-matched healthy volunteers as measured by ASL-MRI, especially in the temporal-parietal and posterior cingulate cortices (Schuff et al. 2009; Mattson et al. 2014). As with the previously described MRI techniques, ASL-MR can detect CBF changes in the preclinical AD population, and is predictive of future decline (Zhang et al. 2017; Fazlollai et al. 2020).

The acquisition parameters of each sequence, structure, and length of each MRI session and image processing algorithms will be outlined in a separate MRI manual. The central reader will conduct all study-related MRI assessments and readings, including volumetric measurements.

4.3 JUSTIFICATION FOR DOSE AND SCHEDULE

The putative efficacy of gantenerumab in this population is hypothesized to be driven by its ability to reduce brain Aβ burden according to the amyloid hypothesis of AD (Selkoe 1991; Hardy and Selkoe 2002; Selkoe and Hardy 2016).

Gantenerumab treatment reduced mean amyloid burden to a mean near the amyloid positivity threshold (approximately 24 centiloids [Navitsky et al. 2018]) after 2 years of treatment, and to zero centiloids after 3 years of treatment in the OLEs of Studies WN25203 (Scarlet RoAD) and WN28745 (Marguerite RoAD; Klein et al. 2021). It is anticipated that similar rates of amyloid reduction will be obtained in both of the ongoing pivotal studies (i.e., Studies WN29922 and WN39658) and in this study (i.e., Study WN42444). The baseline amyloid burden of the population to be enrolled in the study is expected to be similar in the range of centiloids (interquartile range:

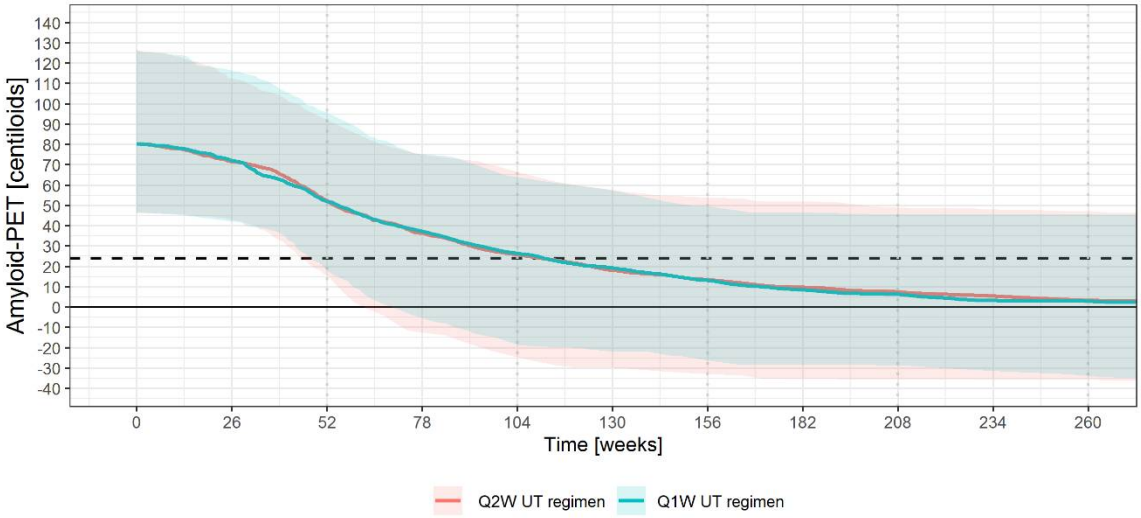
71.6−105.0) to that observed in the population of Studies WN29922 and WN39658 at baseline.

The proposed target dose in Study WN42444 is 1020 mg of gantenerumab per month (i.e., 28 days) administered at 255 mg Q1W or 510 mg Q2W. This target dose was selected based on available clinical data collected through the clinical development program of gantenerumab in early AD, and is supported by PK/PD modeling. The target dose will be administered following the initial dose escalation period of 9 months. The low starting doses and gradual increase in dosing (i.e., slow dose escalation) are expected to reduce the risk of ARIA-E for both *APOE* ε4 carriers and non-carriers based on the ARIA-E hazard model.

The ARIA-E hazard model was first developed using bapineuzumab data (Hutmacher et al. 2013). This model, which includes drug concentrations, time since first dose, and *APOE* ε4 allele status, was applied to the double-blind results in Study WN25203. The model was then tested on publicly available aducanumab data from Study NCT01677572 to predict the incidence of ARIA-E events with a high degree of accuracy, including the observed ARIA-E rate differences across *APOE* ε4 allele groups. The ARIA-E hazard model has been updated with observations from the OLEs of Studies WN25203 and WN28745 with the use of higher doses of gantenerumab. An overall ARIA-E rate of approximately 26% is predicted based on the current ARIA-E hazard model.

An exploratory PK/PD (amyloid PET) model was developed based on PK and amyloid PET data from double-blind Studies WN25203 and WN28745 and their OLEs with use of nonlinear mixed-effects modeling. The model represents the current knowledge of the effects of gantenerumab on amyloid plaque removal. Simulations generated with use of this model, showed amyloid plaque reduction to the targeted amyloid positivity threshold (24 centiloids) as shown in the Figure 4. In addition, the magnitude and time course of amyloid plaque removal are predicted to be comparable for both proposed maintenance dosing regimens, i.e., 1020 mg per month (i.e., 28 days) administered as 510 mg Q2W or 255 mg Q1W.

Figure 4 Median Amyloid PET Over Time Comparing Different Dosing Regimens (Q1W vs. Q2W)



PET = positron emission tomography; Q1W = every 1 week, Q2W = every second week, Q4W = every 4 weeks; UT = dose escalation.

Colored solid lines: median (p50).

Black dotted line: amyloid−positivity threshold at 24 centiloids.

Number of individuals per regimen: 200 participants.

Q2W UT regimen (mg): 120 Q4W (3×) → 255 Q4W (3×) → 510 Q4W (3×) → 510 Q2W (up to Week 209).

Q1W UT regimen (mg): 120 Q4W (3×) → 255 Q4W (3×) → 255 Q2W (6×) → 255 Q1W (up to Week 210).

Note: The predictions of plaque removal in the low centiloid range may have a higher uncertainty due to the paucity of observed data in this range, lack of long-term information (with high gantenerumab doses) and the fact that individual centiloid values can become negative.

Participants may choose 1 of 2 dosing regimens for maintenance dosing; either 255 mg Q1W or 510 mg Q2W. If a participant chooses not to make a selection by Week 25, then they will continue on the 510 mg Q2W dosing regimen by default. Participants will use the selected dosing regimen throughout the study duration following the initial, 9-month dose escalation period. The regimen may differ between participants in dosing frequency from Week 25 on, but the total dose of gantenerumab will remain the same at 1020 mg per month (i.e., 28 days). The option to choose between 2 dosing regimens (Q1W or Q2W) allows for factoring in the participant's preference. The Q1W administration schedule will enable some participants to simplify their treatment administration by decreasing the number of abdominal SC injections per administration, from 2 to 1 at the target dose. Alternatively, the Q2W administration schedule will enable other participants to increase the time between SC injections should that be their preference, or better accommodate their activities and/or life events.

Switching between the different dosing regimens is not permitted.

Gantenerumab exerts its mechanism of action primarily via microglia–mediated clearance of amyloid plaques. A change in the dosing frequency, while maintaining average exposure to gantenerumab, is expected to have no impact on the extent of amyloid plaque removal and thus, a dose of 1020 mg per month administered either as 510 mg Q2W, or 255 mg SC Q1W is expected to result in a similar treatment effect.

When evaluating the efficacy and pharmacodynamics of gantenerumab compared with the control arm, the comparison will be made irrespective of the dosing frequency.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study, including the safety follow-up visit shown in the schedule of activities (see Section 1.3).

The end of this study is defined as the date of the last visit of the last participant in the study or the date at which the last data point required for safety analyses or safety follow-up is received from the last participant, whichever occurs later. The end of the study is expected to occur 227 weeks after the last participant is randomized.

In addition, the Sponsor may decide to terminate the study at any time.

4.5 DURATION OF PARTICIPATION

The total duration of study participation for each participant is expected to be 244 weeks, which includes the screening period (up to 17 weeks), the double-blind treatment period (211 weeks), and the subsequent safety follow-up visit 16 weeks after the final safety and efficacy assessment at Week 211.

5. STUDY POPULATION

Study WN42444 will enroll approximately 1200 participants aged 60–80, who are cognitively unimpaired and at risk for or are at the earliest stages of AD during the global enrollment phase of this study. Additional criteria for the study population are detailed in Sections 5.1, 5.2, and 5.3. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

5.1.1 Optional Blood-Based Biomarker Prescreening Procedure

Potential participants are eligible to participate in the optional BBBM prescreening procedure only if all of the following criteria apply:

- Capable of giving signed informed consent as described in Appendix 1
- Aged 60–80 years (inclusive) at the time of signing the Blood-Based Biomarker Prescreening ICF

- Participants who do not have a known clinical diagnosis of cognitive impairment, MCI, prodromal AD, or any form of dementia

5.1.2 Main Study

Potential participants are eligible to be included in the study only if all of the following criteria apply, irrespective of participation in the optional BBBM prescreening procedure:

- Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol
- Age 60–80 years (inclusive) at the time of signing the ICF
- Willing and able to comply with the study protocol and complete all aspects of the study (including cognitive and functional assessments, physical and neurological examinations, MRI, CSF collection, genotyping, and PET imaging)
- Cognitively unimpaired with a screening CDR–GS of 0, and RBANS DMI $\geq$80
- Evidence of cerebral amyloid accumulation: amyloid-based eligibility can be established by any one of the following 3 methods:
  - CSF $pTau_{181}/A\beta_{1-42}$ ratio $>$0.04 measured in CSF collected at screening with use of Elecsys immunoassays.
  - Qualitative visual read of the amyloid PET scan performed during screening by the core/central PET laboratory
  - Qualitative visual read of prior, off-protocol amyloid PET scan with either [^{18}F]-Florbetapir, [^{18}F]-Florbetaben, or [^{18}F]-Flutemetamol obtained up to 12 months prior to Study WN42444 screening period. Off-protocol PET scans will be centrally read, which will determine if the participant meets the amyloid-based eligibility criteria for Study WN42444.
- Participants who have an available person (referred to as a “study partner” throughout the protocol) who:
  - Has frequent and sufficient contact (e.g., minimum twice a week in-person, via telephone, video calls, by e-mail or other electronic means) with the participant, and is willing and able to provide accurate information regarding the participant’s cognitive and functional abilities, signs the necessary ICF(s), and has sufficient cognitive capacity to accurately report on the participant’s cognitive and functional abilities
  - Is in sufficiently good general health to have a high likelihood of maintaining the same level of interaction with the participant and participation in study procedures throughout the duration of the study
  - Is fluent in the language of the tests used at the study site
  - Every effort should be made to have same study partner participate throughout the duration of the study
- Fluent in the language of the tests used at the study site

- Adequate visual and auditory acuity, sufficient to perform neuropsychological testing (eye glasses and hearing aids are permitted)
- Agreed not to donate blood or blood products for transfusion for the duration of the study and for 1 year after the final dose of study drug
- Agreed not to participate in other interventional research studies for the duration of this trial
- 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 17 weeks after the final dose of study treatment

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  The following are examples of contraceptive methods with a failure rate of $<1\%$ per year: 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 trial and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.

  If required per local guidelines or regulations, locally-recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local ICF.

5.2 EXCLUSION CRITERIA

5.2.1 Exclusions Related to CNS Disorders

Potential participants are excluded from the study if any of the following criteria apply:

- Any evidence of an underlying neurological or neurodegenerative condition that may lead to cognitive impairment other than AD, including, but not limited to, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, Parkinson's disease, corticobasal syndrome, Creutzfeldt-Jakob disease, progressive supranuclear palsy, frontotemporal lobar degeneration, Huntington disease, normal pressure hydrocephalus, seizure disorder, delirium, hypoxia, or encephalopathy related to prior COVID-19 infection
- Clinical diagnosis of MCI, prodromal AD, or any form of dementia

- History or presence of intracranial or intracerebral vascular malformations, aneurysm, subarachnoid hemorrhage, or intracerebral macrohemorrhage
- History or presence of posterior reversible encephalopathy syndrome
- History of ischemic stroke with clinical symptoms or an acute event that is consistent with a transient ischemic attack within 12 months of screening
- History of severe, clinically significant (i.e., resulting in persistent neurologic deficit or structural brain damage) CNS trauma (e.g., cerebral contusion)
- History or presence of intracranial mass lesion (e.g., glioma, meningioma) that could potentially impair cognition or lead to progressive neurological deficits
- Infections that may affect brain function or a history of infections that resulted in neurologic sequelae (e.g., HIV, syphilis, neuroborreliosis, and viral or bacterial meningitis and encephalitis)
- History of major depression, schizophrenia, schizoaffective disorder, or bipolar disorder

  History or presence of major depression is acceptable if the participant is considered to be in remission or depression is controlled by treatment and the participant has had no episode of major depression within 12 months of screening.
- At risk for suicide
- History of alcohol and/or substance abuse or dependence (according to the criteria specified in the Diagnostic and Statistical Manual of Mental Disorders, Version 5) within 2 years of screening

5.2.2 Exclusions Related to Imaging Findings

Potential participants are excluded from the study if any of the following criteria apply:

- According to the MRI central reader, show MRI evidence of any of the following:
  - >1 lacunar infarcts
  - Any territorial infarct >1 cm^3
  - Any white matter lesion that corresponds to an overall Fazekas score of 3, i.e., one or more confluent hyperintense lesion on the fluid-attenuated inversion recovery (FLAIR) sequence, which is ≥ 20 mm in any dimension
- A combined number of microbleeds and areas of leptomeningeal hemosiderosis (i.e., cumulative ARIA-H) on the MRI of >5 (and should not include any disseminated leptomeningeal hemosiderosis) based on the review of the screening MRI performed by the central reader prior to randomization
- Presence of any other significant cerebral abnormalities, including ARIA-E, as assessed in the screening MRI scan
- Inability to tolerate MRI procedures or who have a contraindication to MRI, including, but not limited to, presence of pacemakers not compatible with MRI, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the

eyes, skin, or body that would contraindicate an MRI scan, or any other clinical history or examination finding that would pose a potential hazard in combination with MRI

5.2.3 Exclusions Related to Cardiovascular Disease

Potential participants are excluded from the study if any of the following criteria apply:

- History or presence of clinically significant systemic vascular disease (e.g., $\geq$70% stenosis of the carotid or vertebral arteries, symptomatic aortic aneurysm)
- History or presence of atrial fibrillation
- Within the last year, experienced unstable or clinically significant cardiovascular disease (e.g., myocardial infarction)
- History or presence of heart failure, even if the heart failure is clinically asymptomatic
- Uncontrolled hypertension (e.g., blood pressure $>$160 mmHg systolic or $>$95 mmHg diastolic)

5.2.4 Exclusions Related to Hepatic and Renal Disorders

Potential participants are excluded from the study if any of the following criteria apply:

- Chronic kidney disease, indicated by creatinine clearance $<$30 mL/min to be calculated by the central laboratory with use of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (Levey et al. 2009) at screening, which remains $<$30 mL/min if retested
- Confirmed and unexplained impaired hepatic function as indicated by screening AST or ALT $\geq 3\times$ the upper limit of normal (ULN) or total bilirubin $\geq 2\times$ ULN

5.2.5 Exclusions Related to Infections and Immune Disorders

Potential participants are excluded from the study if any of the following criteria apply:

- History of, or are known to currently have an HIV infection, or hepatitis B or hepatitis C virus infection that has not been adequately treated, or history of spirochete infection of the CNS (e.g., syphilis, Lyme disease, or borreliosis)
- History or presence of systemic autoimmune disorders that may lead to progressive neurological impairment with associated cognitive deficits (e.g., multiple sclerosis, lupus erythematosus, anti-phospholipid antibody syndrome, and Behçet disease)
- Systemic immunosuppression or immunomodulation due to the continuing effects of immunosuppressant or immunomodulating medications
- Current COVID-19 infection

5.2.6 Exclusions Related to Metabolic and Endocrine Disorders

Potential participants are excluded from the study if any of the following criteria apply:

- Abnormal thyroid function as indicated by abnormal screening tests, or abnormal thyroid function that requires a new treatment or an adjustment of current treatment

A participant may be rescreened after 3 months of adequate treatment for abnormal thyroid function.

- Evidence of folic acid deficiency (as indicated by folic acid level below the lower limit of normal by the central laboratory's measurement) or vitamin B-12 deficiency (as indicated by vitamin B-12 level below the lower limit of normal and/or methylmalonic acid levels above the ULN by the central laboratory's measurements)

  Participants may be rescreened after 3 months of adequate treatment for folic acid or vitamin B-12 deficiency.

- Screening hemoglobin A1c (HbA_{1c}) $> 8\%$ (retesting is permitted if $HbA_{1c} \leq 8.4\%$) or poorly controlled insulin-dependent diabetes with hypoglycemic episodes

  Participants may be rescreened after 3 months to allow optimization of diabetic control.

5.2.7 Exclusions Related to Medications

The following medications are prohibited at screening and during the study. Potential participants who start any of the exclusionary medications during the study could be withdrawn from study treatment.

- Any previous administration of gantenerumab is exclusionary at screening
- Any previous administration of active immunotherapy (vaccine) that is being evaluated to prevent or postpone cognitive decline is exclusionary at screening and prohibited during the entire period of study participation
- Any passive immunotherapy (Ig) or other long-acting biologic agent to prevent or postpone cognitive decline within 1 year of screening are exclusionary. Use of passive immunotherapy (Ig) or other long-acting biologic agents agent to prevent or postpone cognitive decline is also prohibited during the entire period of study participation.
- Any other investigational treatment within 5 half-lives or 6 months (whichever is longer) prior to screening is exclusionary and prohibited during the entire period of study participation
- Any previous administration of sodium oligomannate (GV-971) is exclusionary at screening. The use of GV-971 is prohibited during the entire period of study participation.
- Any previous treatment with medications specifically intended to treat symptoms related to Parkinson's disease or any other neurodegenerative disorder is exclusionary at screening and the use of these medications is prohibited during the study. Certain medications are acceptable, if the participant is taking the medication for a non-neurodegenerative disorder (e.g., pramipexole for restless leg syndrome).
- Anticonvulsant medications are exclusionary at screening and throughout the study, except as treatment for an approved pain indication or an adverse event after study start

- Typical anti-psychotic or neuroleptic medications are exclusionary at screening and throughout the study, except as brief treatment for a non-psychiatric indication (e.g., emesis)
- Atypical anti-psychotic medications are exclusionary at screening and during the study except for intermittent short-term use
- Anticoagulation medications within 3 months of screening with no plans to initiate any prior to randomization
  - Anti-platelet treatments (e.g., aspirin, clopidogrel, dipyridamol) and low dose low-molecular-weight heparin for prophylaxis are permitted
- Psychedelic drugs and substances (e.g., psilocybin, LSD), recreational cannabis and illicit use of opioids (e.g., opium, morphine, fentanyl or diacetylmorphine/heroin) or ketamine are exclusionary at screening and during the entire study
- Medical marijuana (licensed and/or standardized marijuana or its derivatives, as prescribed or recommended by a healthcare professional in the treatment of a medical condition) is allowed if on a stable dose for at least 1 month prior to screening. Medical marijuana does not have to be discontinued prior to cognitive testing if on a stable dose for at least 1 month prior to cognitive testing.
- Chronic use of prescribed opiates or opioids for pain management is allowed if on a stable dose for at least 1 month prior to screening. Chronically used, prescribed opioids do not have to be discontinued prior to cognitive testing if on a stable dose for at least 1 month prior to cognitive testing.
- Chronic use of prescribed benzodiazepines, barbiturates and hypnotic medications are allowed if on a stable dose for at least 1 month prior to screening. Chronically used, prescribed benzodiazepines, barbiturates and hypnotic medications do not have to be discontinued prior to cognitive testing if on a stable dose for at least 1 month prior to cognitive testing.
- Nootropics and stimulant medications (e.g., piracetam, amphetamine, methylphenidate preparations, or modafinil) are exclusionary within 1 month of screening and throughout the study
- Medical food supplements (e.g., Axona®, Souvenaid®) are allowed if on a stable dose for at least 1 month prior to screening
- Any previous treatment with cholinesterase inhibitors (e.g., donepezil, galantamine, rivastigmine) and *N*-methyl-D-aspartate receptor antagonists (e.g., memantine) are exclusionary at screening. Cholinesterase inhibitors (e.g., donepezil, galantamine, rivastigmine) and *N*-methyl-D-aspartate receptor antagonists (e.g., memantine) are prohibited during the study until the participant is determined to have progressed dementia due to AD as determine by the iCAC.

5.2.8 Additional Exclusions

Potential participants are excluded from the study if any of the following criteria apply:

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 17 weeks after the final dose of gantenerumab

Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.

- Deformity of the lumbosacral region of the spine that would contraindicate lumbar puncture (LP) in participants who will receive a LP
- Clinically significant abnormal screening blood, CSF (with the exception of CSF Aβ and tau levels) or urine results that remain abnormal at retest
- Impaired coagulation (screening PT $> 1.2\times$ the ULN that remains abnormal on retest)
- History of cancer, with the following exceptions:
  - If considered to be cured
  - If not being actively treated with anti-cancer therapy or radiotherapy and is not likely to require treatment in the ensuing 5 years
  - For prostate cancer or basal cell carcinoma, no significant progression over the previous 2 years
- Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins, including gantenerumab
- Hypersensitivity to any gantenerumab excipients
- Any other severe or unstable medical conditions that could be expected to progress, recur, or change to such an extent that it could put the participant at special risk, interfere with the participant's ability to complete the study assessments, or would require the equivalent of institutional or hospital care
- Reside in a skilled nursing facility such as a convalescent home or long-term care facility
- Require residence in such facilities during the study may continue in the study and be followed for efficacy and safety, provided that they have a study partner who meets the study partner requirements
- Planned or recent (within 12 months prior to screening) exposure to ionizing radiation that in combination with the planned administrations of the radioligand would result in a cumulative exposure that exceeds recommended local guidelines

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

This study has no meal or dietary restrictions.

5.3.2 Caffeine, Alcohol, and Tobacco

This study has no caffeine, alcohol, or tobacco restrictions.

5.3.3 Activity

This study has no activity restrictions.

5.3.4 Contraception Requirements

During the study, female participants of childbearing potential must use contraception or take other precautions as described in Section 5.1.

5.4 SCREEN FAILURES

Individuals who do not meet the cognition or amyloid-based inclusion criteria for participation in this study (screen failure) cannot be rescreened. Rescreening on other criteria may be allowed as detailed in Section 5.2. The investigator will maintain a record of reasons for screen failure (see Section 8).

6. STUDY TREATMENT(S) AND CONCOMITANT THERAPY

Study treatment is defined as any investigational treatment, marketed product, placebo, or medical device intended to be administered to a study participant according to the study protocol.

The term 'study drug' in Study WN42444 refers to gantenerumab or placebo. Gantenerumab and placebo are also designated as investigational medicinal products (IMPs). According to E.U. guidance, the PET tracers, as used in the context of this study, are designated as non-IMPs. In some regions, according to local regulations, these PET tracers may be considered to be IMPs (see Section 6.1.3).

6.1 STUDY TREATMENTS ADMINISTERED

Table 8 provides a description of assigned study treatments for this study.

Table 8 Study Treatment Description

	Gantenerumab	Placebo	[^{18}F]-Florbetaben	[^{18}F]-Flutemetamol	[^{18}F]-MK-6240
Use	Experimental	Placebo comparator	Amyloid PET tracer		Tau PET tracer
Type of medicinal product	IMP	IMP	According to E.U. guidance, the PET tracers, as used in the context of this study, are designated as non-IMPs. In some regions, according to local regulations, these PET tracers may be considered to be IMPs.		
Drug form	Solution for SC injection	Solution for SC injection	Solution for IV injection	Solution for IV injection	Solution for IV injection
Unit dose strength(s)	120 mg/0.8 mL 255 mg/1.7 mL	Not applicable	Approximately 20 mL of sterile solution for approximately 300 MBq (see Investigator's Brochure)	Approximately 20 mL of sterile solution for approximately 185 MBq (see Investigator's Brochure)	Approximately 20 mL of sterile solution for approximately 185 MBq (see Investigator's Brochure)
Dosage level(s)	See Section 6.1.1	See Section 6.1.2	300 ± 10% MBq	185 ± 10% MBq	185 ± 10% MBq
Formulation(s)	Refer to Investigator's Brochure	Not applicable	Refer to Investigator's Brochure	Refer to Investigator's Brochure	Refer to Investigator's Brochure
Packaging	Refer to Investigator's Brochure	Refer to Investigator's Brochure	Syringe or glass vial sealed with a synthetic rubber closure and aluminum overseal	Syringe or glass vial sealed with a synthetic rubber closure and aluminum overseal	Syringe or glass vial sealed with a synthetic rubber closure and aluminum overseal
Labeling	Per local requirements				
Route of administration	SC injection	SC injection	IV injection	IV injection	IV injection
Source	Sponsor	Sponsor	Life Molecular Imaging	GE Healthcare	Cerveau Technologies, Inc

IMP = investigational medicinal product; PET = positron emission tomography.

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

Guidelines for dose modification and treatment interruption or discontinuation for participants who experience adverse events are provided in Appendix 3.

6.1.1 Gantenerumab

The active treatment under investigation for this study is gantenerumab. Gantenerumab will be administered by SC injections to all participants.

Participants who choose the Q1W dosing regimen at the target dose, and are randomized to the active treatment arm will receive a dose of gantenerumab 120 mg SC every 4 weeks (Q4W) three times, 255 mg SC Q4W three times, and 255 mg SC Q2W six times, regardless of *APOE* ε4 status, prior to reaching the target dose of 255 mg Q1W (i.e., 1020 mg per month) as detailed in Table 1.

Participants who choose the Q2W dosing regimen at the target dose, and are randomized to the active treatment arm will receive a dose of gantenerumab 120 mg SC Q4W three times, 255 mg SC Q4W three times, and 510 mg SC Q4W three times, regardless of *APOE* ε4 status, prior to reaching the target dose of 510 mg Q2W (i.e., 1020 mg per month) as detailed in Table 4.

> Note: the minimum number of study drug doses, as outlined above, must be administered during each titration step prior to dose escalation.

Following the initial dose escalation period, study drug will be administered at a Q1W (Table 2) or Q2W (Table 5) dosing regimen. Participants will use their selected dosing regimen throughout the maintenance dosing phase of the study.

For Q4W injections, a visit window of ±7 days is allowed for dosing visits. Once study drug is administered Q1W or Q2W, the visit window for dosing visits is ±3 days. It is recommended not to administer more than 1020 mg (i.e., 4×255 mg Q1W or 2×510 mg for Q2W) within 28 days. Always return to the initial planned dosing regimen for subsequent visits. If administration is not possible on the scheduled dosing day, the study drug should be administered as soon as possible within the time window from the scheduled dosing date. If the study drug cannot be administered within the time window, the dose should be skipped, and the participant should receive the next dose at the next scheduled time with the study drug dosing resumed in accordance with the original dosing schedule.

During the initial dose escalation, the maintenance dosing periods, and the post-progression dose escalation period (if applicable), injections will be administered SC into the abdomen as a single injection, 2 or 3 injections as any combination of the following:

- 0.8 mL injection for the 120 mg dose or placebo
- 1.7 mL injection for the 255 mg dose or placebo

Participants on the Q1W dosing regimen will receive 1 SC study drug injection per dosing visit during the initial dose escalation and maintenance dosing periods (Table 1 and Table 2). However, participants on the Q1W dosing regimen will receive 2 SC study drug injections per dosing visit at Week 1P, Week 5P, and Week 9P, and 1 SC study drug injection per dosing visit at all other dosing visits during the post-progression dose escalation period (Table 3).

Participants on the Q2W dosing regimen will receive 1 SC study drug injection per dosing visit until Week 25 during the initial dose escalation period (Table 4). Starting at Week 25, participants will receive 2 SC study drug injections per dosing visit during the initial dose escalation, maintenance dosing, and post-progression dose escalation periods with the exception of dosing at Week 1P, Week 5P, and Week 9P (Table 4, Table 5, and Table 6) when they will receive 3 SC study drug injections per dosing visit (Table 6).

During pre-specified visits, the study drug may be administered by the participant or their study partner (non-professional caregiver) at the participant's home or another suitable location depending on the individual participant's/study partner's preference, if appropriately trained and certified by the investigator or delegate, and allowed by local regulations.

During the initial dose escalation period, participants will receive SC injections of study drug by the investigator or an appointed qualified study staff for the first 3 doses at the clinic. If the participant or their study partner is willing and determined capable of administering SC injections by the investigator or delegate, this participant or study partner will receive observer and dose administration training at the first 3 dosing visits (i.e., Weeks 1, 5, 9). At the next 4 visits (i.e., Weeks 13, 17, 21, and 25) the injections will be administered by the participant or study partner under the site staff's supervision. Following the supervised dosing visits at the clinic, subsequent dosing may be administered by the participant or study partner at home except for doses that coincide with a clinic visit, in which case the participant or study partner should administer the injection in the clinic, under investigator/study staff supervision. Study staff will document the outcome of the supervised administrations. Training and supportive materials will be provided to the site and the participant and/or their study partner. Following the in-person instructional training and supervised administrations at the site, adequate supply of study drug will be provided. Participants should be observed for at least 2 hours after dosing for the first 4 administrations of study drug (corresponding to the injections at Week 1, Week 5, Week 9 and Week 13); the observation time may be reduced to at least 1 hour following all other administrations. However, participants must be observed for a minimum of 1 hour after each injection by their study partner or another suitably trained individual (i.e., "postdose observer") even if they are self-administering the study drug. Study partners and postdose observers will be trained by the site staff to recognize signs and symptoms of allergic reactions and the appropriate actions to be taken if the participant were to develop those signs and

symptoms. Postdose observers must also sign the Postdose Observer ICF prior to the initiation of the training.

At subsequent visits as specified in the schedule of activities (see Section 1.3), the investigator or appointed qualified study staff will determine if the participant or study partner continues to be qualified to perform home administrations. If at any time the investigator, participant, or study partner determines that home administration by the participant or study partner is unqualified, then the study drug must be administered at home or in the clinic by an alternative trained study drug administrator.

Starting from the fifth dose, at applicable sites, study drug may also be administered by a trained healthcare professional (mobile nurse) at the participant's home or another suitable location, if the participant has given written informed consent.

During the post-progression dose escalation period (Section 1.3 [Table 3 and Table 6]), participants must be observed for at least 2 hours after the first 4 'definitely active doses' (i.e., dosing at Week 1P, Week 5P, Week 9P and Week 13P). The observation time may be reduced to at least 1 hour following all other administrations. Participant or study partner administration is prohibited during the post-progression dose escalation period. The study drug administration by the participant or their study partner may resume after Week 37P following assessment and adequate training, if necessary, by the site. Sites must verify participant/study partner readiness for study drug administration.

A vial adapter will be available in countries where it has been approved to withdraw the medication from the vial into a disposable syringe (this device will be optional for health care professionals and for participants and study partners [non-professional caregivers]).

For study drug administration days that include efficacy assessments, study drug must be administered at the clinical site by the site staff or the participants/study partner. Study personnel preparing and administering study drug must not be involved with any efficacy or safety assessments.

Any cases of overdose, medication error, drug abuse, or drug misuse of study treatment should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose, medication error, drug abuse, or drug misuse of study treatment should be recorded on the Adverse Event eCRF (see Section A2–7.13).

Refer to the Pharmacy Manual and/or the Home Administration Manual and the Gantenerumab Investigator's Brochure for information on study drug handling, including preparation and storage, and accountability.

6.1.2 Placebo

A placebo of identical composition (except gantenerumab) and volume to gantenerumab will be administered by SC injection to the abdomen. The dosing schedule of the placebo and gantenerumab will also be identical throughout the duration of the study as detailed in Section 1.3.

Additional details on dosing in Study WN42444 are provided in Section 4.1.3.

6.1.3 Positron Emission Tomography Tracers

For screening, the possible amyloid PET ligands will be [^{18}F]-Florbetaben and [^{18}F]-Flutemetamol. [^{18}F]-Flutemetamol is only allowed for screening if access to [^{18}F]-Florbetaben at the imaging site is not possible. If during screening, the amyloid-based eligibility is established based on an off-protocol (i.e., historical) amyloid PET scan, the participant will not be allowed to participate in the optional longitudinal amyloid PET assessments, unless a repeat [^{18}F]-Florbetaben amyloid PET scan is obtained at baseline. Such participants may still participate in the optional longitudinal tau PET assessments.

For the optional longitudinal amyloid PET assessments only [^{18}F]-Florbetaben will be used, except that, the use of [^{18}F]-Flutemetamol will be allowed in Japan due to insufficient availability of [^{18}F]-Florbetaben. Participants who will be assessed with [^{18}F]-Flutemetamol will not be accounted for in the 200 participant target sample size for the longitudinal amyloid PET assessments.

For the longitudinal tau PET assessment, [^{18}F]-MK-6240 will be used.

In countries where the PET radioligands are approved for marketing, the approved local product information will be provided, and in countries where they are not approved for marketing, the Investigator's Brochures will be provided.

Additional requirements for all participants receiving an amyloid or tau PET scan include:

- Females of childbearing potential will undergo additional pregnancy tests and must have a negative pregnancy test result prior to the tracer injection
- Planned or recent (within 12 months prior to screening) exposure to ionizing radiation that in combination with the planned administrations of the radioligand would result in a cumulative exposure equal to or less than recommended local guidelines

For the safety reporting requirements dealing with the PET tracers used in this study, please see Section 8.3.4).

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

Investigational medicinal products required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel such as 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, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for 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, with use of an 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 and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs 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 be administered the IMP, only authorized staff may dispense the IMP, and only authorized healthcare professionals or trained participants/study partners may administer the IMP.

Investigational medicinal products 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.

If applicable, participants or study partners will confirm completed administration in the home (nonclinical) setting with use of a diary. Further details will be described in the Home Administration Manual.

Refer to the Pharmacy Manual and/or the Home Administration Manual and the Gantenerumab Investigator's Brochure for information on IMP handling, including preparation and storage, and accountability.

6.3 TREATMENT ASSIGNMENT AND BLINDING

6.3.1 Treatment Assignment

This is a randomized, double-blind study. After the main study written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site will obtain the participant's identification number and treatment kit assignment from an IxRS. Participants will be randomly assigned to 1 of 2 treatment arms. The ratio will be 1:1, 1 experimental to 1 control. The randomization method will be stratified block-randomization. Randomization to treatment allocation will be stratified by the following criteria: geographic region (Western Europe, Australia, and New Zealand), the participant's *APOE* ε4 carrier status (non-carrier vs. heterozygote carrier vs. homozygote carrier), the method used to determine amyloid positivity (PET vs. CSF), and participation in the optional longitudinal amyloid PET and tau PET assessments.

6.3.2 Blinding

The study is to be conducted in a double-blinded manner to minimize potential bias from investigators and participants. The Sponsor, participants and their study partners, and the site staff will remain blinded to treatment assigned at randomization, even after a participant *progresses to MCI or dementia due to AD* and starts active treatment.
In order to protect study blinding, no one administering or with the potential to administer drug to participants will be permitted to conduct any efficacy assessments.
Study partners will only be permitted to support 1 participant in the trial *and may not be enrolled as study participants at the same time*.

The Master Randomization or Master Medication List will not be available at the study center to Roche monitors, Roche project statisticians, or to the project team at Roche. Unblinding should not occur except in the case of emergency situations where knowledge of the study drug assigned would affect participant care. The investigator should make every effort to contact the Medical Monitor before unblinding a participant. If unblinding is necessary for participant management, the investigator will be able to break the treatment code by contacting the IxRS. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event). Any request from the investigator for information about the treatment administered to study participants for another purpose must be discussed with the Medical Monitor.

While PK and immunogenicity samples must be collected from participants not exposed to gantenerumab to maintain the blinding of treatment assignment, PK and ADA assay results for such participants are generally not needed for the safe conduct or proper interpretation of the study data. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to participant treatment assignments to identify appropriate samples for analysis. Pharmacokinetic and ADA samples from participants

not exposed to gantenerumab will not be analyzed for study drug PK concentration or ADAs except by request (e.g., to evaluate a possible error in dosing).

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 8.3.4) that are considered by the investigator or Sponsor to be related to an IMP (defined in Section 6). The participant may continue to receive treatment, and the investigator, participant, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to participant treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

6.4 STUDY TREATMENT COMPLIANCE

When participants are dosed at the site, they will receive study treatment directly from the investigator, their designee or via self/study partner administration under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded on the eCRF. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

When participants self-administer study treatment at home, compliance with study treatment will be assessed via regular phone calls per Section 6.1.1 and the dosing diary per Section 6.2.

Details on treatment administration (e.g., dose and timing) should be noted in the source documents and on the Study Drug Administration eCRF. Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Appendix 2.

6.5 DOSE MODIFICATION

Rules regarding dose interruptions or modifications in participants who develop ARIA events are provided in Section A3–1. Discontinuation from study treatment is detailed in Section 7.1. Participant non-compliance and other potential reasons to discontinue a participant from the study are detailed under Section 7.2.

6.6 CONTINUED ACCESS TO STUDY TREATMENT AFTER THE END OF THE STUDY

The Sponsor will offer continued access to 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 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 gantenerumab 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 gantenerumab after completing the study if any of the following conditions are met:

- The gantenerumab 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 gantenerumab or data suggest that the gantenerumab is not effective for the prevention of symptomatic AD and/or the treatment of prodromal to mild AD
- The Sponsor has reasonable safety concerns regarding the gantenerumab as a treatment for AD
- Provision of the gantenerumab is not permitted under the laws and regulations of the participant's country

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

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

6.7 TREATMENT OF OVERDOSE

An overdose is the administration of a drug in a quantity that is higher than the assigned dose. There is no known antidote for treating gantenerumab. Cases of medication error, including overdoses, along with any associated adverse events, should be reported as described in Appendix 2.

In the event of an overdose, the investigator should take the following steps:

- Contact the Medical Monitor immediately
- Closely monitor the participant for any adverse event or serious adverse event and laboratory abnormalities. The investigator may choose to perform additional MRI monitoring for ARIA at any time (see Section A3–1).

Supportive treatment, in line with local regulations and guidelines, for any noted symptoms is recommended.

6.8 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, herbal and homeopathic remedies, and nutritional supplements) used by a participant in addition to protocol-mandated treatment from 3 months prior to the screening visit until the study completion or discontinuation visit must be recorded on the Concomitant Medications eCRF along with the following information:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

The Medical Monitor may be consulted if there are any questions related to concomitant or prior therapy.

6.8.1 Permitted Therapy

The following medications are permitted if the dose and dosing regimen have been stable for at least 3 months (unless otherwise specified below) prior to the screening visit, and are expected to remain stable after screening or if required for treatment of an adverse event after study start:

- Anticonvulsant medications for an approved pain indication
- Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) for the treatment of depressive symptoms
- Chronic use of prescribed opiates or opioids for pain management is allowed if on a stable dose for at least 1 month prior to screening. Chronically used, prescribed opioids do not have to be discontinued prior to cognitive testing if on a stable dose for at least 1 month prior to cognitive testing.
- Chronic use of prescribed benzodiazepines, barbiturates and hypnotic medications are allowed if on a stable dose for at least 1 month prior to screening. Chronically used, prescribed benzodiazepines, barbiturates and hypnotic medications do not have to be discontinued prior to cognitive testing if on a stable dose for at least 1 month prior to cognitive testing.
- Intermittent, short-term use of prescribed opiates or opioids for pain, as well as benzodiazepines, buspirone, and short-acting hypnotic medication for sleep or anxiety are allowed, except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment
- Medical marijuana (licensed and/or standardized marijuana or its derivatives, as prescribed or recommended by a healthcare professional in the treatment of a medical condition) is allowed if on a stable dose for at least 1 month prior to screening. Medical marijuana does not have to be discontinued prior to cognitive testing if on a stable dose for at least 1 month prior to cognitive testing.
- Intermittent use of centrally acting antihistamine medications except within 2 days or 5 half-lives (whichever is the longer) prior to any cognitive assessment

- Anti-platelet treatments (e.g., aspirin, clopidogrel, dipyridamol) and low dose low-molecular-weight heparin for prophylaxis are permitted
- Participants who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use
- Medical food supplements (e.g., Axona®, Souvenaid®) are allowed if on a stable dose for at least 1 month prior to cognitive testing including at screening

Whenever possible, one of the medications listed below should be used if appropriate. Concomitant and excluded therapies for determination of participant eligibility are described in Section 5.2.7.

6.8.1.1 *COVID-19 Vaccination*

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 Alzheimer's disease.

However, the published safety data show that overlapping adverse events between gantenerumab/placebo and the vaccines can occur: the timing and the nature of local injection reactions (occurring within 24 hours) as well as of systemic injection reactions may be similar for both products.

Just as with other vaccinations (e.g., influenza), the administration of COVID-19 vaccines will be considered as a concomitant medication in these studies.

In the situation that vaccination of a study participant with a COVID-19 vaccine is considered:

- *COVID-19 vaccines that have been approved or authorized for temporary use can be administered to study participants according to the national and local guidance, and their use should be documented on the "Concomitant Medication" eCRF. Only those administered during the time of the protocol specified reporting window for concomitant medications should be collected. Sites should collect as much information as is available regarding the vaccine received on the concomitant medication page of the eCRF. The following should be included where available:*
  - *Manufacturer or proprietary name*
  - *Vaccine type*
  - *Date of administration (if 2 or more doses are received, sites should record each administration as a separate entry)*
  - *If different COVID-19 vaccines are administered (e.g., Pfizer-BioNTech COVID-19 Vaccine at first dose and the Oxford University/AstraZeneca COVID-19 Vaccine at second dose) this should be clearly captured*
- *To facilitate the correct clinical assessment of any adverse events and to continue correct attribution of adverse events related to study drug (gantenerumab/placebo)*

or to the vaccination, namely of local and systemic reactions following the injections, the Sponsor recommends to vaccinate study participants at least 24–48 hours after an injection of study drug. Similarly, vaccination in the 48 hours preceding a study drug administration should also preferably be avoided. However, the timing of the study visits and study drug administration should not be unduly postponed because of a vaccination.

- *Any adverse events observed in association with the use of vaccines should be documented on the adverse event page in the eCRF and clinically managed, as it is medical practice for any other concomitant vaccination*
- *On the same adverse event page, assign the adverse event causality in the "Other suspected causes" field to "Concomitant medication". The Injection Site Reaction eCRF should not be completed for local injections reactions due to the vaccine.*

6.8.2 Cautionary Therapies

6.8.2.1 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug– interactions are generally unknown.

6.8.3 Prohibited Therapy

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

- Any previous administration of gantenerumab is exclusionary at screening
- Any previous administration of active immunotherapy (vaccine) that is being evaluated to prevent or postpone cognitive decline is exclusionary at screening and prohibited during the entire period of study participation
- Any passive immunotherapy (Ig) or other long-acting biologic agent to prevent or postpone cognitive decline within 1 year of screening are exclusionary. Use of passive immunotherapy (Ig) or other long-acting biologic agents to prevent or postpone cognitive decline is also prohibited during the entire period of study participation.
- Any other investigational treatment within 5 half-lives or 6 months (whichever is longer) prior to screening is exclusionary and prohibited during the entire period of study participation
- Any previous administration of GV-971 is exclusionary at screening. The use of GV-971 is prohibited during the entire period of study participation.
- Any previous treatment with medications specifically intended to treat symptoms related to Parkinson's disease or any other neurodegenerative disorder is exclusionary at screening and the use of these medications is prohibited during the study. Certain medications are acceptable, if the participant is taking the medication for a non-neurodegenerative disorder (e.g., pramipexole for restless leg syndrome).

- Anticonvulsant medications are exclusionary at screening and throughout the study, except as treatment for an approved pain indication or an adverse event after study start
- Typical anti-psychotic or neuroleptic medications are exclusionary at screening and throughout the study, except as brief treatment for a non-psychiatric indication (e.g., emesis)
- Atypical anti-psychotic medications are exclusionary at screening and during the stud except for intermittent short-term use
- Anticoagulation medications within 3 months of screening with no plans to initiate any prior to randomization
  - During the study, short-term use of anti-coagulant medications may not result in permanent discontinuation from the study; however, will require temporary interruption of the study drug.
- Psychedelic drugs and substances (e.g., psilocybin, LSD), recreational cannabis and illicit use of opioids (e.g., opium, morphine, fentanyl or diacetylmorphine/heroin) or ketamine are exclusionary at screening and during the entire study
- Nootropics and stimulant medications (e.g., piracetam, amphetamine, methylphenidate preparations, or modafinil) are exclusionary within 1 month of screening and throughout the study
- Any previous treatment with cholinesterase inhibitors (e.g., donepezil, galantamine, rivastigmine) and *N*-methyl-D-aspartate receptor antagonists (e.g., memantine) are exclusionary at screening. Cholinesterase inhibitors (e.g., donepezil, galantamine, rivastigmine) and *N*-methyl-D-aspartate receptor antagonists (e.g., memantine) are prohibited during the study unless the participant has progressed to dementia as determined by the iCAC

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

Study and site closure is described in Appendix 1.

7.1 DISCONTINUATION OF STUDY TREATMENT

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study treatment. If study treatment is definitively discontinued, the participant will remain in the study for additional assessments. See the schedule of activities (see Section 1.3) for data to be collected at the time of discontinuation of study treatment and for any further follow-up evaluations that need to be completed.

Participants must permanently discontinue study treatment if any of the following criteria are met:

- Any medical condition that the investigator determines (including upon the Sponsor's recommendation) may jeopardize the participant's safety if he or she continues to receive study treatment
- Investigator determination (including upon the Sponsor's recommendation) that treatment discontinuation is in the best interest of the participant
- Pregnancy
- Upon evidence of disseminated leptomeningeal hemosiderosis
- Upon evidence of intracerebral macrobleed

If study treatment is discontinued permanently for participants dosed at home, any remaining study drug doses should be returned to the study site (if applicable).

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

Participants who discontinue from the study treatment for any reason should be encouraged to continue with all remaining assessments until the end of the study. However, participants who are unwilling to return to the clinic will be asked to complete the Early Termination and safety follow-up visits within 2 weeks and 17 weeks, respectively from the final dose of study drug.

7.2 PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his or her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. The participant will then be permanently discontinued both from the study treatment and from the study at that time. Participants who withdraw from the study will not be replaced.

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

If a participant withdraws consent from the study, the Sponsor may retain and continue to use any data collected before withdrawal of consent. Samples collected prior to withdrawal may be analyzed, unless the participant specifically requests that the samples be destroyed (as documented in the source documents) 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.

All participants who discontinue from the study early will be asked to **return 2 weeks after the final dose of study drug** to complete the early termination visit and **17 weeks**

after the final dose of study drug for the safety follow-up visit. If participants dosed at home discontinue the study early, any remaining study drug doses should be returned to the study site (if applicable).

Every effort should be made to obtain a reason for participant discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. However, participants will not be followed for any reason after consent has been withdrawn. If a participant requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.

Reasons for participant discontinuation from the study may include, but are not limited to, the following:

- Participant withdrawal of consent
- 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

Participant non-compliance with the study and/or study procedures, defined as missing more than 3 consecutive dose administrations (with Q4W dosing regimen), more than 6 consecutive dose administrations (with Q2W dosing regimen), or >12 consecutive dose administrations (with Q1W dosing regimen) because of non-safety related reasons or more than half of the dosing visits in a calendar year. See the schedule of activities in Section 1.3 for details on Early Termination and Safety Follow-up visits to be performed for participants who permanently discontinue study treatment. If a participant requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

7.3 PARTICIPANTS LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule. If the participant is unable or unwilling to comply with study visits, site personnel should assess reasons the participant is unable or unwilling to return to the clinic, and determine if there are ways to support participant participation.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone

calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he or she will be considered lost to follow-up and will be withdrawn from the study

8. STUDY ASSESSMENTS AND PROCEDURES

Written informed consent for participation in the study must be obtained from all participants and their study partners (non-professional caregivers) before performing any study-related procedures. Informed Consent Forms for enrolled participants, their study partners, and postdose observers, as well as for those who are not subsequently enrolled, will be maintained at the study site. Written informed consent for participation in the study must be obtained from:

- All participants before performing any study-related procedures (including optional prescreening evaluations)
- All study partners (non-professional caregivers) before performing any study-related screening procedures excluding the optional prescreen
- Each postdose observer before they undertake any study-related procedure, including any training

Informed Consent Forms for enrolled participants, their study partners, and postdose observers, as well as for those who are not subsequently enrolled, will be maintained at the study site.

Study procedures and their timing are summarized in the schedule of activities (see Section 1.3). Prospective approval of protocol deviations, also known as protocol waivers or exemptions, is not permitted.

Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment. Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before enrollment. The investigator will maintain a detailed record of all participants screened, to document eligibility or record reasons for screening failure, as applicable.

Medical history and baseline conditions, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, and use of alcohol and drugs of abuse will be recorded at baseline.
Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, herbal and homeopathic remedies, and nutritional supplements) used by the

participant within 3 months prior to the screening visit will be recorded at baseline. Demographic data, including age, sex, and self-reported race or ethnicity, relationship status of participants and their study partner, living situation and length of acquaintance will also be recorded and updated upon changes. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications, demographic data and allergies should be recorded.

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

Participants will be closely monitored for safety throughout the study. Participants should be assessed for toxicity prior to each dose; treatment will be administered only if the clinical assessment and local laboratory test values are acceptable. Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

At applicable sites, certain study assessments may be performed by a MN professional at the participant's home or another suitable location to improve access and convenience for participants participating in the study. The Sponsor will select a healthcare company that will be responsible for providing MN services for home administration at participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a participant and the participant gives written informed consent to participate in MN visits, the MN network will communicate with the participant and the participant's site. Mobile nursing visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional. The MN Manual will specify the assessments that may be performed by a MN professional.

8.1 EFFICACY ASSESSMENTS

8.1.1 Clinical Outcome Assessments

Clinical outcome assessments (COAs) will be completed to assess the treatment benefit of gantenerumab as outlined in the schedule of activities (see Section 1.3) and in the order specified in Section 8.10. Cognitive, functional, neuropsychiatric and quality of life assessments (i.e., PACC-5, CDR, CFIa, Amsterdam Instrumental Activities of Daily Living Questionnaire Short Version [A-IADL-Q-SV], AD-CGI-S, AD-PGI-S, AD-SPGI-S,

GDS-30, and the EQ-5D-5L) will be administered. Detailed descriptions of COAs included in Study WN42444 are provided in Section 8.10.2.

8.1.2 Pharmacodynamic Assessments

Biomarker efficacy assessments are detailed in Section 8.5.

8.2 SAFETY ASSESSMENTS

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary (optional), and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

A limited physical examination will be symptom-directed. Investigators should pay special attention to clinical signs related to previous serious illnesses. Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

The schedule of activities (see Section 1.3) indicates when complete and limited physical examinations are to be recorded. During unscheduled visits, the investigator or designee may choose the appropriate scope of physical examination (complete vs. limited physical examination) depending on the reason for the unscheduled visit.

8.2.2 Vital Signs

Vital signs will consist of pulse rate and systolic and diastolic blood pressure measurements.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. If obtained manually, the pulse rate will be determined by radial pulse and should be counted for a minimum of 20 seconds.

Blood pressure and pulse measurements should be taken before blood collection for laboratory tests and preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones). The same arm should be used for all blood pressure measurements.

Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

The schedule of activities (see Section 1.3) indicates when vital signs (pulse and blood pressure measurements) are to be recorded.

8.2.3 Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the schedule of activities (see Section 1.3).

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

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

The centrally-provided electrocardiograph machine should record the heart rate, QRS interval, RR interval, PR interval, QT interval, QTcB and QTcF (i.e., the QT interval corrected through use the Bazett formula and Fridericia's formula, respectively).

8.2.4 Clinical Safety Laboratory Tests

See Appendix 24 for the list of clinical laboratory tests to be performed and to the schedule of activities (see Section 1.3) for the timing and frequency. Clinical laboratory tests conducted by a central laboratory must be conducted in accordance with the laboratory manual.

The investigator must review the laboratory report, document this review, and record any clinically-relevant changes occurring during the study in the Adverse Event Case Report Form (CRF) (see Appendix 24).

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 17 weeks of the final dose of study treatment should be repeated until the values return to normal or baseline or are considered to be stable and no longer considered clinically significant by the investigator. If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., serious adverse event or adverse event or dose modification), the results must be recorded on the eCRF.

Samples collected for safety laboratory tests will be destroyed no later than the time of completion of the final Clinical Study Report.

8.2.5 Pregnancy Testing

The schedule for pregnancy testing for enrolled female participants is outlined in Section 1.3 and will be conducted as outlined in Appendix 4.

8.2.6 Monitoring for Suicidal Ideation and Behavior

Participants should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of study drug treatment, or at the time of dose changes. Consideration should be given to discontinuing study drug in participants who experience signs of suicidal ideation or behavior, following a risk assessment.

Study partners, families, and caregivers of participants should be alerted about the need to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior and to report such symptoms immediately to the study investigator. Assessment of suicidal ideation and behavior or treatment-emergent suicidal ideation and behavior will be monitored during Study WN42444 with use of the C-SSRS (Posner et al. 2011).

The C-SSRS (https://www.cssrs.columbia.edu) is an assessment tool used to assess the lifetime suicidality of a participant (C-SSRS assessment at baseline) as well as any new instances of suicidality (C-SSRS assessments after baseline). 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 assessments will be performed as indicated in the schedule of activities (see Section 1.3, Table 1, Table 2, and Table 3 for the QW1 dosing regimen and Table 4, Table 5, and Table 6 for the Q2W dosing regimen).

The assessment will be completed by a certified C-SSRS rater after he or she interviews the participant and their study partner during the study visit.

8.2.7 Brain Magnetic Resonance Imaging

In this study brain MRIs will be performed as outlined in the schedule of activities (see Section 1.3) for screening purposes, to support safety assessments, and to provide baseline information for the PET assessments. A detailed description is provided in Section 8.5.4.

During the initial dose escalation *period (Table 1 and Table 4), MRIs* must be performed after *the* third dose of current dose level *while on the Q4W schedule, or after the sixth dose of the current dose level while on the Q2W schedule. Magnetic resonance imaging scans should be performed* at least 7 days prior to dose escalation to the next dose level *and the results must be available for review by the investigator or their*

qualified designee before the dosing can proceed. It is not recommended that the MRI is performed on the same day as the study drug administration.

During the maintenance dosing period (Table 2 and Table 5), MRIs should be performed at least 7 days but no more than 13 days before the dosing visit that requires a safety MRI result. Results must be available for review by the investigator or their qualified designee before dosing at the visit that requires a safety MRI result can proceed. Magnetic resonance imaging scans should be performed before or at least 3 days following CSF sampling.

During the post-progression dose escalation period ***of the Q1W dosing schedule*** *(Table 3), a minimum of 3 'definitely active doses' during the first 2 dosing levels and minimum of 6 'definitely active doses' during the third dosing level must be administered before the participant is eligible for the next dose escalation. If required by the schedule of activities, MRIs should be performed at least 7 days prior to dose escalation to the next dose level, and results* must be available for review by the investigator or their qualified designee before the dosing can proceed.
Magnetic resonance imaging scans should be performed before or at least 3 days following CSF sampling.

During the *post-progression dose escalation period* ***of the Q2W dosing schedule*** *(Table 6), a minimum of 3 'definitely active doses' at each dosing level* must be *administered before the participant is eligible for the next dose escalation. If required by the schedule of activities, MRIs should be performed at least 7 days prior to dose escalation to the next dose level,* and results must be available for review by the investigator or their qualified designee before the dosing can proceed.
Magnetic resonance imaging scans should be performed before or at least 3 days following CSF sampling.

In addition to any local reading according to local procedures and requirements, all MRI scans will be reviewed by an expert central reader within approximately 1 week of receipt and a report provided to the site. For the purposes of overall study relevant decisions and recommendations, including participant eligibility as well as for analysis, results from the expert central reader will be used. Any time the central reader identifies a new MRI finding the study center medical staff and the Sponsor will be rapidly notified (see Section 8.5.2).

See Section A3–5 for instructions in the event of new MRI findings (ARIA-E and ARIA-H).

8.3 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of adverse event and serious adverse event can be found in Appendix 2.

Adverse events will be reported by the participant and their study partner (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, are considered related to the study treatment or study procedures, or caused the participant to discontinue the study treatment/study (see Section 7).

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and e-mailing the form using the fax number or e-mail address provided to investigators. All other medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the General Medical History and Baseline Conditions eCRF, not the Adverse Event eCRF.

All adverse events will be reported from the start of treatment until 17 weeks after the final dose of study treatment at the timepoints specified in the schedule of activities (see Section 1.3).

All serious adverse events will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 2. The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse event or serious adverse event information after conclusion of study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been discharged from the study, and he or she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

Adverse events that occur during the participant’s participation in imaging procedures at the imaging center or that are reported at the time of the participant’s visit to the imaging center will be communicated to the referring clinical site. Conversely, any clinically significant adverse events reported to the clinical site that may affect the participation of

any one participant or all participants enrolled in this study will be communicated to the imaging center within 24 hours of learning of the event.

Clinical observations by the responsible physician or designee at the imaging center, as well as vital sign measurements performed at the imaging center, will be recorded in the source data only and will not be part of the clinical study database unless any of these clinical observations/vital signs are clinically significant and constitute adverse events as assessed by the responsible physician or designee at the imaging site.

All adverse events that occur or are reported during the participant's visit at the imaging center will be retrospectively entered into the clinical database by the clinical site without the need to complete an Adverse Event Worksheet.

Additional measures for at-home administration: Every 4 weeks, except when there is an in-person clinic visit, the investigator or an appointed qualified study staff will have a telephone conversation with the participant and study partner to elicit, in a non-leading way, information on medication errors, adverse events, and changes to concomitant medications that may have occurred in the home setting. Therefore, there will be contact between the study staff and the participant/study partner at least every 4 weeks. The study staff is encouraged to have more frequent calls with a particular participant/study partner if considered appropriate by the investigator. Following the first 2 years of study treatment, the frequency of this telephone surveillance may be reduced to occur at least once, at midtime, between the 6-month in-person clinic visits. *However, for participants who enter the post-progression dose escalation period, there will be contact between the study staff and the participant/study partner at least every 4 weeks for 2 years after entering the post-progression dose escalation period (Table 3 and Table 6). Following this 2-year period, the frequency of this telephone surveillance can be reduced again as outlined above.* In addition, the participant and study partner must be instructed to contact the investigator and seek approval for continued study drug dosing in the home setting in case of onset of any new symptoms or symptom worsening, new or changed concomitant medications, or medication errors.

In addition, after administration of a PET ligand, but prior to initiation of study drug, the following adverse events should be reported:

- All adverse events (serious or non-serious) believed to be related to a PET ligand
- All serious adverse events occurring within 48 hours of PET ligand administration regardless of relatedness to the PET ligand

For reporting of serious adverse events, the above-outlined principles apply.
For non-serious PET ligand-related adverse events, a PET ligand-specific non-serious adverse event reporting paper form should be completed and submitted to the Sponsor or its designee, either by faxing or by scanning and e-mailing the form using the fax number or e-mail address provided to investigators.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 2.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about adverse event occurrences.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All adverse events will be followed 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 (as defined in Section 7.3), or the participant withdraws consent. Further information on follow-up procedures is provided in Appendix 2.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification (i.e., within 24 hours of awareness) by the investigator to the Sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC, and investigators.

For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

To determine reporting requirements for serious 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
[^{18}F]-Florbetaben (Neuraceq™)	[^{18}F]-Florbetaben Investigator's Brochure
[^{18}F]-Flutemetamol (Vizamyl™)	[^{18}F]-Flutemetamol Investigator's Brochure
[^{18}F]-MK-6240	[^{18}F]-MK-6240 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.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5 Pregnancy

Female participants of childbearing potential will be instructed through the ICF to immediately inform the investigator if they become pregnant during the study or within 17 weeks after the final dose of gantenerumab.

If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Appendix 4. The Sponsor or a designee may follow-up by telephone, fax, e-mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

8.3.6 Death Events

Information on reporting deaths is provided in Appendix 2.

8.3.7 Anticipated Events Not Qualifying for Expedited Reporting

Events not qualifying for expedited reporting will not be defined for this study.

8.3.8 Adverse Events of Special Interest and Selected Adverse Events

8.3.8.1 Adverse Events of Special Interest

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 the investigator becomes aware of the event; see Section A2–5 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section A2–7.8)
- Suspected transmission of an infectious agent by a study treatment, 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 treatment is suspected.

Descriptions of risks and management of the above-listed adverse events are provided in Appendix 2.

8.3.8.2 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 see Section A2–7.1 for further details on how to report ARIA events.

8.3.9 Reporting Requirements for Medical Device Complaints

In this study, the vial adapter may be provided to the participant or study partner (non-professional caregiver) in countries where it has been approved to aid study drug administration in the home setting is considered a medical device. The investigator must report all medical device complaints and any associated adverse events to the Sponsor, as described in Appendix 5.

8.3.10 Medical Monitors and Emergency Medical Contacts

Contact Information for All Sites

Medical Monitor/Emergency Medical Contact: [redacted], MD

Mobile Telephone No.: [redacted]

Medical Monitor/Emergency Medical Contact: [redacted], MD (Secondary)

Mobile Telephone No.: [redacted]

To ensure the safety of study participants, an Emergency Medical Call Center will be available 24 hours per day, 7 days per week, in case the above-listed contacts cannot be reached. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

8.4 PHARMACOKINETICS

Blood samples will be collected for measurement of plasma concentrations of gantenerumab as specified in the schedule of activities (see Section 1.3).

Samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the Sponsor. The timing of sampling may be altered during the course of the study on the basis of newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

An additional plasma PK sample will be obtained as soon as is feasible (e.g., at an unscheduled visit or the next study visit following a MRI scan showing new occurrence or worsening of ARIA-E or ARIA-H that meets the discontinuation criteria (e.g., during an unscheduled visit).

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded. Accurate recording of the date and time of study drug administration and PK sampling is critical.

Samples will be used to evaluate the pharmacokinetics of gantenerumab. Samples collected for analyses of gantenerumab plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study. Gantenerumab concentrations will be also measured in CSF in a subset of participants (see Section 8.11.4).

Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

Pharmacokinetic samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed to allow for assay development and validation (if needed).

Information on unblinding of personnel responsible for performing PK assays is provided in Section 6.3.

8.5 PHARMACODYNAMICS

The following pharmacodynamics biomarker samples will be collected, as applicable, from participants at all sites. For information on the optional pharmacodynamics biomarker assessments (i.e., blood-based biomarker prescreening, longitudinal amyloid and tau PET scans and longitudinal CSF sampling) please see Section 8.11.

8.5.1 Plasma Biomarker Samples

Plasma samples for the assessment of biomarkers, including but not limited to, $A\beta_{1-42}$, $A\beta_{1-40}$, NfL, and pTau, will be collected as specified in the schedule of activities (see Section 1.3), to provide evidence of gantenerumab activity (i.e., pharmacodynamic biomarkers, safety biomarkers) and further the understanding of AD biology based on change from baseline to the end of the study in longitudinal biomarker samples. These samples will also be used for exploratory research on biomarkers and biomarker assay development.

An additional plasma biomarker sample for the assessment of exploratory biomarkers will be obtained as soon as practical (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until, and including, ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E) or ARIA-H that meets the discontinuation criteria.

8.5.2 Clinical Genotyping Sample

During screening, whole blood samples for DNA extraction will be collected from all participants for evaluation of their *APOE* genotype for risk assessment and stratification purposes.

Eligible participants will be informed about their *APOE* $\varepsilon 4$ genotype at the end of the screening period, unless they opt out. For more details regarding the return of *APOE* genotyping results, please see Section 4.1.1.

8.5.3 CSF Sample (only for Participants who are Enrolled by CSF Amyloid Assessment)

Cerebrospinal fluid will be obtained from participants who choose to provide CSF samples during screening (CSF-enrolled participants) for confirmation of $A\beta$ and tau levels for eligibility purposes.

Cerebrospinal fluid will be collected via LP by an individual who meets all local requirements and is proficient in the procedure. Cerebrospinal fluid sampling and post-LP care will be performed in accordance with local practice. All CSF sampling should be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variability of CSF biomarkers.

Approximately 12 mL of CSF will be collected at screening. The sample will be divided into aliquots onsite and used for the following:

- Biomarker analysis, including, but not limited to: $A\beta_{1-42}$, $A\beta_{1-40}$, tTau, pTau, and NfL
- Measurement of gantenerumab levels in the CSF
- Samples may also be used to support the development of biomarker assays for diagnostic use

8.5.4 Brain Magnetic Resonance Imaging

Magnetic resonance imaging should be performed with use of 1.5-T or 3.0-T scanners. Whenever possible, the same scanner should be used for an individual participant for the entire duration of the study. Magnetic resonance imaging will be conducted at screening to (1) determine whether the exclusion criteria are met (e.g., number of microhemorrhages or presence of mass lesions), (2) serve as a baseline measure of (regional) brain volumes and (3) serve as baseline information for the PET assessments (where applicable). In addition, structural MRI (to assess whole-brain and regional brain atrophy), and optional imaging, including functional resting-state MRI (rs-fMRI), dMRI, and ASL-MRI, will be performed at multiple timepoints to determine potential treatment effects on MRI outcome measures (for the schedule of activities, see Section 1.3).

Magnetic resonance imaging will also be used during the entire study to monitor safety (e.g., occurrence of ARIA-E or ARIA-H). Additional unscheduled MRI scans may be performed to better understand relevant CNS adverse events (such as increased confusion) occurring in the context of ARIA or to follow-up a sign that emerges at a scheduled scan. Contrast agent may be used in such a case of follow-up MRI scans if clinically indicated and administration of contrast agent is considered safe for the participant according to local standards. If a contrast agent is used, the participant's renal function must be checked according to the local standards to ensure that contrast administration is safe.

Magnetic resonance imaging should be performed before or at least 3 days after CSF sampling (i.e., LP), unless and earlier MRI scan is clinically warranted.

Magnetic resonance imaging scans may include all or some of the following sequences:

Core Sequences:

- 3D T_1–weighted
- T_2*–weighted

- T_2–weighted
- T_2–FLAIR
- DWI

Optional Sequences (subset of sites/subjects depends on the scanner specification):

- BOLD rs-fMRI and related fieldmap: optional and if available (to assess resting-state functional connectivity at investigative sites having the required software and sequences)
- dMRI and related fieldmap: optional and if available (to assess fiber tract integrity)
- ASL-MRI and related fieldmap: optional and if available (to assess CBF)

All sequences (except rs-fMRI, dMRI and ASL-MRI) will be used to assess MRI safety and inclusion/exclusion criteria. Additional sequences may be obtained if clinically warranted.

Magnetic resonance imaging scans will be reviewed by a central MRI core laboratory, which will perform both, the clinical reads and assessment of MRI outcome measures. Magnetic resonance imaging scans should preferably be transferred to the central MRI core laboratory electronically. Magnetic resonance imaging results must be made available to investigators before dosing can proceed (see Section 8.2.7 for additional details on MRI safety management).

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

Additional MRI instructions regarding the specific imaging sequences, acquisition times, procedures for MRI scan acquisition and transmittal to the central reading facility can be found in the MRI Manual and Imaging Review Charter.

8.6 GENETICS

See Section 8.5.2 for information on clinical genotyping.

8.7 BIOMARKER ASSESSMENTS

See Section 8.5 for more information on plasma biomarker, clinical genotyping, and CSF assessments.

The following biomarker samples will be collected, as applicable, from participants at all sites:

- Clinical Genotyping Samples
- CSF Sample – only for participants who are enrolled by CSF amyloid assessment
- Plasma Biomarker Samples

Biomarker samples collected at participating sites and biomarker samples requiring separate consent are described in Section 8.11.

Plasma biomarker samples and CSF samples collected at screening, including those collected from individuals who do not enroll in the study, may be used for exploratory research and/or development of disease-related tests or tools.

Biomarker samples will be collected according to the schedule of assessment outlined in Section 1.3. Biomarker samples will be sent to one or several central laboratories or to the Sponsor or a designee. Instructions for the collection and handling of biomarker samples, including sampling procedures, storage conditions, and shipment instructions, are provided in the laboratory manual.

Unless the participant gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 8.11.5) biomarker samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

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. Results of biomarker analyses may be reported outside of the CSR.

8.8 IMMUNOGENICITY ASSESSMENTS

Antibodies to gantenerumab will be evaluated in plasma samples collected from all participants according to the schedule of activities (see Section 1.3).
Additionally, plasma samples should also be collected at the final visit from participants who discontinued study treatment or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Plasma samples will be screened for antibodies binding to gantenerumab and the titer of confirmed positive samples will be reported.

All samples collected for detection of antibodies to study treatment will also be evaluated for gantenerumab plasma concentration to enable interpretation of the antibody data. Samples may be stored for a maximum of 5 years (or according to local regulations) after the final Clinical Study report has been completed at a facility selected by the Sponsor to enable further analysis of immune responses to gantenerumab.

Remaining volumes from these samples may also be used for further characterization of potential immune responses and for any gantenerumab-related exploratory analyses or assay development/validation experiments.

8.9 HEALTH STATUS UTILITY

For all participants throughout the study, the investigator and study site personnel will collect data about health care resource utilization associated with medical encounters.

The data collected will include the reasons and duration of hospitalizations and emergency room visits and exclude procedures, tests, and encounters mandated by the protocol.

The Sponsor may use the collected data to conduct economic analyses.

Exploratory analyses with use of the EQ-5D-5L health states will be defined for each participant at each measurement timepoint according to EuroQol instructions. For more details on the EQ-5D-5L health status evaluation please see Section 8.10.2.9.

The health states will then be converted into a single index value. The index values, presented in country-specific value sets, are a major feature of the EQ-5D instrument, facilitating the calculation of quality-adjusted life-years that are used to inform economic evaluations of healthcare interventions. Note that these exploratory analyses will not be included in the CSR.

8.10 CLINICAL OUTCOME ASSESSMENTS

Performance outcome (PerfO), clinician–reported outcome (ClinRO), Participant-reported outcome (PRO), and observer-reported outcome (ObsRO) measures will be completed to assess the treatment effect of gantenerumab.
In addition, PRO measures will enable the capture of each participant's direct experience with gantenerumab.

- **PerfO data will be collected through use of the following measures**:
  - RBANS
  - PACC-5, including the following 5 subtests:
    1. Logical Memory Immediate + Delayed Recall subtest from the Wechsler Memory Scale (WMS LM I + II)
    2. Free and Cued Selective Reminding Test – Immediate Recall + Delayed Recall (FCSRT–IR + DR)
    3. Coding from the Wechsler Adult Intelligence Scale IV (WAIS–IV Coding)
    4. MMSE
    5. Category Fluency Test (CFT) - 3 categories
- **ClinRO data will be collected through use of the following measures**:
  - CDR
  - AD-CGI-S scale
  - DCF

- **PRO data will be collected through use of the following measures:**
  - CFIa, participant version
  - A-IADL-Q-SV, self-report version
  - GDS–30
  - AD-PGI-S scale
  - EQ-5D-5L
- **ObsRO data will be collected through use of the following measures**:
  - CFIa, study partner version
  - A-IADL-Q-SV study partner version
  - AD-SPGI-S scale
  - EQ-5D-5L Proxy Version 1 (EQ-5D-5L Proxy 1)

8.10.1 Data Collection Methods for Clinical Outcome Assessments

Clinician-reported outcome, PerfO, PRO, and ObsRO measures, translated into the local language as appropriate, will be completed through use of an electronic device provided by the Sponsor via the electronic clinical outcome assessment (eCOA) vendor.
No paper PRO, ObsRO, PerfO nor ClinRO back-up option is allowed in this study.

Potential raters will receive training and be approved by the eCOA vendor prior to being allowed to administer any COAs in the study. These trained raters will administer the measures using the electronic device, which will be distributed to each site.
The electronic device will be pre-programmed to enable the appropriate COAs to be administered in the recommended order and to capture audio recordings of the measures where applicable (e.g., PACC-5 and CDR) at each specified timepoint within the correct time window. According to the endpoint hierarchy, the PACC-5 (primary endpoint) will be prioritized in order to mitigate participant's fatigue. The data will be transmitted to a centralized database maintained by the electronic device vendor and will be subject to an Endpoint Quality Program performed by the eCOA vendor. Audio eCOA recordings will be used for quality assurance purposes. The data will be available for access by appropriate study personnel. Two distinct study rater roles at every site have been created in order to have an independent clinician dedicated to the ClinROs administration (CDR and AD-CGI-S) as defined in Table 9.

The Principal Investigator or a qualified, clinically experienced designee will complete the DCF training at the beginning of the study, and will then be responsible to complete the form at every study visit for each participant at their site. This function should not be delegated to Rater Role 1 (Cognitive/Functional) or Rater Role 2 (Independent) as defined in Table 9.

Table 9 Distinct Study Rater Roles at Sites

Rater Role 1 (Cognitive/Functional)	Type of eCOA	Rater Role 2 (Independent)	Type of eCOA
RBANS	PerfO	CDR	ClinRO
PACC-5	PerfO	AD-CGI-S	ClinRO
CFIa	PRO + ObsRO	–	–
A-IADL-Q-SV	PRO + ObsRO	–	–
AD-PGI-S	PRO	–	–
AD-SPGI-S	ObsRO	–	–
EQ-5D-5L	PRO + ObsRO	–	–
GDS-30	PRO	–	–

AD-CGI-S = Clinician Global Impression of Cognitive Function; AD-PGI-S = Alzheimer's disease Participant Global Impression of Cognitive Function; AD-SPGI-S = Alzheimer's disease Study Partner Global Impression of Cognitive Function; A-IADL-Q-SV = Amsterdam Instrumental Activities of Daily Living Questionnaire Short Version self-report and study partner version; CDR = Clinical Dementia Rating; CFIa = Cognitive Function Instrument acute – participant version and study partner version; ClinRO = clinician-reported outcome; eCOA = electronic clinical outcome assessments; EQ-5D-5L = EuroQol 5-Dimension, 5-Level Questionnaire; GDS-30 = Geriatric Depression Scale; ObsRO = observer-reported outcome; PACC-5 = Preclinical Alzheimer's Cognitive Composite-5; PerfO = performance outcome; PRO = participant-reported outcome; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status.

As much as is feasible, there should be consistency in the trained rater and study partner who complete the measures for each participant throughout the duration of the study. As much as is feasible, the CDR and the AD-CGI-S should be administered to an individual participant by the same rater throughout the study. The CDR rater cannot perform scales other than the CDR and the AD-CGI-S for a study participant.
In addition, efficacy raters should not be involved in study drug administration and safety assessments. Efficacy raters should not receive information about any ARIA findings.

Clinician-reported outcomes and PerfO measures will be completed at the clinic prior to study drug administration at specified timepoints during the study. The AD-CGI-S and DCF may also be administered after study drug administration with the exception of the baseline visit (see schedule of activities in Section 1.3). Clinician-reported outcomes and PerfO measures will be administered by a rater trained for this study by the vendor.

Participant-reported outcomes and ObsRO measures will be rater-administered at the clinic, at specified timepoints during the study and prior to the administration of study treatment with the exception of the AD-SPGI-S (see schedule of activities in Section 1.3).

During clinic visits, PRO and ObsRO measures should be administered as outlined below:

- Participants' health status should not be discussed prior to administration of the instruments
- Sites must administer the official version of each instrument using the study electronic device, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for participants and study partners to complete the instruments
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions
- Participants and study partners should be instructed to answer questions to the best of their ability; there are no right or wrong answers
- Site staff should not interpret or explain questions
- Participants and study partners should not obtain advice or help from others (e.g., family members or friends) when completing the instruments

All cognitive and functional assessments should be performed in the clinic at the visit timepoints indicated in the schedule of activities (Section 1.3). However, in exceptional circumstances for post-randomization visits, if the participant, their study partner or the primary rater cannot perform these assessments as per the schedule of activities, they may be performed within a 28 days' time window (i.e., ±28 days).

8.10.2 Description of Clinical Outcome Assessment Instruments

8.10.2.1 Preclinical Alzheimer's Cognitive Compositive-5

The PACC-5 (Papp et al. 2017) is a rater-administered PerfO composite measure to assess cognitive decline in individuals at risk for or at the earliest stages of AD. It includes the following five components: the Logical Memory Immediate+Delayed Recall subtest from the Wechsler Memory Scale (WMS LM I+II), the Free and Cued Selective Reminding Test Immediate Recall+Delayed Recall (FCSRT–IR+DR), the MMSE, the Coding from the Wechsler Adult Intelligence Scale–IV (WAIS–IV Coding), and the CFT. The selected set of tests provide for a thorough assessment of cognitive domains that are known to likely be affected early in the disease: (1) episodic memory, thereby using 2 different tests for that purpose (a story recall; Logical Memory IIa, as well as a list recall test; FCSRT), (2) attention/speed processing (Coding), and (3) executive function (MMSE and CFT; Papp et al. 2020). The PACC-5 is computed based on z-scores from the five components. More details will be given in the Statistical Analysis Plan (SAP). The components of the PACC-5 are described in more detail as follows.

Mini Mental State Examination

The MMSE is a rater-administered PerfO measure that includes a set of standardized items to assess a participant's cognitive impairment across six domains: orientation,

registration, attention and calculation, short-term recall, language, and constructional praxis/visuospatial abilities (Folstein et al. 1975; Appendix 6). The total score ranges from 0–30, with lower scores indicating greater impairment. The MMSE takes approximately 10–15 minutes to complete.

Free and Cued Selective Reminding Test Immediate Recall+Delayed Recall

The FCSRT–IR+DR is a PerfO measure of verbal episodic memory with use of controlled learning and semantic cueing to assess memory impairment associated with AD (Grober and Buschke 1987; Grober et al. 2018; Appendix 7). The FCSRT–IR+DR begins with a study phase designed to enhance learning and retrieval, enabling a more specific measurement of the characteristic memory impairment of AD (Grober et al. 2010; 2018). The study phase consists of 16 stimulus items from different semantic categories; these are either pictures or words depending on the version used (Grober et al. 2009). Words stimuli will be used in this study. Items are presented in groups of 4 on a card. The participant is given a verbal category cue (e.g., fruit) and the participant selects and names the item on the card that correspond to the cued category (e.g., grape). Once all 4 cued items have been identified, immediate verbal cued recall of the items is tested. This is repeated for the other 3 sets. The study phase is followed by the test phase which consists of 3 recall trials. In each trial the participant must first freely recall as many items as possible. For any items not freely recalled, the participant is tested through cued recall. Free and cued delayed recall is tested after a 30-minute delay, following the same procedure of free and cued immediate recall. The following scores can be derived: free recall (the cumulative sum of free recall from the 3 trials; range: 0–48), total recall (the cumulative sum of free recall+cued recall from the 3 trials, range: 0–48), and Cueing Index (total recall-free recall)/(48-free recall, range: 0.0–1.0), delayed free recall (number of words at the delayed free recall, range: 0–16), and the delayed total recall (sum of delayed free recall+delayed cued recall, range: 0–16). Higher scores indicate better cognitive performance. The FCSRT–IR+DR takes approximately 45–50 minutes to be administered.

Logical Memory Immediate Recall+Delayed Recall

The Logical Memory Immediate Recall+Delayed Recall (WMS LM I+II) subtest from the Wechsler Memory Scale (Wechsler 2008) is an individually administered assessment that measures verbal episodic memory (Appendix 8). The LM consists of 3 parts: Logical Memory Immediate Recall (LM I), Logical Memory Delayed Recall (LM II), and Logical Memory Delayed Recognition. The participant reads through two passages. The LM I requires participants to immediately recall as many details from the passages as they can. The LM II is the same but is administered after a 20–30 minute delay. In LM Recognition, the participant is asked 15 yes/no recognition memory questions about the passages. The number of free recalls and thematic units are recorded for LM I and II. A total raw score for the LM I and LM II is obtained by the sum of the item scores, ranging from 0–25. The score for LM Recognition is determined by how many questions were answered correctly ranging from 0–15. Higher scores indicate less cognitive impairment. The total raw scores can be converted into subtest scaled scores

with mean of 10 and standard deviation of 3 with use of the conversion table. The LM takes approximately 30 minutes to complete.

Coding

Coding is a performance-based outcome measure used to assess associative learning, motor speed, attention and visuoperceptual functions and is a subtest of the Wechsler Adult Intelligence Scale IV (WAIS–IV; Wechsler 1939; 2008; Jaeger 2018; Appendix 9). The test requires the participant to match certain symbols to numbers based on a given key. They must correctly match as many as they can within the time limit of 120 seconds. The number of correct symbols within the allowed time constitutes the score, with higher scores indicating better performance. It takes approximately 5 minutes to complete the test.

Category Fluency

Verbal fluency is the ability to generate words under certain stimulus constraints (e.g., letter, category). The category verbal fluency (e.g., animals) is a PerfO measure assessing speed and flexibility of verbal thought (Appendix 10). Verbal fluency tests are sensitive tools for detecting dementia (Pasquier et al. 1995; Lezak et al. 2004) and for monitoring cognitive decline over time (Clark et al. 2009). They imply to give a category to the subject (e.g. animals, fruits, vegetables). The principle of the verbal fluency task is always the same: the participant is given 60 seconds to generate as many words starting with the given letter (letter/phonemic fluency) or pertaining to the given category (category/semantic fluency). Total score is determined by how many words are correctly given and higher scores indicate better cognitive performance.

8.10.2.2 Clinical Dementia Rating Scale

The CDR (Morris 1993) is a ClinRO measure used to stage the severity of AD dementia based on a semi-structured interview with the participant and a reliable informant (e.g., caregiver/study partner; Appendix 11). The CDR characterizes the participant's level of cognitive and functional impairment across six domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care) on a 5-point rating scale in which 0 = "None", 0.5 = "questionable", 1 = "mild", 2 = "moderate", 3 = "severe" (with the exception of personal care, which is rated on a 4-point rating scale and excludes the questionable impairment level).

Two scores can be generated; the CDR-GS and the CDR Sum of Boxes (CDR-SB). The CDR-GS is calculated based on the Washington University CDR-assignment algorithm and characterizes a participant's level of global impairment/stage of dementia according to the following categories: 0 (normal), 0.5 (very mild dementia), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia). The CDR-SB is calculated by summing the ratings across each of the six domains (total score: 0–18), with higher scores indicating greater impairment. The CDR-SB score is a detailed quantitative general index that provides more information than the CDR-GS in participants with mild dementia (Berg 1988; Morris et al. 2001; O'Bryant et al. 2010).

Administration of the CDR should be undertaken by a trained clinician and takes approximately 60 minutes to complete (approximate 20-minute interview with the participant and approximate 40-minute interview with the study partner).

8.10.2.3 Amsterdam Instrumental Activity of Daily Living Questionnaire Short Version

The A-IADL-Q-SV (Jutten et al. 2017) is an ObsRO measure designed to assess a participant's ability to perform instrumental activities of daily living (including household/leisure activities, use of household appliances, management of finances, etc.) in early stages of AD (Appendix 12 [participant] and Appendix 13 [study partner]). The A-IADL-Q-SV includes 30 items rated by the study partner/caregiver, with each item divided into 2 questions; the initial question asks whether the activity was performed by the participant during the past 4 weeks ("Yes", "No", "Don't know"). If the activity was performed, the second question captures the level of difficulty experienced while performing the activity on a 5-point Likert scale ("no difficulty" to "no longer able to perform the activity"). If the activity was not performed, the second question captures why the activity was not performed ("never done before", "no longer able to do so due to physical problems", "no longer able to do so due to difficulties with memory, planning, or thinking", or "other", including a free text response). If the response option "Don't know" is selected for the initial question, no follow-up question is administered and the item is scored as missing. The total score for the A-IADL-Q-SV is calculated as a weighted average or with use of item response theory methods, with higher scores indicating better functioning. The A-IADL-Q-SV takes approximately 15 minutes to complete. The self-report (PRO) version of the A-IADL-Q-SV will also be used in this study and will be completed by the study participant.

8.10.2.4 Cognitive Function Instrument acute

The CFIa (Walsh et al. 2006; Amariglio et al. 2015; Li et al. 2017), is an outcome measure developed to assess memory-related cognitive and functional decline in non-demented elderly individuals (Appendix 14 [participant] and Appendix 15 [study partner). The CFIa is a modified version of the original CFI (Walsh et al. 2006), and differs in terms of recall period and item response options. The CFIa consists of 14 items, rated on a 5-point Likert scale ranging from "Never" to "Always" and referring to the participant's current ability (most recent experience). The CFIa takes approximately 10 minutes to complete. A total sum score is calculated with higher scores indicating greater cognitive impairment. The participant (PRO) and study partner (ObsRO) versions of the CFIa will be used in this study. The CFIa participant version will be completed by the study participant, while the CFIa study partner version will be completed by the study partner.

8.10.2.5 Geriatric Depression Scale-30

The GDS-30 is a PRO measure, developed by Yesavage et al. (1983; Appendix 16) as a screening instrument to measure depression in older adults. The GDS includes 30 items

relating to sad mood, lack of energy, positive mood, agitation, and social withdrawal (Sheik et al. 1991). Items are rated on a dichotomous scale ("yes"/"no") with a recall period "over the past week". The total score ranges from 0–30, with higher scores indicating greater depression. A score between 0 and 9 is considered normal, a score between 10 and 19 indicates mild depression, and a score between 20 and 30 indicates severe depression. The GDS-30 takes approximately 10 minutes to complete.

8.10.2.6 Clinician Global Impression of Cognitive Function

The AD-CGI-S is a ClinRO global impression of severity measure designed to assess the impact of cognitive impairment on daily function (Appendix 17). This study-specific AD-CGI-S was developed in house by the Sponsor for use in clinical trials assessing those at risk for or at the earliest stages of AD (Guy 1976). The AD-CGI-S consist of a single item, asking the clinician to rate the severity of their cognitive problems and their impact on the participant's ability to perform daily activities at this time (current status). The item includes six response categories ranging from "no problems" to "severe cognitive problems and functionally dependent in daily activities inside and outside home". The item is scored from 0–5 with higher scores indicating more severe cognitive and functional problems. This AD-CGI-S takes approximately 5 minutes to complete.

8.10.2.7 Participant Global Impression of Cognitive Function

The AD-PGI-S is a self-reported (PRO) global impression of severity measure designed to assess the impact of cognitive impairment on daily function (Appendix 18).
This study-specific AD-PGI-S was developed in house by the Sponsor for use in clinical trials assessing those at risk for or at the earliest stages of AD (FDA 2018b).
The AD-PGI-S consist of a single item, asking the participant to rate the severity of their cognitive problems and their impact on the participant's ability to perform daily activities over the past 7 days (recall period). The item includes six response categories ranging from "no problems" to "severe thinking problems that mean I rely on someone for daily activities inside and outside of my home". The item is scored from 0–5 with higher scores indicating more severe cognitive and functional problems. This AD-PGI-S takes approximately 5 minutes to complete.

8.10.2.8 Study Partner Global Impression of Cognitive Function

The AD-SPGI-S is a study partner-reported (ObsRO) global impression of severity measure designed to assess the impact of cognitive impairment on daily function (Appendix 19). This study-specific AD-SPGI-S was developed in house by the Sponsor for use in clinical trials assessing those at risk for or at the earliest stages of AD (FDA 2018b). The AD-SPGI-S consists of a single item, asking the study partner to rate the severity of their cognitive problems and their impact on the participant's ability to perform daily activities over the past 7 days (recall period). The item includes six response categories ranging from "no problems" to "severe thinking problems that mean he/she relies on someone for daily activities inside and outside of his/her home".
The item is scored from 0–5 with higher scores indicating more severe cognitive and functional problems. This AD-SPGI-S takes approximately 5 minutes to complete.

8.10.2.9 EuroQol EQ-5D-5L

The EQ-5D-5L is a widely used measure to assess health status (EuroQol Group 1990; Appendix 20). There are 2 parts to the EQ-5D-5L which asks the individual to select a response that best describes their health 'today'. The first part consists of a 5-item health state profile used to assess mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Items are rated on a 5-point Likert scale ranging from 1 (no problems) to 5 (extreme problems/unable to do). The second part consists of a visual analogue scale (VAS) that measures health state ranging from 0 (worth health imaginable) to 100 (best health imaginable). A total index value can be calculated with use of published weighting (EuroQoL website) typically ranging from 0 (equivalent to dead; negative values representing worse than dead) to 1 (full health). The EQ-5D-5L takes approximately 5 minutes to complete and will be used in this study for informing pharmacoeconomic evaluations. The EQ-5D is a family of instruments to describe and value health.

The following 2 versions are used in this study:

- EQ-5D-5L interview-administered proxy version 1 (ObsRO): the study partner (the proxy) is asked to rate the participant's health-related QoL in his/her (the proxy's) opinion (Appendix 21)
- EQ-5D-5L, interview-administered version (PRO): the participant is asked to rate his or her own health-related QoL

8.10.2.10 Repeatable Battery for the Assessment of Neuropsychological Status

The RBANS (Randolph 1998) is a rater-administered PerfO measure (Appendix 22). It is a standardized brief neurocognitive battery that has undergone population-based norming in North America for individuals aged 12–89 years. There are twelve subtests across five domains: immediate memory (list learning and story memory), visuospatial/constructional (figure copy and line orientation), language (picture naming and semantic fluency), attention (digit span and coding), delayed memory (list recall, list recognition, story memory, and figure recall). A total scale index score is calculated. These index scores are age-based, with a normal mean of 100 and standard deviation of 15 (which corresponds to one standard deviation) based on the scale normative data. Lower scores indicate higher cognitive decline. It takes approximately 30 minutes to complete.

8.10.2.11 Diagnostic Classification Form

The DCF (Appendix 23) is a ClinRo that is designed to capture the study participant's diagnostic status at each clinic visit within the study by the Principal Investigator (or designee) at the site. If there is a change in diagnosis from the previous visit (e.g., change from "cognitively unimpaired" to "MCI due to AD"), supporting information for the change in diagnosis will need to be captured in the body of the form.

8.11 ADDITIONAL ASSESSMENTS AND PROCEDURES REQUIRING SEPARATE CONSENT AT PARTICIPATING SITES

8.11.1 Optional Blood-Based Biomarker Prescreening

Evidence of abnormal cerebral amyloid deposition is expected to be present in approximately 15%–30% cognitively unimpaired individuals aged 60–80 years (Jansen et al. 2015). Therefore, the screen failure rate based on the amyloid inclusion criterion is expected to be around 85% in Study WN42444.

In order to enable a more efficient and less burdensome screening process, sites, where approved, and participants will have the opportunity to participate in BBBM prescreening. For more details on the optional blood-based biomarker prescreening process please see Section 4.1.1.

Collection and submission of the prescreening blood samples for biomarker testing is contingent upon the review and approval by each site's IRB or EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval to use the BBBM prescreening, this part of the protocol will not be applicable at that site.

Approximately 20 mL (equivalent to 1–1.5 tablespoons) of blood will be collected during prescreening, processed and sent to a central laboratory to test for biomarkers that may help to indicate levels of amyloid the participant's brain and to evaluate the likelihood of a participant to meet the amyloid-based inclusion criteria for Study WN42444. The blood samples collected at prescreening, along with the associated information provided (date of birth, sex, and whether the participant has ever been diagnosed with cognitive impairment) may also be used for future research related to Alzheimer's disease, common pathways among diseases and/or the development of tests or tools that help with detecting or understanding Alzheimer's disease, even if the participant is not eligible for or decides not to take part in Study WN42444, unless the participant specifically asks for the samples to be destroyed.

Instructions for the collection and handling of biomarker samples, including sampling procedures, storage conditions, and shipment instructions, are provided in the laboratory manual.

Unless the participant gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 8.11.5) biomarker samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

Due to the experimental nature of the assay, results for the BBBM prescreening test will not be returned to participants or sites. To further mask the results of the experimental BBBM prescreening test, approximately 10% of participants who are identified to be less likely to meet the amyloid-based inclusion criteria for Study WN42444, will also be invited to continue with the main study screening procedures.

See Section 8.7 for information on availability of data from biomarker analyses.

8.11.2 Optional Longitudinal Amyloid PET Imaging (Only for Participants Who Enrolled via Amyloid PET at Screening)

8.11.2.1 Participants

Participants will be eligible for this assessment if they are eligible for the main study and have had an amyloid PET scan assessment at screening with use of [^{18}F]-Florbetaben ([^{18}F]-Flutemetamol is permitted in Japan only) during screening. Participation in both the optional amyloid and tau PET longitudinal assessments is encouraged but subject to local radiation limits.

Participants that enrolled in the study by providing an off-protocol PET scan are not eligible for the optional longitudinal amyloid PET assessments.

The planned number of participants for the longitudinal amyloid PET assessment is approximately 400 participants.

8.11.2.2 Design

For the longitudinal amyloid PET assessments, only florbetaben will be used in all countries except Japan, where use of [^{18}F]-Flutemetamol will also be permitted at sites without access to [^{18}F]-Florbetaben. Participants who will be assessed with [^{18}F]-Flutemetamol will not be accounted for in the 400-participant target sample size. Moreover, the same PET tracer ([^{18}F]-Florbetaben or [^{18}F]-Flutemetamol) has to be used for the same participant throughout all longitudinal amyloid PET assessments.

Each participant will receive up to 5 injections of amyloid radioligands (including 1 injection at screening) and will undergo an amyloid PET scan after each injection. Participants will undergo an amyloid PET scan (see Section 1.3).

A minimum of 10 half-lives is required between the 2 tracer injections (i.e., a minimum of 18 hours must elapse between injections) for those who are participating in both, longitudinal amyloid PET and tau PET assessments. Therefore, it is not possible to perform the amyloid and tau PET scans on the same day.

8.11.2.3 Preparation and Administration of the Radioligand

8.11.2.3.1 [^{18}F]-Florbetaben Injection and Administration

The recommended dose of florbetaben is 300 MBq (8.1 mCi, effective radiation dose 5.8 mSv), with a maximum 30 μg mass dose, administered to participants as a single slow IV bolus within 40 seconds in a total volume of up to 10 mL. Injection into a large vein is recommended, followed by a flush with approximately 10 mL of 0.9% sterile sodium chloride. In countries where [^{18}F]-Florbetaben PET radioligand is approved for marketing, see the approved local product information for more information. In countries where the [^{18}F]-Florbetaben PET radioligand is not approved for marketing, the [^{18}F]-Florbetaben Investigator's Brochure will be provided.

8.11.2.3.2 Flutemetamol Injection and Administration

The recommended dose of [^{18}F]-Flutemetamol is 185 MBq (5.0 mCi, effective radiation dose 5.9 mSv), with a maximum of 20 μg mass dose, administered to participants as a single slow IV bolus at 6 seconds/mL in a total volume of up to 10 mL. Injection into a large vein is recommended, followed by a flush with approximately 5–15 mL of 0.9% sterile sodium chloride. In countries where [^{18}F]-Flutemetamol PET radioligand is approved for marketing, for more information see the approved local product information. In countries where the [^{18}F]-Flutemetamol PET radioligand is not approved for marketing, the Investigator's Brochure will be provided.

[^{18}F]-Florbetaben or [^{18}F]-Flutemetamol will be provided in accordance with approved national and/or local standards. For additional information on amyloid radioligands, refer to their respective Investigator Brochures and to the Technical Operations Manual.

8.11.2.4 Amyloid PET-Specific Assessments

Detailed procedures for participant preparations and amyloid PET data collection are specified in the amyloid PET Technical Operations Manual. Key aspects of the amyloid PET examination include:

- The PET scan should not be performed if the participant has an ongoing ARIA-E
- For women of childbearing potential (including those who have had a tubal ligation), a urine pregnancy test will be conducted within 24 hours before the PET scan

  The result must be negative for the participant to receive the amyloid tracer.
- At selected sites that can support dynamic imaging and imaging starting at the time of tracer injection, an early-frame PET scan of up to 60 minutes in length will be acquired as soon as the injection is completed to allow assessment of cerebral perfusion. The initial scan will be followed by another 20-minute scan (as described below) with a short break in between.
- A 20-minute amyloid brain PET scan will be acquired after an uptake period targeting 90 minutes for florbetaben and flutemetamol
- Further acquisition details, including allowable deviation from target uptake time, participant preparation, required computed tomography (CT), transmission or MRI scans used for attenuation correction are described in the PET Technical Operations Manual

8.11.2.5 Imaging Processing and Analysis

The Sponsor in conjunction with the imaging Contract Research Organization (CRO) will prepare and distribute a detailed scanning manual for image acquisition and reconstruction procedures and parameters for each center prior to the start of the study. All imaging data will be transferred to the imaging CRO for quality control, qualitative image assessment, and quantitative image analysis as documented in the amyloid PET Technical Operations Manual.

8.11.3 Tau PET Imaging

8.11.3.1 Participants

Participants will be eligible for optional longitudinal tau PET assessments if they are eligible for the main study. The planned number of participants for the optional longitudinal tau PET is 600 participants. Participation in both the amyloid and tau PET longitudinal assessments is encouraged but subject to local radiation limits.

8.11.3.2 Design

Each participant will receive up to 5 injections of [^{18}F]–MK-6240 in this optional longitudinal PET assessment and will undergo a PET scan after each injection. Participants will undergo an [^{18}F]–MK-6240 PET scan (see Section 1.3).

Enrollment in the longitudinal tau PET assessment does not preclude enrollment in other longitudinal assessments. Given that participants enrolled in this study may also participate in the longitudinal amyloid PET assessment, a minimum of 10 half-lives is required between 2 tracer injections (i.e., 18 hours must elapse between injections) for those who are participating in both longitudinal amyloid and tau PET assessment. Therefore, it is not possible to perform the amyloid and tau PET scans on the same day.

8.11.3.3 Preparation and Administration of [18F]–MK-6240

According to E.U. guidance, [^{18}F]–MK-6240 as used in the context of this study is considered a non-IMP in the E.U. In some regions, according to local regulations, [^{18}F]–MK-6240 may be considered an IMP.

[^{18}F]–MK-6240 Injection and Administration

The recommended dose of [^{18}F]–MK-6240 is 185 MBq (5 mCi, effective radiation dose 5.4 mSv), with a maximum 20 μg dose, administered to participants as a single IV bolus. Injection into a large vein is recommended, followed by a flush with approximately 10 mL of sterile saline flush.

The [^{18}F]–MK-6240 injection will be provided in accordance with approved national and/or local standards. For additional information, refer to the respective Investigator Brochures and to the Technical Operations Manual.

8.11.3.4 Tau PET-Specific Assessments

Detailed procedures for participant preparations and [^{18}F]–MK-6240 tau PET data collection are specified in the Tau PET Technical Operations Manual. Key aspects of the tau PET examination include:

- The PET scan should not be performed if the participant has an ongoing ARIA-E

- For women of childbearing potential (including those who have had a tubal ligation), a urine pregnancy test will be conducted within 24 hours before the PET scan

  The result must be negative for the participant to receive the amyloid tracer.
- A 20-minute tau brain PET scan will be acquired after an uptake period targeting 90 minutes
- Further acquisition details, including allowable deviation from target uptake time, participant preparation, required CT, transmission or MRI scans used for attenuation correction are described in the PET Technical Operations Manual

8.11.3.5 Imaging Processing and Analysis

The Sponsor in conjunction with the imaging CRO will prepare and distribute a detailed scanning manual for image acquisition and reconstruction procedures and parameters for each center prior to the start of the study. All imaging data will be transferred to the imaging CRO for quality control, qualitative image assessment, and quantitative image analysis as documented in the Tau PET Technical Operations Manual.

8.11.4 Optional Longitudinal Cerebrospinal Fluid Sampling (Only for Participants Enrolled via CSF at Screening)

Participants who provide a CSF sample during screening (i.e., CSF-enrolled participants) can participate in optional longitudinal CSF sampling for monitoring Aβ and tau levels, PK measurements as well as other CSF biomarkers.

Each participant will undergo a total of up to 4 CSF sample collections (see Section 1.3). The planned number of participants for the optional longitudinal CSF sampling is approximately 400 participants.

Cerebrospinal fluid will be collected via LP by an individual who meets all local requirements and is proficient in the procedure. Cerebrospinal fluid sampling and post-LP care will be performed in accordance with local practice. All CSF sampling should be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variability of CSF biomarkers.

Approximately 12 mL of CSF will be collected at each timepoint. The sample will be divided into aliquots onsite and used for the following:

- Biomarker analysis, including, but not limited to: $A\beta_{1-42}$, $A\beta_{1-40}$, tTau, pTau, and NfL
- Measurement of gantenerumab levels in the CSF
- Samples may also be used to support the development of biomarker assays for diagnostic use

Cerebrospinal fluid samples will be sent to one or several central laboratories or to the Sponsor or a designee. Instructions for the collection and handling of biomarker samples, including sampling procedures, storage conditions, and shipment instructions, are provided in the laboratory manual.

Cerebrospinal fluid samples, including those collected from individuals who do not enroll in the study, may be used for future research and/or development of disease-related tests or tools.

Unless the participant gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 8.11.5), biomarker samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

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.

8.11.5 Overview of the Research Biosample Repository and External Research Entities

The Research Biosample Repository (RBR) is a centrally administered group of facilities managed by Roche and 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 patients in the future.

Samples for the RBR will be collected from participants who give specific consent to participate in this optional research. Roche is planning to also collaborate with external research entities (e.g., the National Centralized Repository for Alzheimer's Disease and Related Dementias [NCRAD] and the Alzheimer's Therapeutic Research Institute [ATRI]). Some of the RBR samples will be shared with these external research entities that will store and use them for the same type of research activities.

Alongside samples, the information collected from the participants during the trial may also be shared with the external research entities, but only after personal information that can identify the participant has been removed. Participants of the optional BBBM prescreening may give a separate consent to participate in this optional long-term storage, regardless of whether they enroll in Study WN42444 or not.

The RBR 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

8.11.5.1 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 8.11.5) will not be applicable at that site.

8.11.5.2 Sample Collection

The following samples will be stored in the RBR and external research entities (e.g., NCRAD, ATRI) and used for research purposes, including, but not limited to, research on biomarkers related to gantenerumab, diseases, or drug safety:

- Leftover blood from the clinical genotyping sample, BBBM prescreening sample, plasma biomarker sample, CSF samples and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole-genome sequencing, whole-exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. Whole-genome sequencing and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which participants are more likely to respond to a drug or develop adverse events.

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.

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

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

8.11.5.3 Data Protection, Use, and Sharing

The RBR samples, as well as their associated data will be labeled with a unique participant identification number.

Participant's information associated with RBR samples is confidential and may only be disclosed to third parties 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.

Data generated from RBR samples will be analyzed in aggregate rather than on an individual participant basis. Thus, there will be no identification and reporting of incidental findings to investigators or participants. In addition, 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, with the exception of data generated from blood samples collected for WGS or WES as described below.

If permitted by local law, a patient may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a participant wishes to access these data, the investigator must inform the Sponsor, using the following e-mail address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file, but will not provide any interpretation of the data. The investigator should not include the data file in the participant's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

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 and external research entities (e.g., NCRAD, ATRI) data will become and remain the exclusive and unburdened property of the Sponsor or the external research entities (e.g., NCRAD, ATRI), except where agreed otherwise.

8.11.5.4 Consent to Participate in the Research Biosample Repository

The ICFs for the main study and the optional prescreening will contain a separate section that addresses participation in the RBR with the samples collected during prescreening and the main study screening regardless of whether they enroll in the main study or not. 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 choose not to provide optional RBR samples 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 choose not to provide optional RBR samples will not provide a separate signature. The investigator should document whether or not the participant has given consent to provide optional RBR samples and (if applicable) the date of consent, by completing the Sample Informed Consent/Withdrawal 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 and external research entities (e.g., NCRAD, ATRI) research.

8.11.5.5 Withdrawal from the Research Biosample Repository

Participants who give consent to provide RBR samples have the right to withdraw their consent for their prescreening samples and/or their main study samples at any time for any reason. After withdrawal of consent, any remaining prescreening samples and/or main study samples will be destroyed. 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 Participant Withdrawal Form and must enter the date of withdrawal on the Sample Informed Consent/Withdrawal 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 e-mailing the study number and participant number to the following e-mail 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.

8.11.5.6 Monitoring and Oversight

The RBR 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 an individual's 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.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will follow the estimand framework. More details on the statistical analyses will be provided in the SAP. In the event of any discrepancy between this protocol and the SAP, the SAP prevails.

9.1 STATISTICAL HYPOTHESES

The change from baseline to Year 4 in cognition, as measured by the PACC-5 score will be the primary endpoint as defined in Section 3.

The primary efficacy analysis will compare the change from baseline to Year 4 in the PACC-5 between the experimental and control arms.

The null and alternative hypotheses for the primary endpoint are as follows:

- H_0 (null hypothesis): there is no difference in the change from baseline to Year 4 in the PACC-5 between the experimental and control arms
- H_1 (alternative hypothesis): there is a difference in the change from baseline to Year 4 in the PACC-5 between the experimental and control arms

9.2 SAMPLE SIZE DETERMINATION

In this study, approximately 1200 participants will be enrolled and randomized in a 1:1 ratio to each study arm. The study is powered to compare the change from baseline to Year 4 in the PACC-5 between the experimental and control arms. Assuming a 35% dropout rate at Year 4, two-sided testing at the overall 0.05 level, a control arm coefficient of variation (CV) of 1.99 for the Year 4 change scores (=standard deviation of control participant change scores/mean of control participant change scores) and 600 participants per arm, the study will have at least 80% power to detect a true effect of 40% reduction of the mean PACC-5 decline in the control arm.

The assumption for the control arm CV is based on data from a population with similar inclusion and exclusion criteria in 4 observational cohorts (ADNI, AIBL; Biomarkers for Identifying Neurodegenerative Disorders Early and Reliably Study [BioFINDER], HABS).

An increase in sample size and/or duration of the study may be considered if factors external to the study or blinded study data analysis warrant a change to the sample size assumption. As a result, the sample size may be increased from 1200 up to 1800 participants (900 participants per arm). Further details will be described in the SAP. The assessment will be performed by the Sponsor at a specified timepoint. The Sponsor will remain blinded and the sample size will not be reduced on the basis of this assessment.

The planned number of participants who take part in the optional longitudinal amyloid PET assessment is approximately 400 participants (200 participants per study arm). The planned number of participants was selected primarily based on practical feasibility.

The planned number of participants who take part in the optional longitudinal tau PET assessment is approximately 600 participants (300 participants per study arm). The planned number of participants was selected primarily based on practical feasibility. Subject to operational feasibility, this number may be increased to a maximum of 800 participants (400 participants per study arm).

The planned number of participants who take part in the optional longitudinal CSF assessment is approximately 400 participants (200 participants per study arm). The planned number of participants was selected primarily based on practical feasibility and not based on power calculations.

9.3 ANALYSIS SETS

The analysis sets are defined in Table 10.

Table 10 Analysis Sets and Description

Participant Analysis Set	Description
All Randomized Participants	All participants randomly assigned to study treatment
Safety	All participants randomly assigned to study treatment and who receive at least 1 dose of study drug

All analyses will be performed on the all randomized participant population, unless specified otherwise.

All safety analyses will be performed on the safety population and participants will be grouped according to the treatment they actually received. For all efficacy analyses, participants will be grouped according to the treatment assigned at randomization.

9.4 STATISTICAL ANALYSES

The SAP will be finalized prior to the locking and unblinding of the study database, and it will include a more technical and detailed description of the statistical analyses described in this section.

In particular, supplementary estimands and details concerning the estimand strategy will be defined in the SAP, as well as any sensitivity analyses to the estimands of study endpoints, and any pre-specified subgroup analyses.

The following sections present the planned statistical analyses of the most important endpoints, including the primary endpoint.

9.4.1 General Considerations

In addition to the analyses detailed in the following sections, study results will be presented by study arm (with total when appropriate) and summarized according to the type of the variables:

- For continuous variables, using descriptive statistics such as the mean, standard deviation, median, and range, as appropriate, including the number of participants contributing to these statistics
- For categorical variables, using the frequency and proportion of participants falling into each category, grouped by study arm (and total). The percentages reported in these tables will be rounded; therefore, may not always sum to 100%.

The type I error will be controlled at a 2-sided 0.05 level for multiplicity across the primary and confirmatory secondary endpoints. The confirmatory secondary endpoints, a subset of the secondary endpoints described in Section 3, will be specified in the SAP.

9.4.2 Primary Endpoint

9.4.2.1 Primary Estimand

The change from baseline to Year 4 in cognition, as measured by the PACC-5 score is the primary endpoint.

If a participant withdraws from study treatment, the reason for withdrawal will be classified as either study drug or condition-related (SDCR) or not study drug or condition-related (NSDCR). More details of this classification will be given in the SAP.

The primary comparison of interest is the difference between the experimental and control arms in the change from baseline to Year 4 in cognition, as measured by the PACC-5 score. The primary comparison will be made regardless of whether:

- A participant initiates a symptomatic treatment for AD (e.g., acetylcholinesterase inhibitors and memantine) after progression to dementia due to AD as determined by the iCAC
- A participant has a treatment interruption due to ARIA-E or safety reasons (e.g., short-term anticoagulation)
- A participant withdraws from the study treatment due to a SDCR reason

Further, the primary comparison will be made in the hypothetical scenario that a NSDCR withdrawal from the study treatment would not have occurred.

Note that the control arm will contain both participants who do not meet the clinical progression criteria and remain on placebo throughout the duration of the study and participants who meet the clinical progression criteria and initiate active gantenerumab at the time of the clinical progression.

The elements of the primary estimand as per the estimand framework introduced in the ICH-E9 (R1) addendum (ICH 2019) as well as the intercurrent events and the handling strategies are defined in Table 11. A full list of intercurrent events will be specified in the SAP.

Table 11 Primary Estimand and Estimand Framework

Primary Estimand	Estimand Framework
Population	Participants at risk for or at the earliest stages of AD as defined by the study inclusion and exclusion criteria
Primary efficacy variable	Change from baseline to Year 4 in the PACC-5
Treatment	Gantenerumab treatment with a target dose of 255 mg Q1W or 510 mg Q2W versus placebo followed by gantenerumab upon the diagnosis of MCI or dementia due to AD by the iCAC
Summary measure	The difference in variable means between study arms
Intercurrent events	• SDCR withdrawal from study treatment: a treatment policy strategy will be applied • NSDCR withdrawal from study treatment: a hypothetical strategy will be applied • Treatment interruption due to ARIA-E or safety reasons: a treatment policy strategy will be applied • Initiation of symptomatic treatment for AD (e.g., acetylcholinesterase inhibitors and memantine) after progression to dementia due to AD as determined by the iCAC: a treatment policy strategy will be applied A full list of intercurrent events will be specified in the SAP.

AD = Alzheimer's disease; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; iCAC = independent Clinical Adjudication Committee; MCI = mild cognitive impairment; NSDCR = not study drug or condition-related; PACC-5 = Preclinical Alzheimer's Cognitive Composite-5; Q1W = every 1 week; Q2W = every 2 weeks; SAP = Statistical Analysis Plan; SDCR = study drug or condition-related.

9.4.2.2 Primary Estimator

The difference in mean change from baseline to Year 4 in the PACC-5 will be estimated with use of a longitudinal data model adjusting for the randomization stratification factors. Formal statistical testing of the difference between the two arms will be performed for the Year 4 visit. When applying the treatment policy strategy, all the available data will be included in the analysis. When applying the hypothetical strategy, data will be censored at the time of the intercurrent events (i.e., NSDCR withdrawal from study treatment) and data after the intercurrent events will be imputed. The imputation rules will be described in the SAP.

9.4.3 Secondary Endpoints

The secondary endpoints are described in Section 3. The confirmatory secondary endpoints, a subset of the secondary endpoints described in Section 3, will be specified in the SAP.

A multiple testing procedure will be applied to adjust for multiple statistical testing of the confirmatory secondary endpoints. The overall type I error rate will thereby be controlled. Details about the multiple statistical testing procedure will be given in the SAP.

The remaining secondary endpoints will not be adjusted for multiple testing.

The following continuous secondary efficacy endpoints will be analyzed in the same way as the primary efficacy endpoint:

- Change from baseline to Year 4 in cognitive functional activities of daily living, as measured by the CFIa and the A-IADL-Q-SV
- Change from baseline to Year 4 in cognition and function, as measured by the CDR-SB

The following time to event secondary efficacy endpoints will be analyzed with use of an estimand whose elements, as per the estimand framework introduced in the ICH-E9 (R1) addendum (ICH 2019), will be described in the SAP:

- Time to onset of confirmed clinical progression, defined as the time from randomization to the first occurrence of 2 consecutive visits (approximately 6 months apart) with a CDR−GS$>$0
- Time from randomization to clinical progression to MCI or dementia due to AD based on the diagnosis of the independent Clinical Adjudication Committee (iCAC)

The comparison of interest is between the experimental and control arms.

The appropriate statistical methods for time to event secondary efficacy endpoints will be described in the SAP and could include, for example, Cox proportional hazards regression.

9.4.4 Safety Endpoints

Safety will be assessed through descriptive summaries of the endpoints listed in Table 7.

9.4.5 Other Analyses

9.4.5.1 Summaries of Conduct of Study

The number of participants who enroll, discontinue, or complete the study will be summarized by study arm. Reasons for premature study withdrawal and study treatment discontinuation will be listed and summarized. Intercurrent events will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

9.4.5.2 Summaries of Demographics and Baseline Characteristics

Demographics and baseline characteristics (including age, sex, race, *APOE* ε4 status) will be summarized by study arm. The baseline value will be defined as the last available value recorded prior to the initiation of study treatment. Descriptive statistics (mean, standard deviation, median, and range) will be presented for continuous variables and counts and percentages will be presented for categorical variables.

9.4.5.3 Pharmacokinetic Analyses

Plasma concentration data for gantenerumab will be tabulated and summarized. Descriptive summary statistics will include the arithmetic mean, median, range, standard deviation, and CV, as appropriate. Because a sparse PK sampling design is being used, population (nonlinear mixed-effects) modeling will be used to analyze the dose concentration-time data of gantenerumab. Information from other clinical studies may be incorporated to establish the PK model. The selection of parameters and the derivation of individual measures of exposure, such as area under the concentration-time curve (AUC), C_{max}, and trough concentration, will depend on the final PK model used for this analysis. The results of this modeling analysis may be reported separately in the Clinical Study Report.

Cerebrospinal fluid concentrations of gantenerumab will be tabulated and summarized as appropriate.

The influence of background medication on the pharmacokinetics of gantenerumab will be explored and, if appropriate, concentration-effect relationships may be assessed post-hoc for PD, efficacy, immunogenicity or safety measures.

Additional PK analyses will be conducted as appropriate and may be reported separately in the CSR.

9.4.5.4 Immunogenicity Analyses

The numbers and proportions of ADA-positive participants and ADA-negative participants at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be summarized for participants exposed to gantenerumab. When determining post-baseline incidence, participants are considered to be ADA-positive if they are ADA-negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA-positive at baseline and the titer of 1 or more post-baseline samples is at least 4–fold higher in comparison to the titer at the baseline (treatment-enhanced ADA response). Participants are considered to be ADA-negative if they are ADA-negative or have missing data at baseline and all post-baseline samples are negative, or if they are ADA-positive at baseline but do not have any post-baseline samples with a titer that is at least 4–fold greater than the titer of the baseline sample (treatment-unaffected ADA response).

The relationship between ADA status and safety, efficacy, pharmacokinetics, and biomarker endpoints may be analyzed and reported via descriptive statistics.

9.5 INTERIM ANALYSIS

9.5.1 Optional Interim Analysis

Based on availability of information pertaining to gantenerumab or other compounds with a similar mode of action that may emerge during the course of this study, the Sponsor may choose to conduct an interim analysis once participants have completed at least 2 years of treatment.

An independent data coordinating center will be responsible for the interim analysis and study results will only be reviewed by the iDMC. The Sponsor will remain blinded. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter. Details of the interim analysis, including the decision to conduct the optional interim analysis, the rationale, timing, and statistical details for the analysis (such as the data that would be reviewed by the iDMC and futility or efficacy thresholds) will be documented in the SAP, and the SAP will be submitted to relevant health authorities as required at least 2 months prior to conducting the interim analysis.

9.6 INDEPENDENT DATA MONITORING COMMITTEE

A formal iDMC will be used for this study. The iDMC will be unblinded and evaluate participant safety and select efficacy on a regular basis. In addition to the data defined in the iDMC Charter (e.g., the incidence, severity, and nature of adverse events, serious adverse events, ARIA-E and ARIA-H, ISRs, adverse events of special interest, and the MMSE), the iDMC will review all necessary cumulative data at regular intervals during the study, including further efficacy data when needed.

The frequency of these assessments is specified in the iDMC Charter. At the time of each review, the iDMC will make appropriate recommendations (e.g., the study should continue as planned, enrollment in a specific arm should be discontinued, the treatment regimen should be modified, the protocol should be amended, and enrollment should be held pending further safety evaluations). The iDMC will also evaluate planned or unplanned interim analyses for efficacy or futility.

Decisions will be made in consideration of the totality of the available data.
Ad-hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues.
Specific operational details such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities are detailed in the iDMC Charter.

Final decisions will rest with the Sponsor.

REFERENCES

Aizenstein HJ, Nebes RD, Saxton JA, et al. Frequent amyloid deposition without significant cognitive impairment among the elderly. Arch Neurol 2008;65:1509–17.

Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging and Alzheimer's Association Workgroup. Alzheimer's Dement 2011;7:270–9.

Amariglio RE, Donohue MC, Marshall GA, et al. Tracking early decline in cognitive function in older individuals at risk for Alzheimer disease dementia: the Alzheimer's Disease Cooperative Study Cognitive Function Instrument. JAMA Neurol 2015;72:446–54.

Bachurin SO, Bovina EV, Ustyugov AA. Drugs in clinical trials for Alzheimer's disease: the major trends. Med Res Rev 2017;37:1186–225.

Barthélemy N, Horie K, Sato C, et al. Blood plasma phosphorylated-tau isoforms track CNS change in Alzheimer's disease. J Exp Med 2020;217:e20200861.

Bateman RJ, Xiong C, Benzinger TLS, et al. Clinical biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med 2012;367:795–804.

Berg L. Clinical Dementia Rating (CDR). Psychopharmacol Bull 1988;24:637–9.

Binnewijzend MA, Schoonheim MM, Sanz-Arigita E, et al. Resting-state fMRI changes in Alzheimer's disease and mild cognitive impairment. Neurobiol Aging 2012;33:2018–28.

Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. Lancet 2006;368:387–403.

Bloom GS. Amyloid-β and tau: the trigger and the bullet in Alzheimer disease pathogenesis. JAMA Neurol 2014;71:505–8.

Bouwman FH, Schoonenboom NSM, Verwey NA, et al. CSF biomarker levels in early and late onset Alzheimer's disease. Neurobiol Aging 2009;30:1895–901.

Brier MR, Thomas JB, Snyder AZ, et al. Loss of intranetwork and internetwork resting state functional connections with Alzheimer's disease progression. J Neurosci 2012;32:8890–9.

Clark LJ, Gatz M, Zheng L, et al. Longitudinal verbal fluency in normal aging, preclinical, and prevalent Alzheimer's disease. Am J Alzheimers Dis Other Demen 2009;24:461–8.

Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol 2010;9:1118–27.

Eisai Co, Ltd. Eisai and Biogen announce positive topline results of the final analysis for BAN2401 at 18 months. News release: 2018. (accessed 24 September 2020) Available from: https://www.eisai.com/news/2018/news201858.html.

EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.

Farlow M, Arnold SE, van Dyck CH, et al. Safety and biomarker effects of solaneuzmab in patients with Alzheimer's disease. Alzheimer's Dement 2012;8:261–71.

Fazlollahi A, Calamante F, Liang X, et al. Increased cerebral blood flow with increased amyloid burden in the preclinical phase of alzheimer's disease. J Magn Reson Imaging 2020;51(2):505–13.

FDA. Early Alzheimer's Disease: Developing drugs for treatment, draft guidance for industry [resource on the Internet] 2018a.

FDA. Patient-focused drug development guidance public workshop: Methods to identify what is important to patients and select, develop, or modify fit-for-purpose clinical outcomes assessments. [resource on the Internet] 2018b. Available from: https://www.fda.gov/media/116277/download.

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

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

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

Franzmeier N, Dewenter A, Frontzkowski L, et al. Patient-centered connectivity-based prediction of tau pathology spread in Alzheimer's disease. Sci Adv 2020;6:eabd1327.

Goveas JS, Xie C, Ward BD, et al. Recovery of hippocampal network connectivity correlates with cognitive improvement in mild Alzheimer's disease patients treated with donepezil assessed by resting-state fMRI. J Magn Reson Imaging 2011;34:764–73.

Graham WV, Bonito-Oliva A, Sakmar TP. Update on Alzheimer's disease therapy and prevention strategies. Annu Rev Med 2017;68:413–30.

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

Grobert E, Ocepek-Welikson K, Teresi JA. The Free and Cued Selective Reminding Test: evidence of psychometric adequacy. Psychology Science Quarterly 2009;51:266–82.

Grober E, Sanders AE, Hall C, et al. Free and cued selective reminding identifies very mild dementia in primary care. Alzheimer Dis Assoc Disord 2010;24:284–90.

Grober E, Veroff AE, Lipton RB. Temporal unfolding of declining episodic memory on teh Free and Cued Selective Reminding Test in the predementia phase of Alzheimer's disease: implications for clinical trials. Alzheimer's Dement (Amst). 2018;10:161–71.

Grothe MJ, Moscoso A, Ashton NJ, et al. Associations of fully automated CSF and novel plasma biomarkers with alzheimer's disease neuropathology at autopsy. Neurology 2021;10.1212/WNL.0000000000012513.

Guy W, editor. ECDEU Assessment Manual for Pschopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education and Welfare.

Hampton OL, Buckley RF, Manning LK, et al. Resting-state functional connectivity and amyloid burden influence longitudinal cortical thinning in the default mode network in preclinical Alzheimers' disease. Neuroimage Clin 2020;28:102407.

Hansson O, Seibyl J, Stomrud E, et al. CSF biomarkers of Alzheimer's disease concord with amyloid-β PET and predict clinical progression: a study of fully automated immunoassays in BioFINDER and ADNI cohorts. Alzheimer's Dement 2018;14:1470–81.

Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 2002;297:353–6.

Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:172–36.

Hoy AR, Ly M, Carlsson CM, et al. Microstructural white matter alterations in preclinical Alzheimer's disease detected using free water elimination diffusion tensor imaging. PLoS One 2017;12:e0173982.

International Council for Harmoinsation (ICH). Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials E9(R1) [resource on the Internet]. 2019. Available from: https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf.

Ingelsson M, Fukumoto H, Newell KL, et al. Early abeta accumulation and progressive synaptic loss, gliosis, and tangle formation in AD brain. Neurology 2004;62:925–31.

Jack CR, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010;9:119–28.

Jack CR, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol 2013;12:207–16.

Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. Alzheimer's Dement 2018;14:535–62.

Jaeger J. Digit Symbol Substitution Test: the case for sensitivity over specificity in neuropsychological testing. J Clin Psychopharmacol 2018;38:513–9.

Jansen WJ, Ossenkoppele R, Knol DL, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. JAMA 2015;313:1924–38.

Jutten RJ, Peeters CFW, Leijdesdorff SMJ, et al. Detecting functional decline from normal aging to dementia: Development and validation of a short version of the Amsterdam IADL Questionnaire. Alzheimers Dement (Amst) 2017;8:26–35.

Karantzoulis S, Novitski J, Gold M, et al. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): utility in detection and characterization of mild cognitive impairment due to Alzheimer's disease. Arch Clin Neuropsychol 2013;28:837–44.

Klein G, Delmar P, Voyle N, et al. Gantenerumab reduces amyloid-β plaques in patients with prodromal to moderate Alzheimer's disease: a PET substudy interim analysis. Alzheimer's Res Ther 2019;11:101.

Klein G, Delmar P, Kerchner GA, et al. Thirty-six-month amyloid positron emission tomography results show continued reduction in amyloid burden with subcutaneous gantenerumab. J Prev Alzheimers Dis 2021;8:3–6.

Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.

Lezak MD, Howieson DB, Loring DW. Neuropsychological assessment (4th revised edition). New York: Oxford University Press, 2004.

Li C, Neugroschl J, Luo X,et al. The utility of the Cognitive Function Instrument (CFI) to detect cognitive decline in non-demented older adults. J Alzheimers Dis 2017;60:427–37.

Li T, Wahlund L. The search for neuroimaging biomarkers of Alzheimer's disease with advanced MRI techniques. Acta Radiol 2011;52:211–22.

Lorenzi M, Beltramello A, Mercuri NB, et al. Effect of mematine on resting state default mode network activity in Alzheimer's disease. Drugs Aging 2011;28:205–17.

Ly M, Canu E, Xu G, et al. Midlife measurements of white matter microstructure predict subsequent regional white matter atrophy in healthy adults. Hum Brain Mapp 2014;35:2044–54.

Mattson N, Cullen NC, Andreasson U, et al. Association between longitudinal plasma neurofilament light and neurodegeneration patients with alzheimer's disease. JAMA Neurol 2019;76:791–9.

Mattson N, Tosun D, Insel PS, et al. Association of brain amyloid-β with cerebral perfusion and structure in Alzheimer's disease and mild cognitive impairment. Brain 2014;137(Pt 5):1550–61.

McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement 2011;7:263–9.

Mielke MM, Hagen CE, Wennberg AMV, et al. Association of plasma total tau level with cognitive decline and risk of mild cognitive impairment or dementia in the Mayo Clinic study on aging. JAMA Neurol 2017;74:1073–80.

Mintun MA, Larossa GN, Sheline YI, et al. [^{11}C]-PIB in a non-demented population: potential antecedent marker of Alzheimer's disease. Neurology 2006;67:446–52.

Mintun MA, Lo AC, Evans CD, et al. Donanemab in early Alzheimer's disease. N Engl J Med 2021;384:1691–1704.

Mormino EC, Kluth JT, Madison CM, et al. Episodic memory loss is related to hippocampal-mediated beta-amyloid deposition in elderly subjects. Brain 2009;132(Pt 5):1310–23.

Morris JC. The clinical dementia rating (CDR): current version and scoring rules. Neurology 1993;43:2412–4.

Morris JC. Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. Int Psychogeriatr 1997:9 Suppl 1:173–6.

Morris JC, Storandt M, Miller JP, et al. Mild cognitive impairment represents early-stage Alzheimer's disease. Arch Neurol 2001;58:397–405.

Navitsky M, Joshi AD, Kennedy I, et al. Standardization of amyloid quantitation with florbetapir standardized uptake value ratios to the Centiloid scale. Alzheimer's Dement 2018;14:1565–71.

Nir TM, Jahanshad N, Villalon-Reina J, et al. Effectiveness of regional DTI measures in distinguishing Alzheimer's disease, MCI, and normal aging. Neuroimage Clin 2013;3:180–95.

O'Bryant SE, Lacritz LH, Hall J, et al. Validation of the new interpretive guidelines for the clinical dementia rating scale sum of boxes score in the national Alzheimer's coordinating center database. Arch Neurol 2010;67:746–9.

Ossenkoppele R, Smith R, Mattsson-Carlgren N, et al. Accuracy of tau positron emission tomography as a prognostic marker in preclinical and prodromal Alzheimer's disease: a head-to-head comparison against amyloid poistron emission tomography and magnetic resonance imaging. JAMA Neurol 2021;e211858.

Ossenkoppele R, Smith R, Ohlsson T, et al. Associations between tau, Aβ, and cortical thickness with cognition in Alzheimer disease. Neurology 2019;92:e601–12.

Ostrowitzki S, Deptula D, Thurfjell L, et al. Mechanism of amyloid removal in patients with Alzheimer disease treated with gantenerumab. Arch Neurol 2012;69:198–207.

Ostrowitzki S, Lasser RA, Dorflinger E, et al. A Phase III randomized trial of gantenerumab in prodromal Alzheimer's disease. Alzheimer's Res Ther. 2017:9:95.

Ovod V, Ramsey KN, Mawuenyega KG, et al. Amyloid β concentrations and stable isotope labeling kinetics of human plasma specific to central nervous system amyloidosis. Alzheimers Dement 2017;13:841–9.

Papp KV, Rentz DM, Orlovsky I, et al. Optimizing the preclinical Alzheimer's cognitive composite with semantic processing: the PACC5. Alzheimer's Dement (NY) 2017;3:668–77.

Papp KV, Buckley R, Mormino E, et al. Clinical meaningfulness of subtle cognitive decline on longitudinal testing in preclinical AD. Alzheimer's Dement 2020;16:552–60.

Parnetti L, Chipi E, Salvadori N, et al. Prevalence and risk of progression of preclinical Alzheimer's disease stages: a systematic review and meta-analysis. Alzheimer's Res Ther 2019;11:7.

Pasquier F, Lebert F, Grymonprez L, et al. Verbal fluency in dementia of frontal lobe type and dementia of Alzheimer type. J Neurol Neurosurg Psychiatry1995;58:81–4.

Peskind ER, Li G, Shofer J, et al. Age and apolipoprotein E*4 allele effects on cerebrospinal fluid beta-amyloid 42 in adults with normal cognition. Arch Neurol 2006;63:936–9.

Petersen RC, Smith GE, Waring SC, et al. Aging, memory, and mild cognitive impairment. Int Psychogeriatr 1997;9 Suppl 1:65–9.

Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011;168):1266–77.

Randolph C, Tierney MC, Mohr E, et al. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. J Clin Exp Neuropsychol 1998;20:310–9.

Salloway S, Sperling R, Fox NC, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N Engl J Med 2014;370:322–33.

Salloway S, Sperling R, Gilman S, et al. A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease. Neurology 2009;73:2061–70.

Schuff N, Matsumoto S, Kmiecik J, et al. Cerebral blood flow in ischemic vascular dementia and Alzheimer's disease, measured by arterial spin-labeling magnetic resonance imaging. Alzheimer's Dement 2009;5:454–62.

Selkoe DJ. Alzheimer's disease. In the beginning. Nature 1991;354:432–3.

Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med 2016;8:595–608.

Sevigny J, Chiao P, Bussière T, et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature 2016;537:50–6.

Shaw LM, Vanderstichele H, Knapik-Czajka M, et al. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimging intiative subjects. Ann Neurol 2009;65:403–13.

Sheikh JI, Yesavage JA, Brooks JO, et al. Proposed factor structure of the Geriatric Depression Scale. Int Psychogeriatr 1991;3:23–8.

Sheline YI, Raichle ME, Snyder AZ, et al. Amyloid plaques disrupt resting state default mode network connectivity in cognitively normal elderly. Biol Psychiatry 2010;67:584–7.

Sheline YI, Raichle ME. Resting state functional connectivity in preclinical Alzheimer's disease. Biol Psychiatry 2013;74:340–7.

Solé-Padullés C, Bartrés-Faz D, Lladó A, et al. Donepezil treatment stabilizes functional connectivity during resting state and brain activity during memroy encoding in Alzheimer's disease. J Clin Psychopharmacol 2013;33:199–205.

Sperling R, Aisen P, Beckett L, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement 2011;7:280–92.

Vandenberghe R, Adamczuk K, Dupont P, et al. Amyloid PET in clinical practice: its place in the multidimensional space of Alzheimer's disease. Neuroimage Clin 2013;2:497–511.

Vandenberghe R, Rinne JO, Boada M, et al. Bapineuzumab for mild to moderate Alzheimer's disease in two global, randomized, phase 3 trials. Alzheimers Res Ther 2016;8:18.

Walsh SP, Raman R, Jones KB, et al. ADCS Prevention Instrument Project: the Mail-In Cognitive Function Screening Instrument (MCFSI). Alzheimer Dis Assoc Disord 2006;20:S170–8.

Wechsler, D. The measurement and appraisal of adult intelligence (1st edition) 1939. Baltimore: Williams and Wilkins Corporation.

Wechsler D. Wechsler adult intelligence scale. Fourth Edition (WAISIV). 2008. San Antonio, TX: NCS Pearson.

Wechsler, D. Wechsler Memory Scale–Fourth Edition (WMS–IV) technical and interpretive manual. 2009. San Antonio, TX: Pearson.

Westfall PH, Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. J Stat Plan Infer 2001;99:25–41.

Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment—beyond controversies, torwards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 2004;256:240–6.

Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982–1983;17:37–49.

Younes L, Albert M, Moghekar A, et al. Identifying changepoints in biomarkers during the preclinical phase of Alzheimer's disease. Front Aging Neurosci 2019;11:74.

Zhang X, Mormino EC, Sun N, et al. Bayesian model reveals latent atrophy factors with dissociable cognitive trajectories in Alzheimer's disease. Proc Natl Acad Sci USA 2016;113:E6535–44.

Zhang N, Gordon ML, Goldberg TE. Cerebral blood flow measured by arterial spin-labeling MRI at resting state in normal aging and Alzheimer's disease. Neurosci Biobehav Rev 2017;72:168–75.

Appendix 1 Regulatory, Ethical, and Study Oversight Considerations

TABLE OF CONTENTS

A1–1. REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP)
- Applicable laws and regulations

The protocol, Informed Consent Form (ICF), Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB) or Ethics Committee (EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- 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
- Notifying the IRB/EC of serious adverse events or other significant safety findings, as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and ensuring adherence to requirements of 21 Code of Federal Regulations (CFR; U.S. sites only), the ICH Guideline for GCP, the IRB/EC, Regulation (E.U.) No. 536/2014 (E.U. sites only), and all other applicable local regulations

A1–2. 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 study and for 1 year after completion of the study (see definition of end of study in Section 4.4).

A1–3. INFORMED CONSENT PROCESS

This section relates to the informed consent process for the optional blood-based biomarker (BBBM) prescreening and the main study.

Participation in the optional BBBM prescreening requires signing of a separate BBBM prescreening ICF. The investigator or authorized designee will explain the nature of the optional BBBM prescreening to the participant and answer all questions regarding the optional BBBM prescreening.

For participation in the main study, the investigator or authorized designee will explain the nature of the study to the participant, to the participant's study partner, and to the participant's postdose observer(s) (if applicable). The investigator or authorized designee will also answer all questions regarding study participation during the informed consent process for the Main Participant, Study Partner, Postdose Observer, and Mobile Nursing ICFs.

Participants, the participant's study partner, and the participant's postdose observer(s) must be informed that their participation is voluntary. The participant, the participant's study partner, and the participant's postdose observer(s) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (U.S. sites only), the ICH Guideline for GCP, and the IRB/EC.

The medical record must include a statement that written informed consent was obtained before the participant, the participant's study partner, and the participant's post-dose observer(s) were enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

If any of the ICFs are revised (through an amendment or an addendum) to communicate information that may affect a participant's, participant's study partner's, or the participant's postdose observer(s)' willingness to continue in the study, the participant, the participant's study partner, or the participant's postdose observer(s) must re-consent by signing the most current version of the ICF or the addendum, in accordance with applicable laws and IRB/EC policy.

A copy of each ICF must be provided to the participant, the participant's study partner and the participant's postdose observer(s). A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 90 days from the previous ICF signature date.

The BBBM prescreening ICF and the Main Participant ICF will each contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the

objectives of the exploratory research. 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 signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

A1–4. DATA PROTECTION

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; the participant's name or any information that would make the participant identifiable will not be transferred.

Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to participants, who will be required to give consent for their data to be used as described in the ICF.

Participants must be informed that their medical records may be examined by auditors or other authorized individuals representing the Sponsor or Sponsor collaborators and licensees, by appropriate IRB/EC members, and by inspectors from health authorities.

A1–5. ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 200 sites globally will participate to enroll approximately 1200 participants. Enrollment will occur through an interactive voice or Web-based response system.

Central facilities will be used for certain assessments throughout the study (e.g., specified laboratory tests, biomarker and pharmacokinetic analyses), as specified in Section 8 and Appendix 24.

An independent Data Monitoring Committee (iDMC) will be employed to monitor and evaluate participant safety throughout the study. An Independent Review Facility will collect, store, and review imaging data.

A1–6. DISSEMINATION OF CLINICAL STUDY DATA

Study data, which may include imaging data and data on genomic variants, 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. 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

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 Roche policy on study data publication.

A1–7. DATA QUALITY ASSURANCE

All participant data relating to the study will be recorded on printed or electronic Case Report Forms (eCRFs) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the Case Report Form (CRF).

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or onsite monitoring), are provided prior to study initiation, in the various functional monitoring plans (including, but not limited to, Quality Tolerance Limit Management Plan and Trial Monitoring Plan).

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing monitoring activities as specified in the Trial Monitoring Plan to confirm that data entered into the CRF by authorized site

personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH Guideline for GCP, and all applicable regulatory requirements.

Records and documents pertaining to the conduct of this study, including signed ICFs, must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A1–8. SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in the Trial Monitoring Plan.

A1–9. STUDY AND SITE CLOSURE

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to, the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or the ICH Guideline for GCP
- Inadequate recruitment of participants by the investigator

- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

A1–10. PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results.
In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of results of multicenter studies only in their entirety and not as individual site 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.

A1–11. 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.

Appendix 2 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

TABLE OF CONTENTS

A2–1 DEFINITION OF ADVERSE EVENT

Adverse Event Definition

An adverse event is any untoward medical occurrence in a patient or clinical study participant temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

Note: An adverse event can; therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the Adverse Event Definition

The following events meet the definition of adverse event:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study treatment administration, even though it may have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected drug– interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concomitant medication

  Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of sequelae.

  "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Definition of Adverse Event

The following events do not meet the definition of adverse event:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy)

  The condition that leads to the procedure is the adverse event.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of a preexisting disease or condition present or detected at the start of the study that do not worsen

A2–2 DEFINITION OF SERIOUS ADVERSE EVENT

If an event is not an adverse event per the definition in Section A2–1, it cannot be a serious adverse event even if serious conditions are met (e.g., hospitalization for signs or symptoms of the disease under study).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious.

  Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.

- Results in persistent disability or incapacity

  The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect
- Other situations:

  Medical or scientific judgment should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section A2–3.2); 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 electronic Case Report Form (eCRF).

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A2–5 for reporting instructions).

A2–3. RECORDING AND FOLLOW-UP OF ADVERSE EVENTS AND/OR SERIOUS ADVERSE EVENTS

A2–3.1 ADVERSE EVENT AND SERIOUS ADVERSE EVENT RECORDING

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant adverse event or serious adverse event information on the eCRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs or symptoms) will be documented as the adverse event or serious adverse event.

A2–3.2 ASSESSMENT OF SEVERITY

The investigator will assess the severity of each adverse event reported during the study through use of the NCI CTCAE (v5.0) grading scale. The investigator will use the grading scale in Table A2–1 for assessing the severity of adverse events that are not specifically listed in the NCI CTCAE.

Table A2–1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

Table A2–1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE (cont.)

CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.
Note: Based on the most recent version of NCI CTCAE (v 5.0), which can be found at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

[a] Examples of instrumental activities of daily living include preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

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

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section A2–5 for reporting instructions), per the definition of serious adverse event in Section A2–2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section A2–5 for reporting instructions), per the definition of serious adverse event in Section A2–2.

A2–3.3 ASSESSMENT OF CAUSALITY

The investigator is obligated to assess the relationship between study treatment and each occurrence of each adverse event or serious adverse event.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or prescribing information (for marketed products) in his or her assessment.

For each adverse event or serious adverse event, the investigator **must** document in the medical notes that he or she has reviewed the adverse event or serious adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data to the Sponsor.

The investigator may change his or her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

A2–3.4 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A2–3.4.1 Investigator Follow-Up

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor with a copy of any post-mortem findings, including histopathology.

New or updated information should be recorded on the originally-completed Adverse Event eCRF. 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 the investigator becomes 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

During the adverse event reporting period (defined in Section 8.3.1), 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.

For reporting of pregnancies, see Appendix 4.

A2–3.4.2 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, e-mail, and/or a monitoring visit

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

A2–4. REPORTING OF SERIOUS ADVERSE EVENTS

A2–4.1 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA AN ELECTRONIC COLLECTION TOOL

The primary mechanism for reporting a serious adverse event to the Sponsor will be the electronic data collection tool, as described in Section A2–5.

If the electronic system is unavailable, the site will use the paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A2–5, to report the event within 24 hours.

The site will enter the serious adverse event data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new serious adverse event from a study participant or receives updated data on a previously reported serious adverse event after the electronic data collection tool has been taken offline, the site can report this information on a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A2–5.

A2–4.2 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA PAPER CRF

Under certain circumstances, serious adverse events may be reported to the Sponsor through use of a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A2–5.

A2–5. REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS OF SPECIAL INTEREST

A2–5.1 EVENTS THAT OCCUR PRIOR TO STUDY TREATMENT INITIATION

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., cerebrospinal fluid sampling or lumbar puncture, discontinuation of medications) should be reported.

In addition, the following serious adverse events should be reported after administration of a positron emission tomography (PET) ligand and prior to initiation of study drug:

- All serious adverse events believed to be related to the PET ligand (non-serious adverse events believed to be related to the PET ligand should also be reported; see Section 8.3.1)
- All serious adverse events occurring within 48 hours of the PET ligand administration, regardless of relatedness to the PET ligand

The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and e-mailing the form, using the fax number or e-mail address provided to investigators.

A2–5.2 EVENTS THAT OCCUR AFTER STUDY TREATMENT INITIATION

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 17 weeks after the final dose of study treatment (i.e., the participant's safety follow-up visit). Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and e-mailing the form, using the fax number or e-mail 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 more than 17 weeks after the final dose of study treatment are provided in Section A2–6.

A2–6. REPORTING 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 17 weeks after the final dose of study treatment), if the event is believed to be related to be prior to exposure to study 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 e-mailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form, using the fax number or e-mail address provided to investigators.

A2–7. PROCEDURES FOR RECORDING ADVERSE EVENTS

When an adverse event occurs, it is the responsibility of the investigator to review all documentation related to the event (e.g., hospital progress notes, laboratory reports, and diagnostics reports). The investigator will then record all relevant adverse event information on the Adverse Event eCRF. It is not acceptable for the investigator to send photocopies of the participant's medical records to the Medical Monitor in lieu of completion of the eCRF. Investigators should use correct medical terminology and concepts when recording adverse events on the Adverse Event eCRF.
Avoid colloquialisms and abbreviations. Only 1 adverse event term should be recorded in the event field of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

A2–7.1 ARIA FINDINGS

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

- Symptomatic ARIA-E (i.e., onset or worsening of CNS symptom[s] that is/are attributable to ARIA-E magnetic resonance imaging (MRI) findings in the judgment of the investigator), and/or
- ARIA findings that result in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation), and/or
- Findings that are 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 A2–7.5 for details on recording persistent adverse events).

A2–7.2 INJECTION REACTIONS

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

If a participant experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded separately on the Adverse Event eCRF.

For local reactions, the diagnosis of “injection-site reaction” 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 captured as a single diagnosis on the Adverse Event eCRF (e.g., "anaphylactic reaction"). If possible, avoid ambiguous terms such as "systemic reaction".

A2–7.3 DIAGNOSIS VERSUS 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 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 1 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.

A2–7.4 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
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF

- If dizziness leads to a fall and consequent fracture, all 3 events should be reported separately on the eCRF
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF

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

A2–7.5 PERSISTENT OF 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 the investigator becomes aware that the event became serious; see Section A2–5 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.

A2–7.6 ABNORMAL LABORATORY VALUES

Not every abnormal laboratory value qualifies as an adverse event. A laboratory value abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected.
A laboratory value abnormality that is not associated with the underlying disease 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., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × 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 A2–7.5 for details on recording persistent adverse events).

A2–7.7 ABNORMAL VITAL SIGN VALUES

Not every abnormal vital sign value qualifies as an adverse event. A vital sign abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A vital sign abnormality that is not associated with the underlying disease 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., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

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

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (e.g., 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 A2–7.5 for details on recording persistent adverse events).

A2–7.8 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 Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section A2–7.6) and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either as a serious adverse event or an adverse event of special interest (see Section A2–5).

A2–7.9 DEATHS

All deaths that occur during the protocol-specified adverse event reporting period (see Section 8.3.1), regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section A2–5). This includes death attributed to progression of Alzheimer's disease (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.

Autopsy reports, including cause of death, for all participants who die during the study should be requested.

Deaths that occur after the adverse event reporting period should be reported as described in Section A2–6.

A2–7.10 PREEXISTING MEDICAL CONDITIONS

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

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

A2–7.11 LACK OF EFFICACY OR WORSENING OF ALZHEIMER'S DISEASE

Deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) should be recorded as an adverse event. When recording an unanticipated worsening of AD on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of Alzheimer's disease").
Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

A2–7.12 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 A2–2), except as outlined below.

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

- Hospitalization for respite care

- Planned hospitalization required by the protocol
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The participant was hospitalized for an elective procedure that was planned prior to the study, was scheduled during the study despite the fact that the condition had not worsened, or was scheduled during the study when treatment became necessary because of the expected normal progression of the condition
  - The participant has not experienced an adverse event
- Hospitalization due solely to the expected progression of AD

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

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

A2–7.13 CASES OF OVERDOSE, MEDICATION ERROR, DRUG ABUSE, OR DRUG MISUSE

Special situations (overdoses, medication errors, drug abuse, or drug misuse) are to be reported for study treatment.

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (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
- Intentional overdose: intentional 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.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the participant, drug misuse could involve the drug being administered to someone other than the participant. Note: 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 the investigator becomes aware of the event; see Section A2–5). For study treatment, adverse events associated with special situations should be recorded as described below for each situations' boxes:

- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- 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.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

As an example, an accidental overdose that resulted in a headache would require 2 entries on the Adverse Event eCRF, 1 entry to report the accidental overdose and 1 entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

All special situations associated with study treatment, 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.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- 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.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the participant: Enter the drug name and "participant supplied drug to third party" as the event term. Check the "Drug misuse" box.

A2–7.14 CASES OF MEDICATION ERROR

A medication error is defined as an accidental deviation in the administration of a drug (e.g., wrong drug dose administered, sham procedure performed in participant assigned to active drug, drug administered in wrong location, sham procedure performed incorrectly, expired drug administered). In some cases, a medication error may be intercepted prior to administration of the drug.

Medication errors are not in themselves adverse events, but may result in adverse events. 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 the investigator becomes aware of the event; see Section A2–5).

As an example, a medication error that resulted in a headache would require 2 entries on the Adverse Event eCRF, 1 entry to report a medication error and 1 entry to report the headache. The "Medication error" boxes would need to be checked for both entries.

A2–7.15 PARTICIPANT-REPORTED OR OBSERVER-REPORTED OUTCOME DATA

Adverse event reports will not be derived from PRO or ObsRO data by the Sponsor (detailed list of PROs and ObsROs included in the study is provided in Section 8.10). Sites are not expected to review the PRO or ObsRO data for adverse events.

A2–7.16 SAFETY BIOMARKER DATA

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on participant management.

Appendix 3 Safety Plan: Management of Identified and Potential Risks

TABLE OF CONTENTS

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 current Gantenerumab Investigator's Brochure for a complete summary of safety information.

A3–1 AMYLOID-RELATED IMAGING ABNORMALITIES

Amyloid-related imaging abnormalities are one of the most significant adverse events reported in therapies against aggregated forms of amyloid β (Aβ). These findings appear to be dependent on dose-, time-, and apolipoprotein E (*APOE)* ε4 status (Piazza and Winblad 2016).

The mechanism underlying the development of amyloid-related imaging abnormalities–edema/effusion (ARIA-E) and amyloid-related imaging abnormalities–hemosiderin deposition (ARIA-H) during anti-amyloid treatment is not yet fully understood. Because anti-Aβ antibodies remove 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). An anti-Aβ therapy that effectively maintains vascular Aβ clearance would allow vascular remodeling and might, over time, decrease the risk of such extravasation events (Sperling et al. 2012). This hypothesis is consistent with experiences in previous and ongoing studies and with reported data from the long-term extension study of aducanumab treatment (Haeberlein et al. 2019; Lin et al. 2021).

Understanding of the clinical significance of ARIA by study Sponsors, investigators, and regulators has substantially evolved since ARIA events were first seen on MRI scans in a Phase I clinical trial with bapineuzumab (Black et al. 2010). The accrued clinical evidence with gantenerumab and other *N*-terminus anti-amyloid antibodies has shown that ARIA events tend to occur early in treatment, are dose and *APOE* ε4 dependent, and can be monitored by MRI and managed with dose intervention algorithms.

In the double-blind phase of Study WN25203, ARIA events were time (duration of treatment), dose, and *APOE* ε4 allele status-dependent. The incidence of ARIA-E was 0.8% in the placebo, 6.6% in the 105 mg gantenerumab, and 13.5% in the 225 mg gantenerumab groups. For ARIA-H, the incidence was 13.2% in the placebo, and 22.9% and 16.2% in the 105 mg and 225 mg gantenerumab treatment groups, respectively. The rates of new ARIA-E were highest between 3 and 6 months of treatment (3.8% and 7.5% in the 105 mg and 225 mg gantenerumab groups, respectively) and decreased substantially after the first 9 months of treatment (incidence of up to 2.3% in the 225 mg

gantenerumab group in approximately 2 years). The median MRI Barkhof Grand Total Score (BGTS; Barkhof et al. 2013) of these findings was 3. Most ARIA events were asymptomatic and did not lead to clinically significant consequences. A total of 5 participants (1.8%) from the 105 mg gantenerumab group and 6 participants (2.3%) from the 225 mg gantenerumab group experienced symptoms related to ARIA findings; the most commonly reported symptom was headache (5 participants). Other symptoms reported with ARIA-E included visual disturbances (left eye diplopia and upper left quadrantanopia), focal seizure (dysarthria/ aphasia that lasted for 10 minutes), anxiety, hyperreflexia, confusional state, disturbance in attention, cognitive disorder, malaise, and dizziness.

Symptomatic ARIAs were of mild severity and were non-serious except for 1 serious adverse event of focal seizure.

Following the futility analysis for Study WN25203, treatment in the double-blind phase was discontinued in July 2017 (median double-blind treatment duration: 68 weeks) and consenting participants transitioned into an open-label extension (OLE).

In the double-blind phase of Study WN28745, the frequency of ARIA-E was 1.5% and 11.5% in the placebo and gantenerumab groups, respectively. The frequency of ARIA-H was 11.8% and 15.1% in the placebo and gantenerumab groups, respectively. The median BGTS of ARIA-E was 3. Most ARIAs were asymptomatic and did not lead to clinically significant consequences. Two participants reported CNS adverse events as symptoms of ARIAs: 1 participant (0.5%) in the placebo group reported irritability that was mild in intensity and non-serious, and 1 participant (0.5%) in the gantenerumab group reported headache that was moderate in intensity and non-serious.

The OLEs of Studies WN25203 and WN28745 were recently completed (last participant, last visit [LPLV] occurred and databases are closed). As of 3 December 2020, in the OLE part of the Study WN25203, all 154 patients dosed with gantenerumab in the OLE had at least 1 post-OLE baseline MRI scan. Of these, 47 patients (30.5%) had new ARIA-E and 51 patients (33.1%) had new ARIA-H. Additionally, 31 patients (20.1%) had new ARIA-E and new ARIA-H at any point during the OLE.

The majority of ARIA-E findings were asymptomatic, with 19 of 47 participants (40.4%) with ARIA-E reporting associated CNS adverse events. The CNS adverse events were mostly mild to moderate in intensity, non-serious, did not require permanent cessation of study treatment, and resolved with protocol-defined ARIA management rules. In 4 of 19 patients with ARIA-E MRI findings who reported associated CNS adverse events, the events were reported as serious. Three patients reported events of seizure ($n=2$) and cerebral hematoma which was severe in intensity and one patient reported confusion

that was moderate in intensity. Three serious adverse events were assessed as related to study treatment by the investigator.

Up to 11 January 2021, 219 of 225 participants dosed with gantenerumab in the OLE phase of Study WN28745 had a post-baseline MRI scan; 71 of 219 participants (32.4%) had new ARIA-E (with or without ARIA-H), 75 patients (34.24%) had new ARIA-H (with or without ARIA-E), and 49 patients (22.3%) had both ARIA-E and ARIA-H. The majority of ARIA-E events were asymptomatic, with 22 out of 71 participants (31%) with ARIA-E reporting associated CNS adverse events. 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. Four of the 22 participants (18%) reported serious events associated with ARIA findings (2 participants had seizure events which resolved without anti-epileptic medication, 1 participant had hemiplegia which resolved after treatment with dexamethasone, and 1 participant had ischemic stroke which improved [most of the symptoms, with the exception of disorientation, resolved]).

Study WN42444 will require an MRI scan documenting the absence of ARIA-E, >5 ARIA-H, or disseminated leptomeningeal hemosiderosis prior to the first study drug dose. If ARIA findings occur during the study, MRI monitoring, temporary dose holding, or permanent study drug discontinuation will be implemented according to an ARIA management plan, as described in Section A3–5.

Safety findings, including individual participant and aggregate data, will be reviewed on a regular basis by an unblinded iDMC.

To date, clinical experience with gantenerumab has shown that ARIA events are dose- and *APOE* ε4-dependent. These events are manageable with MRI monitoring and dose intervention algorithms. In addition, in case of clinical symptoms, the use of IV glucorticosteroids may be considered.

Rules for management of participants who develop ARIA-E or ARIA-H are provided in in Section A3–5.

A3–2 INJECTION REACTIONS AND HYPERSENSITIVITY

Gantenerumab may cause a local injection-site reaction (ISR) when given as an SC injection. In studies with gantenerumab, the most common 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.

In the double-blind phase 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 groups,

respectively. All ISRs were non-serious, and the majority were mild in intensity and resolved without treatment. The most common signs and symptoms of ISRs included injection-site erythema, pruritus, and rash. Two participants (0.3%) discontinued study treatment due to an ISR.

In the double-blind phase of Study WN28745, the incidence of ISRs was 1.0% and 9.4% in the placebo and gantenerumab groups, respectively. All ISRs were non-serious and mild in intensity; the vast majority resolved without treatment. The most common signs and symptoms of ISRs included injection-site erythema, pruritus, hemorrhage, and rash. No participants discontinued study treatment due to an ISR.

Up to 11 January 2021 ISRs have been reported in 36.4% of participants (56 of 154 participants) treated with gantenerumab in the OLE phase of Study WN25203. The most frequently reported ISRs (≥ 10%) were injection-site erythema (49 participants [31.8%]) and injection-site swelling (18 participants [11.7%]). All ISRs were non-serious and mild except 1 which was of moderate intensity, and the majority resolved without treatment. Overall, 3 of 56 participants (5.4%) who had an ISR received treatment, which included topical steroids and antihistamines.

Up to 11 Jan 2021 March 2020, ISRs have been reported in 40.0 % of participants (90 of 225 participants) treated with gantenerumab in the OLE phase of Study WN28745. The most frequently reported ISRs (≥ 10%) were injection-site erythema (67 participants [29.8%]). All ISRs were non-serious, with the majority being mild and resolving without treatment. One participant (0.4%) experienced a severe event (injection-site pain after receiving a 600 mg dose via a pump, resulting in dose modification [i.e., dose escalation was delayed]); this ISR resolved within 24 hours. Overall, 10 of 90 participants (11.1%) who had an ISR received treatment, which included topical steroids and antihistamines.

Detailed information on the characteristic signs and symptoms of ISRs (e.g., erythema, pruritus) will be recorded on a dedicated electronic Case Report Form (eCRF) page (see Section A2–7.2 for details on recording of ISRs).

As with administration of any exogenous protein, a potential exists for the development of hypersensitivity reactions, including anaphylaxis. A hypersensitivity reaction may present during any injection, although typically would not present during the first injection. For subsequent injections, more severe injection reaction symptoms than previously experienced, or new severe symptoms, should prompt consideration of a potential hypersensitivity reaction.

A potential exists for the occurrence of systemic injection reactions, which are related to cytokine release and/or other chemical mediators. These may be clinically

indistinguishable from hypersensitivity reactions, including anaphylaxis. In comparison to hypersensitivity reactions, systemic injection reactions could occur on first exposure to study drug in participants with no history of prior opportunities for sensitization.

On each dosing day, after all assessments prior to dosing have been completed (see the schedule of activities in Section 1.3), the study drug will be administered SC at room temperature (full details are provided in the Pharmacy Manual). Study site personnel administering study drug must not be involved with any efficacy assessments or safety evaluations.

During the initial dose escalation period, participants should be observed for a minimum of 2 hours after dosing for the first 4 doses of study drug administration, and then for a minimum of 1 hour after all remaining doses (i.e., dose 5 and beyond). During the post-progression dose escalation period, participants should be observed for at least 2 hours after injections at Week 1P, Week 5P, Week 9P and Week 13P. The observation time may be reduced to at least 1 hour following all other administrations. Participants should leave the study center after injections only if they appear to be tolerating the injections. When doses are to be administered remotely from the clinical sites, the drug administrator must remain with the participant for a minimum of 1 hour after each injection. Participants self-administering the study drug must also be observed for a minimum of 1 hour after each injection by their study partner or another suitably trained individual (i.e., postdose observer).

Rescue medications to treat anaphylactic and anaphylactoid reactions must be available at the clinical trial site. Participants and their study partners will be alerted to watch for signs of anaphylactic and anaphylactoid reactions, and given emergency contact information to use as soon as possible if any such signs are noted.

The investigator may order any pertinent laboratory tests, including an unscheduled anti-drug antibody (ADA) test, in the event any hypersensitivity reaction occurs.

If anaphylaxis or a serious hypersensitivity reaction occurs, the study drug must be discontinued permanently, and any remaining study drug doses should be returned to the study site (if applicable). Blood samples for the presence of ADAs and PK/PD will be obtained.

A3–3 IMMUNOGENICITY

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

For the management of suspected immunogenicity-associated hypersensitivity/anaphylaxis, see section above.

A3–4 RISKS ASSOCIATED WITH PET TRACERS

A3–4.1 RISKS ASSOCIATED WITH RADIATION

The risks associated with radiation in Study WN42444 are considered minimal, owing to the low dose of tracer that is administered and based on nonclinical and clinical experience available to date. The principal risks associated with positron emission tomography (PET) imaging are those associated with IV line placement, the discomfort associated with acquisition of the images while keeping the head stable in the scanner, and radiation exposure because of the radiotracer dose and transmission or CT scanning. The most frequently reported adverse events with amyloid radioligands are described in Sections A3–4.2 and A3–4.3, and the most frequently reported adverse events with the tau radioligand MK-6240 are described in Section A3–4.4).

Other adverse reactions could be related in part to the PET scan apparatus and procedures; careful attention should be taken to make the participant aware of the planned procedures and to maximize participant comfort in the scanner.
Venous catheter insertion can be associated with bruising, infection, or clot formation. Using proper placement techniques will minimize such risks. Experience in previous human clinical trials has revealed no clinically-meaningful changes in vital signs, electrocardiogram, or laboratory changes following treatment with PET tracers.

The potential for drug-drug interactions with PET tracers is not presently known. Since PET tracers are administered at trace-level doses, no clinically-relevant drug interactions with concomitant medications is expected.

A3–4.1.1 Radiation Exposure

The dose of whole-body effect radiation resulting from the recommended injected radioactivity is similar for [^{18}F]-Florbetaben, [^{18}F]-Flutemetamol, and [^{18}F]-MK-6240 and is well-below the maximum annual effective dose limitations recommended in the United States, the European Union, and other countries where PET imaging will be used. The recommended 300 MBq dose of [^{18}F]-Florbetaben results in a 5.8-mSv absorbed dose, the 185-MBq dose of [^{18}F]-Flutemetamol results in 5.9 mSv, and the 185-MBq dose of [^{18}F]-MK-6240 results in 5.4 mSv. Additional radiation dose results from CT or transmission scan used for attenuation correction of the PET emission data. The CT scan in PET/CT scanners will be configured as a low-dose CT and will add approximately 0.1 mSv to the dose from PET tracers. In dedicated PET scanners without CT scans, the transmission scan adds only a negligible amount of radiation dose.

Radiation exposure for [^{18}F]-Florbetaben, [^{18}F]-Flutemetamol, and [^{18}F]-MK-6240 doses can be found in their respective Investigator's Brochures and in the Technical Operations Manual. Refer to local and national guidelines for recommended annual radiation exposure. For comparison, the annual dose associated with the natural background is 2.4 mSv. The recommended maximum annual whole-body dose from research scans in the United States is 50 mSv. In the European Union, 10 mSv per year is the recommended maximum dose for research scans, corresponding to a risk category "Category IIb" with a "minor to intermediate" level of risk (Verbruggen et al. 2008). Positron emission tomography scans should only be performed if the investigator has determined that a participant's total past and planned annual radiation exposure does not exceed local guidelines.

A3–4.2 [^{18}F]-FLORBETABEN (AMYLOID PET TRACER)

The most commonly reported adverse reactions after injection of [^{18}F]-Florbetaben (occurring in at least 1% of subjects) are injection-site pain (3.1%), and injection or application-site erythema (1.4%). [^{18}F]-Florbetaben contains up to 33 mg (i.e., 1.4 mmol) of sodium per dose. This should be taken into account for participants on a sodium-controlled diet. [^{18}F]-Florbetaben contains up to 1200 mg of ethanol per dose, which is equivalent to 30 mL of beer or 12.5 mL of wine per dose.

In countries where [^{18}F]-Florbetaben PET radioligand is approved for marketing, for more information see the approved local product information. In countries where the [^{18}F]-Florbetaben PET radioligand is not approved for marketing, the Investigator's Brochure will be provided.

A3–4.3 [^{18}F]-FLUTEMETAMOL (AMYLOID PET TRACER)

The most commonly reported adverse reactions after injection of flutemetamol are flushing (2%), chest discomfort (1%), dizziness (1%), headache (1%), increased blood pressure (1%), nausea (1%), and anaphylactic reaction ($<$0.5%). [^{18}F]-Flutemetamol contains up to 41 mg (i.e., 1.8 mmol) of sodium per dose. This should be taken into account for participants on a sodium-controlled diet. [^{18}F]-Flutemetamol contains up to 552 mg of ethanol per dose, which is equivalent to 14 mL of beer or 6 mL of wine per dose.

In countries where [^{18}F]-Flutemetamol PET radioligand is approved for marketing, for more information see the approved local product information. In countries where the [^{18}F]-Flutemetamol PET radioligand is not approved for marketing, the Investigator's Brochure will be provided.

A3–4.4 [^{18}F]-MK-6240 (TAU PET TRACER)

There are no adverse reactions to [^{18}F]-MK-6240. Potential risks include pain and bleeding from venous or arterial catheterization or an IV infusion reaction ([^{18}F]-MK-6240 Investigator's Brochure, Version F, dated June 2021). [^{18}F]-MK-6240 contains up to 32.4 mg of sodium (81 mg of sodium chloride) and 1 mL of ethanol per dose.

The [^{18}F]-MK-6240 PET radioligand is not approved for marketing in any country. For more information, the Investigator's Brochure will be provided.

A3–5 MANAGEMENT RULES FOR AMYLOID-RELATED IMAGING ABNORMALITIES

Participants on target dose 510 mg SC Q2W: Before reaching the maximum target dose 510 mg Q2W, a minimum of 3 doses during 120 mg Q4W, 255 mg Q4W, and 510 mg Q4W dosing periods must be administered prior to dose escalation. Participants will undergo brain MRI examinations prior to dose increases (predose escalation MRI scans) to 510 mg Q4W and 510 mg Q2W and according to the schedule of activities once the target dose is achieved (see Section 1.3). These predose escalation MRI scans will determine eligibility for the next dose escalation dose. The investigators may choose to perform additional MRI monitoring for ARIA at any time.

Participants on target dose 255 mg SC Q1W: Before reaching the maximum target dose 255 mg Q1W, a minimum of 3 doses during 120 mg Q4W and 255 mg Q4W dosing periods, and a minimum of 6 doses during the 255 mg Q2W dosing period must be administered prior to dose escalation. Participants will undergo brain MRI examinations prior to dose increases (predose escalation MRI scans) to 255 mg Q2W and 255 mg Q1W and according to the schedule of activities once the target dose is achieved (see Section 1.3). These predose escalation MRI scans will determine eligibility for the next dose escalation dose. The investigators may choose to perform additional MRI monitoring for ARIA at any time.

Participants will be eligible for dose escalation if there is no new ARIA-E; or if the new ARIA-E is mild (Bioclinica severity = 1) and asymptomatic; or if the ARIA-E is resolved (Bioclinica severity = 0, asymptomatic), and if the criteria for permanent treatment discontinuation because of ARIA-H have not been met.

In addition, the dose adjustment and discontinuation rules for MRI findings specified in Table A3–1 will apply.

Additional measures for at-home administration: Every 4 weeks, except when there is an in-person clinic visit, the investigator or an appointed qualified study staff will have

a telephone conversation with the participant and/or study partner to elicit, in a non-leading way, information on medication errors and adverse events that may have occurred in the home setting. Therefore, there will be frequent contact between the study staff and the participant/study partner. Following the first 2 years of study treatment, the frequency of this telephone surveillance may be reduced to occur at least once, at midtime, between the 6-month in-person clinic visits. *However, for participants who enter the post-progression dose escalation period, there will be contact between the study staff and the participant/study partner at least every 4 weeks for 2 years after entering the post-progression dose escalation period (Table 3 and Table 6). Following this 2-year period, the frequency of this telephone surveillance can be reduced again as outlined above.* In addition, the participant and study partner must be instructed to contact the investigator and seek approval for continued study drug dosing in the home setting in case of onset of any new symptoms or symptom worsening. These requirements will aid symptomatic ARIA-E detection and dose intervention, as described below, in the case of an asymptomatic ARIA-E that becomes symptomatic at a later date.

The iDMC will review the incidence and other characteristics of ARIA in an unblinded manner and may recommend adjustment of dosing regimen and/or ARIA management for the overall study population or for a specific *APOE* ε4 genotype.

Table A3–1 Management Rules for Amyloid-Related Imaging Abnormalities

Finding	Characteristics	Action to be Taken
ARIA-E	**Asymptomatic** **Bioclinica severity** 1 (radiologically mild)	• Continue study drug according to the schedule of administration (including dose escalation) • Perform MRI scans at 4-week intervals until ARIA-E resolves • Then, resume the standard MRI schedule
	Asymptomatic **Bioclinica severity 2** (radiologically mild +) or **Bioclinica severity 3** (radiologically moderate)	**During *initial and post-progression* dose escalation periods:** • Continue study drug at the same dose level and do not up titrate • Perform MRI scans at 4-week intervals until ARIA-E resolves • Once ARIA-E resolves, continue dose escalation and resume the standard MRI schedule **During treatment period (at target dose):** • Continue study drug according to the schedule of administration • Perform MRI scans at 4-week intervals until ARIA-E resolves, Then, resume the standard MRI schedule.

Table A3–1 Management Rules for Amyloid-Related Imaging Abnormalities (cont.)

Finding	Characteristics	Action to be Taken
	Asymptomatic **Bioclinica severity 4** (radiologically moderate +) or **Bioclinica 5** (radiologically severe) OR **Symptomatic of any severity (Bioclinica 1–5)**	**During *initial and post-progression* dose escalation periods:** • Temporarily interrupt study drug • Perform MRI scans at 4-week intervals until ARIA-E (and any ARIA-E symptom/s) resolves • Once ARIA-E (and any ARIA-E symptom/s) resolves, reintroduce study drug at the dose level given at the time the event was detected • *Once dosing has been resumed, perform an MRI scan after the first dose while participants are on a Q4W dosing frequency, or after the second dose while participants are on a Q2W dosing frequency or after the third or fourth dose for participants on a Q1W dosing frequency* • If no new ARIA-E is detected, continue dose escalation and resume the standard MRI schedule **During treatment period (at target dose):** • Temporarily interrupt study drug • Perform MRI scans at 4-week intervals until ARIA-E (and any ARIA-E symptom/s) resolves • Once ARIA-E (and any ARIA-E symptom/s) resolves, reintroduce IMP • *Once dosing has been resumed, perform an MRI scan after the second dose while participants are on a Q2W dosing frequency or after the third or fourth dose for participants on a Q1W dosing frequency* • If no new ARIA-E is detected, resume the standard MRI schedule
	Any recurrence of ARIA-E	Treat as above
ARIA-H	**Without disseminated LH**	• Continue study drug according to the schedule of administration (including dose escalation) • Perform MRI scans according to the standard MRI schedule
	Disseminated LH	Permanently discontinue study drug

Table A3–1 Management Rules for Amyloid-Related Imaging Abnormalities (cont.)

Source: Bracoud et al. 2017.

ARIA-E = amyloid-related imaging abnormality–edema/effusion; ARIA-H = amyloid-related imaging abnormality–microhemorrhage/hemosiderin deposition; LH = leptomeningeal hemosiderosis; MRI = magnetic resonance imaging; PK = pharmacokinetic; Q1W = every week; Q2W = every 2 weeks; Q4W = every 4 weeks.

Notes:

- The investigator may choose to perform additional MRI monitoring for ARIA at any time
- Symptomatic ARIA-E is defined as onset or worsening of CNS symptom(s) that is/are attributable to ARIA-E MRI findings in the judgment of the Principal Investigator
- Disseminated LH is defined as more than 3 focal leptomeningeal hemosiderosis *cumulatively*
- If ARIA-E and disseminated LH co-occur, the more conservative management rule will apply
- Any other new significant MRI findings will be reviewed by the *investigator* and appropriate dose action will be taken
- In exceptional cases, as determined by the investigator:

  1) Q4W MRI monitoring may no longer be necessary in case of an ARIA-E that is asymptomatic with Bioclinica severity 1 and considered stable over consecutive MRI images; or a symptomatic ARIA-E for which the imaging evidence of ARIA-E has resolved but the CNS symptoms continue

  2) study drug can be either reintroduced or up-titrated, as applicable, in case of an asymptomatic ARIA-E that has stabilized at Bioclinica severity 1; or a symptomatic ARIA-E for which the imaging evidence of ARIA-E has resolved but the CNS symptoms continue.
- A PK sample will be obtained as soon as soon as practicable (e.g., at an unscheduled visit or the next study visit) following a MRI scan showing new occurrence or worsening of ARIA-E or ARIA-H that meets the discontinuation criteria (e.g., during an unscheduled visit)
- A plasma biomarker sample for the assessment of exploratory biomarkers will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E).

REFERENCES

Barkhof F, Daams M, Scheltens P, et al. AJNR Am J Neuroradiol 2013;34:1550–5.

Black RS, Sperling RA, Safirstein B, et al. A single ascending dose study of bapineuzumab in pateints with Alzheimer's disease. Alzheimer Dis Assoc Disord 2010;24:198–203.

Bracoud L, Fiebach JB, Purcell DD, et al. [P1–047]: Validation of a simple severity scale for assessing ARIA-E. Alzheimer's Assoc 2017;13:P253–4.

Haeberlein SB, von Hehn C, Tian Y, et al. EMERGE and ENGAGE topline results: two Phase 3 studies to evaluate aducanumab in patients with early alzheimer's

disease [resource on the Internet] 2019. Available from : https://investors.biogen.com/static-files/8e58afa4-ba37-4250-9a78-2ecfb63b1dcb.

Lin GA, Whittington MD, Synnott PG, et al. Aducanumab for alzheimer's disease: effectiveness and value. Draft evidence report. Institute for Clinical and Economic Review. [resource on the Internet] 2021. Available from: https://icer.org/wp-content/uploads/2020/10/ICER_ALZ_Draft_Evidence_Report_050521.pdf.

Piazza F, Winblad B. Amyloid-Related Imaging Abnormalities (ARIA) in immunotherapy trials for Alzheimer's disease: need for prognostic biomarkers? J Alzheimer's Dis 2016;52:417–20.

Sperling R, Salloway S, Brooks DJ, et al. Amyloid-related imaging abnormalities in patients with Alzheimer's disease treated with bapineuzumab: a retrospective anaysis. Lancet Neurol 2012;11:241–9.

Verbruggen A, Coenen HH, Deverre J, et al. Guideline to regulations for radiopharmaceuticals in early phase clinical trials in the EU. Eur J Nucl Med Mol Imaging 2008;35:2144–51.

Appendix 4 Contraceptive and Barrier Guidance

TABLE OF CONTENTS

A4–1. 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 17 weeks after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the pregnancy), either by faxing or by scanning and e-mailing the form, using the fax number or e-mail address provided to investigators. Pregnancy should not be recorded on the Adverse Event electronic Case Report Form (eCRF). The investigator should discontinue study treatment 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 events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly or 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.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A4–2. 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 the investigator becomes aware of the event; see Section A2–5).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal 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 the investigator becomes aware of the event; see Section A2–5). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

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

A4–3. ABNORMAL PREGNANCY OUTCOMES

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomaly, birth defect, ectopic pregnancy) in a female participant exposed to study treatment 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 the investigator becomes aware of the event; see Section A2–5).

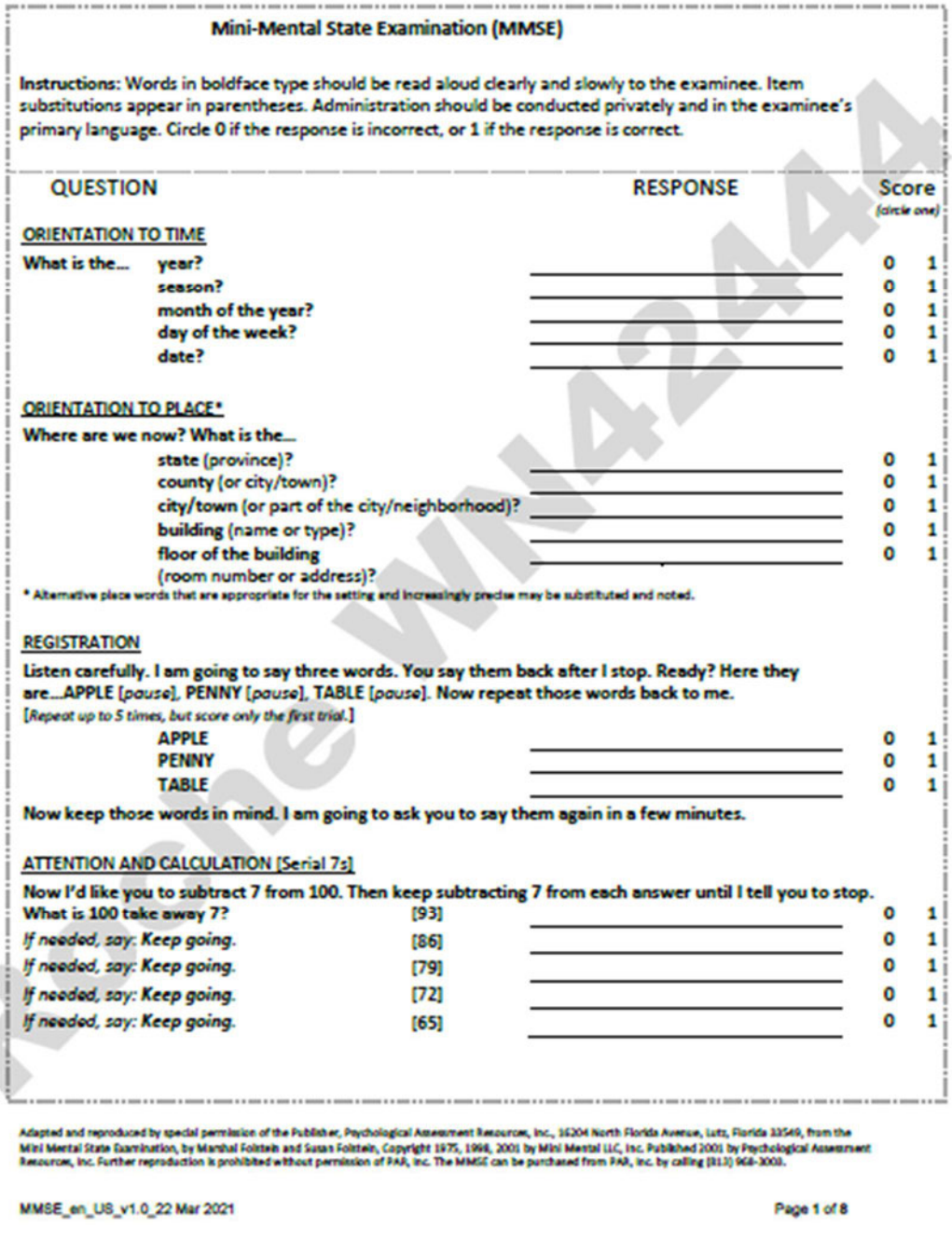
Appendix 5 Reporting Requirements for Medical Device Complaints

In this study, the vial adapter may be provided to the participant or study partner (non-professional caregiver), in countries where it has been approved, to aid study drug administration in the home setting is considered a medical device. The investigator must report all device deficiencies to the Sponsor in the form of a medical device complaint. A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance, and it can include malfunctions, use errors, and inadequate labeling. In reporting a medical device complaint, the investigator should document as much information as possible on the Investigational Medicinal Product Deviation Form, including the product batch number, as reported on the blister, and forward the form to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; refer to the Pharmacy Manual for further details). If the medical device deficiency results in an adverse event to the study participant, the event must be reported on the Adverse Event electronic Case Report Form (CRF) and submitted through the EDC system. If the event fulfills seriousness criteria, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), as outlined in Section A2–5.

Appendix 6 Mini-Mental State Examination (Preclinical Alzheimer's Cognitive Composite–5) — Form A, B, and C

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

FORM A



Mini-Mental State Examination (MMSE)

Instructions: Words in boldface type should be read aloud clearly and slowly to the examinee. Item substitutions appear in parentheses. Administration should be conducted privately and in the examinee's primary language. Circle 0 if the response is incorrect, or 1 if the response is correct.

QUESTION			RESPONSE	Score (circle one)
ORIENTATION TO TIME				
What is the...	year?		_____	0 1
	season?		_____	0 1
	month of the year?		_____	0 1
	day of the week?		_____	0 1
	date?		_____	0 1
ORIENTATION TO PLACE*				
Where are we now? What is the...				
	state (province)?		_____	0 1
	county (or city/town)?		_____	0 1
	city/town (or part of the city/neighborhood)?		_____	0 1
	building (name or type)?		_____	0 1
	floor of the building (room number or address)?		_____	0 1
REGISTRATION				
Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are...APPLE [*pause*], PENNY [*pause*], TABLE [*pause*]. Now repeat those words back to me. [*Repeat up to 5 times, but score only the first trial.*]				
	APPLE		_____	0 1
	PENNY		_____	0 1
	TABLE		_____	0 1
Now keep those words in mind. I am going to ask you to say them again in a few minutes.				
ATTENTION AND CALCULATION [Serial 7s]				
Now I'd like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop.				
What is 100 take away 7?		[93]	_____	0 1
If needed, say: Keep going.		[86]	_____	0 1
If needed, say: Keep going.		[79]	_____	0 1
If needed, say: Keep going.		[72]	_____	0 1
If needed, say: Keep going.		[65]	_____	0 1

* Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted.

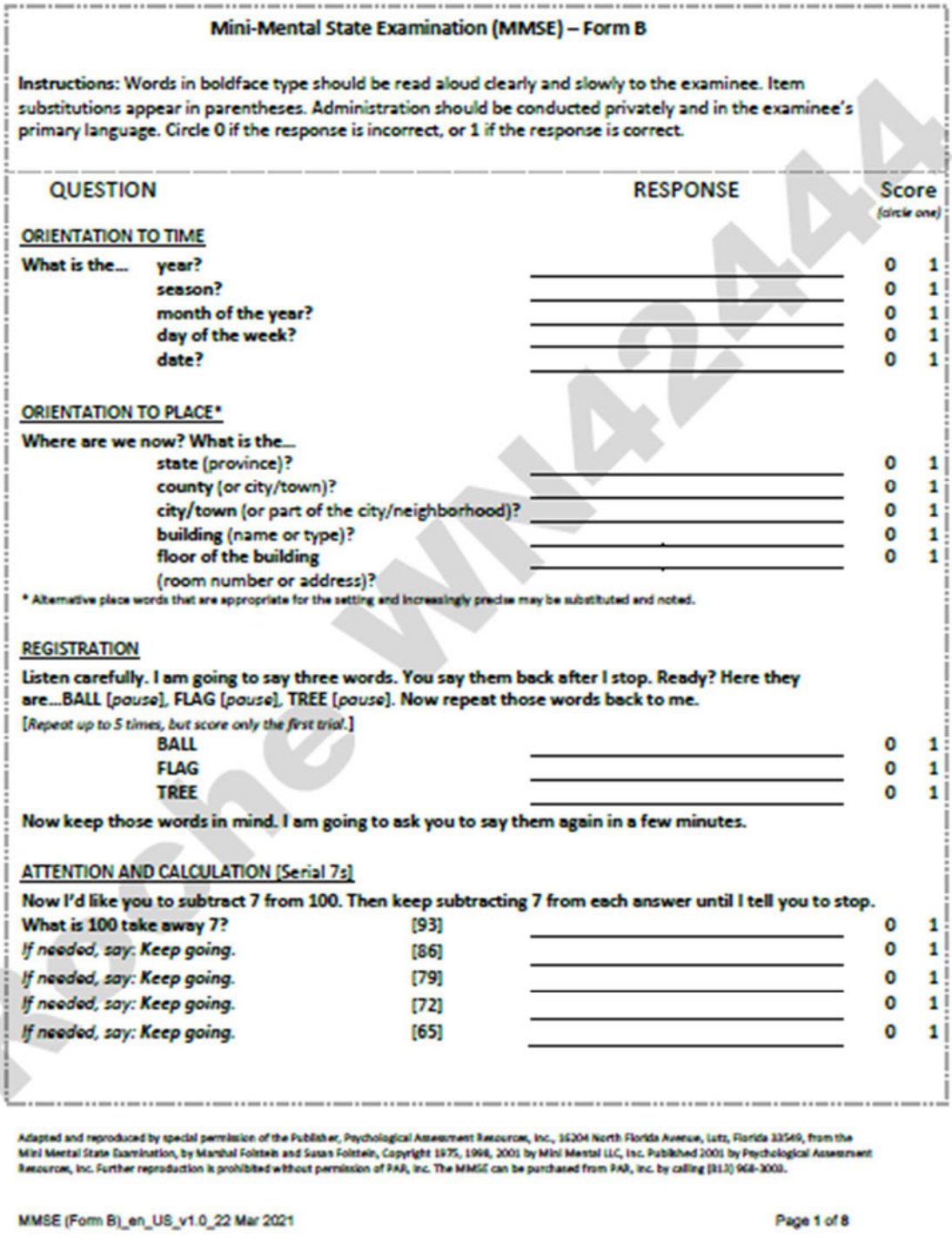
Appendix 6: Mini-Mental State Examination (Preclinical Alzheimer's Cognitive Composite–5) — Form A, B, and C

QUESTION	RESPONSE	Score (circle one)
RECALL		
What were those three words I asked you to remember? [Do not offer any hints.]		
APPLE	_____	0 1
PENNY	_____	0 1
TABLE	_____	0 1
NAMING		
What is this? [*Point to a pencil or pen*]	_____	0 1
What is this? [*Point to a watch*]	_____	0 1
REPETITION		
Now I am going to ask you to repeat what I say. Ready? "NO IFS, ANDS, OR BUTS." Now you say that. [*Repeat up to 5 times, but score only the first trial.*]		
NO IFS, ANDS, OR BUTS.	_____	0 1
COMPREHENSION		
Listen carefully because I am going to ask you to do something. **Take this paper in your right hand** [*pause*], **fold it in half** [*pause*], **and put it on the floor** (*or* **table**).		
TAKE IN RIGHT HAND	_____	0 1
FOLD IN HALF	_____	0 1
PUT ON FLOOR (*or* TABLE)	_____	0 1
READING		
Please read this and do what it says. [*Show examinee the words on the stimulus form.*]		
CLOSE YOUR EYES	_____	0 1
WRITING		
Please write a sentence. [*If examinee does not respond, say*: **Write about the weather.**] Place the blank piece of paper in front of the examinee and provide a pen. Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar and spelling.		0 1
DRAWING		
Please copy this design. [*Display the intersecting pentagons on the stimulus form.*] Score 1 point if the drawing consists of two 5-sided figures that intersect to form a 4-sided figure.		0 1
MMSE Total Score: (*Sum all item scores*)		☐
		(*30 points max*)

CLOSE YOUR EYES

Appendix 6: Mini-Mental State Examination (Preclinical Alzheimer's Cognitive Composite–5) — Form A, B, and C

FORM B



Mini-Mental State Examination (MMSE) – Form B

Instructions: Words in boldface type should be read aloud clearly and slowly to the examinee. Item substitutions appear in parentheses. Administration should be conducted privately and in the examinee's primary language. Circle 0 if the response is incorrect, or 1 if the response is correct.

QUESTION			RESPONSE	Score (circle one)
ORIENTATION TO TIME				
What is the...	year?			0 1
	season?			0 1
	month of the year?			0 1
	day of the week?			0 1
	date?			0 1
ORIENTATION TO PLACE*				
Where are we now? What is the...				
	state (province)?			0 1
	county (or city/town)?			0 1
	city/town (or part of the city/neighborhood)?			0 1
	building (name or type)?			0 1
	floor of the building (room number or address)?			0 1
REGISTRATION				
Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are...BALL [*pause*], FLAG [*pause*], TREE [*pause*]. Now repeat those words back to me. [*Repeat up to 5 times, but score only the first trial.*]				
	BALL			0 1
	FLAG			0 1
	TREE			0 1
Now keep those words in mind. I am going to ask you to say them again in a few minutes.				
ATTENTION AND CALCULATION [Serial 7s]				
Now I'd like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop.				
What is 100 take away 7?		[93]		0 1
If needed, say: Keep going.		[86]		0 1
If needed, say: Keep going.		[79]		0 1
If needed, say: Keep going.		[72]		0 1
If needed, say: Keep going.		[65]		0 1

* Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted.

QUESTION	RESPONSE	Score (circle one)
RECALL		
What were those three words I asked you to remember? [Do not offer any hints.]		
BALL	_____	0 1
FLAG	_____	0 1
TREE	_____	0 1
NAMING		
What is this? [*Point to a pencil or pen*]	_____	0 1
What is this? [*Point to a watch*]	_____	0 1
REPETITION		
Now I am going to ask you to repeat what I say. Ready? "NO IFS, ANDS, OR BUTS." Now you say that. [*Repeat up to 5 times, but score only the first trial.*]		
NO IFS, ANDS, OR BUTS.	_____	0 1
COMPREHENSION		
Listen carefully because I am going to ask you to do something. **Take this paper in your right hand** [*pause*], **fold it in half** [*pause*], **and put it on the floor** (*or* **table**).		
TAKE IN RIGHT HAND	_____	0 1
FOLD IN HALF	_____	0 1
PUT ON FLOOR (*or* TABLE)	_____	0 1
READING		
Please read this and do what it says. [*Show examinee the words on the stimulus form.*]		
CLOSE YOUR EYES	_____	0 1
WRITING		
Please write a sentence. [*If examinee does not respond, say*: **Write about the weather.**] Place the blank piece of paper in front of the examinee and provide a pen. Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar and spelling.		0 1
DRAWING		
Please copy this design. [*Display the intersecting pentagons on the stimulus form.*] Score 1 point if the drawing consists of two 5-sided figures that intersect to form a 4-sided figure.		0 1
MMSE Total Score: *(Sum all item scores)*		☐ *(30 points max)*

CLOSE YOUR EYES

Appendix 6: Mini-Mental State Examination (Preclinical Alzheimer's Cognitive Composite–5) — Form A, B, and C

FORM C

Mini-Mental State Examination (MMSE) – Form C

Instructions: Words in boldface type should be read aloud clearly and slowly to the examinee. Item substitutions appear in parentheses. Administration should be conducted privately and in the examinee's primary language. Circle 0 if the response is incorrect, or 1 if the response is correct.

QUESTION		RESPONSE	Score (circle one)
ORIENTATION TO TIME			
What is the...	year?	_____	0 1
	season?	_____	0 1
	month of the year?	_____	0 1
	day of the week?	_____	0 1
	date?	_____	0 1
ORIENTATION TO PLACE*			
Where are we now? What is the...			
	state (province)?	_____	0 1
	county (or city/town)?	_____	0 1
	city/town (or part of the city/neighborhood)?	_____	0 1
	building (name or type)?	_____	0 1
	floor of the building (room number or address)?	_____	0 1

* Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted.

REGISTRATION

Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are...PONY [*pause*], QUARTER [*pause*], ORANGE [*pause*]. Now repeat those words back to me.
[*Repeat up to 5 times, but score only the first trial.*]

PONY	_____	0 1
QUARTER	_____	0 1
ORANGE	_____	0 1

Now keep those words in mind. I am going to ask you to say them again in a few minutes.

ATTENTION AND CALCULATION [Serial 7s]

Now I'd like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop.

What is 100 take away 7?	[93]	_____	0 1
If needed, say: Keep going.	[86]	_____	0 1
If needed, say: Keep going.	[79]	_____	0 1
If needed, say: Keep going.	[72]	_____	0 1
If needed, say: Keep going.	[65]	_____	0 1

Appendix 6: Mini-Mental State Examination (Preclinical Alzheimer's Cognitive Composite–5) — Form A, B, and C

QUESTION	RESPONSE	Score (circle one)
RECALL		
What were those three words I asked you to remember? [Do not offer any hints.]		
PONY	_____	0 1
QUARTER	_____	0 1
ORANGE	_____	0 1
NAMING		
What is this? [*Point to a pencil or pen*]	_____	0 1
What is this? [*Point to a watch*]	_____	0 1
REPETITION		
Now I am going to ask you to repeat what I say. Ready? "NO IFS, ANDS, OR BUTS." Now you say that. [*Repeat up to 5 times, but score only the first trial.*]		
NO IFS, ANDS, OR BUTS.	_____	0 1
COMPREHENSION		
Listen carefully because I am going to ask you to do something. Take this paper in your right hand [*pause*], **fold it in half** [*pause*], **and put it on the floor** (*or* **table**).		
TAKE IN RIGHT HAND	_____	0 1
FOLD IN HALF	_____	0 1
PUT ON FLOOR (*or* TABLE)	_____	0 1
READING		
Please read this and do what it says. [*Show examinee the words on the stimulus form.*]		
CLOSE YOUR EYES	_____	0 1
WRITING		
Please write a sentence. [*If examinee does not respond, say:* **Write about the weather.**] Place the blank piece of paper in front of the examinee and provide a pen. Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar and spelling.		0 1
DRAWING		
Please copy this design. [*Display the intersecting pentagons on the stimulus form.*] Score 1 point if the drawing consists of two 5-sided figures that intersect to form a 4-sided figure.		0 1
MMSE Total Score: (*Sum all item scores*)		(*30 points max*)

CLOSE YOUR EYES

Appendix 6: Mini-Mental State Examination (Preclinical Alzheimer's Cognitive Composite–5) — Form A, B, and C

REFERENCES

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

Jaeger J. Digit Symbol Substitution Test: the case for sensitivity over specificity in neuropsychological testing. J Clin Psychopharmacol 2018;38:513–9.

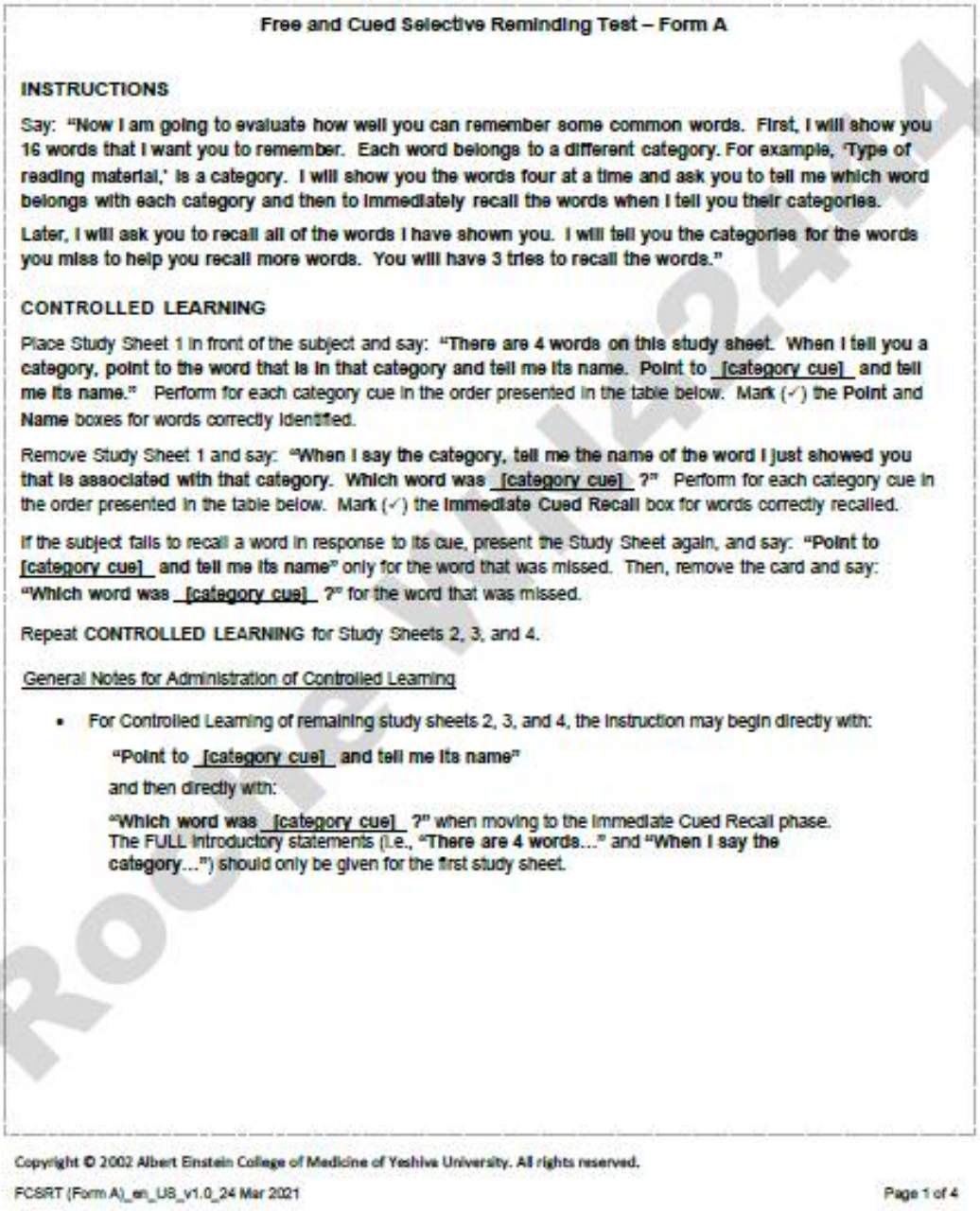
Papp KV, Rentz DM, Orlovsky I, et al. Optimizing the preclinical Alzheimer's cognitive composite with semantic processing: the PACC5. Alzheimer's Dement (NY) 2017;3:668–77.

Papp KV, Buckley R, Mormino E, et al. Clinical meaningfulness of subtle cognitive decline on longitudinal testing in preclinical AD. Alzheimer's Dement 2020;16:552–60.

Appendix 7 FCSRT–IR+DR (Preclinical Alzheimer's Cognitive Composite–5) — Form A, B, and C

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

FORM A



Free and Cued Selective Reminding Test – Form A

INSTRUCTIONS

Say: **"Now I am going to evaluate how well you can remember some common words. First, I will show you 16 words that I want you to remember. Each word belongs to a different category. For example, 'Type of reading material,' is a category. I will show you the words four at a time and ask you to tell me which word belongs with each category and then to immediately recall the words when I tell you their categories.**

Later, I will ask you to recall all of the words I have shown you. I will tell you the categories for the words you miss to help you recall more words. You will have 3 tries to recall the words."

CONTROLLED LEARNING

Place Study Sheet 1 in front of the subject and say: **"There are 4 words on this study sheet. When I tell you a category, point to the word that is in that category and tell me its name. Point to [category cue] and tell me its name."** Perform for each category cue in the order presented in the table below. Mark (✓) the **Point** and **Name** boxes for words correctly identified.

Remove Study Sheet 1 and say: **"When I say the category, tell me the name of the word I just showed you that is associated with that category. Which word was [category cue] ?"** Perform for each category cue in the order presented in the table below. Mark (✓) the **Immediate Cued Recall** box for words correctly recalled.

If the subject fails to recall a word in response to its cue, present the Study Sheet again, and say: **"Point to [category cue] and tell me its name"** only for the word that was missed. Then, remove the card and say: **"Which word was [category cue] ?"** for the word that was missed.

Repeat **CONTROLLED LEARNING** for Study Sheets 2, 3, and 4.

General Notes for Administration of Controlled Learning

- For Controlled Learning of remaining study sheets 2, 3, and 4, the instruction may begin directly with:

  "Point to [category cue] and tell me its name"

  and then directly with:

  "Which word was [category cue] ?" when moving to the Immediate Cued Recall phase. The FULL introductory statements (i.e., **"There are 4 words..."** and **"When I say the category..."**) should only be given for the first study sheet.

FCSRT (Form A)_en_US_v1.0_24 Mar 2021 Page 1 of 4

- If at any point in the FCSRT the rater accidentally provides the name of the word when intending to cue with the category name, make note of the occurrence on the worksheet and give the participant benefit of the doubt, awarding credit for recall of that word.

	Category Cue	Word	Point	Name		Immediate Cued Recall
Sheet 1	Fruit	Grapes				
	Sports Equipment	Racquet				
	Bird	Owl				
	Furniture	Desk				
Sheet 2	Part of a Building	Chimney				
	Type of Boat	Submarine				
	Office Supplies	Paper Clip				
	A Fish	Shark				
Sheet 3	Used for Measuring	Ruler				
	For Seeing	Binoculars				
	Kind of Plant	Cactus				
	Used by Babies	Rattle				
Sheet 4	Part of a Car	Steering Wheel				
	For Holding Liquids	Pitcher (jug)				
	A Toiletry	Razor				
	Musical Instrument	Guitar				

INTERFERENCE: Before TRIAL 1 FREE RECALL, say: **"Now count backwards from 100 by 3's."** Allow the subject to count backwards for 20 seconds.

FREE RECALL: Say: **"Tell me all the words you can remember, in any order."**

Allow 90 seconds for Free Recall of all words. Stop if no words have been recalled for 15 seconds. Mark (✓) the F box for words freely recalled. Proceed to CUED RECALL for each word that was not freely recalled.

CUED RECALL: (as needed) Say: **"Which word was [category cue] ?"**

Allow up to 10 seconds for Cued Recall of each word. Mark (✓) the C box for words recalled following a cue.

If the subject does not correctly recall the word following its category cue, say: **"The [category cue] was a/an [word] ."** and mark (✓) the **SR** (i.e., selective reminding) box. Then, proceed to the next word that requires cued recall. When cued recall with selective reminding is completed, proceed to TRIAL 2.

TRIAL 2: Repeat the **INTERFERENCE, FREE RECALL,** and **CUED RECALL** with **SELECTIVE REMINDING** procedures.

TRIAL 3: Repeat the **INTERFERENCE, FREE RECALL,** and **CUED RECALL** with **SELECTIVE REMINDING** procedures.

		Trial 1			Trial 2			Trial 3			
Category Cue	Word	F	C	SR	F	C	SR	F	C	SR	Word
Fruit	Grapes										Grapes
Sports Equipment	Racquet										Racquet
Bird	Owl										Owl
Furniture	Desk										Desk
Part of a Building	Chimney										Chimney
Type of Boat	Submarine										Submarine
Office Supplies	Paper Clip										Paper Clip
A Fish	Shark										Shark
Used for Measuring	Ruler										Ruler
For Seeing	Binoculars										Binoculars
Kind of Plant	Cactus										Cactus
Used by Babies	Rattle										Rattle
Part of a Car	Steering Wheel										Steering Wheel
For Holding Liquids	Pitcher (jug)										Pitcher (jug)
A Toiletry	Razor										Razor
Musical Instrument	Guitar										Guitar
	TOTAL FREE		↓			↓			↓		
	TOTAL CUED										

Time Trial 3 of FCSRT Free and Cued Recall ended: _____:_____ (24-hour clock)
(HH : MM)

DELAYED RECALL

Wait 20-30 minutes after the completion of Trial 3 of Free and Cued Recall (i.e., at least 20 minutes but no more than 30 minutes) to assess Delayed Recall. Record the clock time below to indicate the time that Delayed Recall procedures began. Do not use count down interference before Delayed Recall. Do not provide selective reminding during the Delayed Recall procedures.

Time FCSRT Delayed Recall began: _____:_____ (24-hour clock)
(HH : MM)

FREE RECALL: Say: **"Do you remember the words I showed you on the 4 sheets earlier? Tell me all of the words you can remember now, in any order."**

Allow 90 seconds for Free Recall of all words. Stop if no words have been recalled for 15 seconds. Mark (✓) the **Free Recall** box for words freely recalled. Proceed to CUED RECALL for each word that was not freely recalled.

CUED RECALL: (as needed) Say: **"Which word was [category cue] ?"**

Allow up to 10 seconds for Cued Recall of each word. Mark (✓) the **Cued Recall** box for words recalled following a cue.

		Delayed	
Category Cue	**Word**	**Free Recall**	**Cued Recall**
Fruit	Grapes		
Sports Equipment	Racquet		
Bird	Owl		
Furniture	Desk		
Part of a Building	Chimney		
Type of Boat	Submarine		
Office Supplies	Paper Clip		
A Fish	Shark		
Used for Measuring	Ruler		
For Seeing	Binoculars		
Kind of Plant	Cactus		
Used by Babies	Rattle		
Part of a Car	Steering Wheel		
For Holding Liquids	Pitcher (jug)		
A Toiletry	Razor		
Musical Instrument	Guitar		
	TOTAL FREE		↓
	TOTAL CUED		

FORM B

Free and Cued Selective Reminding Test – Form B

INSTRUCTIONS

Say: **"Now I am going to evaluate how well you can remember some common words. First, I will show you 16 words that I want you to remember. Each word belongs to a different category. For example, 'Type of reading material,' is a category. I will show you the words four at a time and ask you to tell me which word belongs with each category and then to immediately recall the words when I tell you their categories.**

Later, I will ask you to recall all of the words I have shown you. I will tell you the categories for the words you miss to help you recall more words. You will have 3 tries to recall the words."

CONTROLLED LEARNING

Place Study Sheet 1 in front of the subject and say: **"There are 4 words on this study sheet. When I tell you a category, point to the word that is in that category and tell me its name. Point to [category cue] and tell me its name."** Perform for each category cue in the order presented in the table below. Mark (✓) the **Point** and **Name** boxes for words correctly identified.

Remove Study Sheet 1 and say: **"When I say the category, tell me the name of the word I just showed you that is associated with that category. Which word was [category cue] ?"** Perform for each category cue in the order presented in the table below. Mark (✓) the **Immediate Cued Recall** box for words correctly recalled.

If the subject fails to recall a word in response to its cue, present the Study Sheet again, and say: **"Point to [category cue] and tell me its name"** only for the word that was missed. Then, remove the card and say: **"Which word was [category cue] ?"** for the word that was missed.

Repeat **CONTROLLED LEARNING** for Study Sheets 2, 3, and 4.

General Notes for Administration of Controlled Learning

- For Controlled Learning of remaining study sheets 2, 3, and 4, the instruction may begin directly with:

  "Point to [category cue] and tell me its name"

  and then directly with:

  "Which word was [category cue] ?" when moving to the Immediate Cued Recall phase. The FULL introductory statements (i.e., **"There are 4 words..."** and **"When I say the category..."**) should only be given for the first study sheet.

- If at any point in the FCSRT the rater accidentally provides the name of the word when intending to cue with the category name, make note of the occurrence on the worksheet and give the participant benefit of the doubt, awarding credit for recall of that word.

	Category Cue	Word	Point	Name		Immediate Cued Recall
Sheet 1	Like an Insect	Spider				
	Part of the Body	Foot				
	Something that Makes Noise	Bell				
	Found in Hospitals	Wheelchair				
Sheet 2	Weather Phenomenon	Clouds				
	Part of a Ship	Anchor				
	Jewelry	Watch				
	Vegetable	Onion				
Sheet 3	Clothing	Vest				
	Toy	Kite				
	A Number	Nine				
	For Sitting	Bench				
Sheet 4	Type of Light	Candle				
	Weapon	Sword				
	For Sewing	Thread				
	Kitchen Appliance	Toaster				

INTERFERENCE: Before TRIAL 1 FREE RECALL, say: **"Now count backwards from 100 by 3's."** Allow the subject to count backwards for 20 seconds.

FREE RECALL: Say: **"Tell me all the words you can remember, in any order."**

Allow 90 seconds for Free Recall of all words. Stop if no words have been recalled for 15 seconds. Mark (✓) the F box for words freely recalled. Proceed to CUED RECALL for each word that was not freely recalled.

CUED RECALL: (as needed) Say: **"Which word was [category cue] ?"**

Allow up to 10 seconds for Cued Recall of each word. Mark (✓) the C box for words recalled following a cue.

If the subject does not correctly recall the word following its category cue, say: **"The [category cue] was a/an [word] ."** and mark (✓) the SR (i.e., selective reminding) box. Then, proceed to the next word that requires cued recall. When cued recall with selective reminding is completed, proceed to TRIAL 2.

TRIAL 2: Repeat the **INTERFERENCE, FREE RECALL, and CUED RECALL with SELECTIVE REMINDING** procedures.

TRIAL 3: Repeat the **INTERFERENCE, FREE RECALL, and CUED RECALL with SELECTIVE REMINDING** procedures.

		Trial 1			Trial 2			Trial 3			
Category Cue	Word	F	C	SR	F	C	SR	F	C	SR	Word
Like an Insect	Spider										Spider
Part of the Body	Foot										Foot
Something that Makes Noise	Bell										Bell
Found in Hospitals	Wheelchair										Wheelchair
Weather Phenomenon	Clouds										Clouds
Part of a Ship	Anchor										Anchor
Jewelry	Watch										Watch
Vegetable	Onion										Onion
Clothing	Vest										Vest
Toy	Kite										Kite
A Number	Nine										Nine
For Sitting	Bench										Bench
Type of Light	Candle										Candle
Weapon	Sword										Sword
For Sewing	Thread										Thread
Kitchen Appliance	Toaster										Toaster
	TOTAL FREE		↓			↓			↓		
	TOTAL CUED										

Time Trial 3 of FCSRT Free and Cued Recall ended: _____:_____ (24-hour clock)
(HH : MM)

DELAYED RECALL

Wait 20-30 minutes after the completion of Trial 3 of Free and Cued Recall (i.e., at least 20 minutes but no more than 30 minutes) to assess Delayed Recall. Record the clock time below to indicate the time that Delayed Recall procedures began. Do not use count down interference before Delayed Recall. Do not provide selective reminding during the Delayed Recall procedures.

Time FCSRT Delayed Recall began: _____:_____ **(24-hour clock)**
(HH : MM)

FREE RECALL: Say: **"Do you remember the words I showed you on the 4 sheets earlier? Tell me all of the words you can remember now, in any order."**

Allow 90 seconds for Free Recall of all words. Stop if no words have been recalled for 15 seconds. Mark (✓) the **Free Recall** box for words freely recalled. Proceed to CUED RECALL for each word that was not freely recalled.

CUED RECALL: (as needed) Say: **"Which word was [category cue] ?"**

Allow up to 10 seconds for Cued Recall of each word. Mark (✓) the **Cued Recall** box for words recalled following a cue.

		Delayed	
Category Cue	**Word**	**Free Recall**	**Cued Recall**
Like an Insect	Spider		
Part of the Body	Foot		
Something that Makes Noise	Bell		
Found in Hospitals	Wheelchair		
Weather Phenomenon	Clouds		
Part of a Ship	Anchor		
Jewelry	Watch		
Vegetable	Onion		
Clothing	Vest		
Toy	Kite		
A Number	Nine		
For Sitting	Bench		
Type of Light	Candle		
Weapon	Sword		
For Sewing	Thread		
Kitchen Appliance	Toaster		
	TOTAL FREE		↓
	TOTAL CUED		

FORM C

Free and Cued Selective Reminding Test – Form C

INSTRUCTIONS

Say: **"Now I am going to evaluate how well you can remember some common words. First, I will show you 16 words that I want you to remember. Each word belongs to a different category. For example, 'Type of reading material,' is a category. I will show you the words four at a time and ask you to tell me which word belongs with each category and then to immediately recall the words when I tell you their categories.**

Later, I will ask you to recall all of the words I have shown you. I will tell you the categories for the words you miss to help you recall more words. You will have 3 tries to recall the words."

CONTROLLED LEARNING

Place Study Sheet 1 in front of the subject and say: **"There are 4 words on this study sheet. When I tell you a category, point to the word that is in that category and tell me its name. Point to [category cue] and tell me its name."** Perform for each category cue in the order presented in the table below. Mark (✓) the **Point** and **Name** boxes for words correctly identified.

Remove Study Sheet 1 and say: **"When I say the category, tell me the name of the word I just showed you that is associated with that category. Which word was [category cue] ?"** Perform for each category cue in the order presented in the table below. Mark (✓) the **Immediate Cued Recall** box for words correctly recalled.

If the subject fails to recall a word in response to its cue, present the Study Sheet again, and say: **"Point to [category cue] and tell me its name"** only for the word that was missed. Then, remove the card and say: **"Which word was [category cue] ?"** for the word that was missed.

Repeat **CONTROLLED LEARNING** for Study Sheets 2, 3, and 4.

General Notes for Administration of Controlled Learning

- For Controlled Learning of remaining study sheets 2, 3, and 4, the instruction may begin directly with:

  "Point to [category cue] and tell me its name"

  and then directly with:

  "Which word was [category cue] ?" when moving to the Immediate Cued Recall phase. The FULL introductory statements (i.e., **"There are 4 words..."** and **"When I say the category..."**) should only be given for the first study sheet.

- If at any point in the FCSRT the rater accidentally provides the name of the word when intending to cue with the category name, make note of the occurrence on the worksheet and give the participant benefit of the doubt, awarding credit for recall of that word.

	Category Cue	Word	Point	Name		Immediate Cued Recall
Sheet 1	4-footed Animal	Bear				
	Worn on Feet	Skate (Roller Skate)				
	A Kitchen Utensil	Rolling Pin				
	For Cleaning Up	Broom				
Sheet 2	Earth Formation	Volcano				
	Transportation	Train				
	A Game	Dominoes				
	Something Sweet to Eat	Cake (Piece of Cake)				
Sheet 3	Worn on the Head	Crown				
	A Shape	Triangle				
	Kind of Building	Cabin				
	A Flower	Tulip				
Sheet 4	Tool	Axe				
	For Smoking	Pipe				
	Party Decoration	Balloons				
	For Carrying Things	Basket				

INTERFERENCE: Before TRIAL 1 FREE RECALL, say: **"Now count backwards from 100 by 3's."** Allow the subject to count backwards for 20 seconds.

FREE RECALL: Say: **"Tell me all the words you can remember, in any order."**

Allow 90 seconds for Free Recall of all words. Stop if no words have been recalled for 15 seconds. Mark (✓) the F box for words freely recalled. Proceed to CUED RECALL for each word that was not freely recalled.

CUED RECALL: (as needed) Say: **"Which word was [category cue] ?"**

Allow up to 10 seconds for Cued Recall of each word. Mark (✓) the C box for words recalled following a cue.

If the subject does not correctly recall the word following its category cue, say: **"The [category cue] was a/an [word] ."** and mark (✓) the SR (i.e., selective reminding) box. Then, proceed to the next word that requires cued recall. When cued recall with selective reminding is completed, proceed to TRIAL 2.

TRIAL 2: Repeat the **INTERFERENCE, FREE RECALL, and CUED RECALL with SELECTIVE REMINDING** procedures.

TRIAL 3: Repeat the **INTERFERENCE, FREE RECALL, and CUED RECALL with SELECTIVE REMINDING** procedures.

		Trial 1			Trial 2			Trial 3			
Category Cue	Word	F	C	SR	F	C	SR	F	C	SR	Word
4-footed Animal	Bear										Bear
Worn on Feet	Skate (Roller Skate)										Skate (Roller Skate)
A Kitchen Utensil	Rolling Pin										Rolling Pin
For Cleaning Up	Broom										Broom
Earth Formation	Volcano										Volcano
Transportation	Train										Train
A Game	Dominoes										Dominoes
Something Sweet to Eat	Cake (Piece of Cake)										Cake (Piece of Cake)
Worn on the Head	Crown										Crown
A Shape	Triangle										Triangle
Kind of Building	Cabin										Cabin
A Flower	Tulip										Tulip
Tool	Axe										Axe
For Smoking	Pipe										Pipe
Party Decoration	Balloons										Balloons
For Carrying Things	Basket										Basket
	TOTAL FREE		↓			↓			↓		
	TOTAL CUED										

Time Trial 3 of FCSRT Free and Cued Recall ended: _____:_____ (24-hour clock)
(HH : MM)

DELAYED RECALL

Wait 20-30 minutes after the completion of Trial 3 of Free and Cued Recall (i.e., at least 20 minutes but no more than 30 minutes) to assess Delayed Recall. Record the clock time below to indicate the time that Delayed Recall procedures began. Do not use count down interference before Delayed Recall. Do not provide selective reminding during the Delayed Recall procedures.

Time FCSRT Delayed Recall began: _____:_____ (24-hour clock)
(HH : MM)

FREE RECALL: Say: **"Do you remember the words I showed you on the 4 sheets earlier? Tell me all of the words you can remember now, in any order."**

Allow 90 seconds for Free Recall of all words. Stop if no words have been recalled for 15 seconds. Mark (✓) the **Free Recall** box for words freely recalled. Proceed to CUED RECALL for each word that was not freely recalled.

CUED RECALL: (as needed) Say: **"Which word was [category cue] ?"**

Allow up to 10 seconds for Cued Recall of each word. Mark (✓) the **Cued Recall** box for words recalled following a cue.

		Delayed	
Category Cue	**Word**	**Free Recall**	**Cued Recall**
4-footed Animal	Bear		
Worn on Feet	Skate (Roller Skate)		
A Kitchen Utensil	Rolling Pin		
For Cleaning Up	Broom		
Earth Formation	Volcano		
Transportation	Train		
A Game	Dominoes		
Something Sweet to Eat	Cake (Piece of Cake)		
Worn on the Head	Crown		
A Shape	Triangle		
Kind of Building	Cabin		
A Flower	Tulip		
Tool	Axe		
For Smoking	Pipe		
Party Decoration	Balloons		
For Carrying Things	Basket		
	TOTAL FREE		↓
	TOTAL CUED		

REFERENCES

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

Grobert E, Ocepek-Welikson K, Teresi JA. The Free and Cued Selective Reminding Test: evidence of psychometric adequacy. Psychology Science Quarterly 2009;51:266–82.

Grober E, Sanders AE, Hall C, et al. Free and cued selective reminding identifies very mild dementia in primary care. Alzheimer Dis Assoc Disord 2010;24:284–90.

Grober E, Veroff AE, Lipton RB. Temporal unfolding of declining episodic memory on teh Free and Cued Selective Reminding Test in the predementia phase of Alzheimer's disease: implications for clinical trials. Alzheimer's Dement (Amst). 2018;10:161–71.

Papp KV, Rentz DM, Orlovsky I, et al. Optimizing the preclinical Alzheimer's cognitive composite with semantic processing: the PACC5. Alzheimer's Dement (NY) 2017;3:668–77.

Papp KV, Buckley R, Mormino E, et al. Clinical meaningfulness of subtle cognitive decline on longitudinal testing in preclinical AD. Alzheimer's Dement 2020;16:552–60.

Appendix 8 LM I+II – WMS–IV (Preclinical Alzheimer's Cognitive Composite–5) — Form A, B, and C

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

FORM A

WMS-IV Logical Memory I & II – Form A

Logical Memory I (Immediate Recall)

The subject listens to a story and immediately after hearing it is asked to retell it from memory.

Directions:

- Say: **"I am going to read a short story to you. Listen carefully and try to remember it just the way I say it, as close to the same words as you can remember. When I am through, I want you to tell me everything I read to you. You should tell me all you can remember even if you are not sure. Ready?"**

  Read the story to the subject: **"Anna Thompson of South Boston, employed as a cook in a school cafeteria, reported at the police station that she had been held up on State Street the night before and robbed of fifty-six dollars. She had four small children, the rent was due, and they had not eaten for two days. The police, touched by the woman's story, took up a collection for her."**

- Then say: **"Tell me everything you can remember about this story. Start at the beginning."**

Recording:

- Record the subject's response below. Write in the subject's recall within the lines of the segmented story below. Or, to simplify the recording, the examiner may underline any words of the story that the subject repeats verbatim and write in only those words that vary from the exact wording printed on the page.
- The words and phrases separated by diagonal lines in the passage represent key details of the story. Each detail correctly recalled is worth one point.

Anna / Thompson / of South / Boston /, employed /
as a cook / in a school / cafeteria /, reported / at the police /
station / that she had been held up / on State Street / the night before /
and robbed / of fifty-six dollars /. She had four / small children /,
the rent was due /, and they had not eaten / for two days /. The police /,
touched by the woman's story /, took up a collection / for her.

Time Logical Memory I (Immediate Recall) ended: _____:_____ (24-hour clock)
(HH : MM)

Scoring: Detailed scoring rules are given below in the Story Scoring Criteria table. Record either 0 or 1 for each story element.

STORY SCORING CRITERIA: Logical Memory I (Immediate Recall)		
Story Detail	**Score 0 or 1**	**1-Point Scoring Criteria**
Anna		*Anna* or variant of the name
Thompson		*Thompson* is required
of South		*South* (in any context)
Boston,		*Boston* (in any context)
employed		indication that she held a job
as a cook		*cook* or some form of the word (e.g., cooked) is required
in a school		*school* is required
cafeteria,		*cafeteria* is required
reported		indication that a formal statement was made to someone in authority (in any context)
at the police		*police* (in any context)
station		*station* (in any context) or a word or phrase denoting a police station
that she had been held up		indication that she had been held up (i.e., gunpoint or knife)
on State Street		*State Street* (in any context)
the night before		indication that the hold-up occurred the previous night
and robbed		indication that a robbery took place
of fifty-six dollars.		indication that an amount of money greater than $49 but less than $60 was taken from her
She had four		*four* is required, together with an indication that the children were hers
small children,		*children* or a synonym is required
the rent was due,		indication that the rent was due
and they had not eaten		indication that her children or the family were without food
for two days.		*two days* is required or a phrase meaning about two days (e.g., couple of days)
The police,		word or phrase signifying one or more members of the police department (in any context)
touched by the woman's story,		indication that her story evoked sympathy
took up a collection		indication that money was collected
for her.		indication that the money collected was for her or her children
Total Score:		**Logical Memory I (Immediate Recall)**

Logical Memory II (Delayed Recall)

Administer 20-30 minutes after completing Logical Memory I

Time Logical Memory II (Delayed Recall) began: _____:_____ (24-hour clock)
(HH : MM)

Directions:

- Administer this subtest at least 20-30 minutes after completion of Logical Memory I. If necessary, pause or provide a brief break to the subject to ensure that 20-30 minutes have elapsed.
- Say, **"Do you remember the story I read to you a little while ago? I want you to tell me the story again. Tell me everything that you can remember about the story. Start at the beginning."**
- If the subject does not recall any story details, say, **"The story was about a woman who was robbed."** Do not give any further help other than general encouragement.
- Note below whether a reminder was given and, if so, do not give a point for the corresponding story detail during scoring.

Recording:

- Record the subject's response below. Write in the subject's recall within the lines of the segmented story below. Or, to simplify the recording, the examiner may underline any words of the story that the subject repeats verbatim and write in only those words that vary from the exact wording printed on the page.
- The words and phrases separated by diagonal lines in the passage represent key details of the story. Each detail correctly recalled is worth one point.

Anna / Thompson / of South / Boston /, employed /
as a cook / in a school / cafeteria /, reported / at the police /
station / that she had been held up / on State Street / the night before /
and robbed / of fifty-six dollars /. She had four / small children /,
the rent was due /, and they had not eaten / for two days /. The police /,
touched by the woman's story /, took up a collection / for her.

Reminder given? _____ YES _____ NO.

Scoring: Detailed scoring rules are given below in the Story Scoring Criteria table. Record either **0** or **1** for each story element.

STORY SCORING CRITERIA: Logical Memory II (Delayed Recall)		
Story Detail	**Score 0 or 1**	**1-Point Scoring Criteria**
Anna		*Anna* or variant of the name
Thompson		*Thompson* is required
of South		*South* (in any context)
Boston,		*Boston* (in any context)
employed		indication that she held a job
as a cook		*cook* or some form of the word (e.g., cooked) is required
in a school		*school* is required
cafeteria,		*cafeteria* is required
reported		indication that a formal statement was made to someone in authority (in any context)
at the police		*police* (in any context)
station		*station* (in any context) or a word or phrase denoting a police station
that she had been held up		indication that she had been held up (i.e., gunpoint or knife)
on State Street		*State Street* (in any context)
the night before		indication that the hold-up occurred the previous night
and robbed		indication that a robbery took place (note: do not give a point for this story detail if a reminder was given)
of fifty-six dollars.		indication that an amount of money greater than $49 but less than $60 was taken from her
She had four		*four* is required, together with an indication that the children were hers
small children,		*children* or a synonym is required
the rent was due,		indication that the rent was due
and they had not eaten		indication that her children or the family were without food
for two days.		*two days* is required or a phrase meaning about two days (e.g., couple of days)
The police,		word or phrase signifying one or more members of the police department (in any context)
touched by the woman's story,		indication that her story evoked sympathy
took up a collection		indication that money was collected
for her.		indication that the money collected was for her or her children
Total Score:		**Logical Memory II (Delayed Recall)**

FORM B

WMS-IV Logical Memory I & II – Form B

Logical Memory I (Immediate Recall)

The subject listens to a story and immediately after hearing it is asked to retell it from memory.

Directions:

- Say: **"I am going to read a short story to you. Listen carefully and try to remember it just the way I say it, as close to the same words as you can remember. When I am through, I want you to tell me everything I read to you. You should tell me all you can remember even if you are not sure. Ready?"**

  Read the story to the subject: **"At 6:00 on Monday evening, Joe Garcia of Chicago was watching television as he dressed to go out. A weather bulletin interrupted the program to warn that thunderstorms would move into the area within the next two to three hours and remain until morning. The announcer said the storm could bring hail and up to four inches of rain and cause the temperature to drop by fifteen degrees. Joe decided to stay home. He took off his coat and sat down to watch old movies."**

- Then say: **"Tell me everything you can remember about this story. Start at the beginning."**

Recording:

- Record the subject's response below. Write in the subject's recall within the lines of the segmented story below. Or, to simplify the recording, the examiner may underline any words of the story that the subject repeats verbatim and write in only those words that vary from the exact wording printed on the page.

- The words and phrases separated by diagonal lines in the passage represent key details of the story. Each detail correctly recalled is worth one point.

At 6:00 / on Monday / evening /. Joe / Garcia / of Chicago /
was watching television / as he dressed / to go out /. A weather bulletin /
interrupted the program / to warn that thunderstorms / would move into the area /
within the next two to three hours / and remain until morning /. The announcer said /
the storm could bring hail / and up to four inches / of rain /
and cause the temperature to drop / by fifteen degrees /. Joe decided to stay home /.
He took off his coat / and sat down / to watch old movies.

Time Logical Memory I (Immediate Recall) ended: _____ : _____ (24-hour clock)
(HH : MM)

Scoring: Detailed scoring rules are given below in the Story Scoring Criteria table. Record either 0 or 1 for each story element.

STORY SCORING CRITERIA: Logical Memory I (Immediate Recall)		
Story Detail	**Score 0 or 1**	**1-Point Scoring Criteria**
At 6:00		*6:00* required
on Monday		*Monday* is required
evening,		*evening* (in any context)
Joe		*Joe* or variant of the name
Garcia		*Garcia* is required
of Chicago		*Chicago* is required
was watching television		indication that he was watching/listening to the television
as he dressed		indication that he was getting dressed
to go out.		indication that he was going out
A weather bulletin		indication that there was an announcement about the weather
interrupted the program		indication of a break in the regularly-scheduled program
to warn that thunderstorms		indication that there was a warning about a storm
would move into the area		indication that a storm was coming
within the next two to three hours		phrase meaning about two or three hours
and remain until morning.		indication that the storm would stay until morning
The announcer said		indication that someone was reporting about a storm
the storm could bring hail		indication that hail was possible
and up to four inches		*four inches* is required
of rain		*rain* is required
and cause the temperature to drop		indication that the temperature would drop or decrease
by fifteen degrees.		relative decrease of 15 degrees is required*
Joe decided to stay home.		indication that he decided to stay home
He took off his coat		indication that he took off outer clothing
and sat down		indication that he sat down
to watch old movies		indication of viewing movies is required
Total Score:		**Logical Memory I (Immediate Recall)**

*If the examinee mentions a temperature change without specifying increase or decrease but including the correct amount of change (e.g., the examinee says, there would be a 15-degree change in temperature), you may assume the direction is a decrease and score 1 point for "by fifteen degrees." However, without a specific mention that the change is a decrease, score 0 points for "and cause the temperature to drop."

Logical Memory II (Delayed Recall)

Administer 20-30 minutes after completing Logical Memory I

Time Logical Memory II (Delayed Recall) began: _____:_____ (24-hour clock)
(HH : MM)

Directions:

- Administer this subtest at least 20-30 minutes after completion of Logical Memory I. If necessary, pause or provide a brief break to the subject to ensure that 20-30 minutes have elapsed.
- Say, **"Do you remember the story I read to you a little while ago? I want you to tell me the story again. Tell me everything that you can remember about the story. Start at the beginning."**
- If the subject does not recall any story details, say, **"The story was about a weather bulletin."** Do not give any further help other than general encouragement.
- Note below whether a reminder was given and, if so, do not give a point for the corresponding story detail during scoring.

Recording:

- Record the subject's response below. Write in the subject's recall within the lines of the segmented story below. Or, to simplify the recording, the examiner may underline any words of the story that the subject repeats verbatim and write in only those words that vary from the exact wording printed on the page.
- The words and phrases separated by diagonal lines in the passage represent key details of the story. Each detail correctly recalled is worth one point.

At 6:00 / on Monday / evening /, Joe / Garcia / of Chicago /
was watching television / as he dressed / to go out /. A weather bulletin /
interrupted the program / to warn that thunderstorms / would move into the area /
within the next two to three hours / and remain until morning /. The announcer said /
the storm could bring hail / and up to four inches / of rain /
and cause the temperature to drop / by fifteen degrees /. Joe decided to stay home /.
He took off his coat / and sat down / to watch old movies.

Reminder given? _____ YES _____ NO.

Scoring: Detailed scoring rules are given below in the Story Scoring Criteria table. Record either 0 or 1 for each story element.

STORY SCORING CRITERIA: Logical Memory II (Delayed Recall)		
Story Detail	**Score 0 or 1**	**1-Point Scoring Criteria**
At 6:00		*6:00* required
on Monday		*Monday* is required
evening,		*evening* (in any context)
Joe		*Joe* or variant of the name
Garcia		*Garcia* is required
of Chicago		*Chicago* is required
was watching television		indication that he was watching/listening to the television
as he dressed		indication that he was getting dressed
to go out.		indication that he was going out
A weather bulletin		indication that there was an announcement about the weather (note: do not give a point for this story detail if a reminder was given)
interrupted the program		indication of a break in the regularly-scheduled program
to warn that thunderstorms		indication that there was a warning about a storm
would move into the area		indication that a storm was coming
within the next two to three hours		phrase meaning about two or three hours
and remain until morning.		indication that the storm would stay until morning
The announcer said		indication that someone was reporting about a storm
the storm could bring hail		indication that hail was possible
and up to four inches		*four inches* is required
of rain		*rain* is required
and cause the temperature to drop		indication that the temperature would drop or decrease
by fifteen degrees.		relative decrease of 15 degrees is required*
Joe decided to stay home.		indication that he decided to stay home
He took off his coat		indication that he took off outer clothing
and sat down		indication that he sat down
to watch old movies		indication of viewing movies is required
Total Score:		**Logical Memory II (Delayed Recall)**

*If the examinee mentions a temperature change without specifying increase or decrease but including the correct amount of change (e.g., the examinee says, there would be a 15-degree change in temperature), you may assume the direction is a decrease and score 1 point for "by fifteen degrees." However, without a specific mention that the change is a decrease, score 0 points for "and cause the temperature to drop."

FORM C

WMS-IV Logical Memory I & II – Form C

Logical Memory I (Immediate Recall)

The subject listens to a story and immediately after hearing it is asked to retell it from memory.

Directions:

- Say: **"I am going to read a short story to you. Listen carefully and try to remember it just the way I say it, as close to the same words as you can remember. When I am through, I want you to tell me everything I read to you. You should tell me all you can remember even if you are not sure. Ready?"**

  Read the story to the subject: **"Robert Miller was driving a ten-ton truck down a highway at night in the Mississippi Delta carrying eggs to Nashville, when his axle broke. His truck skidded off the road, into a ditch. He was thrown against the dashboard and was badly shaken. There was no traffic and he doubted that help would come. Just then his two-way radio buzzed. He quickly answered, "This is Grasshopper."**

- Then say: **"Tell me everything you can remember about this story. Start at the beginning."**

Recording:

- Record the subject's response below. Write in the subject's recall within the lines of the segmented story below. Or, to simplify the recording, the examiner may underline any words of the story that the subject repeats verbatim and write in only those words that vary from the exact wording printed on the page.
- The words and phrases separated by diagonal lines in the passage represent key details of the story. Each detail correctly recalled is worth one point.

Robert / Miller / was driving / a ten-ton / truck /

down a highway / at night / in the Mississippi / Delta /, carrying eggs /

to Nashville /, when his axle / broke /. His truck skidded / off the road /,

into a ditch /. He was thrown / against the dashboard / and was badly shaken /.

There was no traffic / and he doubted that help would come /.

Just then his two-way radio / buzzed /. He quickly answered /,

"This is Grasshopper."

Time Logical Memory I (Immediate Recall) ended: _____:_____ (24-hour clock)
(HH : MM)

Scoring: Detailed scoring rules are given below in the Story Scoring Criteria table. Record either 0 or 1 for each story element.

STORY SCORING CRITERIA: Logical Memory I (Immediate Recall)		
Story Detail	**Score 0 or 1**	**1-Point Scoring Criteria**
Robert		*Robert* or a variant of the name is required
Miller		*Miller* is required
was driving		an indication that Miller was the driver of the truck
a ten-ton		*ten-ton* is required
truck		*truck* is required
down a highway		an indication that the truck was being driven on a road (but not an unpaved road) or other intercity or interstate artery
at night		an indication that it was after nightfall
in the Mississippi		*Mississippi* (in any context)
Delta,		*Delta* is required
carrying eggs		*eggs* is required together with an indication that they were part of a shipment
to Nashville,		*Nashville* (in any context)
when his axle		*axle* is required
broke.		a word or phrase meaning "broke"
His truck skidded		an expression indicating that the truck was out of control
off the road,		an expression meaning that the truck left the road
into a ditch.		*ditch* is required, or a word or phrase describing a ditch
He was thrown		an indication that he was forcibly propelled
against the dashboard		*dashboard* or *dash* is required
and was badly shaken.		a word or phrase indicating that he was jarred or upset, but not indicating injury
There was no traffic		a statement that no other vehicles were passing by
and he doubted that help would come.		a phrase expressing doubt that someone would assist him
Just then his two-way radio		an indication that he has a (two-way) radio
buzzed.		any word or phrase indicating that an audible signal of any type was received (sound or voice)
He quickly answered,		an expression signifying that he responded by voice
"This is Grasshopper."		*Grasshopper* (in any context)
Total Score:		**Logical Memory I (Immediate Recall)**

Logical Memory II (Delayed Recall)

Administer 20-30 minutes after completing Logical Memory I

Time Logical Memory II (Delayed Recall) began: _____:_____ (24-hour clock)
(HH : MM)

Directions:

- Administer this subtest at least 20-30 minutes after completion of Logical Memory I. If necessary, pause or provide a brief break to the subject to ensure that 20-30 minutes have elapsed.
- Say, **"Do you remember the story I read to you a little while ago? I want you to tell me the story again. Tell me everything that you can remember about the story. Start at the beginning."**
- If the subject does not recall any story details, say, **"The story was about a man who had trouble on the highway."** Do not give any further help other than general encouragement.
- Note below whether a reminder was given and, if so, do not give a point for the corresponding story detail during scoring.

Recording:

- Record the subject's response below. Write in the subject's recall within the lines of the segmented story below. Or, to simplify the recording, the examiner may underline any words of the story that the subject repeats verbatim and write in only those words that vary from the exact wording printed on the page.
- The words and phrases separated by diagonal lines in the passage represent key details of the story. Each detail correctly recalled is worth one point.

Robert / Miller / was driving / a ten-ton / truck /

down a highway / at night / in the Mississippi / Delta /, carrying eggs /

to Nashville /, when his axle / broke /. His truck skidded / off the road /,

into a ditch /. He was thrown / against the dashboard / and was badly shaken /.

There was no traffic / and he doubted that help would come /.

Just then his two-way radio / buzzed /. He quickly answered /,

"This is Grasshopper."

Reminder given? _____ YES _____ NO.

Scoring: Detailed scoring rules are given below in the Story Scoring Criteria table. Record either 0 or 1 for each story element.

STORY SCORING CRITERIA: Logical Memory II (Delayed Recall)		
Story Detail	**Score 0 or 1**	**1-Point Scoring Criteria**
Robert		*Robert* or a variant of the name is required
Miller		*Miller* is required
was driving		an indication that Miller was the driver of the truck
a ten-ton		*ten-ton* is required
truck		*truck* is required
down a highway		an indication that the truck was being driven on a road (but not an unpaved road) or other intercity or interstate artery (note: do not give a point for this story detail if a reminder was given)
at night		an indication that it was after nightfall
in the Mississippi		*Mississippi* (in any context)
Delta,		*Delta* is required
carrying eggs		*eggs* is required together with an indication that they were part of a shipment
to Nashville,		*Nashville* (in any context)
when his axle		*axle* is required
broke.		a word or phrase meaning "broke"
His truck skidded		an expression indicating that the truck was out of control
off the road,		an expression meaning that the truck left the road
into a ditch.		*ditch* is required, or a word or phrase describing a ditch
He was thrown		an indication that he was forcibly propelled
against the dashboard		*dashboard* or *dash* is required
and was badly shaken.		a word or phrase indicating that he was jarred or upset, but not indicating injury
There was no traffic		a statement that no other vehicles were passing by
and he doubted that help would come.		a phrase expressing doubt that someone would assist him
Just then his two-way radio		an indication that he has a (two-way) radio
buzzed.		any word or phrase indicating that an audible signal of any type was received (sound or voice)
He quickly answered,		an expression signifying that he responded by voice
"This is Grasshopper."		*Grasshopper* (in any context)
Total Score:		**Logical Memory II (Delayed Recall)**

REFERENCES

Papp KV, Rentz DM, Orlovsky I, et al. Optimizing the preclinical Alzheimer's cognitive composite with semantic processing: the PACC5. Alzheimer's Dement (NY) 2017;3:668–77.

Papp KV, Buckley R, Mormino E, et al. Clinical meaningfulness of subtle cognitive decline on longitudinal testing in preclinical AD. Alzheimer's Dement 2020;16:552–60.

Wechsler D. Wechsler adult intelligence scale. Fourth Edition (WAISIV). 2008. San Antonio, TX: NCS Pearson.

Appendix 9 Coding – WAIS–IV (Preclinical Alzheimer's Cognitive Composite–5) — Form A, B, and C

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

CODING MANUAL

WAIS-IV Digit Symbol-Coding

Administration Instructions

- This test should be timed using a stopwatch. Accurate timing is essential.
- The subject's performance after 120 seconds will be recorded and scored.
- Discontinue the test after 120 seconds.

General Directions:

- A smooth drawing surface must be provided. If the table has a rough surface, the Digit Symbol-Coding Record Form should be placed on a clipboard or another flat surface.
- Use the demonstration items to explain and illustrate the task to the subject, then allow the subject to practice by completing the sample items. If the subject appears confused, repeat the explanation and demonstrate the task again using the sample items. Proceed with the test items only when the examinee clearly understands the task.
- If a subject asks what to do if he or she makes a mistake, say, ***That's OK. Just keep working as fast as you can.*** However, do not discourage a subject from making spontaneous corrections unless he or she does so repeatedly and it impedes performance.
- If a subject omits an item or begins to complete a row in reverse order (from his or her right to left), say, ***Do them in order. Don't skip any.*** Point to the first omitted item and say, ***Do this one next.***
- Provide no further assistance on this subtest except to remind the subject to continue until told to stop (if necessary).

Test Instructions:

To introduce the test, say: ***Next, I'm going to ask you to copy some symbols.***

Demonstration Items

Place the Digit Symbol-Coding Record Form in front of the subject. Point to the key above the test items, and say: ***Look at these boxes. Each box has a number in the top part*** (point across the numbers from 1 to 9) ***and a special mark in the bottom part*** (point across the symbols). ***Each number has its own mark*** (point to 1 and its symbol in the key, then 2 and its symbol).

Point to the demonstration items and say, ***Down here, the boxes have numbers in the top parts but are empty in the bottom parts. You are to draw the marks that belong in the empty boxes, like this.***

Point to the first demonstration item (6) and say, ***Here is a 6. The 6 has this mark*** (point to the key to show its corresponding symbol), ***so I draw that mark in the box, like this*** (write the symbol).

Point to the second demonstration item (8) and say, ***Here is an 8. The 8 has this mark*** (point to the key to show its corresponding symbol), ***so I draw that mark in the box*** (write the symbol).

Point to the third demonstration item (3) and say, ***Here is a 3. The 3 has this mark*** (point to the key to show its corresponding symbol), ***so I draw that mark in the box*** (write the symbol).

Proceed to the Sample Items.

Sample Items

Hand the subject a pen and say, ***Now you do these*** (point to the sample items). ***Stop when you get to this line*** (point to the heavy line that separates the Sample Items from the Test Items).

Allow the subject to work alone on the remaining sample items. If a left-handed subject partially blocks the key with his or her left hand while completing the sample items, stop the administration. Place an extra Record Form to the right of the subject's Record Form. Position it so the extra key is aligned with the key the subject's hand is blocking. Have the subject complete the remaining sample items using the extra key, so he or she will be accustomed to the arrangement when completing the test items.

If the subject completes the sample items correctly, offer praise such as ***Yes*** or ***Right*** and, finally, ***Now you know how to do them.***

If the subject makes a mistake on a Sample Item, correct the error immediately. Use the item to review the use of the key. Continue to help the subject, if necessary, until the subject correctly completes the Sample Items. Use explanations such, ***You see, this is a 9. The 9 has this mark, so I draw that mark in the box*** (write the symbol).

Do not proceed with the Test Items until the subject understands the task.

When the subject has successfully completed the Sample Items, proceed to the Test Items.

Test Items

Say, ***When I say go, do these the same way. Start here*** (point to the first test item), ***go in order, and do not skip any. Work as fast as you can without making any mistakes until I tell you to stop. Are you ready?***

Explain further, if necessary, then say, ***Go***. Begin timing and allow 120 seconds.

If necessary, remind the subject to go in order and continue working. Give no further assistance.

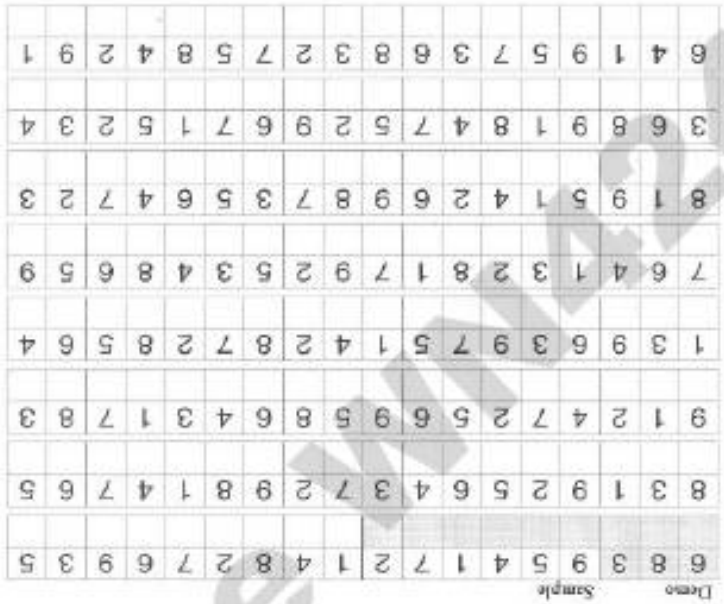
If the subject is still working at 120 seconds, stop timing and say, ***Stop.***

Visually note where the subject is on the Record Form when he or she is told to stop. Mark the 120-second performance on the image below by drawing a vertical line just past the last symbol completed when the timer reached 120 seconds.

If a subject draws a symbol after the 120-second time limit has expired, write an "X" over the additional symbol on the image below as well as on the subject's Record Form and do not count it as correct.

Recording Performance

Indicate the subject's 120-second performance on the image below by drawing a vertical line just past the last symbol completed when the timer reached 120 seconds.



Record the clock time below at which the Digit Symbol-Coding test was completed.

Scoring Guidelines

Use the Coding Scoring Template to score the subject's responses. Align the template so that the correct responses are above the subject's responses. Each test-item number is indicated on the scoring template.

A response is scored as correct if it is correctly drawn, of if drawn imperfectly, it is clearly identifiable as the keyed symbol. The marks do not need to be identical to the keyed symbol but must be clearly distinguishable from other symbols.

Score 1 point for each correctly drawn symbol completed within the time limit.

Score 1 point if the subject, after realizing a mistake, spontaneously draws the correct symbol next to or on top of the incorrect response.

Do not include responses to the sample items in the subject's score.

Items that the subject did not attempt (either skipped or did not reach before the time limit expired) should not be counted.

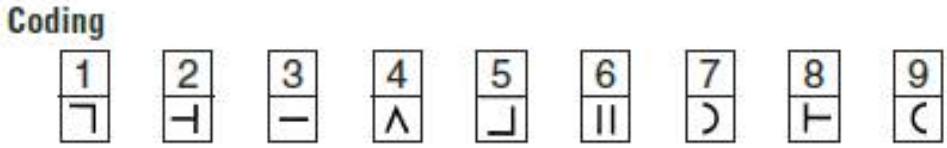
If the subject completed all test items before the 120-second time limit expired, record the total number of correct symbols at 120 seconds as 135, minus any incorrect or omitted symbols.

Score

Total number of correct symbols at 120 seconds:	

FORM A

FORM B



Demo Sample

6	8	3	9	5	4	1	7	2	1	4	8	2	7	6	9	3	5
8	3	1	9	2	5	6	4	3	7	2	9	8	1	4	7	6	5
9	1	2	4	7	2	5	6	9	5	8	6	4	3	1	7	8	3
1	3	9	6	3	9	7	5	1	4	2	8	7	2	8	5	6	4
7	6	4	1	3	2	8	1	7	9	2	5	3	4	8	6	5	9
8	1	9	5	1	4	2	6	9	8	7	3	5	6	4	7	2	3
3	6	8	9	1	8	4	7	5	2	9	6	7	1	5	2	3	4
6	4	1	9	5	7	3	6	8	3	2	7	5	8	4	2	9	1

Form B

FORM C

Coding

Demo Sample

6	8	3	9	5	4	1	7	2	1	4	8	2	7	6	9	3	5
8	3	1	9	2	5	6	4	3	7	2	9	8	1	4	7	6	5
9	1	2	4	7	2	5	6	9	5	8	6	4	3	1	7	8	3
1	3	9	6	3	9	7	5	1	4	2	8	7	2	8	5	6	4
7	6	4	1	3	2	8	1	7	9	2	5	3	4	8	6	5	9
8	1	9	5	1	4	2	6	9	8	7	3	5	6	4	7	2	3
3	6	8	9	1	8	4	7	5	2	9	6	7	1	5	2	3	4
6	4	1	9	5	7	3	6	8	3	2	7	5	8	4	2	9	1

Form C

REFERENCES

Papp KV, Rentz DM, Orlovsky I, et al. Optimizing the preclinical Alzheimer's cognitive composite with semantic processing: the PACC5. Alzheimer's Dement (NY) 2017;3:668–77.

Papp KV, Buckley R, Mormino E, et al. Clinical meaningfulness of subtle cognitive decline on longitudinal testing in preclinical AD. Alzheimer's Dement 2020;16:552–60.

Wechsler, D. The measurement and appraisal of adult intelligence (1st edition) 1939. Baltimore: Williams and Wilkins Corporation.

Wechsler D. Wechsler adult intelligence scale. Fourth Edition (WAISIV). 2008. San Antonio, TX: NCS Pearson.

Appendix 10 Category Fluency (Preclinical Alzheimer's Cognitive Composite–5) — Form A, B, and C

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

FORM A

Category Fluency – Form A

Materials

Please make sure you have **a stopwatch** available BEFORE beginning this assessment.

Remember: Time Limit = **60 seconds**

General Guidelines

- Only score responses that are relevant to the task.
- If the subject makes a phonemic error e.g. guinea fig (for animals) and you can understand what they mean, mark as Correct Response.
- If subject corrects self or takes their comments back, it doesn't count as a Correct Response.
- If subject forgets and asks what category they are on, you can remind him.
- **However, you cannot correct them unless they specifically ask,** i.e. don't correct the subject unless they ask for guidance.

Instructions to Subject

ADMINISTRATION:

Start timer after completing instructions. Write actual responses as legibly as possible. **Stop the procedure at 1 minute**

Say:

I am going to give you a category and I want you to name, as fast as you can, all of the things that belong in that category.

For example, if I say, "articles of clothing," you could say, "shirt, tie, hat, etc." Can you think of other articles of clothing?

(Wait for subject to name two or three items)

That's fine. I want you to name things that belong to another category. You will have a minute to do this.

PROMPTS:

1. If the subject pauses for 15 seconds:
   - ***Keep going***
   - ***What other [category] can you think of?***

2. If subject gives 3 consecutive words that do not belong to the category: (Provide this prompt only once.)
   - ***We are now naming [category].***

Category: Animals

Say: ***Now go ahead and tell me all the different ANIMALS you can think of. Ready? Begin.*** (START TIMING: 60 seconds)

☐ No responses Provided

	Correct		Correct
1.	☐	21.	☐
2.	☐	22.	☐
3.	☐	23.	☐
4.	☐	24.	☐
5	☐	25.	☐
6.	☐	26.	☐
7.	☐	27.	☐
8.	☐	28.	☐
9.	☐	29.	☐
10.	☐	30.	☐
11.	☐	31.	☐
12.	☐	32.	☐
13.	☐	33.	☐
14.	☐	34.	☐
15.	☐	35.	☐
16.	☐	36.	☐
17.	☐	37.	☐
18.	☐	38.	☐
19.	☐	39.	☐
20.	☐	40.	☐

Category: Vegetables

Say: ***Now go ahead and tell me all the different VEGETABLES you can think of. Ready? Begin.*** (START TIMING: 60 seconds)

☐ No responses Provided

	Correct		Correct
1.	☐	21.	☐
2.	☐	22.	☐
3.	☐	23.	☐
4.	☐	24.	☐
5	☐	25.	☐
6.	☐	26.	☐
7.	☐	27.	☐
8.	☐	28.	☐
9.	☐	29.	☐
10.	☐	30.	☐
11.	☐	31.	☐
12.	☐	32.	☐
13.	☐	33.	☐
14.	☐	34.	☐
15.	☐	35.	☐
16.	☐	36.	☐
17.	☐	37.	☐
18.	☐	38.	☐
19.	☐	39.	☐
20.	☐	40.	☐

Category: Fruits

Say: ***Now go ahead and tell me all the different FRUITS you can think of. Ready? Begin.*** (START TIMING: 60 seconds)

☐ No responses Provided

	Correct		Correct
1.	☐	21.	☐
2.	☐	22.	☐
3.	☐	23.	☐
4.	☐	24.	☐
5	☐	25.	☐
6.	☐	26.	☐
7.	☐	27.	☐
8.	☐	28.	☐
9.	☐	29.	☐
10.	☐	30.	☐
11.	☐	31.	☐
12.	☐	32.	☐
13.	☐	33.	☐
14.	☐	34.	☐
15.	☐	35.	☐
16.	☐	36.	☐
17.	☐	37.	☐
18.	☐	38.	☐
19.	☐	39.	☐
20.	☐	40.	☐

Scoring Summary

Animals:

Total Generated Words ☐

Total Admissible Words ☐

Vegetables:

Total Generated Words ☐

Total Admissible Words ☐

Fruits:

Total Generated Words ☐

Total Admissible Words ☐

Rosen, WG (1980). Verbal fluency in aging and dementia. Journal of Clinical Neuropsychology, 2 (1980), pp. 135-146
Strauss, E., Sherman, E. M. S., & Spreen, O. (Eds.). (2006). A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary, Oxford, New York, Oxford University Press

FORM B

Category Fluency – Form B

Materials

Please make sure you have **a stopwatch** available BEFORE beginning this assessment.

Remember: Time Limit = **60 seconds**

General Guidelines

- Only score responses that are relevant to the task.
- If the subject makes a phonemic error e.g. guinea fig (for animals) and you can understand what they mean, mark as Correct Response.
- If subject corrects self or takes their comments back, it doesn't count as a Correct Response.
- If subject forgets and asks what category they are on, you can remind him.
- **However, you cannot correct them unless they specifically ask,** i.e. don't correct the subject unless they ask for guidance.

Instructions to Subject

ADMINISTRATION:

Start timer after completing instructions. Write actual responses as legibly as possible. **Stop the procedure at 1 minute**

Say:

I am going to give you a category and I want you to name, as fast as you can, all of the things that belong in that category.

For example, if I say, "articles of clothing," you could say, "shirt, tie, hat, etc." Can you think of other articles of clothing?

(Wait for subject to name two or three items)

That's fine. I want you to name things that belong to another category. You will have a minute to do this.

PROMPTS:

1. If the subject pauses for 15 seconds:
   - ***Keep going***
   - ***What other [category] can you think of?***

2. If subject gives 3 consecutive words that do not belong to the category: (Provide this prompt only once.)
   - ***We are now naming [category].***

Category: Vegetables

Say: ***Now go ahead and tell me all the different VEGETABLES you can think of. Ready? Begin.*** (START TIMING: 60 seconds)

☐ No responses Provided

	Correct		Correct
1.	☐	21.	☐
2.	☐	22.	☐
3.	☐	23.	☐
4.	☐	24.	☐
5	☐	25.	☐
6.	☐	26.	☐
7.	☐	27.	☐
8.	☐	28.	☐
9.	☐	29.	☐
10.	☐	30.	☐
11.	☐	31.	☐
12.	☐	32.	☐
13.	☐	33.	☐
14.	☐	34.	☐
15.	☐	35.	☐
16.	☐	36.	☐
17.	☐	37.	☐
18.	☐	38.	☐
19.	☐	39.	☐
20.	☐	40.	☐

Category: Fruits

Say: ***Now go ahead and tell me all the different FRUITS you can think of. Ready? Begin.*** (START TIMING: 60 seconds)

☐ No responses Provided

	Correct		Correct
1.	☐	21.	☐
2.	☐	22.	☐
3.	☐	23.	☐
4.	☐	24.	☐
5	☐	25.	☐
6.	☐	26.	☐
7.	☐	27.	☐
8.	☐	28.	☐
9.	☐	29.	☐
10.	☐	30.	☐
11.	☐	31.	☐
12.	☐	32.	☐
13.	☐	33.	☐
14.	☐	34.	☐
15.	☐	35.	☐
16.	☐	36.	☐
17.	☐	37.	☐
18.	☐	38.	☐
19.	☐	39.	☐
20.	☐	40.	☐

Category: Animals

Say: ***Now go ahead and tell me all the different ANIMALS you can think of. Ready? Begin.*** (START TIMING: 60 seconds)

☐ No responses Provided	Correct		Correct
1.	☐	21.	☐
2.	☐	22.	☐
3.	☐	23.	☐
4.	☐	24.	☐
5	☐	25.	☐
6.	☐	26.	☐
7.	☐	27.	☐
8.	☐	28.	☐
9.	☐	29.	☐
10.	☐	30.	☐
11.	☐	31.	☐
12.	☐	32.	☐
13.	☐	33.	☐
14.	☐	34.	☐
15.	☐	35.	☐
16.	☐	36.	☐
17.	☐	37.	☐
18.	☐	38.	☐
19.	☐	39.	☐
20.	☐	40.	☐

Scoring Summary

Vegetables:

Total Generated Words ☐

Total Admissible Words ☐

Fruits:

Total Generated Words ☐

Total Admissible Words ☐

Animals:

Total Generated Words ☐

Total Admissible Words ☐

Rosen, WG (1980). Verbal fluency in aging and dementia. Journal of Clinical Neuropsychology, 2 (1980), pp. 135-146
Strauss, E., Sherman, E. M. S., & Spreen, O. (Eds.). (2006). A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary, Oxford, New York, Oxford University Press

FORM C

Category Fluency – Form C

Materials

Please make sure you have **a stopwatch** available BEFORE beginning this assessment.

Remember: Time Limit = **60 seconds**

General Guidelines

- Only score responses that are relevant to the task.
- If the subject makes a phonemic error e.g. guinea fig (for animals) and you can understand what they mean, mark as Correct Response.
- If subject corrects self or takes their comments back, it doesn't count as a Correct Response.
- If subject forgets and asks what category they are on, you can remind him.
- **However, you cannot correct them unless they specifically ask,** i.e. don't correct the subject unless they ask for guidance.

Instructions to Subject

ADMINISTRATION:

Start timer after completing instructions. Write actual responses as legibly as possible. **Stop the procedure at 1 minute**

Say:

I am going to give you a category and I want you to name, as fast as you can, all of the things that belong in that category.

For example, if I say, "articles of clothing," you could say, "shirt, tie, hat, etc." Can you think of other articles of clothing?

(Wait for subject to name two or three items)

That's fine. I want you to name things that belong to another category. You will have a minute to do this.

PROMPTS:

1. If the subject pauses for 15 seconds:
   - ***Keep going***
   - ***What other [category] can you think of?***

2. If subject gives 3 consecutive words that do not belong to the category: (Provide this prompt only once.)
   - ***We are now naming [category].***

Category: Fruits

Say: ***Now go ahead and tell me all the different FRUITS you can think of. Ready? Begin.*** (START TIMING: 60 seconds)

☐ No responses Provided	Correct		Correct
1.	☐	21.	☐
2.	☐	22.	☐
3.	☐	23.	☐
4.	☐	24.	☐
5	☐	25.	☐
6.	☐	26.	☐
7.	☐	27.	☐
8.	☐	28.	☐
9.	☐	29.	☐
10.	☐	30.	☐
11.	☐	31.	☐
12.	☐	32.	☐
13.	☐	33.	☐
14.	☐	34.	☐
15.	☐	35.	☐
16.	☐	36.	☐
17.	☐	37.	☐
18.	☐	38.	☐
19.	☐	39.	☐
20.	☐	40.	☐

Category: Animals

Say: ***Now go ahead and tell me all the different ANIMALS you can think of. Ready? Begin.*** (START TIMING: 60 seconds)

☐ No responses Provided

	Correct		Correct
1.	☐	21.	☐
2.	☐	22.	☐
3.	☐	23.	☐
4.	☐	24.	☐
5	☐	25.	☐
6.	☐	26.	☐
7.	☐	27.	☐
8.	☐	28.	☐
9.	☐	29.	☐
10.	☐	30.	☐
11.	☐	31.	☐
12.	☐	32.	☐
13.	☐	33.	☐
14.	☐	34.	☐
15.	☐	35.	☐
16.	☐	36.	☐
17.	☐	37.	☐
18.	☐	38.	☐
19.	☐	39.	☐
20.	☐	40.	☐

Category: Vegetables

Say: ***Now go ahead and tell me all the different VEGETABLES you can think of. Ready? Begin.*** (START TIMING: 60 seconds)

☐ No responses Provided

	Correct		Correct
1.	☐	21.	☐
2.	☐	22.	☐
3.	☐	23.	☐
4.	☐	24.	☐
5	☐	25.	☐
6.	☐	26.	☐
7.	☐	27.	☐
8.	☐	28.	☐
9.	☐	29.	☐
10.	☐	30.	☐
11.	☐	31.	☐
12.	☐	32.	☐
13.	☐	33.	☐
14.	☐	34.	☐
15.	☐	35.	☐
16.	☐	36.	☐
17.	☐	37.	☐
18.	☐	38.	☐
19.	☐	39.	☐
20.	☐	40.	☐

Scoring Summary

Fruits:

Total Generated Words ☐

Total Admissible Words ☐

Animals:

Total Generated Words ☐

Total Admissible Words ☐

Vegetables:

Total Generated Words ☐

Total Admissible Words ☐

Rosen, WG (1980). Verbal fluency in aging and dementia. Journal of Clinical Neuropsychology, 2 (1980), pp. 135-146
Strauss, E., Sherman, E. M. S., & Spreen, O. (Eds.). (2006). A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary, Oxford, New York, Oxford University Press

REFERENCES

Clark LJ, Gatz M, Zheng L, et al. Longitudinal verbal fluency in normal aging, preclinical, and prevalent Alzheimer's disease. Am J Alzheimers Dis Other Demen 2009;24:461–8.

Lezak MD, Howieson DB, Loring DW. Neuropsychological assessment (4th revised edition). New York: Oxford University Press, 2004.

Papp KV, Rentz DM, Orlovsky I, et al. Optimizing the preclinical Alzheimer's cognitive composite with semantic processing: the PACC5. Alzheimer's Dement (NY) 2017;3:668–77.

Papp KV, Buckley R, Mormino E, et al. Clinical meaningfulness of subtle cognitive decline on longitudinal testing in preclinical AD. Alzheimer's Dement 2020;16:552–60.

Pasquier F, Lebert F, Grymonprez L, et al. Verbal fluency in dementia of frontal lobe type and dementia of Alzheimer type. J Neurol Neurosurg Psychiatry1995;58:81–4.

Appendix 11 Clinical Dementia Rating Scale

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Clinical Dementia Rating Worksheet

This is a semi-structured interview. Please ask all of these questions. Ask any additional questions necessary to determine the subject's CDR. Please note information from the additional questions.

Memory Questions for Informant:

1. Does he/she have a problem with his/her memory or thinking? ☐ Yes ☐ No
1a. If yes, is this a consistent problem (as opposed to inconsistent)? ☐ Yes ☐ No
2. Can he/she recall recent events? ☐ Usually ☐ Sometimes ☐ Rarely
3. Can he/she remember a short list of items (shopping)? ☐ Usually ☐ Sometimes ☐ Rarely
4. Has there been some decline in memory during the past year? ☐ Yes ☐ No
5. Is his/her memory impaired to such a degree that it would have interfered with his/her activities of daily life a few years ago (or pre-retirement activities)? (collateral sources opinion) ☐ Yes ☐ No
6. Does he/she completely forget a major event (e.g., trip, party, family wedding) within a few weeks of the event? ☐ Usually ☐ Sometimes ☐ Rarely
7. Does he/she forget pertinent details of the major event? ☐ Usually ☐ Sometimes ☐ Rarely
8. Does he/she completely forget important information of the distant past (e.g., birthdate, wedding date, place of employment)? ☐ Usually ☐ Sometimes ☐ Rarely
9. Tell me about some recent event in his/her life that he/she should remember. (For later testing, obtain details such as location of the event, time of day, participants, how long the event was, when it ended and how the subject or other participants got there).

   Within 1 week:_____

   _____

   Within 1 month:_____

   _____
10. Question 10 removed because it contains protected health information (PHI)._____
11. Where was he/she born?_____
12. What was the last school he/she attended?_____

    Name_____

    Place_____

    Grade_____
13. What was his/her main occupation/job (or spouse's job if subject was not employed)?_____
14. What was his/her last major job (or spouse's job if subject was not employed)?_____
15. When did he/she (or spouse) retire and why?_____

Clinical Dementia Rating Worksheet

Orientation Questions for Informant:

How often does he/she know of the exact:

1. Date of the Month?

   ☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

2. Month?

   ☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

3. Year?

   ☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

4. Day of the Week?

   ☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

5. Does he/she have difficulty with time relationships (when events happened in relation to each other)?

   ☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

6. Can he/she find his/her way about familiar streets?

   ☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

7. How often does he/she know how to get from one place to another outside his/her neighborhood?

   ☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

8. How often can he/she find his/her way about indoors?

   ☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

Clinical Dementia Rating Worksheet

Judgment and Problem Solving Questions for Informant:

1. In general, if you had to rate his/her abilities to solve problems at the present time, would you consider them:
   - ☐ As good as they have ever been
   - ☐ Good, but not as good as before
   - ☐ Fair
   - ☐ Poor
   - ☐ No ability at all
2. Rate his/her ability to cope with small sums of money (e.g., make change, leave a small tip):
   - ☐ No loss
   - ☐ Some loss
   - ☐ Severe loss
3. Rate his/her ability to handle complicated financial or business transactions (e.g., balance check-book, pay bills):
   - ☐ No loss
   - ☐ Some loss
   - ☐ Severe loss
4. Can he/she handle a household emergency (e.g., plumbing leak, small fire)?
   - ☐ As well as before
   - ☐ Worse than before because of trouble thinking
   - ☐ Worse than before, another reason (why)_____
5. Can he/she understand situations or explanations?
   ☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know
6. Does he/she behave* appropriately [i.e., in his/her usual (premorbid) manner] in social situations and interactions with other people?
   ☐ Usually ☐ Sometimes ☐ Rarely ☐ Don't Know

*This item rates behavior, not appearance.

Clinical Dementia Rating Worksheet

Community Affairs Questions for Informant:

Occupational

1. Is the subject still working? ☐ Yes ☐ No ☐ N/A
   If not applicable, proceed to item 4
   If yes, proceed to item 3
   If no, proceed to item 2
2. Did memory or thinking problems contribute to the subject's decision to retire? ☐ Yes ☐ No ☐ D/K
   (Question 4 is next)
3. Does the subject have significant difficulty in his/her job because of problems with memory or thinking?

   ☐ Rarely or Never ☐ Sometimes ☐ Usually ☐ Don't Know

Social

4. Did he/she ever drive a car? ☐ Yes ☐ No

   Does the subject drive a car now? ☐ Yes ☐ No

   If no, is this because of memory or thinking problems? ☐ Yes ☐ No
5. If he/she is still driving, are there problems or risks because of poor thinking? ☐ Yes ☐ No

*6. Is he/she able to independently shop for needs?

☐ Rarely or Never	☐ Sometimes	☐ Usually	☐ Don't Know
(Needs to be accompanied on any shopping trip)	(Shops for limited number of items; buys duplicate items or forgets needed items)		

7. Is he/she able to independently carry out activities outside the home?

☐ Rarely or Never	☐ Sometimes	☐ Usually	☐ Don't Know
(Generally unable to perform activities without help)	(Limited and/or routine, e.g., superficial participation in church or meetings; trips to beauty parlor)	(Meaningful participation in activities, e.g., voting)	

8. Is he/she taken to social functions outside a family home? ☐ Yes ☐ No
   If no, why not?_____
9. Would a casual observer of the subject's behavior think the subject was ill? ☐ Yes ☐ No
10. If in nursing home, does he/she participate well in social functions (thinking)? ☐ Yes ☐ No

IMPORTANT:
Is there enough information available to rate the subject's level of impairment in community affairs?
If not, please probe further.

Community Affairs: Such as going to church, visiting with friends or family, political activities, professional organizations such as bar association, other professional groups, social clubs, service organizations, educational programs.

_____

***Please add notes if needed to clarify subject's level of functioning in this area.**

Clinical Dementia Rating Worksheet

Home and Hobbies Questions for Informant:

1a. What changes have occurred in his/her abilities to perform household chores?_____

1b. What can he/she still do well?_____

2a. What changes have occurred in his/her abilities to perform hobbies?_____

2b. What can he/she still do well?_____

3. If in nursing home, what can he/she no longer do well (H and H)?_____

Everyday Activities (Blessed):

	No Loss		Severe Loss
4. Ability to perform household tasks	0	0.5	1

Please describe:_____

5. Is he/she able to perform household chores at the level of:
(Pick one. Informant does not need to be asked directly).

- ☐ No meaningful function.
  (Performs simple activities, such as making a bed, only with much supervision)
- ☐ Functions in limited activities only.
  (With some supervision, washes dishes with acceptable cleanliness; sets table)
- ☐ Functions independently in some activities.
  (Operates appliances, such as a vacuum cleaner; prepares simple meals)
- ☐ Functions in usual activities but not at usual level.
- ☐ Normal function in usual activities.

IMPORTANT:
Is there enough information available to rate the subject's level of impairment in HOME & HOBBIES?
If not, please probe further.

Homemaking Tasks: Such as cooking, laundry, cleaning, grocery shopping, taking out garbage, yard work, simple car maintenance, and basic home repair.

Hobbies: Sewing, painting, handicrafts, reading, entertaining, photography, gardening, going to theater or symphony, woodworking, participation in sports.

Clinical Dementia Rating Worksheet

Personal Care Questions for Informant:

*What is your estimate of his/her mental ability in the following areas:

	Unaided	Occasionally misplaced buttons, etc.	Wrong sequence commonly forgotten items	Unable to dress
A. Dressing (Blessed)	0	1	2	3

	Unaided	Needs prompting	Sometimes needs help	Always or nearly always needs help
B. Washing, grooming	0	1	2	3

	Cleanly; proper utensils	Messily; spoon	Simple solids	Has to be fed completely
C. Eating habits	0	1	2	3

	Normal complete control	Occasionally wets bed	Frequently wets bed	Doubly incontinent
D. Sphincter control (Blessed)	0	1	2	3

* A box-score of 1 can be considered if the subject's personal care is impaired from a previous level, even if they do not receive prompting.

Clinical Dementia Rating Worksheet

Memory Questions for Subject:

1. Do you have problems with memory or thinking? ☐ Yes ☐ No

2. A few moments ago your (spouse, etc.) told me a few recent experiences you had. Will you tell me something about those? (Prompt for details, if needed such as location of the event, time of day, participants, how long the event was, when it ended and how the subject or other participants got there).

Within 1 week

1.0 – Largely correct _____
0.5 – Partially correct _____
0.0 – Largely incorrect _____

Within 1 month

1.0 – Largely correct _____
0.5 – Partially correct _____
0.0 – Largely incorrect _____

3. I will give you a name and address to remember for a few minutes. Repeat this name and address after me: (Repeat until the phrase is correctly repeated or to a maximum of three trials).

Elements	1	2	3	4	5
	John	Brown,	42	Market Street,	Chicago
	John	Brown,	42	Market Street,	Chicago
	John	Brown,	42	Market Street,	Chicago

(Underline elements repeated correctly in each trial).

4. Question 4 removed because it contains protected health information (PHI)._____

5. Where were you born?_____

6. What was the last school you attended?
Name_____
Place_____Grade_____

7. What was your main occupation job (or spouse if not employed)?_____

8. What was your last major job (or spouse if not employed)?_____

9. When did you (or spouse) retire and why?_____

10. . Repeat the name and address I asked you to remember:

Elements	1	2	3	4	5
	John	Brown,	42	Market Street,	Chicago

(Underline elements repeated correctly).

Clinical Dementia Rating Worksheet

Orientation Questions for Subject:

Record the subject's answer verbatim for each question

1. What is the date today? ☐ Correct ☐ Incorrect

   _____

2. What day of the week is it? ☐ Correct ☐ Incorrect

   _____

3. What is the month? ☐ Correct ☐ Incorrect

   _____

4. What is the year? ☐ Correct ☐ Incorrect

   _____

5. What is the name of this place? ☐ Correct ☐ Incorrect

   _____

6. What town or city are we in? ☐ Correct ☐ Incorrect

   _____

7. What time is it? ☐ Correct ☐ Incorrect

   _____

8. Does the subject know who the informant is (in your judgment)? ☐ Correct ☐ Incorrect

   _____

Clinical Dementia Rating Worksheet

Judgment and Problem Solving Questions for Subject:

Instructions: If initial response by subject does not merit a grade 0, press the matter to identify the subject's best understanding of the problem. Circle nearest response.

Similarities:

Example: "How are a pencil and pen alike? (writing instruments)

How are these things alike?" Subject's Response

1. turnip……cauliflower _____
   (0 = vegetables)
   (1 = edible foods, living things, can be cooked, etc.)
   (2 = answers not pertinent; differences; buy them)

2. desk……bookcase _____
   (0 = furniture, office furniture; both hold books)
   (1 = wooden, legs)
   (2 = not pertinent, differences)

Differences:

Example: "What is the difference between sugar and vinegar? (sweet vs. sour)

What is the difference between these things?"

3. lie……mistake _____
   (0 = one deliberate, one unintentional)
   (1 = one bad the other good – or explains only one)
   (2 = anything else, similarities)

4. river……canal _____
   (0 = natural - artificial)
   (2 = anything else)

Calculations:

5. How many nickels in a dollar? ☐ Correct ☐ Incorrect
6. How many quarters in $6.75? ☐ Correct ☐ Incorrect
7. Subtract 3 from 20 and keep subtracting 3 from each new number all the way down. ☐ Correct ☐ Incorrect

Judgment:

8. Upon arriving in a strange city, how would you locate a friend that you wished to see?

   (0 = try the telephone book, city directory, Internet search, call a mutual friend)
   (1 = call the police, call operator (usually will not give address)
   (2 = no clear response)

9. Subject's assessment of disability and station in life and understanding of why he/she is present at the examination (may have covered, but rate here):

   ☐ Good Insight ☐ Partial Insight ☐ Little Insight

CLINICAL DEMENTIA RATING (CDR)

CLINICAL DEMENTIA RATING (CDR):	0	0.5	1	2	3

	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.

REFERENCES

Berg L. Clinical Dementia Rating (CDR). Psychopharmacol Bull 1988;24:637–9.

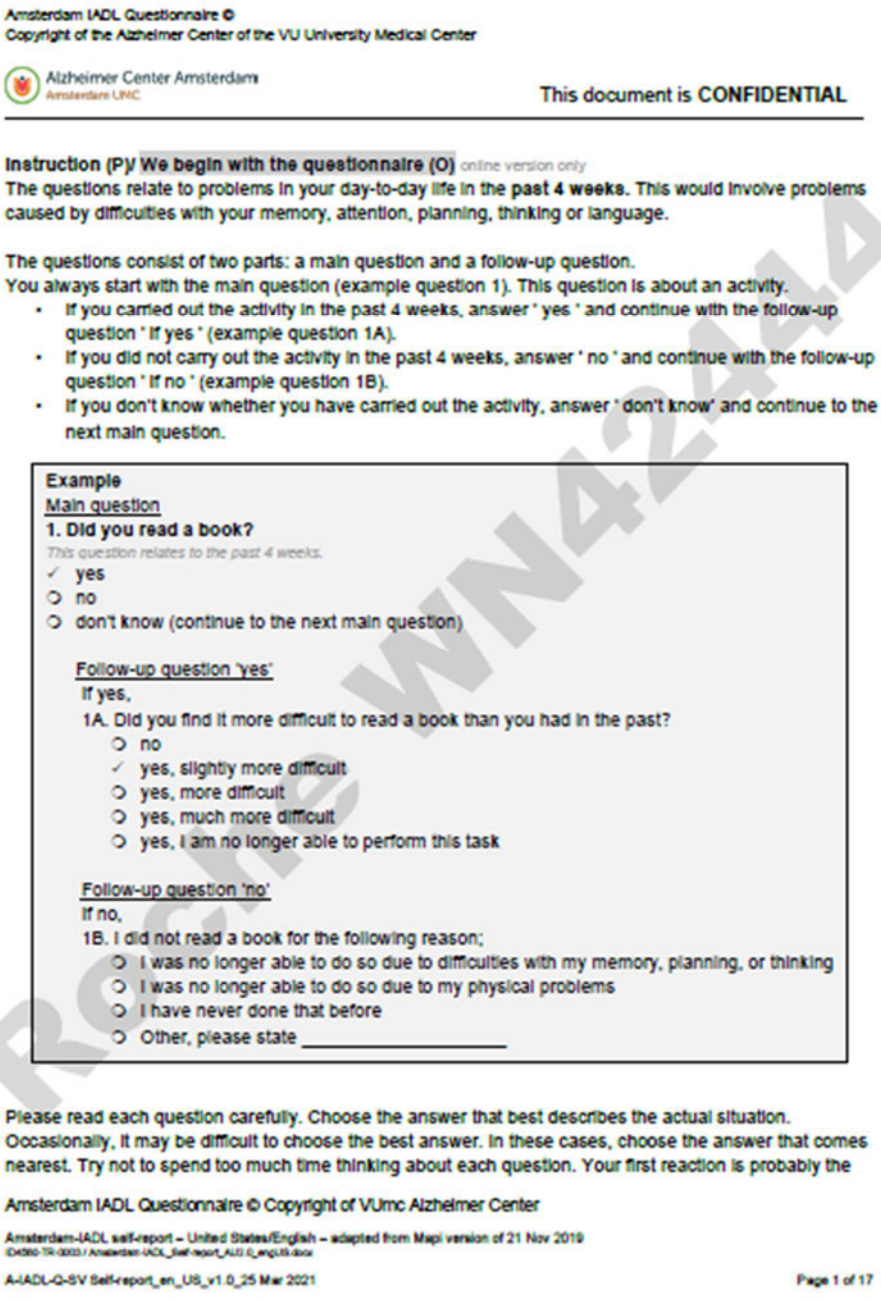
Morris JC. The clinical dementia rating (CDR): current version and scoring rules. Neurology 1993;43:2412–4.

Morris JC, Storandt M, Miller JP, et al. Mild cognitive impairment represents early-stage Alzheimer's disease. Arch Neurol 2001;58:397–405.

O'Bryant SE, Lacritz LH, Hall J, et al. Validation of the new interpretive guidelines for the clinical dementia rating scale sum of boxes score in the national Alzheimer's coordinating center database. Arch Neurol 2010;67:746–9.

Appendix 12 Amsterdam Instrumental Activity of Daily Living Questionnaire–Short Version (A-IADL-Q-SV) Participant Version

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.



Amsterdam IADL Questionnaire ©
Copyright of the Alzheimer Center of the VU University Medical Center

Alzheimer Center Amsterdam
Amsterdam UMC

This document is **CONFIDENTIAL**

Instruction (P)/ We begin with the questionnaire (O) online version only
The questions relate to problems in your day-to-day life in the **past 4 weeks.** This would involve problems caused by difficulties with your memory, attention, planning, thinking or language.

The questions consist of two parts: a main question and a follow-up question.
You always start with the main question (example question 1). This question is about an activity.

- If you carried out the activity in the past 4 weeks, answer ' yes ' and continue with the follow-up question ' If yes ' (example question 1A).
- If you did not carry out the activity in the past 4 weeks, answer ' no ' and continue with the follow-up question ' If no ' (example question 1B).
- If you don't know whether you have carried out the activity, answer ' don't know' and continue to the next main question.

Example
Main question
1. Did you read a book?
This question relates to the past 4 weeks.
✓ yes
○ no
○ don't know (continue to the next main question)

Follow-up question 'yes'
If yes,
1A. Did you find it more difficult to read a book than you had in the past?
○ no
✓ yes, slightly more difficult
○ yes, more difficult
○ yes, much more difficult
○ yes, I am no longer able to perform this task

Follow-up question 'no'
If no,
1B. I did not read a book for the following reason;
○ I was no longer able to do so due to difficulties with my memory, planning, or thinking
○ I was no longer able to do so due to my physical problems
○ I have never done that before
○ Other, please state _____

Please read each question carefully. Choose the answer that best describes the actual situation. Occasionally, it may be difficult to choose the best answer. In these cases, choose the answer that comes nearest. Try not to spend too much time thinking about each question. Your first reaction is probably the

Amsterdam IADL Questionnaire © Copyright of VUmc Alzheimer Center

Amsterdam-IADL self-report – United States/English – adapted from Mapi version of 21 Nov 2019

A-IADL-Q-SV Self-report_en_US_v1.0_25 Mar 2021 Page 1 of 17

***Important:** Pages are printed on both sides.*

most accurate. Press "next" to start the questionnaire. By pressing "back" you return to the previous question (O) online version only

Important: Pages are printed on both sides.

1. Did you carry out household chores?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 2)

If yes,

1A. Did you find it more difficult to carry out household chores than you had in the past?

- o No
- o Yes, slightly more difficult
- o Yes, more difficult
- o Yes, much more difficult
- o Yes, I am no longer able to perform this task

If no,

1B. I did not carry out household chores for the following reason;

- o I was no longer able to do so due to difficulties with my memory, planning, or thinking
- o I was no longer able to do so due to my physical problems
- o I have never done that before
- o Other, please state _____

2. Did you do the shopping?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 3)

If yes,

2A. Did you find it more difficult to do the shopping than you had in the past?

- o No
- o Yes, slightly more difficult
- o Yes, more difficult
- o Yes, much more difficult
- o Yes, I am no longer able to perform this task

If no,

2B. I did not do the shopping for the following reason;

- o I was no longer able to do so due to difficulties with my memory, planning, or thinking
- o I was no longer able to do so due to my physical problems
- o I have never done that before
- o Other, please state _____

Important: Pages are printed on both sides.

3. Did you buy the correct items when doing the shopping?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 4)

If yes,

3A. Did you find it more difficult to buy the correct items than you had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, I am no longer able to perform this task

If no,

3B. I did not buy the correct items for the following reason;

- ○ I was no longer able to do so due to difficulties with my memory, planning, or thinking
- ○ I was no longer able to do so due to my physical problems
- ○ I have never done that before
- ○ Other, please state _____

4. Did you do the cooking?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 5)

If yes,

4A. Did you find it more difficult to do the cooking than you had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, I am no longer able to perform this task

If no,

4B. I did not do the cooking for the following reason;

- ○ I was no longer able to do so due to difficulties with my memory, planning, or thinking
- ○ I was no longer able to do so due to my physical problems
- ○ I have never done that before
- ○ Other, please state _____

Important: Pages are printed on both sides.

5. Did you prepare sandwiches?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 6)

If yes,

5A. Did you find it more difficult to prepare sandwiches than you had in the past?

- o No
- o Yes, slightly more difficult
- o Yes, more difficult
- o Yes, much more difficult
- o Yes, I am no longer able to perform this task

If no,

5B. I have not prepared sandwiches for the following reason:

- o I was no longer able to do so due to difficulties with my memory, planning, or thinking
- o I was no longer able to do so due to my physical problems
- o I have never done that before
- o Other, please state: _____

6. Did you make minor repairs to the house?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 7)

If yes,

6A. Did you find it more difficult to perform minor repairs to the house than you had in the past?

- o No
- o Yes, slightly more difficult
- o Yes, more difficult
- o Yes, much more difficult
- o Yes, I am no longer able to perform this task

If no,

6B. I have not performed minor repairs to the house for the following reason;

- o I was no longer able to do so due to difficulties with my memory, planning, or thinking
- o I was no longer able to do so due to my physical problems
- o I have never done that before
- o Other, please state _____

Important: Pages are printed on both sides.

7. Did you use household appliances?
This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 8)

If yes,
7A. Did you find it more difficult to use household appliances than you had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, I am no longer able to perform this task

If no,
7B. I did not use household appliances for the following reason;

- ○ I was no longer able to do so due to difficulties with my memory, planning, or thinking
- ○ I was no longer able to do so due to my physical problems
- ○ I have never done that before
- ○ Other, please state _____

8. Did you use the microwave?
This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 9)

If yes,
8A. Did you find it more difficult to use the microwave than you had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, I am no longer able to perform this task

If no,
8B. I did not use the microwave for the following reason;

- ○ I was no longer able to do so due to difficulties with my memory, planning, or thinking
- ○ I was no longer able to do so due to my physical problems
- ○ I have never done that before
- ○ Other, please state _____

Important: Pages are printed on both sides.

9. Did you use the coffee maker?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 10)

If yes,

9A. Did you find it more difficult to use the coffee maker than you had in the past?

- o No
- o Yes, slightly more difficult
- o Yes, more difficult
- o Yes, much more difficult
- o Yes, I am no longer able to perform this task

If no,

9B. I did not use the coffee maker for the following reason;

- o I was no longer able to do so due to difficulties with my memory, planning, or thinking
- o I was no longer able to do so due to my physical problems
- o I have never done that before
- o Other, please state _____

10. Did you use the washing machine?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 11)

If yes,

10A. Did you find it more difficult to use the washing machine than you had in the past?

- o No
- o Yes, slightly more difficult
- o Yes, more difficult
- o Yes, much more difficult
- o Yes, I am no longer able to perform this task

If no,

10B. I did not use the washing machine for the following reason;

- o I was no longer able to do so due to difficulties with my memory, planning, or thinking
- o I was no longer able to do so due to my physical problems
- o I have never done that before
- o Other, please state _____

***Important:** Pages are printed on both sides.*

11. Did you pay your bills?
This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 12)

If yes,

11A. Did you find it more difficult to pay your bills than you had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, I am no longer able to perform this task

If no,

11B. I did not pay my bills for the following reason;

- ○ I was no longer able to do so due to difficulties with my memory, planning, or thinking
- ○ I was no longer able to do so due to my physical problems
- ○ I have never done that before
- ○ Other, please state _____

12. Did you use a cell phone?
This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 13)

If yes,

12A. Did you find it more difficult to use a cell phone than you had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, I am no longer able to perform this task

If no,

12B. I did not use a cell phone for the following reason;

- ○ I was no longer able to do so due to difficulties with my memory, planning, or thinking
- ○ I was no longer able to do so due to my physical problems
- ○ I have never done that before
- ○ Other, please state _____

Important: Pages are printed on both sides.

13. Did you manage your paperwork?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 14)

If yes,

13A. Did you find it more difficult to manage your paperwork than you had in the past?

- o No
- o Yes, slightly more difficult
- o Yes, more difficult
- o Yes, much more difficult
- o Yes, I am no longer able to perform this task

If no,

13B. I did not manage my paperwork for the following reason;

- o I was no longer able to do so due to difficulties with my memory, planning, or thinking
- o I was no longer able to do so due to my physical problems
- o I have never done that before
- o Other, please state _____

14. Did you use online banking?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 15)

If yes,

14A. Did you find it more difficult to use online banking than you had in the past?

- o No
- o Yes, slightly more difficult
- o Yes, more difficult
- o Yes, much more difficult
- o Yes, I am no longer able to perform this task

If no,

14B. I did not use online banking for the following reason;

- o I was no longer able to do so due to difficulties with my memory, planning, or thinking
- o I was no longer able to do so due to my physical problems
- o I have never done that before
- o Other, please state _____

Important: Pages are printed on both sides.

15. Did you use a PIN code?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 16)

If yes,

15A. Did you find it more difficult to use a PIN code than you had in the past?

- o No
- o Yes, slightly more difficult
- o Yes, more difficult
- o Yes, much more difficult
- o Yes, I am no longer able to perform this task

If no,

15B. I did not use a PIN code for the following reason;

- o I was no longer able to do so due to difficulties with my memory, planning, or thinking
- o I was no longer able to do so due to my physical problems
- o I have never done that before
- o Other, please state _____

16. Did you withdraw money from a cash machine (ATM)?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 17)

If yes,

16A. Did you find it more difficult to withdraw the correct amount from a cash machine (ATM) than you had in the past?

- o No
- o Yes, slightly more difficult
- o Yes, more difficult
- o Yes, much more difficult
- o Yes, I am no longer able to perform this task

If no,

16B. I have not withdrawn money from a cash machine (ATM) for the following reason;

- o I was no longer able to do so due to difficulties with my memory, planning, or thinking
- o I was no longer able to do so due to my physical problems
- o I have never done that before
- o Other, please state _____

***Important:** Pages are printed on both sides.*

17. Did you pay with cash?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 18)

If yes,

17A. Did you find it more difficult to pay with cash than you had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, I am no longer able to perform this task

If no,

17B. I did not pay with cash for the following reason;

- ○ I was no longer able to do so due to difficulties with my memory, planning, or thinking
- ○ I was no longer able to do so due to my physical problems
- ○ I have never done that before
- ○ Other, please state _____

18. Did you make appointments?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 19)

If yes,

18A. Did you find it more difficult to keep appointments than you had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, I am no longer able to perform this task

If no,

18B. I did not make appointments for the following reason;

- ○ I was no longer able to do so due to difficulties with my memory, planning, or thinking
- ○ I was no longer able to do so due to my physical problems
- ○ I have never done that before
- ○ Other, please state _____

Important: Pages are printed on both sides.

19. Did you fill in forms?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 20)

If yes,

19A. Did you find it more difficult to fill in forms than you had in the past?

- o No
- o Yes, slightly more difficult
- o Yes, more difficult
- o Yes, much more difficult
- o Yes, I am no longer able to perform this task

If no,

19B. I did not fill in forms for the following reason;

- o I was no longer able to do so due to difficulties with my memory, planning, or thinking
- o I was no longer able to do so due to my physical problems
- o I have never done that before
- o Other, please state _____

20. Did you work?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 21)

If yes,

20A. Did you find it more difficult to work than you had in the past?

- o No
- o Yes, slightly more difficult
- o Yes, more difficult
- o Yes, much more difficult
- o Yes, I am no longer able to perform this task

If no,

20B. I did not work for the following reason;

- o I was no longer able to do so due to difficulties with my memory, planning, or thinking
- o I was no longer able to do so due to my physical problems
- o I have never done that before
- o Other, please state _____

Important: Pages are printed on both sides.

21. Did you use a computer?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 22)

If yes,

21A. Did you find it more difficult to use a computer than you had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, I am no longer able to perform this task

If no,

21B. I did not use a computer for the following reason;

- ○ I was no longer able to do so due to difficulties with my memory, planning, or thinking
- ○ I was no longer able to do so due to my physical problems
- ○ I have never done that before
- ○ Other, please state _____

22. Did you use e-mail?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 23)

If yes,

22A. Did you find it more difficult to use e-mail than you had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, I am no longer able to perform this task

If no,

22B. I did not use e-mail for the following reason;

- ○ I was no longer able to do so due to difficulties with my memory, planning, or thinking
- ○ I was no longer able to do so due to my physical problems
- ○ I have never done that before
- ○ Other, please state _____

Important: Pages are printed on both sides.

23. Did you print documents?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 24)

If yes,

23A. Did you find it more difficult to print documents than you had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, I am no longer able to perform this task

If no,

23B. I did not print documents for the following reason;

- ○ I was no longer able to do so due to difficulties with my memory, planning, or thinking
- ○ I was no longer able to do so due to my physical problems
- ○ I have never done that before
- ○ Other, please state _____

24. Did you use electronic devices?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 25)

If yes,

24A. Did you find it more difficult to use electronic devices than you had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, I am no longer able to perform this task

If no,

24B. I did not use electronic devices for the following reason;

- ○ I was no longer able to do so due to difficulties with my memory, planning, or thinking
- ○ I was no longer able to do so due to my physical problems
- ○ I have never done that before
- ○ Other, please state _____

Important: Pages are printed on both sides.

25. Did you use the television remote control?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 26)

If yes,

25A. Did you find it more difficult to use the television remote control than you had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, I am no longer able to perform this task

If no,

25B. I did not use the television remote control for the following reason;

- ○ I was no longer able to do so due to difficulties with my memory, planning, or thinking
- ○ I was no longer able to do so due to my physical problems
- ○ I have never done that before
- ○ Other, please state _____

26. Did you play card and board games?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 27)

If yes,

26A. Did you find it more difficult to play card and board games than you had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, I am no longer able to perform this task

If no,

26B. I did not play card and board games for the following reason;

- ○ I was no longer able to do so due to difficulties with my memory, planning, or thinking
- ○ I was no longer able to do so due to my physical problems
- ○ I have never done that before
- ○ Other, please state _____

Important: Pages are printed on both sides.

27. Did you drive a car?

This question relates to the past 4 weeks.

- ❍ Yes
- ❍ No
- ❍ Don't know (continue with question 28)

If yes,

27A. Did you find it more difficult to drive a car than you had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, I am no longer able to perform this task

If no,

27B. I did not drive a car for the following reason;

- ○ I was no longer able to do so due to difficulties with my memory, planning, or thinking
- ○ I was no longer able to do so due to my physical problems
- ○ I have never done that before
- ○ Other, please state _____

28. Did you use GPS (navigation system)?

This question relates to the past 4 weeks.

- ❍ Yes
- ❍ No
- ❍ Don't know (continue with question 29)

If yes,

28A. Did you find it more difficult to use GPS (navigation system) than you had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, I am no longer able to perform this task

If no,

28B. I did not use GPS (navigation system) for the following reason;

- ○ I was no longer able to do so due to difficulties with my memory, planning, or thinking
- ○ I was no longer able to do so due to my physical problems
- ○ I have never done that before
- ○ Other, please state _____

Important: Pages are printed on both sides.

29. Did you use public transport?

This question relates to the past 4 weeks.

- ❍ Yes
- ❍ No
- ❍ Don't know (continue with question 30)

If yes,

29A. Did you find it more difficult to use public transport than you had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, I am no longer able to perform this task

If no,

29B. I did not make use of public transport for the following reason;

- ○ I was no longer able to do so due to difficulties with my memory, planning, or thinking
- ○ I was no longer able to do so due to my physical problems
- ○ I have never done that before
- ○ Other, please state _____

30. Did you use medication?

This question relates to the past 4 weeks.

- ❍ Yes
- ❍ No
- ❍ Don't know

If yes,

30A. Did you have more trouble being responsible for your own medication than in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, I am no longer able to perform this task

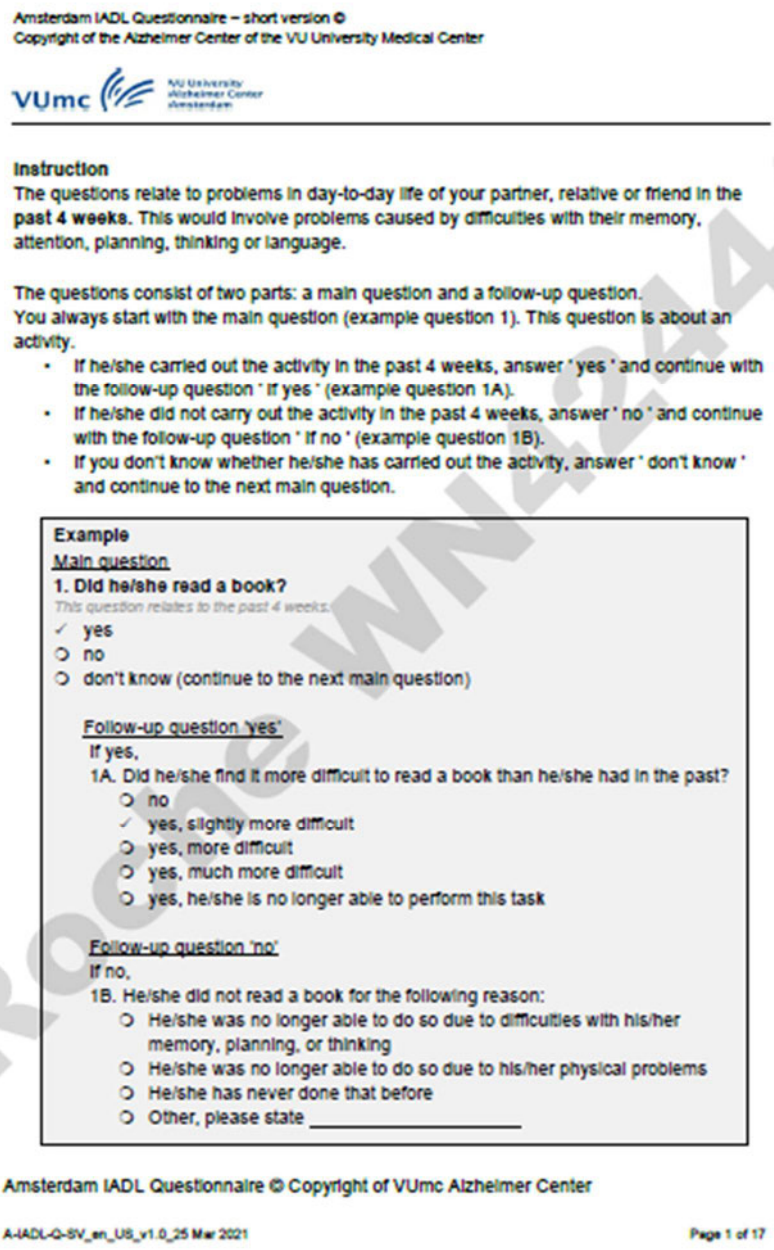
Thank you for completing this questionnaire!

REFERENCE

Jutten RJ, Peeters CFW, Leijdesdorff SMJ, et al. Detecting functional decline from normal aging to dementia: Development and validation of a short version of the Amsterdam IADL Questionnaire. Alzheimers Dement (Amst) 2017;8:26–35.

Appendix 13 Amsterdam Instrumental Activity of Daily Living Questionnaire–Short Version (A-IADL-Q-SV) Study Partner Version

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.



Amsterdam IADL Questionnaire – short version ©
Copyright of the Alzheimer Center of the VU University Medical Center

VUmc VU University Alzheimer Center Amsterdam

Instruction
The questions relate to problems in day-to-day life of your partner, relative or friend in the **past 4 weeks**. This would involve problems caused by difficulties with their memory, attention, planning, thinking or language.

The questions consist of two parts: a main question and a follow-up question.
You always start with the main question (example question 1). This question is about an activity.

- If he/she carried out the activity in the past 4 weeks, answer ' yes ' and continue with the follow-up question ' If yes ' (example question 1A).
- If he/she did not carry out the activity in the past 4 weeks, answer ' no ' and continue with the follow-up question ' If no ' (example question 1B).
- If you don't know whether he/she has carried out the activity, answer ' don't know ' and continue to the next main question.

Example
Main question
1. Did he/she read a book?
This question relates to the past 4 weeks.
✓ yes
○ no
○ don't know (continue to the next main question)

Follow-up question 'yes'
If yes,
1A. Did he/she find it more difficult to read a book than he/she had in the past?
○ no
✓ yes, slightly more difficult
○ yes, more difficult
○ yes, much more difficult
○ yes, he/she is no longer able to perform this task

Follow-up question 'no'
If no,
1B. He/she did not read a book for the following reason:
○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
○ He/she was no longer able to do so due to his/her physical problems
○ He/she has never done that before
○ Other, please state _____

Amsterdam IADL Questionnaire © Copyright of VUmc Alzheimer Center

A-IADL-Q-SV_en_US_v1.0_25 Mar 2021 Page 1 of 17

Please read each question carefully. Choose the answer that best describes the actual situation. Occasionally, it may be difficult to choose the best answer. In these cases, choose the answer that comes nearest. Try not to spend too much time thinking about each question. Your first reaction is probably the most accurate.

1. Did he/she carry out household chores?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 2)

If yes,

1A. Did he/she find it more difficult to carry out household chores than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

1B. He/she did not carry out household chores for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

2. Did he/she do the shopping?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 3)

If yes,

2A. Did he/she find it more difficult to do the shopping than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

2B. He/she did not do the shopping for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

3. Did he/she buy the correct items when doing the shopping?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 4)

If yes,

3A. Did he/she find it more difficult to buy the correct items than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

3B. He/she did not buy the correct items for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

4. Did he/she do the cooking?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 5)

If yes,

4A. Did he/she find it more difficult to do the cooking than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

4B. He/she did not do the cooking for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

5. Did he/she prepare sandwiches?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 6)

If yes,

5A. Did he/she find it more difficult to prepare sandwiches than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

5B. He/she has not prepared sandwiches for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

6. Did he/she make minor repairs to the house?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 7)

If yes,

6A. Did he/she find it more difficult to perform minor repairs to the house than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

6B. He/she has not performed minor repairs to the house for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

7. Did he/she use household appliances?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 8)

If yes,

7A. Did he/she find it more difficult to use household appliances than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

7B. He/she did not use household appliances for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

8. Did he/she use the microwave?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 9)

If yes,

8A. Did he/she find it more difficult to use the microwave than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

8B. He/she did not use the microwave for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

9. Did he/she use the coffee maker?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 10)

If yes,

9A. Did he/she find it more difficult to use the coffee maker than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

9B. He/she did not use the coffee maker for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

10. Did he/she use the washing machine?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 11)

If yes,

10A. Did he/she find it more difficult to use the washing machine than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

10B. He/she did not use the washing machine for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

11. Did he/she pay his/her bills?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 12)

If yes,

11A. Did he/she find it more difficult to pay his/her bills than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

11B. He/she did not pay his/her bills for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

12. Did he/she use a cell phone?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 13)

If yes,

12A. Did he/she find it more difficult to use a cell phone than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

12B. He/she did not use a cell phone for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

13. Did he/she manage his/her paperwork?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 14)

If yes,

13A. Did he/she find it more difficult to manage his/her paperwork than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

13B. He/she did not manage his/her paperwork for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

14. Did he/she use online banking?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 15)

If yes,

14A. Did he/she find it more difficult to use online banking than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

14B. He/she did not use online banking for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

15. Did he/she use a PIN code?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 16)

If yes,

15A. Did he/she find it more difficult to use a PIN code than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

15B. He/she did not use a PIN code for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

16. Did he/she withdraw money from a cash machine (ATM)?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 17)

If yes,

16A. Did he/she find it more difficult to withdraw the correct amount from a cash machine (ATM) than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

16B. He/she has not withdrawn money from a cash machine (ATM) for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

17. Did he/she pay with cash?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 18)

If yes,

17A. Did he/she find it more difficult to pay with cash than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

17B. He/she did not pay with cash for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

18. Did he/she make appointments?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 19)

If yes,

18A. Did he/she find it more difficult to keep appointments than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

18B. He/she did not make appointments for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

19. Did he/she fill in forms?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 20)

If yes,

19A. Did he/she find it more difficult to fill in forms than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

19B. He/she did not fill in forms for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

20. Did he/she work?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 21)

If yes,

20A. Did he/she find it more difficult to work than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

20B. He/she did not work for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

21. Did he/she use a computer?

This question relates to the 4 four weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 22)

If yes,

21A. Did he/she find it more difficult to use a computer than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

21B. He/she did not use a computer for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

22. Did he/she use e-mail?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 23)

If yes,

22A. Did he/she find it more difficult to use e-mail than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

22B. He/she did not use e-mail for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

23. Did he/she print documents?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 24)

If yes,

23A. Did he/she find it more difficult to print documents than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

23B. He/she did not print documents for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

24. Did he/she use electronic devices?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 25)

If yes,

24A. Did he/she find it more difficult to use electronic devices than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

24B. He/she did not use electronic devices for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

25. Did he/she use the television remote control?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 26)

If yes,
25A. Did he/she find it more difficult to use the television remote control than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,
25B. He/she did not use the television remote control for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

26. Did he/she play card and board games?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 27)

If yes,
26A. Did he/she find it more difficult to play card and board games than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,
26B. He/she did not play card and board games for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

27. Did he/she drive a car?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 28)

If yes,

27A. Did he/she find it more difficult to drive a car than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

27B. He/she did not drive a car for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

28. Did he/she use GPS (navigation system)?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 29)

If yes,

28A. Did he/she find it more difficult to use GPS (navigation system) than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

28B. He/she did not use GPS (navigation system) for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

29. Did he/she use public transport?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know (continue with question 30)

If yes,

29A. Did he/she find it more difficult to use public transport than he/she had in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

If no,

29B. He/she did not make use of public transport for the following reason;

- ○ He/she was no longer able to do so due to difficulties with his/her memory, planning, or thinking
- ○ He/she was no longer able to do so due to his/her physical problems
- ○ He/she has never done that before
- ○ Other, please state _____

30. Did he/she use medication?

This question relates to the past 4 weeks.

- ○ Yes
- ○ No
- ○ Don't know

If yes,

30A. Did he/she have more trouble being responsible for his/her own medication than in the past?

- ○ No
- ○ Yes, slightly more difficult
- ○ Yes, more difficult
- ○ Yes, much more difficult
- ○ Yes, he/she is no longer able to perform this task

Thank you for completing this questionnaire!

REFERENCE

Jutten RJ, Peeters CFW, Leijdesdorff SMJ, et al. Detecting functional decline from normal aging to dementia: Development and validation of a short version of the Amsterdam IADL Questionnaire. Alzheimers Dement (Amst) 2017;8:26–35.

Appendix 14 CFIa – Participant Version

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

CFI-Acute (CFIa) – Participant Version

Please complete these questions thinking about your current ability (most recent experience) by selecting the response for the one best answer for each question.

1. How often do you have difficulty with your memory? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
2. How often do others tell you that you repeat questions over and over? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
3. How often do you misplace things? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
4. How often must you rely on written reminders? ☐ Never ☐Rarely ☐ Sometimes ☐ Often ☐ Always
5. How often do you need help from other people to remember appointments, family occasions or holidays? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
6. How often do you have trouble recalling names, finding the right word or completing sentences? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
7. How often do you have trouble driving (slowly or too fast, trouble at night, get lost, have accidents)? ☐ Never ☐Rarely ☐ Sometimes ☐ Often ☐ Always ☐ I do not drive
8. How often do you have difficulty managing money (paying bills, calculating change, completing tax forms)? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always ☐ Does not apply
9. How often do you participate in social activities? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
10. How often do you have problems with work performance (paid or volunteer) ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always ☐ I do not work or volunteer
11. How often do you have trouble following the news or the plots of books, movies or TV shows? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
12. How often do you have difficulty with activities for example, hobbies, card games, or crafts? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
13. How often do you get disoriented or lost? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
14. How often do you have difficulty using your usual household appliances (such as washing machine or microwave) or familiar electronic devices (computer or cell phone)? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

CFI-Acute – Participant version, adapted from ADCS-CFI – Participant, Version 3, US-English, 17Sept2015

Used with permission from the NIA-funded Alzheimer's Disease Cooperative Study (NIA Grant U19 AG10483).

Walsh, S.; Raman, R.; Jones, K.; Aisen, P.; and the ADCS; "ADCS Prevention Instrument Project: The Mail-In Cognitive Function Screening Instrument (MCFSI)." *Alzheimer's Disease and Associated Disorders*, 2006. Vol 20(3) S170-S178.

Amariglio, R., Donohue, M., Marshall, G., Rentz, D., Salmon, D., Ferris, S., Karantzoulis, S., Aisen, P., Sperling, R. and the ADCS. "Tracking early decline in cognitive function in older individuals at risk for Alzheimer's disease dementia: the ADCS-Cognitive Function Instrument." JAMA Neurology, 2015. Vol. 72(4):446-454

REFERENCES

Amariglio RE, Donohue MC, Marshall GA, et al. Tracking early decline in cognitive function in older individuals at risk for Alzheimer disease dementia: the Alzheimer's Disease Cooperative Study Cognitive Function Instrument. JAMA Neurol 2015;72:446–54.

Li C, Neugroschl J, Luo X,et al. The utility of the Cognitive Function Instrument (CFI) to detect cognitive decline in non-demented older adults. J Alzheimers Dis 2017;60:427–37.

Walsh SP, Raman R, Jones KB, et al. ADCS Prevention Instrument Project: the Mail-In Cognitive Function Screening Instrument (MCFSI). Alzheimer Dis Assoc Disord 2006;20:S170–8.

Appendix 15 CFIa – Study Partner Version

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

CFI-Acute (CFIa) – Study Partner Version

Please complete these questions without asking the study participant's opinion. You may ask other family members, friends or colleagues of the participant. Select the one best answer for each question thinking about the participant's current ability (most recent experience).

1. How often does the participant have difficulty with memory? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
2. How often does the participant repeat questions over and over? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
3. How often does the participant misplace things? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
4. How often must the participant rely on written reminders? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
5. How often does the participant need help from other people to remember appointments, family occasions or holidays? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
6. How often does the participant have trouble recalling names, finding the right word or completing sentences? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
7. How often does the participant have trouble driving (slowly or too fast, trouble at night, gets lost, has accidents)? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always ☐ Does not drive
8. How often does the participant have difficulty managing money (paying bills, calculating change, completing tax forms)? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always ☐ Does not apply
9. How often does the participant participate in social activities? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
10. How often does the participant have problems with work performance (paid or volunteer)? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always ☐ Does not work or volunteer
11. How often does the participant have trouble following the news or the plots of books, movies or TV shows? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
12. How often does the participant have difficulty with activities for example, hobbies, card games, crafts? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
13. How often does the participant get disoriented or lost? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always
14. How often does the participant have difficulty using usual household appliances (such as washing machine or microwave) or familiar electronic devices (computer or cell phone)? ☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

CFI-Acute – Study Partner version, adapted from ADCS-CFI – Study Partner, Version 3, US-English, 17Sept2015

Used with permission from the NIA-funded Alzheimer's Disease Cooperative Study (NIA Grant U19 AG10483).

Walsh, S.; Raman, R.; Jones, K.; Aisen, P.; and the ADCS; "ADCS Prevention Instrument Project: The Mail-In Cognitive Function Screening Instrument (MCFSI)." *Alzheimer's Disease and Associated Disorders*, 2006. Vol 20(3) S170-S178.

Amariglio, R., Donohue, M., Marshall, G., Rentz, D., Salmon, D., Ferris, S., Karantzoulis, S., Aisen, P., Sperling, R. and the ADCS. "Tracking early decline in cognitive function in older individuals at risk for Alzheimer's disease dementia: the ADCS-Cognitive Function Instrument." JAMA Neurology, 2015. Vol. 72(4):446-454

REFERENCES

Amariglio RE, Donohue MC, Marshall GA, et al. Tracking early decline in cognitive function in older individuals at risk for Alzheimer disease dementia: the Alzheimer's Disease Cooperative Study Cognitive Function Instrument. JAMA Neurol 2015;72:446–54.

Li C, Neugroschl J, Luo X,et al. The utility of the Cognitive Function Instrument (CFI) to detect cognitive decline in non-demented older adults. J Alzheimers Dis 2017;60:427–37.

Walsh SP, Raman R, Jones KB, et al. ADCS Prevention Instrument Project: the Mail-In Cognitive Function Screening Instrument (MCFSI). Alzheimer Dis Assoc Disord 2006;20:S170–8.

Appendix 16 Geriatric Depression Scale–30

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Geriatric Depression Scale (GDS) 30-Item Version

Instructions for the interviewer: Read each of the following questions verbatim to the subject and mark (✓) either Yes or No based on the subject's response to each question. Provide the following instruction to the subject before asking the first question: **"Choose the best answer for how you have felt over the past week:"**

Question	Response	
1. Are you basically satisfied with your life?	○ yes	☐ ***NO***
2. Have you dropped many of your activities and interests?	☐ ***YES***	○ no
3. Do you feel that your life is empty?	☐ ***YES***	○ no
4. Do you often get bored?	☐ ***YES***	○ no
5. Are you hopeful about the future?	○ yes	☐ ***NO***
6. Are you bothered by thoughts you can't get out of your head?	☐ ***YES***	○ no
7. Are you in good spirits most of the time?	○ yes	☐ ***NO***
8. Are you afraid that something bad is going to happen to you?	☐ ***YES***	○ no
9. Do you feel happy most of the time?	○ yes	☐ ***NO***
10. Do you often feel helpless?	☐ ***YES***	○ no
11. Do you often get restless and fidgety?	☐ ***YES***	○ no
12. Do you prefer to stay at home, rather than going out and doing new things?	☐ ***YES***	○ no
13. Do you frequently worry about the future?	☐ ***YES***	○ no
14. Do you feel you have more problems with memory than most?	☐ ***YES***	○ no
15. Do you think it is wonderful to be alive now?	○ yes	☐ ***NO***
16. Do you often feel downhearted and blue?	☐ ***YES***	○ no
17. Do you feel pretty worthless the way you are now?	☐ ***YES***	○ no
18. Do you worry a lot about the past?	☐ ***YES***	○ no
19. Do you find life very exciting?	○ yes	☐ ***NO***
20. Is it hard for you to get started on new projects?	☐ ***YES***	○ no

21. Do you feel full of energy?	○ yes	☐ ***NO***
22. Do you feel that your situation is hopeless?	☐ ***YES***	○ no
23. Do you think that most people are better off than you are?	☐ ***YES***	○ no
24. Do you frequently get upset over little things?	☐ ***YES***	○ no
25. Do you frequently feel like crying?	☐ ***YES***	○ no
26. Do you have trouble concentrating?	☐ ***YES***	○ no
27. Do you enjoy getting up in the morning?	○ yes	☐ ***NO***
28. Do you prefer to avoid social gatherings?	☐ ***YES***	○ no
29. Is it easy for you to make decisions?	○ yes	☐ ***NO***
30. Is your mind as clear as it used to be?	○ yes	☐ ***NO***
TOTAL SCORE (0-30):	_____	

Scoring: The GDS Total Score is the sum (1 point each) of the responses in ***BOLD, ITALIC, CAPITALS***.

- Items 1, 5, 7, 9, 15, 19, 21, 27, 29, and 30 → score 1 point if the response is "***NO***".
- Items 2, 3, 4, 6, 8, 10, 11, 12, 13, 14, 16, 17, 18, 20, 22, 23, 24, 25, 26, and 28 → score 1 point if the response is "***YES***".

Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey MB, Leirer VO: Development and validation of a geriatric depression screening scale: A preliminary report. *Journal of Psychiatric Research 17:* 37-49, 1983.

REFERENCES

Sheikh JI, Yesavage JA, Brooks JO, et al. Proposed factor structure of the Geriatric Depression Scale. Int Psychogeriatr 1991;3:23–8.

Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982–1983;17:37–49.

Appendix 17 Alzheimer's Disease Clinical Global Impression of Cognitive Function – Severity (AD-CGI-S)

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Clinician Global Impression of Cognitive Function (CGI-S)

Instructions for the rater: This form is intended to capture a clinician global impression of severity (CGI-S). Please read carefully through the descriptive language for each anchor and on the last page choose the descriptor that best fits the participant's current status.

Clinician Global Impression of Cognitive Function (CGI-S) – Descriptors

1 No problems: The participant has no cognitive problems and appears to have no concerns about his/her current cognitive abilities. He/She is able to perform all activities as usual, without any problems or changes.

2 Minor but noticeable cognitive problems that do not require modifications to his/her daily activities: The participant experiences minor cognitive problems that cause some concern (e.g. occasional forgetfulness, losing his/her train of thought, feeling overwhelmed making plans or decisions). However, he/she is still able to perform all his/her daily activities as usual, without difficulties or need to rely upon additional reminders or help.

3 Minor cognitive problems that require minor modification to daily activities, but he/she is functionally independent: The participant has minor cognitive problems that impact his/her ability to perform certain activities of daily living (e.g. it takes more effort or longer to perform certain activities like paying bills, calculating the tip at a restaurant, and organizing his/her daily schedule) and/or the participant needs to make minor lifestyle changes (e.g. He/she takes additional steps that were not needed before to complete activities, such as writing notes, reminders, or lists). However, he/she is still able to perform all of his/her daily activities independently, without any additional help.

4 Mild cognitive problems with functional impairment noticeable and needs some support: The participant has mild cognitive problems that mean he/she needs support with some activities that he/she used to be able to carry out independently (e.g. taking care finances, going shopping, or the participant had to retire early because of memory/thinking problems) and/or the participant has given up some activities due to his/her cognitive problems (e.g. driving or hobbies).

5 Moderate cognitive problems and functionally dependent outside home: The participant needs help for many daily activities (e.g. dressing and/or personal hygiene) and has stopped other activities due to his/her cognitive problems. He/She is no longer independent in his/her daily activities outside of his/her home.

6 Severe cognitive problems and functionally dependent in daily activities inside and outside home: The participant cannot perform his/her daily activities in his/her own home due to cognitive problems. He/She depends on others for some or all activities of daily life including eating, showering or bathing, dressing, toileting.

Please rate the severity of the study participant's cognitive problems and the impact on his/her daily activities at this time:

1	No problems	☐
2	Minor but noticeable cognitive problems that do not require modifications to his/her daily activities	☐
3	Minor cognitive problems that require minor modification to daily activities, but he/she is functionally independent	☐
4	Mild cognitive problems with functional impairment noticeable and needs some support	☐
5	Moderate cognitive problems and functionally dependent outside home	☐
6	Severe cognitive problems and functionally dependent in daily activities inside and outside home	☐

Adapted from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education and Welfare

REFERENCE

Guy W, editor. ECDEU Assessment Manual for Pschopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education and Welfare.

Appendix 18 Alzheimer's Disease Participant Global Impression of Cognitive Function (AD-PGI-S)

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Participant Global Impression of Cognitive Function (PGI-S)

Instructions for the interviewer: Please ensure that a paper copy of the scale, specifically the response options and descriptions, is in front of the participant. Read out loud all six response categories to the participant, including the full descriptions as displayed on the following pages, before asking the participant to choose the category that best applies to him/her. Enter the participant's response on the last page. Repeat the response categories and detailed descriptions, if necessary, but do not provide alternate examples or additional information.

Participant Global Impression of Cognitive Function (PGI-S) – Descriptors

Please rate the severity of any memory/thinking problems you may have had and their impact on your daily activities over the past 7 days:

1 No problems:
I have no memory and/or thinking problems and have no concerns about my current thinking abilities. I am able to perform all my activities as usual, without any problems or changes.

2 Minor but noticeable thinking problems that do not require changes to daily activities:
I experience minor memory and/or thinking problems that cause some concern (e.g. occasional forgetfulness, losing my train of thought, feeling overwhelmed making plans or decisions). However, I am still able to perform all my daily activities as usual, without difficulties or the need to rely upon additional reminders or help.

3 Minor thinking problems that require minor changes to daily activities, but I am independent in daily activities:
I have minor memory and/or thinking problems that impact my ability to perform certain activities of daily living (e.g. it takes more effort or longer to perform certain activities like paying bills, calculating the tip at a restaurant, and organizing my daily schedule) and/or I need to make minor lifestyle changes (e.g. I take additional steps that were not needed before to complete activities, such as writing notes, reminders, or lists). However, I am still able to perform all of my daily activities independently, without any additional help.

4 Mild thinking problems that mean I need help with some daily activities:
I have mild memory and/or thinking problems and as a result need help with some activities that I used to be able to carry out independently (e.g. taking care of finances, going shopping, or I had to retire early because of memory/thinking problems) and/or I have given up some activities due to my memory and/or thinking problems (e.g. driving or hobbies).

5 Moderate thinking problems that mean I rely on someone for daily activities outside of my home:
I need help for many daily activities (e.g. dressing and/or personal hygiene) and have stopped other activities due to my memory and/or thinking problems. I am no longer independent in my daily activities outside of my home.

6 Severe thinking problems that mean I rely on someone for daily activities inside and outside of my home:
I cannot perform my daily activities in my own home due to my memory and/or thinking problems. I rely on others for some or all activities of daily life including eating, showering or bathing, dressing, toileting.

Please rate the severity of any memory/thinking problems you may have had and their impact on your daily activities over the past 7 days:

1.	No problems	☐
2.	Minor but noticeable thinking problems that do not require changes to daily activities	☐
3.	Minor thinking problems that require minor changes to daily activities, but I am independent in daily activities	☐
4.	Mild thinking problems that mean I need help with some daily activities	☐
5.	Moderate thinking problems that mean I rely on someone for daily activities outside of my home	☐
6.	Severe thinking problems that mean I rely on someone for daily activities inside and outside of my home	☐

FDA. Patient-Focused Drug Development Guidance Public Workshop. Methods to Identify What Is Important to Patients & Select, Develop or Modify Fit-for-Purpose Clinical Outcomes Assessments. 2018

REFERENCE

FDA. Patient-focused drug development guidance public workshop: Methods to identify what is important to patients and select, develop, or modify fit-for-purpose clinical outcomes assessments. [resource on the Internet] 2018b. Available from: https://www.fda.gov/media/116277/download.

Appendix 19 Alzheimer's Disease Study Partner Impression of Cognitive Function (AD-SPGI-S)

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Study Partner Global Impression of Cognitive Function (SPGI-S)

Instructions for the interviewer: Please ensure that a paper copy of the scale, specifically the response options and descriptions, is in front of the participant. Read out loud all six response categories to the participant, including the full descriptions as displayed on the following pages, before asking the participant to choose the category that best applies to him/her. Enter the participant's response on the last page. Repeat the response categories and detailed descriptions, if necessary, but do not provide alternate examples or additional information.

Study Partner Global Impression of Cognitive Function (SPGI-S) – Descriptors

Please rate the severity of any memory/thinking problems of your spouse/partner/relative/friend and the impact on his/her daily activities over the past 7 days:

1 No problems:
He/she has no memory and/or thinking problems and appears to have no concerns about his/her current thinking abilities. He/she is able to perform all of his/her activities as usual, without any problems or changes.

2 Minor but noticeable thinking problems that do not require changes to his/her daily activities:
He/she experiences minor memory and/or thinking problems that appear to cause some concern (e.g. occasional forgetfulness, losing his/her train of thought, feeling overwhelmed making plans or decisions). However, he/she is still able to perform all his/her daily activities as usual, without difficulties or the need to rely upon additional reminders or help.

3 Minor thinking problems that require minor changes to daily activities, but he/she is independent in daily activities:
He/she has minor memory and/or thinking problems that impact his/her ability to perform certain activities of daily living (e.g. it takes more effort or longer to perform certain activities like paying bills, calculating the tip at a restaurant, and organizing his/her daily schedule) and/or he/she needs to make minor lifestyle changes (e.g. he/she takes additional steps that were not needed before to complete activities, such as writing notes, reminders, or lists). However, he/she is still able to perform all of his/her daily activities independently, without any additional help.

4 Mild thinking problems that mean he/she needs help with some daily activities:
He/she has mild memory and/or thinking problems and as a result needs help with some activities that he/she used to be able to carry out independently (e.g. taking care of finances, going shopping, or he/she had to retire early because of memory/thinking problems) and/or he/she has given up some activities due to his/her memory and/or thinking problems (e.g. driving or hobbies).

5 Moderate thinking problems that mean he/she relies on someone for daily activities outside of his/her home:
He/she needs help for many daily activities (e.g. dressing and/or personal hygiene) and has stopped other activities due to his/her memory and/or thinking problems. He/she is no longer independent in daily activities outside of his/her home.

6 Severe thinking problems that mean he/she relies on someone for daily activities inside and outside of his/her home:
He/she cannot perform his/her daily activities in his/her own home due to his/her memory and/or thinking problems. He/she relies on others for some or all activities of daily life including eating, showering or bathing, dressing, toileting.

Please rate the severity of any memory/thinking problems of your spouse/partner/relative/friend and the impact on his/her daily activities over the past 7 days:

1.	No problems	☐
2.	Minor but noticeable thinking problems that do not require changes to his/her daily activities	☐
3.	Minor thinking problems that require minor changes to daily activities, but he/she is independent in daily activities	☐
4.	Mild thinking problems that mean he/she needs help with some daily activities	☐
5.	Moderate thinking problems that mean he/she relies on someone for daily activities outside of his/her home	☐
6.	Severe thinking problems that mean he/she relies on someone for daily activities inside and outside of his/her home	☐

FDA. Patient-Focused Drug Development Guidance Public Workshop. Methods to Identify What Is Important to Patients & Select, Develop or Modify Fit-for-Purpose Clinical Outcomes Assessments. 2018

REFERENCE

FDA. Patient-focused drug development guidance public workshop: Methods to identify what is important to patients and select, develop, or modify fit-for-purpose clinical outcomes assessments. [resource on the Internet] 2018b. Available from: https://www.fda.gov/media/116277/download.

Appendix 20 EuroQol EQ-5-D-5L IA

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Health Questionnaire

English version for the UK

VERSION FOR INTERVIEWER ADMINISTRATION

Note to interviewer: although allowance should be made for the interviewer's particular style of speaking, the wording of the questionnaire instructions should be followed as closely as possible. In the case of the EQ-5D-5L descriptive system on page 2 of the questionnaire, the precise wording must be followed.

If the respondent has difficulty choosing a response, or asks for clarification, the interviewer should repeat the question word for word and ask the respondent to answer in a way that most closely resembles his or her thoughts about his or her health today.

INTRODUCTION

(Note to interviewer: please read the following to the respondent.)

We are trying to find out what you think about your health. I will explain what to do as I go along, but please interrupt me if you do not understand something or if things are not clear to you. There are no right or wrong answers. We are interested only in your personal view.

First, I am going to read out some questions. Each question has a choice of five answers. Please tell me which answer best describes your health TODAY.

Do not choose more than one answer in each group of questions.

(Note to interviewer: first read all five options for each question. Then ask the respondent to choose which one applies to him/herself. Repeat the question and options if necessary. Mark the appropriate box under each heading. You may need to remind the respondent regularly that the timeframe is TODAY.)

EQ-5D DESCRIPTIVE SYSTEM

MOBILITY

First, I would like to ask you about mobility. Would you say that:

1. You have no problems in walking about? ❑
2. You have slight problems in walking about? ❑
3. You have moderate problems in walking about? ❑
4. You have severe problems in walking about? ❑
5. You are unable to walk about? ❑

SELF-CARE

Next, I would like to ask you about self-care. Would you say that:

1. You have no problems washing or dressing yourself? ❑
2. You have slight problems washing or dressing yourself? ❑
3. You have moderate problems washing or dressing yourself? ❑
4. You have severe problems washing or dressing yourself? ❑
5. You are unable to wash or dress yourself? ❑

USUAL ACTIVITIES

Next, I would like to ask you about usual activities, for example work, study, housework, family or leisure activities. Would you say that:

1. You have no problems doing your usual activities? ❑
2. You have slight problems doing your usual activities? ❑
3. You have moderate problems doing your usual activities? ❑
4. You have severe problems doing your usual activities? ❑
5. You are unable to do your usual activities? ❑

PAIN / DISCOMFORT

Next, I would like to ask you about pain or discomfort. Would you say that:

1. You have no pain or discomfort? ❑
2. You have slight pain or discomfort? ❑
3. You have moderate pain or discomfort? ❑
4. You have severe pain or discomfort? ❑
5. You have extreme pain or discomfort? ❑

ANXIETY / DEPRESSION

Finally, I would like to ask you about anxiety or depression. Would you say that:

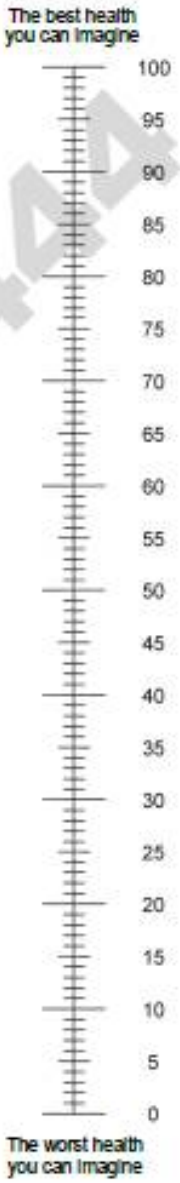
1. You are not anxious or depressed? ❑
2. You are slightly anxious or depressed? ❑
3. You are moderately anxious or depressed? ❑
4. You are severely anxious or depressed? ❑
5. You are extremely anxious or depressed? ❑

EQ-5D VAS

- **Now, I would like to ask you to say how good or bad your health is TODAY.**
- **I would like you to try to picture in your mind a scale that looks like a thermometer.**
  (Note to interviewer: If interviewing face-to-face, please show the person the VAS scale.)
- **The best health you can imagine is marked 100 (one hundred) at the top of the scale and the worst health you can imagine is marked 0 (zero) at the bottom.**
- **I would now like you to tell me the point on this scale where you would put your health TODAY.**
  (Note to interviewer: mark the scale at the point indicating the respondent's 'health today'. Now, please write the number you marked on the scale in the box below.)

THE RESPONDENT'S HEALTH TODAY =

Thank you for taking the time to answer these questions.



REFERENCE

EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.

Appendix 21 EuroQol EQ-5D-5L IA Proxy

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

EQ-5D-5L

Health Questionnaire

English version for the UK

PROXY VERSION FOR INTERVIEWER ADMINISTRATION
OF THE EQ-5D-5L: 1
How the proxy would describe the other person's health.

Note to interviewer: although allowance should be made for the interviewer's particular style of speaking, the wording of the questionnaire instructions should be followed as closely as possible. In the case of the EQ-5D-5L descriptive system on page 2 of the questionnaire, the precise wording must be followed.

If the proxy has difficulty choosing a response, or asks for clarification, the interviewer should repeat the question word for word and ask the proxy to answer in a way that most closely resembles his or her thoughts about the person's health today.

INTRODUCTION

(Note to interviewer: please read the following to the proxy.)

We are trying to find out what you think best describes the health of the person who is being assessed TODAY. I will explain what to do as I go along, but please interrupt me if you do not understand something or if things are not clear to you. There are no right or wrong answers. We are interested only in your personal view.

First, I am going to read out some questions. Each question has a choice of five answers. Please tell me which answer you think best describes the person's health TODAY.

Do not choose more than one answer in each group of questions.

(Note to interviewer: first read all five options for each question. Then ask the proxy to choose which one he/she thinks applies to the person whose health is being assessed. Repeat the question and options if necessary. Mark the appropriate box under each heading. You may need to remind the proxy regularly that the timeframe is TODAY.)

EQ-5D DESCRIPTIVE SYSTEM

First, I would like to ask you about MOBILITY. Do you think that the person:

1. Has no problems in walking about? ☐
2. Has slight problems in walking about? ☐
3. Has moderate problems in walking about? ☐
4. Has severe problems in walking about? ☐
5. Is unable to walk about? ☐

Next, I would like to ask you about SELF-CARE. Do you think that the person:

1. Has no problems washing or dressing him/herself? ☐
2. Has slight problems washing or dressing him/herself? ☐
3. Has moderate problems washing or dressing him/herself? ☐
4. Has severe problems washing or dressing him/herself? ☐
5. Is unable to wash or dress him/herself? ☐

Next, I would like to ask you about USUAL ACTIVITIES, for example work, study, housework, family or leisure activities. Do you think that the person:

1. Has no problems doing his/her usual activities? ☐
2. Has slight problems doing his/her usual activities? ☐
3. Has moderate problems doing his/her usual activities? ☐
4. Has severe problems doing his/her usual activities? ☐
5. Is unable to do his/her usual activities? ☐

Next, I would like to ask you about PAIN OR DISCOMFORT. Do you think that the person:

1. Has no pain or discomfort? ☐
2. Has slight pain or discomfort? ☐
3. Has moderate pain or discomfort? ☐
4. Has severe pain or discomfort? ☐
5. Has extreme pain or discomfort? ☐

Finally, I would like to ask you about ANXIETY OR DEPRESSION. Do you think that the person:

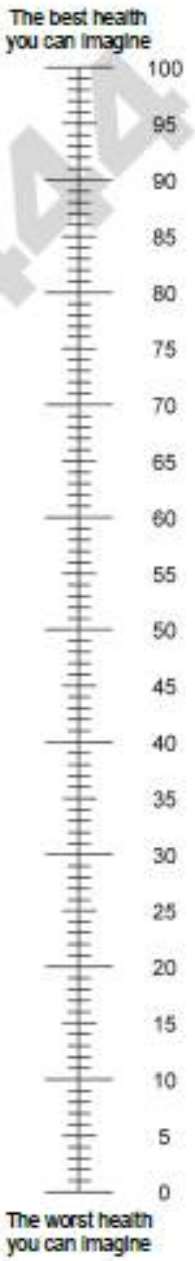
1. Is not anxious or depressed? ☐
2. Is slightly anxious or depressed? ☐
3. Is moderately anxious or depressed? ☐
4. Is severely anxious or depressed? ☐
5. Is extremely anxious or depressed? ☐

EQ-5D VAS

- **Now, I would like to ask you to say how good or bad you think the person's health is TODAY.**
- **I would like you to picture in your mind a vertical line that is numbered from 0 to 100.**
  (Note to interviewer: If interviewing face-to-face, please show the proxy the VAS line.)
- **100 at the top of the line means the <u>best</u> health you can imagine.**

  0 at the bottom of the line means the <u>worst</u> health you can imagine.
- **I would now like you to tell me the point on this line where you would put the person's health TODAY.**
  (Note to interviewer: mark the line to indicate how the proxy thinks the person's health is TODAY. Now, please write the number you marked on the line in the box below.)

THE PERSON'S HEALTH TODAY =



Thank you for taking the time to answer these questions.

REFERENCE

EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.

Appendix 22 Repeatable Battery for the Assessment of Neuropsychological Status

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

1 List Learning

Trial 1

Say *I am going to read you a list of words. I want you to listen carefully and, when I finish, repeat back as many words as you can. You don't have to say them in the same order that I do—just repeat back as many words as you can remember, in any order. Okay?*

Trials 2–4

Say *I am going to read the list again. When I finish, repeat back as many words as you can, even if you have already said them before. Okay?*

Record responses in order.

Scoring: 1 point for each word correctly recalled on each trial.

List	Trial 1	Trial 2	Trial 3	Trial 4
Market				
Package				
Elbow				
Apple				
Story				
Carpet				
Bubble				
Highway				
Saddle				
Powder				

Number Correct	+	+	+	=
	Total Trial 1	Total Trial 2	Total Trial 3	Total Trial 4	Total Score Range=0–40

2 Story Memory

Trial 1

Say ***I am going to read you a short story. I'd like you to listen carefully and, when I finish, repeat back as much of the story as you can remember. Try and use the same wording, if you can. Okay?***

Read the story below, then say ***Now repeat back as much of that story as you can.***

Trial 2

Say ***I am going to read that same story again. When I finish, I want you to again repeat back as much of the story as you can remember. Try to repeat it as exactly as you can.***

Read the story below, then say ***Now repeat back as much of that story as you can.***

Scoring: 1 point for verbatim recall of bold, italic words or alternatives, shown below in color within parentheses. Record intrusions or variations in the Responses column.

Story	Trial 1 Responses	Trial 1 Score (0 or 1)	Trial 2 Responses	Trial 2 Score (0 or 1)	Item Score (0–2)
1. On ***Tuesday,***					
2. ***May***					
3. ***Fourth,***					
4. in ***Cleveland,*** Ohio,					
5. a ***3 alarm***					
6. ***fire*** broke out.					
7. ***Two***					
8. ***hotels***					
9. and a ***restaurant***					
10. were ***destroyed***					
11. before the ***firefighters*** *(firemen)*					
12. were able to ***extinguish it*** *(put it out).*					
				Total Score (Trial 1 + Trial 2) Range=0–24	

3 Figure Copy

Time Limit: 4 minutes

Fold this page back and present the Figure Copy Drawing Page along with the stimulus. Ask the examinee to make an exact copy of the figure. Tell the examinee that he or she is being timed, but that the score is based only on the exactness of his or her copy.

Scoring: 1 point for correctness and completeness (drawing), and 1 point for proper placement. See Appendix 1 in Stimulus Booklet A for complete scoring criteria and scoring examples.

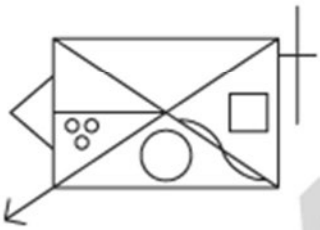


Figure Copy Criteria

(Fold back for use.)

Item	Drawing (0 or 1)	Placement (0 or 1)	Score (0, 1, or 2)	Scoring Criteria
1. rectangle				**Drawing:** lines are unbroken and straight; angles 90 degrees; top/bottom lines 25% longer than sides **Placement:** not rotated more than 15 degrees
2. diagonal cross				**Drawing:** lines are unbroken and straight and should approximately bisect each other **Placement:** ends of lines should meet corners of the rectangle without significant overlap or measurable distance between the ends of the lines and the corners
3. horizontal line				**Drawing:** line is unbroken and straight; should not exceed 1/2 the length of the rectangle **Placement:** should bisect left side of the rectangle at approximately a right angle and intersect the diagonal cross
4. circle				**Drawing:** round, unbroken and closed; diameter should be approximately 1/4–1/3 height of rectangle **Placement:** placed in appropriate segment; not touching any other part of figure
5. 3 small circles				**Drawing:** round, unbroken and closed; equal size; triangular arrangement; not touching each other **Placement:** in appropriate segment; not touching figure; triangle formed not rotated more than 15 degrees
6. square				**Drawing:** must be closed; 90 degree angles; lines straight and unbroken; height is 1/4–1/3 height of rectangle **Placement:** in appropriate segment; not touching any other part of figure; not rotated more than 15 degrees
7. curving line				**Drawing:** 2 curved segments are approximately equal in length and symmetrical; correct direction of curves **Placement:** ends of line touch diagonal; do not touch corner of rectangle or intersection of diagonal lines
8. outside cross				**Drawing:** vertical line of the outside cross is parallel to side of rectangle; >1/2 the height of rectangle; horizontal line crosses vertical at 90 degree angle and is between 20–50% of length of vertical line **Placement:** horizontal line of outside cross touches rectangle higher than 2/3 the height of rectangle, but below top; does not penetrate the rectangle
9. triangle				**Drawing:** angle formed by 2 sides of triangle is between 60–100 degrees; sides are straight, unbroken and meet in a point; distance on vertical side of rectangle subsumed by triangle is approximately 50% of the height of vertical side **Placement:** roughly centered on the left vertical side of the rectangle
10. arrow				**Drawing:** straight and unbroken; lines forming arrow are approximately equal in length and not more than 1/3 length of staff **Placement:** must protrude from appropriate corner of rectangle such that staff appears to be continuation of diagonal cross
	Total Score Range=0–20			

4 Line Orientation

Time Limit: 20 seconds/item

Present the sample item, and say ***These two lines down here*** (indicate) ***match two of the lines on top. Can you tell me the numbers, or point to the lines that they match?*** Correct any errors and make sure the examinee understands the task. Continue with Items 1–10.

Scoring: 1 point for each line correctly identified.

Item	Responses	Correct Responses	Score (0, 1, or 2)
Sample		1, 7	
1.		10, 12	
2.		4, 11	
3.		6, 9	
4.		8, 13	
5.		2, 4	

Item	Responses	Correct Responses	Score (0, 1, or 2)
6.		1, 6	
7.		3, 10	
8.		5, 8	
9.		1, 3	
10.		11, 13	
		Total Score Range=0–20	

5 Picture Naming

Time Limit: 20 seconds/item

Ask the examinee to name each picture. Give the semantic cue only if the picture is obviously misperceived.

Scoring: 1 point for each item that is correctly named spontaneously or following semantic cue.

Item	Semantic Cue	Responses	Score (0 or 1)
1. chair	a piece of furniture		
2. pencil	used for writing		
3. well	you get water from it		
4. giraffe	an animal		
5. sailboat	used on the water (if "boat," query "what kind")		
6. cannon	a weapon, used in war		
7. pliers	a tool		
8. trumpet	a musical instrument ("cornet" okay)		
9. clothespin	used to hold laundry on a line		
10. kite	it's flown in the air		
		Total Score Range=0–10	

6 Semantic Fluency

Time Limit: 60 seconds

Say ***Now I'd like you to tell me the names of all of the different kinds of fruits and vegetables that you can think of. I'll give you one minute to come up with as many as you can. Ready?***

Scoring: 1 point for each correct response.

1. _____	11. _____	21. _____	31. _____
2. _____	12. _____	22. _____	32. _____
3. _____	13. _____	23. _____	33. _____
4. _____	14. _____	24. _____	34. _____
5. _____	15. _____	25. _____	35. _____
6. _____	16. _____	26. _____	36. _____
7. _____	17. _____	27. _____	37. _____
8. _____	18. _____	28. _____	38. _____
9. _____	19. _____	29. _____	39. _____
10. _____	20. _____	30. _____	40. _____

Total Score
Range=0–40

7 Digit Span

Say ***I am going to say some numbers, and I want you to repeat them after me. Okay?***
Read the numbers at the rate of 1 per second. Only read the second string in each set if the first string was failed.
Discontinue after failure of both strings in any set.

Scoring: 2 points for the first string correct, 1 point for the second string correct, and 0 points for both strings failed.

Item	First String	String Score (0 or 2)	Second String	String Score (0 or 1)	Item Score (0–2)
1.	4—9		5—3		
2.	8—3—5		2—4—1		
3.	7—2—4—6		1—6—3—8		
4.	5—3—9—2—4		3—8—4—9—1		
5.	6—4—2—9—3—5		9—1—5—3—7—6		
6.	2—8—5—1—9—3—7		5—3—1—7—4—9—2		
7.	8—3—7—9—5—2—4—1		9—5—1—4—2—7—3—8		
8.	1—5—9—2—3—8—7—4—6		5—1—9—7—6—2—3—6—5		

Total Score
Range=0–16

8 Coding

Time Limit: 90 seconds

Say ***Look at these boxes*** (indicate key). ***For each one of these marks there is a number that goes with it. Down here there are marks, but no numbers. I want you to fill in the number that goes with each mark.***

Demonstrate the first three. Say ***Now I would like you to fill in the rest of these boxes up to the double lines*** (indicate) ***for practice.*** Correct any errors as they are made. Make sure that the examinee understands the task and has correctly completed the sample items before you begin timing.

Say ***Now I would like you to continue to fill in the numbers that match the marks. Go as quickly as you can without skipping any. When you reach the end of the line, go on to the next one. Ready? Go ahead.***

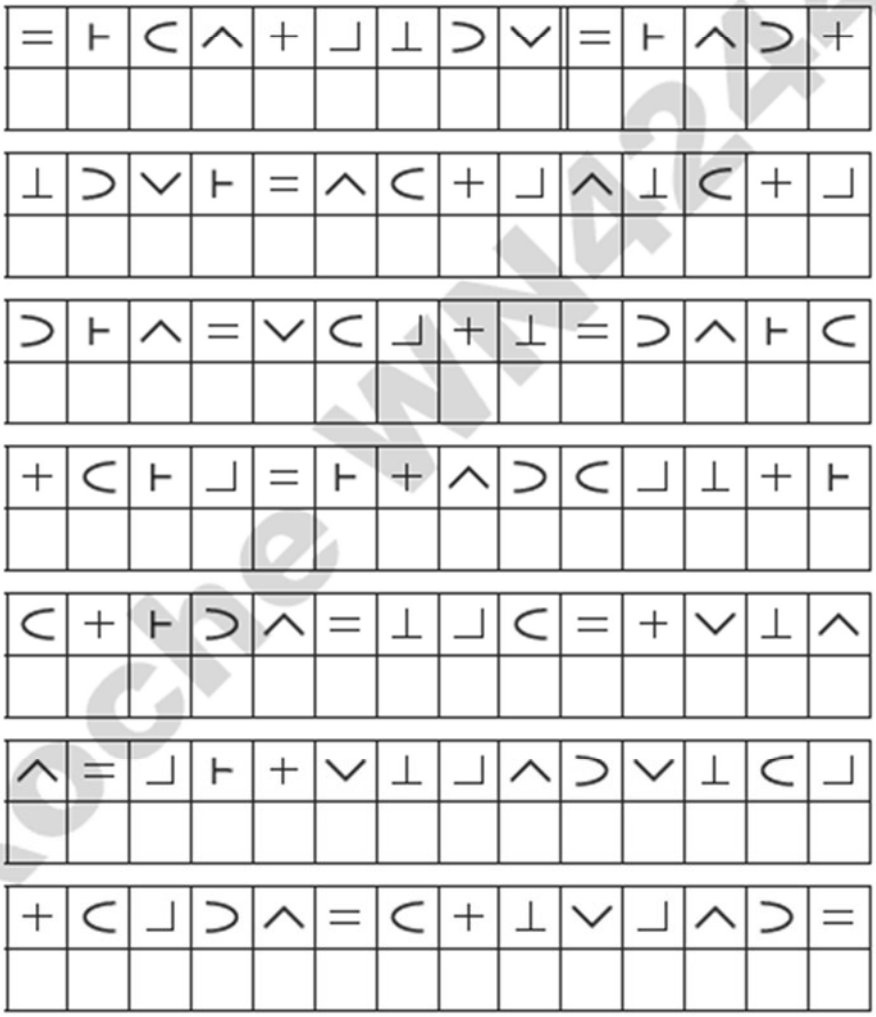
Redirect the examinee to the task if he or she becomes distracted. If the examinee is unable to comprehend the task, the subtest score is 0.

Scoring: 1 point for each item correctly coded within 90 seconds (do not score the sample items).

Note: Familiarize yourself with these instructions before administering this subtest.

Total Score
Range=0–89

SAMPLE_____



9 List Recall

Say ***Do you remember the list of words that I read to you in the beginning? Tell me as many of those words as you can remember now.***

Scoring: 1 point for each word correctly recalled.

List (Do not read)	Response	Score (0 or 1)
Market		
Package		
Elbow		
Apple		
Story		
Carpet		
Bubble		
Highway		
Saddle		
Powder		
	Total Score Range=0–10	

10 List Recognition

Say ***I'm going to read you some words. Some of these words were on that list, and some of them weren't. I want you to tell me which words were on the list.*** For each word, ask ***Was _____ on the list?***

Scoring: 1 point for each word correctly identified. Circle the letter corresponding to examinee's response (y = yes, n = no); bold, capitalized (**Y, N**) letter indicates correct response.

List	Circle One		List	Circle One		List	Circle One		List	Circle One	
1. **Apple**	**Y**	n	6. sailor	y	**N**	11. **Bubble**	**Y**	n	16. **Saddle**	**Y**	n
2. honey	y	**N**	7. velvet	y	**N**	12. prairie	y	**N**	17. **Powder**	**Y**	n
3. **Market**	**Y**	n	8. **Carpet**	**Y**	n	13. **Highway**	**Y**	n	18. angel	y	**N**
4. **Story**	**Y**	n	9. valley	y	**N**	14. oyster	y	**N**	19. **Package**	**Y**	n
5. fabric	y	**N**	10. **Elbow**	**Y**	n	15. student	y	**N**	20. meadow	y	**N**
									Total Score Range=0–20		

11 Story Recall

Say ***Do you remember that story about a fire that I read to you earlier? Tell me as many details from the story as you can remember now.***

Scoring: 1 point for each verbatim recall of bold, italic words or alternatives, shown below in color within parentheses. Record intrusions or variations in the Responses column.

Story (Do not read.)	Responses	Item Score (0 or 1)
1. On ***Tuesday,***		
2. ***May***		
3. ***Fourth,***		
4. in ***Cleveland,*** Ohio,		
5. a ***3 alarm***		
6. ***fire*** broke out.		
7. ***Two***		
8. ***hotels***		
9. and a ***restaurant***		
10. were ***destroyed***		
11. before the ***firefighters*** *(firemen)*		
12. were able to ***extinguish it*** *(put it out).*		
	Total Score Range=0–12	

12 Figure Recall

Say ***Do you remember that figure that I had you copy? I want you to draw as much of it as you can remember now. If you remember a part, but you're not sure where it goes, put it anywhere. Try to draw as much of it as you can.***

Now, present the Figure Recall Drawing Page.

Scoring: 1 point for correctness and completeness (drawing), and 1 point for proper placement. See Appendix 1 in Stimulus Booklet A for complete scoring criteria and scoring examples.

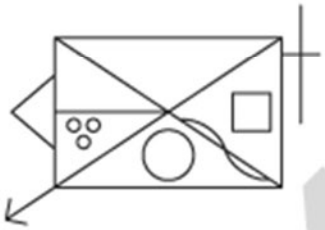
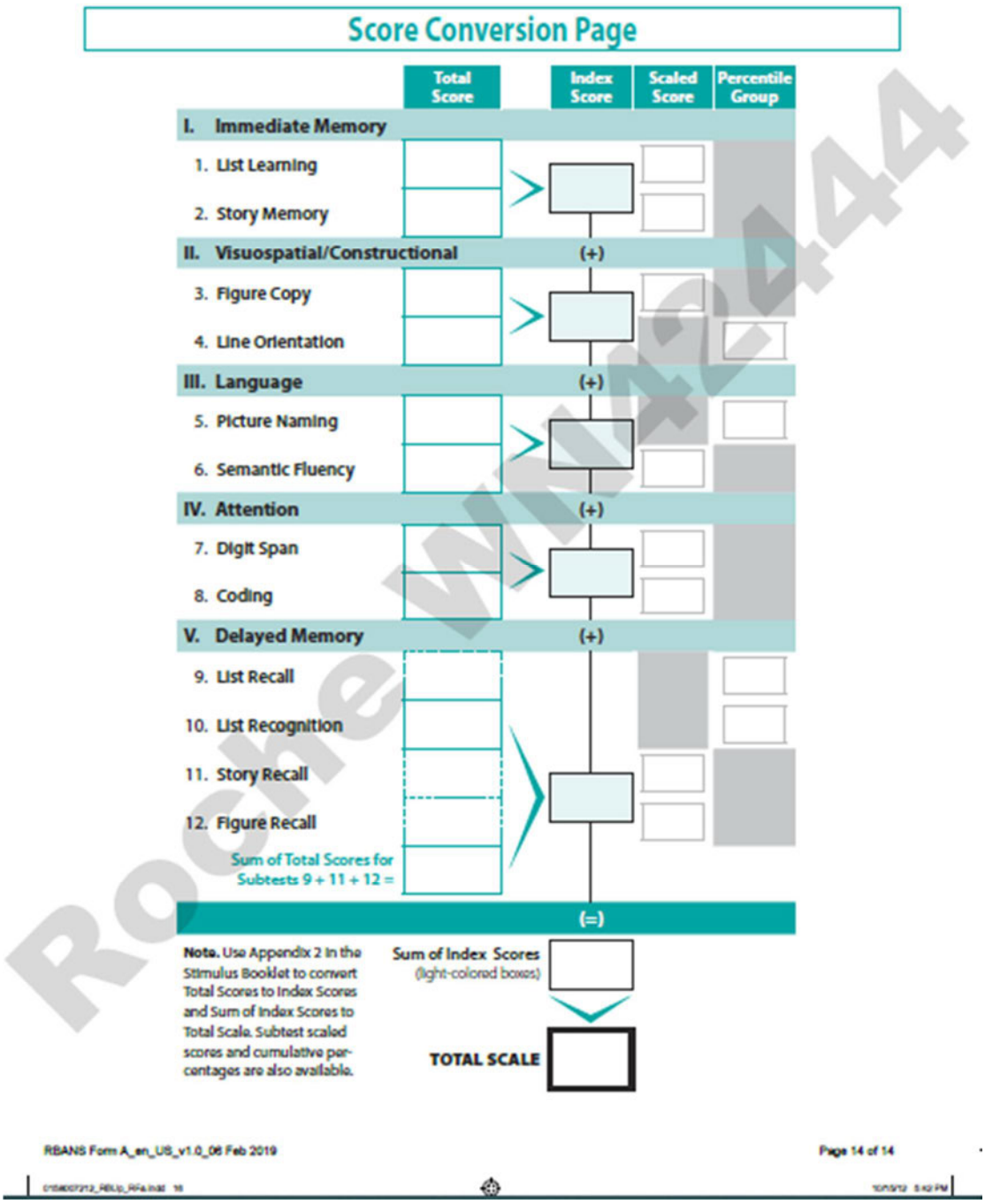


Figure Recall Criteria

(Fold back for use.)

Item	Drawing (0 or 1)	Placement (0 or 1)	Score (0, 1, or 2)	Scoring Criteria
1. rectangle				**Drawing:** lines are unbroken and straight; angles 90 degrees; top/bottom lines 25% longer than sides **Placement:** not rotated more than 15 degrees
2. diagonal cross				**Drawing:** lines are unbroken and straight and should approximately bisect each other **Placement:** ends of lines should meet corners of the rectangle without significant overlap or measurable distance between the ends of the lines and the corners
3. horizontal line				**Drawing:** line is unbroken and straight; should not exceed 1/2 the length of the rectangle **Placement:** should bisect left side of the rectangle at approximately a right angle and intersect the diagonal cross
4. circle				**Drawing:** round, unbroken and closed; diameter should be approximately 1/4–1/3 height of rectangle **Placement:** placed in appropriate segment; not touching any other part of figure
5. 3 small circles				**Drawing:** round, unbroken and closed; equal size; triangular arrangement; not touching each other **Placement:** in appropriate segment; not touching figure; triangle formed not rotated more than 15 degrees
6. square				**Drawing:** must be closed; 90 degree angles; lines straight and unbroken; height is 1/4–1/3 height of rectangle **Placement:** in appropriate segment; not touching any other part of figure; not rotated more than 15 degrees
7. curving line				**Drawing:** 2 curved segments are approximately equal in length and symmetrical; correct direction of curves **Placement:** ends of line touch diagonal; do not touch corner of rectangle or intersection of diagonal lines
8. outside cross				**Drawing:** vertical line of the outside cross is parallel to side of rectangle; >1/2 the height of rectangle; horizontal line crosses vertical at 90 degree angle and is between 20–50% of length of vertical line **Placement:** horizontal line of outside cross touches rectangle higher than 2/3 the height of rectangle, but below top; does not penetrate the rectangle
9. triangle				**Drawing:** angle formed by 2 sides of triangle is between 60–100 degrees; sides are straight, unbroken and meet in a point; distance on vertical side of rectangle subsumed by triangle is approximately 50% of the height of vertical side **Placement:** roughly centered on the left vertical side of the rectangle
10. arrow				**Drawing:** straight and unbroken; lines forming arrow are approximately equal in length and not more than 1/3 length of shaft **Placement:** must protrude from appropriate corner of rectangle such that shaft appears to be continuation of diagonal cross
		Total Score Range=0–20		



REFERENCE

Randolph C, Tierney MC, Mohr E, et al. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. J Clin Exp Neuropsychol 1998;20:310–9.

Appendix 23 Diagnostic Classification Form (DCF)

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Diagnostic Classification Form

Current Diagnosis:

(to be completed after all clinical scales have beenadministered for the visit)

- ☐ **Normal Cognition:** No evidence of decline from baseline on neurocognitive testing or study partner reported cognitive decline.
- ☐ **MCI due to AD:** Evidence of decline in cognition on basis of participant or study partner report, and evidence of decline on neurocognitive testing, but participant remains relatively independent in managing routine activities of daily living.*(Complete supportive narrative on page 2).*
- ☐ **MCI due to other cause:** Evidence of decline in cognition on basis of participant or study partner report, and evidence of decline on neurocognitive testing, but participant remains relatively independent in managing routine activities of daily living.
  Clinical and/or other findings (MRI, labs) suggest an etiology for cognitive impairment other than AD. *(Complete supportive narrative on page 3).*
- ☐ **Dementia due to AD:** Evidence of cognitive decline in multiple cognitive domains of a magnitude sufficient to interfere with routine activities of daily living. *(Complete supportive narrative on page 4).*
- ☐ **Dementia due to other cause:** Evidence of cognitive decline in multiple cognitive domains of a magnitude sufficient to interfere with routine activities of daily living. Clinical and/or other findings (MRI, labs) suggest an etiology for dementia other than AD. *(Complete supportive narrative on page 5).*

MCI due to AD

- **Subjective evidence of decline in cognition** (typically memory), observed since the baseline visit, preferably as reported by the study partner or observed clinically.
- **Evidence of impairment of cognition in one or more cognitive domains as** measured by decline in cognitive functioning from baseline on objective testing.
- **Preservation of independence in functional activities.** Persons with MCI typically have some difficulty managing more complicated activities of daily living and may require some assistance or supervision of things like finances or medications. In general, however, there should be no evidence of significant impairment of activities of daily living or social functioning that would constitute a dementia in the judgment of the Investigator.
- **In the investigator's opinion, the participant's MCI is due to AD.** Other central nervous system etiologies have been ruled out, including other neurodegenerative disorders, toxic, metabolic, or infectious conditions.

Please include an explanation as to why you feel this diagnosis is warranted, providing supporting evidence for <u>each</u> of the criteria above.

Brief supporting narrative *(additional space for notes on page 6)*:

MCI due to cause other than AD

This diagnosis should be reserved for cases of MCI that in the investigator's opinion are due to causes other than AD (e.g., a participant who suffers a thalamic infarct that produces clinically significant impairment of memory).

Please include a narrative that describes the onset, nature and severity of the cognitive impairments and the rationale for the diagnosis, including any relevant laboratory data:

Presumed etiology of MCI due to non-AD cause:

Brief supporting narrative *(additional space for notes on page 6)*:

Dementia due to AD

Participant has cognitive impairments which:

- **Were gradual in onset**
- **Represent a decline from a previous level of cognitive functioning**
- **Include memory impairment as an early and prominent feature**
- **Include impairment in at least one cognitive domain other than memory** (e.g., language, executive, attentional, visuospatial functions)
- **Have progressively worsened over time**
- **Are currently severe enough to significantly impair activities of daily living or social functioning.**

In the Investigator's opinion:

- **The participant's dementia is due to AD.** Other central nervous system disorders have been ruled out, including other neurodegenerative, toxic, metabolic, or infectious conditions.

Please include an explanation as to why you feel this diagnosis is warranted, providing supporting evidence for each of the criteria above.

Brief supporting narrative *(additional space for notes on page 6)*:

Dementia due to other cause

This diagnosis should be reserved for cases of dementia that in the investigator's opinion are due to causes other than AD (e.g., frontotemporal dementia, Lewy body dementia, NPH, etc.).

Please include a narrative that describes the onset, nature and severity of the cognitive and functional impairments and the rationale for the diagnosis, including any relevant clinical and laboratory data:

Presumed etiology of non-AD dementia:

Brief supporting narrative *(additional space for notes on page 6)*:

Notes

Appendix 24 Clinical Safety Laboratory Tests

The tests detailed in Table A24–1 will be performed by the central laboratory. See the schedule of activities (Section 1.3) for the testing timing and frequency. Instruction manuals and supply kits will be provided for all central laboratory assessments.

Local laboratory results are only required in the event that the central laboratory results are not available in time for study treatment administration and/or response evaluation. If a local sample is required, it is important that a sample for central analysis be obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or a response evaluation, the results must be entered on the electronic Case Report Form.

Protocol-specific requirements for inclusion and exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the study if determined to be necessary by the investigator or if required by local regulations.

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

Investigators must document their review of each laboratory safety report.

Table A24–1 Protocol-Required Safety Laboratory Assessments

Central Laboratory Tests
The following laboratory assessments will be performed at screening, baseline, Weeks 25, 53, 79, 105, 131, 157, 183, 211, safety follow-up, unscheduled visits (as applicable), early termination visit as well as during the post-progression dose escalation period at Weeks 1P, 25P and unscheduled visits (as applicable) (Section 1.3): • Serum chemistry: AST, ALT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, bicarbonate, chlorine, calcium, glucose, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory) • Hematology: hemoglobin, hematocrit, red blood cell count (with morphology), white blood cell count, basophils, eosinophils, lymphocytes, monocytes, neutrophils, and platelets Urine for pregnancy test will be performed in women of childbearing potential (including those who have had a tubal ligation) at screening, prior to PET scans, at the safety follow-up visit or early termination study visit, or if suspected to have become pregnant, and 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. In addition, the following laboratory assessments will be performed at screening, Weeks 53, 105, 157, 211, safety follow-up, unscheduled visits (as applicable), early termination visit as well as during the post-progression dose escalation period at Week 1P (Section 1.3): • Metabolic tests: Hemoglobin A_{1C}, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, folic acid, vitamin B-12, methylmalonic acid, total thyroxine, free thyroxine, and thyroid-stimulating hormone levels These test should be collected as fasting samples (i.e. at least 4 hours after meals) • C-reactive protein • *Prothrombin time* The following laboratory assessments will be performed at screening only (Table 1 and Table 4) • Viral serology: HIV, hepatitis B, and hepatitis C • Urine sample for drugs of abuse At screening only, urine samples will be analyzed for the presence of the following drugs of abuse: amphetamine, benzodiazepines, cannabinoids, opiates, cocaine, barbiturates, and methadone. Results will be used to verify participant eligibility pertaining to drugs of abuse. Inconclusive results may be repeated once during the screening period. Investigators should use their best clinical judgment in cases where results may be erroneous (e.g., permitted use of opiates or ingestion of food/food supplements). • Urinalysis At screening only, urinalysis will be performed at the site by dipstick for blood, protein, glucose, and pH. Microscopic examination will be performed by the central laboratory if blood and/or protein results are positive or strongly positive.

PET = positron emission tomography.

Appendix 25 Abbreviations

Abbreviation	Definition
AIBL	Australian Imaging, Biomarker, and Lifestyle
AD	Alzheimer's disease
ADA	anti-drug antibody
ADNI	Alzheimer’s Disease Neuroimaging Initiative
AD-CGI-S	Alzheimer’s disease Clinician Global Impression of Cognitive Function
AD-PGI-S	Alzheimer’s disease Participant Global Impression of Cognitive Function
AD-SPGI-S	Alzheimer’s disease Study Partner Global Impression of Cognitive Function
A-IADL-Q-SV	Amsterdam Instrumental Activities of Daily Living Questionnaire Short Version
APOE	apolipoprotein
ARIA-E	amyloid-related imaging abnormality–edema/effusion
ARIA-H	amyloid-related imaging abnormality–hemosiderin deposition
ATRI	Alzheimer’s Therapeutic Research Institute
BGTS	Barkhof Grand Total Score
CBF	cerebral blood flow
CDR	Clinical Dementia Rating
CDR-GS	Clinical Dementia Rating Global Score
CDR-SB	Clinical Dementia Rating Sum of Boxes
CFIa	Cognitive Function Instrument acute
CFT	category fluency test
ClinRO	clinician-reported outcome
COA	clinical outcome assessments
CRF	Case Report Form
CRO	Contract Research Organization
CSF	cerebrospinal fluid
CV	coefficient of variation
C-SSRS	Columbia-Suicide Severity Rating Scale
DCF	Diagnostic Classification Form
DMI	Delayed Memory Index
DTI	diffusion-tensor imaging
EC	Ethics Committee
eCOA	electronic clinical outcome assessment
eCRF	electronic Case Report Form
EDC	electronic data capture

Appendix 25: Abbreviations

Abbreviation	Definition
EQ-5D-5L	EuroQol 5-Dimension 5-Level Questionnaire
FDA	U.S. Food and Drug Administration
FLAIR	fluid-attenuated inversion recovery
GCP	Good Clinical Practice
GDS-30	Geriatric Depression Scale-30 items
HABS	Harvard Aging Brain Study
iCAC	independent Clinical Adjudication Committee
ICF	Informed Consent Form
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
ISR	injection-site reaction
IxRS	interactive voice or Web-based response system
LP	lumbar puncture
MCI	mild cognitive impairment
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
NCRAD	National Cell Repository for Alzheimer's Disease and Related Dementias
NfL	neurofilament light
NSDCR	not study drug or condition-related
ObsRO	observer-reported outcome
OLE	open-label extension
PACC-5	Preclinical Alzheimer’s Cognitive Composite-5
PerfO	performance outcome
PET	positron emission tomography
PK	pharmacokinetic
PRO	participant-reported outcome
Q1W	every 1 week
Q2W	every 2 weeks
Q4W	every 4 weeks
QoL	quality of life
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RBR	Research Biosample Repository

Appendix 25: Abbreviations

Abbreviation	Definition
SAP	Statistical Analysis Plan
SDCR	study drug or condition-related
ULN	upper limit of normal
WES	whole-exome sequencing