Official Title: A Phase II, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy, and Safety Study of MTAU9937A in Patients With Prodromal to Mild Alzheimer's Disease

NCT Number: NCT03289143

Document Date: Protocol Version 4: 11-June 2019

PROTOCOL

TITLE:	**A PHASE II, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, EFFICACY, AND SAFETY STUDY OF MTAU9937A IN PATIENTS WITH PRODROMAL TO MILD ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	GN39763
VERSION NUMBER:	4
EUDRACT NUMBER:	2017-001800-31
IND NUMBERS:	129270, 125702
TEST PRODUCTS:	MTAU9937A (RO7105705) and [^{18}F]GTP1 (RO6880276)
MEDICAL MONITOR:	[redacted] M.D., Ph.D.
SPONSOR:	Genentech, Inc.
APPROVAL DATE:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
11-Jun-2019 20:44:36	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocols		
Version	**Date Final**	**Country**	**Version**	**Date Final**
3	20 August 2018	European Union	3	6 December 2018
		European Union (only)	2	12 October 2017
1	31 May 2017	—	—	—

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol GN39763, Version 4, encompasses the cumulative changes to the protocol that were made to Version 3 (European Union) (6 Dec 2018), which was only applicable to E.U. countries, along with global changes specific to this amendment.

Changes specific to Protocol GN39763, Version 4, along with a rationale for each change, are summarized below:

- Clinical background information on MTAU9937A clinical studies was updated to include Study GN40040, an ongoing Phase II study in patients with moderate Alzheimer's disease (Section 1.2.2).
- Clinical background information on fluorine-18 Genentech tau probe 1 ([^{18}F]GTP1) has been updated to include reference to ongoing clinical Substudies WN29922/WN39658 and Study GN40040 (Section 1.3.1).
- The total number of patients enrolled and the number of clinical sites has been updated (Sections 3.1.1, 4.1, and 9.4).
- Exclusion criteria have been modified (Section 4.1.2):
  - The exclusion criterion for biologic therapy has been clarified to indicate that any investigational biologic therapy (e.g., therapeutic proteins, monoclonal antibodies, or other active or passive immunotherapy) is prohibited at screening and during the study.
  - The exclusion criterion for systemic immunosuppressive therapy has been revised to indicate that short courses ($\leq$2 weeks) of high-dose corticosteroid therapy are permitted, and that chronic therapy ($>$2 weeks) is permitted as long as the dose is $<$7.5 mg/day prednisolone equivalent and the condition being treated is not expected to deteriorate significantly during the study period.
- The description of the recall time frame for the Caregiver Global Impression of Change Scales has been corrected to align with the time frames used for the assessment (Section 4.5.7.11).
- Language has been added to clarify that, after withdrawal of consent for participation in the Research Biosample Repository (RBR), remaining RBR samples will be destroyed or will no longer linked to the patient (Section 4.5.12.6).
- Examples of clinically significant magnetic resonance imaging (MRI) abnormalities have been provided (Section 5.1.1.2).
- Contact information for Medical Monitor supporting E.U. sites has been updated (Section 5.4.1).
- Language has been added to indicate that the study will comply with applicable local, regional, and national laws (Section 8.1).

- Language has been revised to clarify that data posting will not be limited to two clinical trial registries and to clarify that redacted Clinical Study Reports are provided only if requirements of Roche's global policy on data sharing have been met (Section 9.5).
- The window for postbaseline [^{18}F]GTP1 PET scans has been expanded to $\pm$14 days, and further extensions to the allowed window for the Week 73 [^{18}F]GTP1 PET scan may be granted on a case-by-case basis by the Medical Monitor. Scheduling of the Week 49, Week 169, and Treatment Discontinuation visit [^{18}F]GTP1 PET scans may be coordinated by the [^{18}F]GTP1 distribution network on the basis of tracer availability and may be scheduled outside the $\pm$14 day window around the scheduled visit if appropriate extenuating circumstances arise (Appendices 1 and 2).
- It has been clarified that if additional coagulation panel tests are required per the local standard prior to performing lumbar puncture for cerebrospinal fluid (CSF) collection, these tests may be performed at the central laboratory or at a local laboratory (Appendices 1 and 2). The open-label extension (OLE) schedule of activities was corrected to include coagulation laboratory tests at the Week 169 visit for patients undergoing optional CSF collection (lumbar puncture) (Appendix 2).

Protocol GN39763, Version 3, was amended to address feedback from European Health Authorities resulting in protocol Version 3 (European Union) (6 Dec 2018). Changes to the protocol, along with the rationale for each change, are summarized below:

- Study visits during the protocol safety follow-up period were clarified to state that patients who discontinue from treatment early will have a treatment discontinuation visit (Section 3.1.1.1).
- For visits that include both MRI and study medication dosing, it has been clarified that although the MRI must be performed prior to study medication dosing, dosing can occur following local, real-time assessment and before the site receives the central MRI report if no clinically significant new or worsening abnormalities are identified (Section 5.1.1.2 and Appendices 1 and 2).
- Adverse event reporting was clarified to include reporting of adverse events that occur after the protocol defined adverse event reporting interval following the last dose of [^{18}F]GTP1 or study drug administration for adverse events leading to discontinuation from the study (Section 5.6).
- It has been clarified that coagulation studies must be performed within 90 days prior to a lumbar puncture or within an interval consistent with the local standard of care, whichever is shorter. Guidance was added that for patients taking multiple anti-platelet medications, the investigator should determine (per local standards of care) whether the temporary discontinuation of one or more anti-platelet medications prior to lumbar puncture (LP) is warranted (e.g., continuing aspirin and discontinuing thienopyridine derivatives for 1–2 weeks prior to LP; Appendices 1 and 2).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE II, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, EFFICACY, AND SAFETY STUDY OF MTAU9937A IN PATIENTS WITH PRODROMAL TO MILD ALZHEIMER'S DISEASE**
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MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	Genentech, Inc.

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 Contract Research Associate.

PROTOCOL SYNOPSIS

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TEST PRODUCTS:	MTAU9937A (RO7105705) and [^{18}F]GTP1 (RO6880276)
PHASE:	Phase II
INDICATION:	Alzheimer's Disease
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This study will evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of MTAU9937A in patients with prodromal or mild Alzheimer's disease (AD), ages 50–80, who are amyloid positive by cerebrospinal fluid (CSF) or amyloid positron emission tomography (PET). Specific objectives and corresponding endpoints for the study are outlined below.

Primary	
Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of MTAU9937A compared with placebo	• Change from baseline to Week 73 on the CDR-SB
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety and tolerability of MTAU9937A compared with placebo	• Nature, frequency, severity, and timing of adverse events and serious adverse events. Severity of adverse events will be determined through use of the WHO toxicity grading scale. • Changes from baseline in vital signs, physical findings, neurologic findings, ECG, and clinical laboratory results during and following MTAU9937A administration • Changes from baseline in suicidal ideation and behavior during and following MTAU9937A administration as assessed by the C-SSRS • Nature, frequency, severity, and timing of neuroimaging abnormalities

Secondary	
Efficacy Objective	**Corresponding Endpoints**
• To evaluate the effect of MTAU9937A on cognition compared with placebo	• Change from baseline to Week 73 on the RBANS Total Score • Change from baseline to Week 73 on the ADAS-Cog 13
• To evaluate the effect of MTAU9937A on activities of daily living compared with placebo	• Change from baseline to Week 73 on the Amsterdam iADL questionnaire • Change from baseline to Week 73 on the ADCS-ADL
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the PK of MTAU9937A	• Serum concentrations of MTAU9937A at specified timepoints
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to MTAU9937A	• Presence of ADAs during the study relative to the presence of ADAs at baseline
Exploratory	
Efficacy Objective	**Corresponding Endpoints**
• To evaluate the effect of MTAU9937A on time to decline in functional capacity compared with placebo	• Time from baseline to change in diagnosis or the occurrence of a decline in functional capacity, as assessed by an AD event inventory and other assessments
Pharmacokinetic Objectives	**Corresponding Endpoints**
• To evaluate potential relationships between drug exposure and the safety, PD response, and activity of MTAU9937A	• Relationship between serum PK for MTAU9937A and safety endpoints • Relationship between serum or CSF PK for MTAU9937A and clinical activity or PD endpoints
• To evaluate potential relationships between selected covariates and exposure to MTAU9937A	• Relationship between selected covariates, including but not limited to age, sex, and serum pharmacokinetics for MTAU9937A
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, or PK endpoints
Biomarker Objectives	**Corresponding Endpoints**
• To evaluate the effect of MTAU9937A on pathological burden of tau • To evaluate the effect of MTAU9937A on biomarkers to aid in defining MOA • To evaluate the relationship between changes in biomarkers and efficacy • To evaluate if biomarkers, at baseline, identify a subset of patients with more rapid disease progression and/or enhanced clinical benefit to MTAU9937A	• Changes from baseline in brain tau burden over time as measured by [^{18}F]GTP1 PET • Changes from baseline in levels of soluble tau in plasma or CSF and in levels of other potential disease biomarkers • Changes from baseline in brain structure measured by MRI • Relationship between changes in efficacy endpoints and measures of changes in brain tau burden, soluble tau in biofluids, brain structure, and other potential disease biomarkers • Relationships between biomarkers in blood or CSF (including common and rare genetic variants, identified through genomic analysis on DNA extracted from blood) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

Resource Utilization Objectives	Corresponding Endpoint
• To evaluate resource utilization of caregivers and patients treated with MTAU9937A	• Change from baseline in the RUD-Lite at Week 73

ADA=anti-drug antibody; ADAS-Cog=Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS-ADL=Alzheimer's Disease Cooperative Study Group–Activities of Daily Living Inventory; CSF=cerebrospinal fluid; C-SSRS=Columbia-Suicide Severity Rating Scale; CDR-SB=Clinical Dementia Rating–Sum of Boxes; GTP1= Genentech tau probe 1; iADL=Instrumental Activity of Daily Living; MOA= mechanism of action; MRI=magnetic resonance imaging; PET=positron emission tomography; PD=pharmacodynamic; PK=pharmacokinetic; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; RUD=Resource Utilisation in Dementia; WGS=whole genome sequencing.

Study Design

Description of Study

This Phase II, randomized, double-blind, placebo-controlled, parallel-group study will evaluate the efficacy, safety and tolerability, pharmacokinetics, and pharmacodynamics of MTAU9937A in patients with prodromal AD (pAD) to mild AD (mAD).

The study consists of a screening period, a double-blind treatment period, an optional open-label extension (OLE) period, and a safety follow-up period. An extended baseline visit (up to 15 days) is included in the double-blind treatment period, following randomization and prior to the initiation of study drug. Study drug (MTAU9937A or placebo) will be administered intravenously in the double-blind treatment period, and MTAU9937A will be administered intravenously in the optional OLE period. Study drug administration will occur every 2 weeks (Q2W) for the first three doses of the double-blind treatment period and every 4 weeks (Q4W) thereafter in the double-blind treatment period. MTAU9937A will be administered Q4W in the OLE period.

Study treatment is defined as study drug plus the PET radioligand used during PET imaging procedures ([^{18}F] Genentech tau probe 1 [GTP1] for tau PET imaging and the amyloid radioligand for amyloid PET imaging).

Patients will be randomly assigned to one of three active, IV dose arms (1500 mg, 4500 mg, or 8100 mg MTAU9937A) or to an IV placebo dose arm in a 2:3:2:3 (1500 mg:4500 mg:8100 mg:placebo) ratio. All patients participating in the OLE will receive MTAU9937A 4500 mg IV. To maintain balance in dementia status and *APOE* status between treatment arms, randomization will be stratified by dementia status (pAD vs. mAD) and *APOE* status (ApoE4+ vs. ApoE4–). To ensure adequate representations of each diagnostic group, the Sponsor may operationally manage the proportion of pAD and mAD patients in the study (e.g., no more than approximately 80% of one category).

Patients will be selected on the basis of clinical diagnosis of probable AD (according to the National Institute on Aging/Alzheimer's Association [NIA-AA] Diagnostic Criteria and Guidelines for AD) or pAD (according to the NIA-AA Diagnostic Criteria and Guidelines for AD). pAD is defined in this protocol as a clinical diagnosis of mild cognitive impairment (MCI) due to AD coupled with evidence of cerebral amyloidosis. Clinical diagnosis for each patient must be supported by information provided on a Diagnostic Verification Form (DVF), which must be reviewed and approved by the Sponsor or Sponsor delegate.

Eligible patients must be 50–80 years old at the beginning of screening, meet diagnostic criteria for MCI or probable AD dementia, and have evidence of cerebral amyloidosis as indicated by CSF analysis (i.e., CSF-enrolled patients) *or* positive amyloid PET scan by qualitative read (i.e., PET-enrolled patients). The choice between CSF versus PET for determination of cerebral amyloidosis should be made on the basis of the capability of an individual site and/or the preference of an individual patient. If a patient is amyloid negative based on one of the two modalities (CSF assessment or amyloid PET), then the patient may undergo assessment with the other modality during screening; amyloid positivity by either modality is sufficient for eligibility. Under certain circumstances, a previously acquired amyloid PET scan may be used for study inclusion. If the previously acquired amyloid PET scan is read as amyloid negative by

the core/central PET vendor, the patient may undergo CSF assessment to determine eligibility, but the patient may not undergo an additional amyloid PET scan for enrollment.

At the time of screening, patients must have a Mini-Mental State Examination (MMSE) score of ≥ 20 points and a Clinical Dementia Rating–Global Score (CDR-GS) of 0.5 or 1.0. To confirm objective memory impairment, patients must also have a Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Delayed Recall Index of ≤ 85 at the time of screening. Patients will be eligible for the study whether or not they are receiving standard-of-care symptomatic medications for AD (e.g., cholinesterase inhibitors, memantine, and/or the medical food supplement Souvenaid-®). These medications must have been stable for ≥ 2 months prior to screening, and there should be no a priori planned initiation, discontinuation, or dose changes for these medications during the study (including during the double-blind treatment and OLE treatment periods). However, following the initiation of study drug, standard-of-care symptomatic medications for AD may be initiated, dose adjusted, or discontinued as deemed clinically appropriate.

To monitor patients for safety, the incidence and nature of adverse events, serious adverse event, adverse events of special interest, responses on the Columbia-Suicide Severity Rating Scale (C-SSRS), and abnormalities in standard safety blood and urine tests, ECG, vital signs, physical examination, and magnetic resonance imaging (MRI) will be assessed on a regular basis by the Sponsor and an unblinded independent Data Monitoring Committee (iDMC). Blood samples will be obtained from all patients for the assessment of pharmacokinetics and for the measurement of antibodies directed against MTAU9937A and other components of the drug product.

Baseline measures of clinical outcome assessments (COAs) (for clinical efficacy) and tau biomarkers (for pharmacodynamic [PD] activity) will be obtained prior to the initiation of study drug, either during the screening period (e.g., Clinical Dementia Rating–Sum of Boxes [CDR-SB]) or during the post-randomization baseline visit (e.g., the Amsterdam Instrumental Activity of Daily Living [iADL] or [^{18}F]GTP1 PET imaging). Assessment of clinical efficacy will be determined by changes from baseline to Week 73 on a number of COAs. Changes from baseline to Week 73 on a number of biomarker measurements (e.g., tau burden as measured by [^{18}F]GTP1 PET, plasma/CSF analytes) will be used to assess PD activity in this study. Assessment of COAs and biomarkers will continue into the OLE period, for those patients continuing into the optional OLE period.

All patients must have baseline and longitudinal tau-related biomarker evaluation. If [^{18}F]GTP1 PET imaging is available to a patient, based on site availability of [^{18}F]GTP1 PET imaging and lack of local restriction to such imaging, the patient must undergo [^{18}F]GTP1 PET imaging for tau-related biomarker evaluation. [^{18}F]GTP1 PET imaging will be performed at the baseline visit (after randomization), Week 49, and Week 73 during the double-blind treatment period; those patients continuing into the optional OLE period must also have [^{18}F]GTP1 PET imaging performed at Week 169. In addition, for patients undergoing [^{18}F]GTP1 PET imaging, optional CSF collection at baseline and postbaseline time points is also encouraged.

For sites where [^{18}F]GTP1 PET imaging is not available, or where local restrictions preclude [^{18}F]GTP1 PET imaging, patients must have CSF collected via lumbar puncture (LP) at baseline, Week 49, and Week 73 during the double-blind treatment period; those patients continuing into the optional OLE period are encouraged to have an LP performed at Week 169. If an LP was performed during screening for the assessment of amyloid positivity, CSF from this LP will be used for the baseline measurement; otherwise, an LP must be performed during the baseline visit (after randomization).

[18F]GTP1 PET, amyloid PET, and MRI evaluation will use a standard protocol, provided in the imaging technical operations manuals. Screening amyloid PET and MRIs will be read by a central reader to determine eligibility. Screening amyloid CSF analysis will be performed by a central laboratory.

PET scans should be performed only if the investigator has determined that the total past and planned annual radiation exposure does not exceed local guidelines. Radiation exposure for [18F]GTP1 doses can be found in the [18F]GTP1 Investigator's Brochure. Radiation exposure for doses of the amyloid radioligands can be found in the local labeling instructions or, depending on locality, in the Investigator's Brochures.

Number of Patients

This study *has enrolled 457* patients and *is being* conducted at *97* sites in North America, Europe, and the Asia-Pacific region.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form by the patient (co-signed by the patient's legally authorized representative, if required by the local regulations, guidelines, and independent ethics committee or institutional review board)

  Patients should be judged by the investigator to be lucid and oriented when giving the informed consent.
- Age between 50 and 80 years, inclusive, at time of signing Informed Consent Form
- NIA-AA core clinical criteria for probable AD dementia or pAD (consistent with the NIA-AA diagnostic criteria and guidelines for MCI)
- Evidence of the AD pathological process, by a positive amyloid assessment either on CSF $A\beta_{1-42}$ as measured on Elecsys β-Amyloid(1–42) Test System OR amyloid PET scan by visual read by the core/central PET vendor as specified in the Imaging Review Charter.

  If a patient is amyloid negative based on CSF assessment, they may undergo an amyloid PET scan during screening to potentially be enrolled. The patient may undergo an LP for CSF assessment or an amyloid PET scan, only one time each during screening.

  If a patient is amyloid negative based on an amyloid PET scan, they may undergo an LP for CSF assessment during screening to potentially be enrolled. The patient may undergo an LP for CSF assessment or an amyloid PET scan, only one time each during screening.

  Under certain circumstances, a previously acquired amyloid PET scan may be used for study inclusion. If the previously acquired amyloid PET scan is considered valid and is read negative by the core/central PET vendor, the patient may undergo CSF assessment to potentially enrollment, but the patient may not undergo an additional amyloid PET scan for enrollment.
- mAD symptomatology, as defined by a screening MMSE score of ≥ 20 points and CDR-GS of 0.5 or 1
- Abnormal memory function at screening as demonstrated by an RBANS Delayed Recall Index ≤ 85
- If the patient is receiving non-investigational AD medications, the dosing regimen must have been stable for 2 months prior to the start of screening. There should be no a priori intent to initiate, discontinue, or alter the dose of any AD therapy for the duration of the study. However, following the initiation of study drug, standard-of-care symptomatic medications for AD may be initiated, dose adjusted, or discontinued as deemed clinically appropriate.
- Inclusion is subject to review of clinical criteria at screening (via the DVF)
- Availability of a person (referred to as the "caregiver" throughout this protocol) who in the investigator's judgment:

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

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

Every effort should be made to have same caregiver participate throughout the duration of the study, for the purpose of completing the designated caregiver clinical outcome assessments (COAs)

- Fluency in the language of the tests administered at the study site
- Completion of at least 6 years of formal education after the age of 5 years.
- Willingness and ability to complete all aspects of the study (including MRI, LP [if applicable], clinical genotyping, and PET imaging [if applicable]); the patient should be capable of completing study procedures either alone or with the help of caregiver(s)
- Adequate visual and auditory acuity, in the investigator's judgment, to perform the neuropsychological testing (eye glasses and hearing aids are permitted)
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use of contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for 9 weeks after the last dose of study drug or 4 days after the last dose of [^{18}F]GTP1 or an amyloid radioligand, whichever is longer

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

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

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 9 weeks after the last dose of study drug or 4 days after the last dose of [^{18}F]GTP1 or an amyloid radioligand, whichever is longer, to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

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

<u>Exclusion Criteria</u>

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

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 9 weeks after the last dose of study drug or 4 days after the last dose of [^{18}F]GTP1 or an amyloid radioligand, whichever is longer

  Women of childbearing potential must have a negative serum pregnancy test result during screening and a negative urine pregnancy test result each day of dosing or of PET imaging prior to administration of study drug or radioligand.
- Inability to tolerate MRI procedures or contraindication to MRI, including, but not limited to, presence of pacemakers not compatible with MRI, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin, or body that would contraindicate an MRI scan; or any other clinical history or examination finding that, in the judgment of the investigator, would pose a potential hazard in combination with MRI

- A patient must be able to undergo either PET imaging or lumbar dural puncture, or both, and patients with contraindications to both procedures are ineligible.

    For patients undergoing PET imaging: Planned, or recent (within 12 months prior to screening) exposure to ionizing radiation that in combination with the planned administrations of [^{18}F]GTP1 or an amyloid radioligand would result in a cumulative exposure that exceeds recommended local guidelines

    For patients undergoing LP: contraindication to lumbar dural puncture, including coagulopathy, concomitant anticoagulation (except for a platelet inhibitor such as aspirin or clopidogrel), thrombocytopenia, prior lumbar spinal surgery, significant deformity of the lumbosacral region, or other factor that precludes safe LP in the opinion of the investigator
- Body mass index $>$ 40
- Hospitalization during the 4 weeks prior to screening

    In regions where hospitalization status can be classified as observational or an inpatient admission, this exclusion criterion specifically refers to an inpatient admission.
- Planned procedure or surgery during the study that in the investigator's opinion would affect cognitive assessments or otherwise interfere with compliance with the protocol
- Residence in a skilled nursing facility such as a convalescent home or long-term care facility, except if current residence is in a section of the facility where no assistance is provided for basic activities of daily living

    Patients who subsequently 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 caregiver who meets the minimum requirement
- Blood transfusion within 8 weeks prior to screening or planned transfusion during the study
- Poor peripheral venous access
- Any serious medical condition or abnormality in clinical laboratory tests that remains abnormal on retest and, in the investigator's judgment, precludes the patient's safe participation in and completion of the study, or bias the assessment of the clinical or mental status of the participant to a significant degree. Including, but not limited to:

    Severe chronic kidney disease (Stage 4 or 5, according to National Kidney Foundation guidelines)

    Hypertension not stably controlled by current medication (e.g., sustained systolic blood pressure > 160 mmHg or diastolic blood pressure > 95 mmHg)

    Diabetes not stably controlled by current medication (e.g., hemoglobin A1c $>$ 8%, or any history of clinically significant hypoglycemia, hyperosmolar syndrome, ketoacidosis, or other significant complication of diabetes within 2 years before screening)

    Heart failure (e.g., New York Heart Association Class II or higher)

    Clinically significant, abnormal ECG at screening (e.g., evidence of significant conduction blockade, or evidence of prior myocardial infarction, unless associated with a known myocardial infarction more than 2 years before screening)
- History of cancer, except as follows:

    If considered to be cured

    An appropriately treated carcinoma in situ of the cervix or Stage I uterine cancer

    If there has been no significant clinical progression during the past 5 years, with no active anti-cancer therapy or radiotherapy and, in the opinion of the investigator, is not likely to progress or require treatment in the ensuing 5 years

    Prostate cancer or basal cell carcinoma, where there has been no significant progression over the previous 2 years
- QT interval corrected using Fridericia's formula $>$ 470 ms in females and >450 ms in males, demonstrated by at least two ECGs $>$ 30 minutes apart

- Abnormal screening thyroid function tests or tests that remain abnormal on retest or require a new treatment or an adjustment of current treatment

  Abnormal screening thyroid function tests are defined as a thyroid-stimulating hormone (TSH) level outside the normal range and either a free thyroxine (T4) or a total T4 level outside the normal range.

  A patient may be rescreened if there is no improvement in cognition in the investigator's judgment after 2 months of adequate treatment for thyroid function.
- Screening folic acid or vitamin B12 levels that are sufficiently low or remain low on retest such that deficiency requires initiation or alteration of treatment and/or may be contributing to cognitive impairment

  A patient may be rescreened if there is no improvement in cognition after 2 months of adequate treatment for folic acid or vitamin B12 deficiency.

Cerebrovascular/Neurologic/Psychiatric

Patients who meet any of the following cerebrovascular/neurologic/psychiatric criteria will be excluded from study entry:

- History of seizures, with the exception of childhood febrile seizures or other remote, non-recurrent seizure
- History of prior traumatic brain injury graded as moderate or severe, defined as a head injury resulting in loss of consciousness lasting 30 minutes or longer, an initial Glasgow Coma Scale of 12 or worse at presentation, posttraumatic amnesia or confusion lasting 24 hours or longer, or any associated abnormal brain imaging finding at presentation
- Any evidence of a condition other than AD that may affect cognition, including but not limited to, dementia with Lewy bodies, vascular dementia, Parkinson's disease, corticobasal degeneration, Creutzfeldt-Jakob disease, progressive supranuclear palsy, frontotemporal degeneration, Huntington's disease, normal pressure hydrocephalus, hypoxia, severe sleep apnea or other chronic sleep disturbance, or baseline intellectual disability
- History of schizophrenia, schizoaffective disorder, major depression, or bipolar disorder

  A history of major depression is acceptable if patient has had no episode within the past year, is considered in remission, or depression is controlled by treatment.
- At risk of suicide in the opinion of the investigator
- Substance abuse meeting criteria for alcohol, cannabis, phencyclidine, other hallucinogen, inhalant, opioid, sedative, hypnotic, anxiolytic, or stimulant use disorder of any severity (per the Diagnostic and Statistical Manual of Mental Disorders, Version 5) within the past 2 years

  Investigators may elect to obtain a urine drug screen if clinically indicated.
- History or presence of clinically evident vascular disease potentially affecting the brain (e.g., clinically significant carotid, vertebral stenosis, or plaque; aortic aneurysm; intracranial aneurysm; cerebral hemorrhage; arteriovenous malformation) that, in the opinion of the investigator, has the potential to affect cognitive function
- History or presence of any stroke with clinical symptoms within the past 2 years, or documented history within the last 6 months of an acute event consistent, in the opinion of the investigator, with a transient ischemic attack
- History of cerebral amyloid angiopathy or MRI evidence of >6 microhemorrhages, any macrohemorrhage, or superficial siderosis comprising more than one region or a single region >1 cm
- History or presence of intracranial tumor that is clinically relevant (e.g., glioma, cerebral metastasis) in the opinion of the investigator
- Presence of infections that affect brain function or history of infections that resulted in neurologic sequelae (e.g., HIV, syphilis, neuroborreliosis, viral or bacterial meningitis/encephalitis)

- History or presence of central nervous system or systemic autoimmune disorders potentially causing progressive neurologic disease with associated cognitive deficits (e.g., multiple sclerosis, lupus erythematosus, antiphospholipid antibody syndrome, Behçet disease)
- MRI evidence of 1) more than two lacunar infarcts, 2) any territorial infarct > 1 cm^3, or 3) significant fluid attenuated inversion recovery hyperintense lesions in the cerebral deep white matter corresponding to a Fazekas deep white matter score of 3 or that otherwise may, in the investigator's opinion, contribute to cognitive dysfunction

Infections and Immune Disorders

Patients who meet any of the following infections and immune disorders criteria will be excluded from study entry:

- Systemically, clinically significantly immunocompromised patients, owing to continuing effects of immune-suppressing medication
- Positive for hepatitis C virus antibody at screening
- Positive for hepatitis B surface antigen at screening
- Positive for HIV antibody at screening
- Serious infection requiring oral or IV antibiotics within 30 days prior to screening
- Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins

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

- Use of any experimental therapy within 90 days or 5 half-lives prior to screening, whichever is greater
- Use of any passive immunotherapy (immunoglobulin) against tau, except use of MTAU9937A in Genentech Study GN39058, as long as the last dose was at least 90 days prior to screening.
- Use of any passive immunotherapy (immunoglobulin) against Aβ, unless the last dose was at least 1 year prior to screening.
- Use of any active immunotherapy (vaccine) that is under evaluation to prevent or postpone cognitive decline
- *Investigational* biologic therapy *(e.g., therapeutic proteins, monoclonal antibodies, or other* active or passive immunotherapy*)* within 1 year of screening or any expectation to require *additional investigational* biologic therapy for the duration of the trial
- Any previous treatment with medications specifically intended to treat Parkinsonian symptoms or any other neurodegenerative disorder within 1 year of screening

  Certain medications are acceptable if the patient is taking the medicine for a non-neurodegenerative disorder, such as restless leg disorder (e.g., pramipexole)
- Systemic immunosuppressive therapy within 12 months of screening through the entire study period

  Short courses (≤2 weeks) of high-dose corticosteroid therapy are permitted. Chronic corticosteroid therapy (> 2 weeks) is permitted as long as the dose is < 7.5 mg/day prednisolone equivalent and the condition being treated is not expected to deteriorate significantly during the study period.
- Typical antipsychotic or neuroleptic medication within 6 months of screening, except as brief treatment for a non-psychiatric indication (e.g., emesis)

- Daily treatment with any of the following classes of medication, except for intermittent short-term use, which is permitted except within 2 days or 5 half-lives (whichever is longer) prior to any COA. The investigator should contact the Medical Monitor if there are questions regarding permitted medications.

  Atypical antipsychotics

  Opiates or opioids (including long-acting opioid medication)

  Benzodiazepines, barbiturates, or hypnotics

  Any medication with clinically significant centrally-acting antihistamine or anticholinergic activity (i.e., those medications with significant levels of blood-brain barrier penetration that are likely to affect cognition and/or behavior).
- Stimulant medications (amphetamine, methylphenidate preparations, or modafinil), unless the dose has been stable within the 6 months prior to screening and is expected to be stable throughout the study.

End of Study

The end of this study is defined as the date when the last patient, last visit occurs or the date at which safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur 43 months after the last patient is enrolled.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 63 months.

Investigational Medicinal Products

Test Product (Investigational Drug)

Study treatment is defined as study drug plus the PET radioligand used during PET imaging procedures ([^{18}F]GTP1 for tau PET imaging, and the amyloid radioligand for amyloid PET imaging). Depending on local classification, the [^{18}F]GTP1 tau PET radioligand and/or the amyloid PET radioligand(s) may be considered non-investigational medicinal products or investigational medicinal products.

Study drug (MTAU9937A or placebo) will be administered IV in the double-blind treatment period, and MTAU9937A will be administered IV in the optional OLE period. Study drug administration will occur Q2W for the first three doses of the double-blind treatment period and every 4 weeks (Q4W) thereafter in the double-blind treatment period. Patients will receive 1500 mg, 4500 mg, or 8100 mg MTAU9937A IV or a placebo IV. MTAU9937A will be administered Q4W in the OLE period. All patients participating in the OLE will receive MTAU9937A 4500 mg IV.

[^{18}F]GTP1 and amyloid radioligands will be used for tau PET and amyloid PET imaging, respectively. For each PET imaging procedure, a single dose of the relevant radioligand will be injected prior to the PET scan. Details for radioligand doses and administration are provided in the Technical Operations Manuals for the various radioligands.

Statistical Methods

Primary Analysis

The efficacy analyses will be based on the modified intent-to-treat population, which is defined as all randomized patients who receive at least one dose of study drug and have at least one postbaseline primary efficacy Clinical Dementia Rating–Sum of Boxes (CDR-SB) measurement. For the efficacy analysis, patients will be grouped according to the treatment assigned at randomization. The primary efficacy endpoint is change in CDR-SB score from baseline to Week 73. The difference in mean change from baseline to Week 73 between MTAU9937A- and placebo-treated patients will be estimated using an analysis of covariance model adjusting for *ApoE4* status and baseline *clinical* status (i.e., prodromal AD vs. mild AD dementia). Confidence intervals as well as least squares estimates will be used to aid in interpretation of study results.

The safety analysis will be based on all randomized patients who receive at least one dose of either MTAU9937A or placebo, or GTP1. Patients will be grouped according to MTAU9937A treatment actually received. All adverse events that occur after informed consent is given will

be summarized by mapped term, appropriate thesaurus level, and toxicity grade. In addition, all serious adverse events, including deaths and events leading to discontinuation, will be listed separately and summarized. Laboratory data will be summarized by descriptive statistics by treatment group. In addition, all laboratory abnormalities will be summarized by grade using the WHO grading scale. Dose-limiting adverse events and adverse events of special interest will be listed and summarized by treatment group. Vital signs (pulse rate, blood pressure, body temperature, and respiratory rate), weight, and other disease-specific data will be summarized by descriptive statistics by treatment group. Changes from baseline will be summarized by treatment group.

- A primary analysis will occur after the last patient has completed the Week 73 assessment.
- A final analysis will occur after the last patient has finished the OLE and completed the Week 169 assessment.

Determination of Sample Size

This study *has enrolled 457* patients*,* randomized to one of three active IV dose arms or to an IV placebo dose arm in a 2:3:2:3 ratio. *The prior projected* sample size *of 360 patients* provides reasonable precision for estimating a clinically significant treatment effect on CDR-SB scores when MTAU9937A is compared with placebo. Assuming an observed 0.6-point difference in mean CDR-SB decline between the 4500 mg MTAU9937A arm and placebo at Week 73, a standard deviation across patients of 2, and a 25% dropout rate, a 90% confidence interval on the population treatment effect point estimate for the CDR-SB is approximately 0.08–1.12.

Optional Interim Analysis

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct an interim efficacy analysis. The rationale for conducting an interim analysis will be on the basis of factors and information external to this study such as new, emergent data from other clinical trials.

If an interim analysis is conducted, the Sponsor will remain blinded. The interim analysis will be conducted by an external statistical group and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC charter.

The decision to conduct an optional interim analysis, along with the rationale and timing, will be documented in the protocol. Statistical details for the interim analysis will be contained within the Statistical Analysis Plan (SAP). A substantial protocol amendment (in the European Union) or the SAP (other jurisdictions) will be submitted to relevant health authorities*,* as appropriate, prior to the conduct of the interim analysis. The iDMC charter will also be updated to document potential recommendations the iDMC can make to the Sponsor as a result of this analysis and the iDMC charter will be submitted to relevant Health Authorities. All documents submitted to health authorities would be simultaneously submitted to the study master file to further document this information appropriately. The Clinical Study Report will also document that such an interim analysis occurred.

If the interim analysis plan allows for early assessment of efficacy, the type I error rate will be controlled to ensure statistical validity is maintained. Specifically, the Lan-DeMets α-spending function that approximates the O'Brien-Fleming boundary will be applied to determine the critical value for stopping for positive efficacy at the interim analysis. Additional criteria for recommending that the study be stopped for positive efficacy may be added to the iDMC charter. If the study continues beyond the interim analysis, the critical value at the final analysis would be adjusted accordingly to maintain the overall type I error rate, per standard Lan-DeMets methodology. The select efficacy endpoints provided to the iDMC as part of ongoing safety review do not enable and are not considered sufficient for a formal interim analysis to assess early efficacy or futility.

If the interim analysis plan allows for early assessment of futility, the threshold for declaring futility will include an assessment of the predictive probability that the primary endpoint will achieve statistical significance. An interim analysis that might lead to stopping the study for futility will not occur before at least 50% of the information has been accumulated for the primary endpoint.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
[^{18}F]GTP1	fluorine-18 Genentech tau probe 1
Aβ	β-amyloid
AD	Alzheimer's disease
ADA	anti–drug antibody, also known as anti-therapeutic antibody (ATA)
ADAS-Cog	Alzheimer's Disease Assessment Scale–Cognitive Subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study Group–Activities of Daily Living Inventory
ADL	activities of daily living
AUC	area under the concentration–time curve
CaGI-Alz	*Caregiver Global Impression of Change Scales for Alzheimer's disease*
CDR	Clinical Dementia Rating
CDR-GS	Clinical Dementia Rating–Global Score
CDR-SB	Clinical Dementia Rating–Sum of Boxes
C_{max}	maximum concentration
COA	clinical outcome assessment
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DVF	Diagnostic Verification Form
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
Fc	fragment crystallizable
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration
GLP	Good Laboratory Practices
GTP1	Genentech tau probe 1
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HV	healthy volunteer
iADL	Instrumental Activity of Daily Living
ICH	International Conference on Harmonisation
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (application)

Abbreviation	Definition
IRB	Institutional Review Board
IxRS	interactive voice or web-based response system
LP	lumbar puncture
mAD	mild AD
MCI	mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NIA-AA	National Institute on Aging/Alzheimer's Association
NIMP	Non-investigational medical product
OLE	open-label extension
pAD	prodromal AD
PD	pharmacodynamic
PET	positron emission tomography
PK	pharmacokinetic
Q2W	every 2 weeks
Q4W	every 4 weeks
QTcF	QT interval corrected using Fridericia's formula
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RBR	Research Biosample Repository
RUD	Resource Utilization in Dementia
SAP	Statistical Analysis Plan
SNP	single nucleotide polymorphism
T4	*thyroxine*
TK	toxicokinetic
TSH	*thyroid-stimulating hormone*
ULN	upper limit of normal
URTI	upper respiratory tract infection
WES	whole exome sequencing
WGS	whole genome sequencing
YTE	heavy chain with M249Y, S251T, and T253E mutations

1. BACKGROUND

1.1 BACKGROUND ON ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the most common cause of dementia, affecting an estimated 4.5 million individuals in the United States and 26.6 million worldwide (Hebert et al. 2003; Brookmeyer et al. 2007). The disease is characterized pathologically by the accumulation in the brain neocortex of extracellular β-amyloid (Aβ) peptide-containing plaques and intracellular neurofibrillary tangles containing aggregates of the microtubule associated protein tau. Diagnosis is made through the clinical assessment of the neurologic and neuropsychiatric signs and symptoms of AD and the exclusion of other causes of cognitive dysfunction. AD is commonly classified into preclinical, prodromal, mild, moderate, and severe stages by the presence and severity of clinically relevant functional and/or cognitive decline, and categorization is often facilitated by global measures, such as the Clinical Dementia Rating scale (CDR; Morris 1993) or the Mini-Mental State Examination (MMSE; Folstein et al. 1975). Approved medical therapies that inhibit acetylcholinesterase activity or antagonize *N*-methyl-d-aspartate receptors in the brain may temporarily improve the symptoms of AD in some patients but do not modify the progression of the disease (Cummings 2004).

The deposition of extracellular amyloid plaques and intracellular tau aggregates in the brain are the hallmark pathologic findings in AD, first reported by Alois Alzheimer in 1906. Intracellular neurofibrillary tangles are composed of aggregated and abnormally phosphorylated tau protein. Tau, encoded by the *MAPT* gene, is expressed in the human brain as six splice isoforms, with lengths of 352–441 amino acids. The six isoforms comprise combinations of three variant near-amino-terminal repeat domains (0N, 1N, and 2N) and two variant carboxy-terminal repeat domains (3R and 4R) (Wang and Mandelkow 2016). While the intracellular aggregates are found as neurofibrillary tangles in the neuron soma and as neuropil threads in the dendritic compartment, it is believed that the spread of tau pathology through the brain is mediated by soluble tau in the extracellular brain environment (Braak and Tredici 2015; Wang and Mandelkow 2016).

The spatial distribution of tau pathology in AD patients correlates with decline in the cognitive domains subserved by the affected cortical networks (Ossenkoppele et al. 2016). Knockout of the tau gene in an AD transgenic mouse model is protective against cognitive deficits (Roberson et al. 2007). Therapies that reduce the spread of tau in the brain may alleviate cognitive dysfunction and block further synaptic loss, axon degeneration, and neuronal cell death.

1.2 BACKGROUND ON MTAU9937A

1.2.1 Non-Clinical Information

MTAU9937A is a pan-tau IgG4 monoclonal antibody that has potential to treat tauopathies (including AD and primary tauopathies). MTAU9937A is designed to bind and intercept all extracellular tau isoforms, in order to stop or slow cell-to-cell spread and propagation of tau toxicity and pathology throughout cortical and sub-cortical networks. The IgG4 backbone was chosen for MTAU9937A because it has reduced Fcγ receptor binding affinity compared with the human IgG1 subclass, and thus a reduced immune effector response. MTAU9937A has demonstrated protection of neurons in the presence of microglia, in response to exposure to toxic species of tau in cell-based experiments (see the MTAU9937A Investigator's Brochure for details). MTAU9937A has also been engineered to contain three mutations (M249Y, S251T, and T253E) (YTE) in the heavy chain component of the fragment crystallizable (Fc) region of the antibody that enhance binding to the neonatal Fc receptor (FcRn) and have been shown to slow peripheral antibody clearance in humans, potentially augmenting exposure levels (Robbie et al. 2013).

A murine surrogate of MTAU9937A showed dose-dependent reduction in accumulation of tau pathology in a transgenic model (hTau P301L.Tg) overexpressing human tau. In addition, MTAU9937A prevented toxic tau species from entering cultured neurons and protected these neurons from tau-mediated toxicity and death.

There were no MTAU9937A-related adverse findings in the Good Laboratory Practices (GLP) 5-week, repeat-dose toxicity study in which cynomolgus monkeys were administered MTAU9937A at doses up to 300 mg/kg/week IV. MTAU9937A-related clinical pathology findings were limited to increases in neutrophils, fibrinogen, globulin (possibly because of the presence of high levels of test article), and/or decreases in albumin, suggestive of a mild inflammatory response, as well as mild transient decreases in glucose and mild decreases in platelets. The findings were not considered adverse as they were mild, transient, or both, and no anatomic findings explained or correlated with the findings. On the basis of this 5-week toxicity study in monkeys, the no-observed-adverse-event level was determined to be the highest dose tested, 300 mg/kg/week (mean area under the concentration–time curve [AUC] from toxicokinetic [TK] Day 0 to TK Day 30 of 184,000 μg • day/mL and a maximum concentration [C_{max}; post-first dose] of 7,280 μg/mL).

In addition, MTAU9937A was also locally well tolerated following single SC injection in rabbits.

In support of chronic administration of MTAU9937A in patients, a GLP 26-week, repeat-dose, toxicity study has been conducted in cynomolgus monkeys and is currently in the reporting phase. Preliminary data show that MTAU9937A was well tolerated by cynomolgus monkeys following 27 weekly IV doses up to 300 mg/kg with no

MTAU9937A-related adverse effects noted (refer to the MTAU9937A Investigator's Brochure for additional details regarding results of this study).

Refer to the MTAU9937A Investigator's Brochure for further details regarding the nonclinical studies.

1.2.2 Clinical Information

The experience with MTAU9937A in humans consists of data from one completed Phase I study (GN39058*),* this ongoing Phase II study (GN39763*), and an ongoing Phase II study in patients with moderate AD (GN40040*).

Study GN39058 was a randomized, placebo-controlled, double-blind, Phase I study that assessed the safety, tolerability, and pharmacokinetics of IV and SC MTAU9937A in 65 healthy volunteers (HVs) and 10 patients with mild-to-moderate AD. The study consisted of a single-ascending dose part (6 IV cohorts, with doses from 225 mg to 16,800 mg, and one SC cohort at 1200 mg) and a multiple-dose part (2 IV cohorts each receiving 8400 mg IV once weekly ×4 weeks). All single-dose cohorts consisted of only HVs; one multiple-dose cohort consisted of HVs and the other multiple-dose cohort consisted of patients with AD. The initial single-dose IV cohort consisted of 3 HVs, randomized to a 2:1 ratio (MTAU9937A:placebo). The remainder of the single-dose IV cohorts consisted of 8 HVs, randomized to a 6:2 ratio (MTAU9937A:placebo). The single-dose SC cohort consisted of 12 HVs, all treated with MTAU9937A. Each of the two multiple-dose IV cohorts consisted of 10 subjects, randomized to an 8:2 ratio (MTAU9937A:placebo). A total of 44 HVs received single doses of MTAU9937A with a range of 225–16,800 mg IV or SC (32 HVs received IV doses, 12 HVs received SC doses), and 16 participants (8 HVs and 8 patients with mild-to-moderate AD) each received four doses of 8400 mg IV once a week (except for 1 HV, who was mistakenly given a first dose of 4200 mg, followed by three doses of 8400 mg).

Study GN40040 is a randomized, double-blind, Phase II study that aims to assess the efficacy, safety, pharmacokinetics, and pharmacodynamics of MTAU9937A in patients with moderate AD. The study consists of a screening period, a double-blind treatment period, an optional open-label extension (OLE) period, and a safety follow-up period. This study will include approximately 260 patients from approximately 50 sites in North America and Europe. Patients will be randomized to MTAU9937A (4500 mg) or placebo administered IV in a 1:1 ratio.

MTAU9937A has been generally well tolerated in HVs and patients with AD *(refer to the MTAU9937A Investigator's Brochure for further details).* No adverse drug reactions have been identified with MTAU9937A. Potential risks associated with MTAU9937A are discussed in Section 5.1.1.

The pharmacokinetics of MTAU9937A were evaluated in Study GN39058 following single (225–16,800 mg) or weekly (8400 mg × 4 doses) IV or single (1200 mg) SC

administration to HVs and to patients with mild-to-moderate AD. Upon IV administration, MTAU9937A exhibited biphasic disposition, and the half-life had a range of 22.8–45.7 days. The mean SC bioavailability estimated from the SC cohort (1200 mg) was approximately 69%. Upon weekly IV administration, the pharmacokinetics of MTAU9937A were comparable between HVs and patients with AD. An assessment of dose proportionality demonstrated that serum pharmacokinetics increased proportionally with the dose after a single-dose IV administration. MTAU9937A was detected in the cerebrospinal fluid (CSF), suggesting penetration into the CNS.

Refer to the MTAU9937A Investigator's Brochure for further details on clinical studies, including the numbers of patients that have been exposed to MTAU9937A.

1.3 BACKGROUND ON [^{18}F]GTP1

Tau protein has been identified as one of the key pathological features of AD (Grundke et al. 1986; Kosik et al. 1986; Wood et al. 1986). Tau is the primary protein composing neurofibrillary tangles and postmortem studies have shown that neurofibrillary tangle density correlates with neurodegeneration and cognitive impairment (Duyckaerts et al. 1987; Delaére et al. 1989; Duyckaerts et al. 1990; Arriagada et al. 1992; McLean et al. 1999). Thus, a positron emission tomography (PET) imaging agent that binds to aggregated tau has the potential to serve as a biomarker for disease severity or neurodegeneration and may be useful for monitoring disease progression in therapeutic trials.

Fluorine-18 Genentech tau probe 1 ([^{18}F]GTP1) has been developed as a positron emitting radioligand for in vivo imaging of tau protein aggregates. [^{18}F]GTP1 has been previously evaluated in a first-in-human study (e0040) involving 3 patients with AD, 3 patients with progressive supranuclear palsy, and 2 HVs. The study demonstrated substantial retention of the radioligand in brain regions expected to contain tau pathology in patients with AD. [^{18}F]GTP1 has also been studied in two additional Phase I studies: a test re-test study (e0048) with 5 patients with AD and 5 elderly HVs, and a radiation dosimetry study (e0049) with 6 HVs. In addition, [^{18}F]GTP1 is currently being evaluated in a Phase I longitudinal natural history study (Study GN30009; clinicaltrials.gov identifier NCT02640092).

[18F]GTP1 is also being evaluated in longitudinal PET-imaging substudies of Phase III trials of the anti-Aβ antibodies crenezumab (Studies BN29552 and BN29553; clinicaltrials.gov identifiers NCT02670083 and NCT03114657, respectively), and gantenerumab (Studies WN29922 and WN39658; clinicaltrials.gov identifiers NCT03444870 and NCT03443973, respectively).

1.3.1 Clinical Safety and Tolerability

Available safety data from the completed and ongoing clinical studies (completed: Studies e0040, e0048, e0049; ongoing: Study GN30009, Substudies BN29552/BN29553, *Substudies WN29922/WN39658, Study GN39763,* and

Study *GN40040*) with [18F]GTP1 show that exposure to [18F]GTP1 and imaging procedures are generally well tolerated. One serious adverse event has been reported: a urinary tract infection in Study GN30009, assessed as not related to [18F]GTP1 by the investigator. There have been no deaths, no adverse events of special interest, no hypersensitivity reactions, and no systemic infusion-related reactions reported. Local infusion-related reactions, including hematoma, ecchymosis, and injection-site pain, were reported; all were non-serious and mild in severity. Refer to the [18F]GTP1 Investigator's Brochure for details on these studies and full nonclinical evaluation of the tracer.

1.4 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

MTAU9937A represents a novel potential therapeutic for the treatment of AD. As described in Section 1.1, existing therapies for AD provide only modest symptomatic benefit and fail to slow progression of the underlying neurodegenerative process. Therefore, there is significant unmet medical need among patients with AD, and MTAU9937A may fill that gap by targeting a key pathological protein believed to underlie the degenerative process. Study GN39763 is a proof-of-concept study, using clinical outcome assessments (COAs), a novel tau imaging technology, and other biomarkers to test the hypothesis that MTAU9937A administration to patients with AD improves clinical outcome and stops or slows cell-to-cell spread and propagation of tau pathology in the brain.

There has been no evidence of safety concerns associated with MTAU9937A or its murine surrogate in nonclinical models to date, and there has been no obvious phenotype reported in tau knockout mice (Harada et al. 1994). The completed toxicology program for MTAU9937A was designed to support IV and SC dosing in clinical studies. In a GLP, 5-week, repeat-dose, toxicity study in cynomolgus monkeys, there were no MTAU9937A-related adverse effects following weekly IV doses of up to 300 mg/kg. In support of chronic administration of MTAU9937A in patients, a GLP, 26-week, repeat-dose, toxicity study has been conducted in cynomolgus monkeys and is currently in the reporting phase. MTAU9937A was well tolerated by cynomolgus monkeys following 27 weekly IV doses up to 300 mg/kg with no MTAU9937A-related adverse effects noted (refer to the MTAU9937A Investigator's Brochure for additional details regarding results of this study).

On the basis of results from nonclinical studies and the Phase I study in humans (GN39058), MTAU9937A is expected to be well tolerated by patients with AD in this study (GN39763). There are no known risks to MTAU9937A. Potential risks of MTAU9937A are described in Section 5.1.1. Several measures are being taken in this study to mitigate possible safety concerns, including strict inclusion and exclusion criteria (see Section 4.1), periodic neurologic examinations (Section 4.5.4), magnetic resonance imaging (MRI) and suicidality monitoring (see Section 4.5.7), and regular safety review by an unblinded, independent Data Monitoring Committee (iDMC; Section 3.1.2).

Because of high unmet need for disease-modifying treatments for AD and the benign safety profile of MTAU9937A observed in both nonclinical and clinical studies to date, the benefit–risk of MTAU9937A is favorable and supportive of its use in this clinical study.

Refer to the MTAU9937A Investigator's Brochure for additional details regarding nonclinical pharmacology, pharmacokinetic (PK), and toxicology data, as well as human pharmacology, PK, and safety data.

[^{18}F]GTP1 will be used in this study to evaluate the effect of MTAU9937A on tau burden as measured by tau PET in patients with AD. Measures based on PET imaging with [^{18}F]GTP1 are expected to help in understanding the pharmacodynamic (PD) effects of MTAU9937A on tau pathology (spread of tau protein aggregates) as well as the relationship between change in tau PET and change in other endpoints in this study. On the basis of results from nonclinical studies and completed and ongoing studies in humans, [^{18}F]GTP1 is expected to be well tolerated by patients with AD in this study. There are no known risks to [^{18}F]GTP1; potential risks of [^{18}F]GTP1 are described in Section 5.1.2.

The benefit–risk of [^{18}F]GTP1 is favorable and supportive of its use in this clinical study.

Refer to the [^{18}F]GTP1 Investigator's Brochure for additional details.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of MTAU9937A in patients with prodromal AD (pAD) or mild AD (mAD), ages 50–80, who are amyloid positive by CSF or amyloid PET. Specific objectives and corresponding endpoints for the study are outlined in Table 1.

Table 1 Objectives and Corresponding Endpoints

Primary	
Efficacy Objective	**Corresponding Endpoint**
• To evaluate the efficacy of MTAU9937A compared with placebo	• Change from baseline to Week 73 on the CDR-SB
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety and tolerability of MTAU9937A compared with placebo	• Nature, frequency, severity, and timing of adverse events and serious adverse events. Severity of adverse events will be determined through use of the WHO toxicity grading scale. • Changes from baseline in vital signs, physical findings, neurologic findings, ECG, and clinical laboratory results during and following MTAU9937A administration • Changes from baseline in suicidal ideation and behavior during and following MTAU9937A administration as assessed by the C-SSRS • Nature, frequency, severity, and timing of neuroimaging abnormalities
Secondary	
Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the effect of MTAU9937A on cognition compared with placebo	• Change from baseline to Week 73 on the RBANS Total Score • Change from baseline to Week 73 on the ADAS-Cog 13
• To evaluate the effect of MTAU9937A on activities of daily living compared with placebo	• Change from baseline to Week 73 on the Amsterdam iADL questionnaire • Change from baseline to Week 73 on the ADCS-ADL
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the pharmacokinetics of MTAU9937A	• Serum concentrations of MTAU9937A at specified timepoints
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to MTAU9937A	• Presence of ADAs during the study relative to the presence of ADAs at baseline
Exploratory	
Efficacy Objective	**Corresponding Endpoint**
• To evaluate the effect of MTAU9937A on time to decline in functional capacity compared with placebo	• Time from baseline to change in diagnosis or the occurrence of a decline in functional capacity, as assessed by an AD event inventory and other assessments

Exploratory	
Pharmacokinetic Objectives	**Corresponding Endpoints**
• To evaluate potential relationships between drug exposure and the safety, PD response, and activity of MTAU9937A	• Relationship between serum pharmacokinetics for MTAU9937A and safety endpoints • Relationship between serum or CSF pharmacokinetics for MTAU9937A and clinical activity or PD endpoints
• To evaluate potential relationships between selected covariates and exposure to MTAU9937A	• Relationship between selected covariates, including but not limited to age, sex, and serum pharmacokinetics for MTAU9937A
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, or PK endpoints
Biomarker Objectives	**Corresponding Endpoints**
• To evaluate the effect of MTAU9937A on pathological burden of tau • To evaluate the effect of MTAU9937A on biomarkers to aid in defining MOA • To evaluate the relationship between changes in biomarkers and efficacy • To evaluate if biomarkers, at baseline, identify a subset of patients with more rapid disease progression and/or enhanced clinical benefit to MTAU9937A	• Changes from baseline in brain tau burden over time as measured by [^{18}F]GTP1 PET • Changes from baseline in levels of soluble tau in plasma or CSF and in levels of other potential disease biomarkers • Changes from baseline in brain structure measured by MRI • Relationship between changes in efficacy endpoints and measures of changes in brain tau burden, soluble tau in biofluids, brain structure, and other potential disease biomarkers • Relationships between biomarkers in blood or CSF (including common and rare genetic variants, identified through genomic analysis on DNA extracted from blood) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints
Resource Utilization Objectives	**Corresponding Endpoint**
• To evaluate resource utilization of caregivers and patients treated with MTAU9937A	• Change from baseline in the RUD-Lite at Week 73

AD=Alzheimer's disease; ADA=anti-drug antibody; ADAS-Cog=Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS-ADL=Alzheimer's Disease Cooperative Study Group–Activities of Daily Living Inventory; CSF=cerebrospinal fluid; C-SSRS=Columbia-Suicide Severity Rating Scale; CDR-SB=Clinical Dementia Rating–Sum of Boxes; GTP1= Genentech tau probe 1; iADL=Instrumental Activity of Daily Living; MOA= mechanism of action; MRI=magnetic resonance imaging; PET=positron emission tomography; PD=pharmacodynamic; PK=pharmacokinetic; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; RUD=Resource Utilisation in Dementia.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design and Study Treatment

This Phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group study will evaluate the efficacy, safety and tolerability, pharmacokinetics, and pharmacodynamics of MTAU9937A in patients with pAD to mAD.

The study consists of a screening period, a double-blind treatment period, an optional OLE period, and a safety follow-up period (see Figure 1 for the study schema and in Appendix 1 and Appendix 2 for the schedules of activities). An extended baseline visit (up to 15 days) is included in the double-blind treatment period, following randomization and prior to the initiation of study drug. Study drug (MTAU9937A or placebo) will be administered intravenously in the double-blind treatment period, and MTAU9937A will be administered intravenously in the optional OLE period. Study drug administration will occur every 2 weeks (Q2W) for the first three doses of the double-blind treatment period and every 4 weeks (Q4W) thereafter in the double-blind treatment period. MTAU9937A will be administered Q4W in the OLE period.

Study treatment is defined as study drug plus the PET radioligand used during PET imaging procedures ([^{18}F]GTP1 for tau PET imaging and the amyloid radioligand for amyloid PET imaging). See Section 4.3 for a description of the study treatments used in this study.

This study *has enrolled 457* patients at *97* sites in North America, Europe, and the Asia-Pacific region. Patients will be randomly assigned to one of three active, IV dose arms (1500 mg, 4500 mg, or 8100 mg MTAU9937A) or to an IV placebo dose arm in a 2:3:2:3 (1500 mg:4500 mg:8100 mg:placebo) ratio. All patients participating in the OLE will receive MTAU9937A 4500 mg IV. To maintain balance in dementia status and *APOE* status between treatment arms, randomization will be stratified by dementia status (pAD vs. mAD) and *APOE* status (ApoE4+ vs. ApoE4–). To ensure adequate representations of each diagnostic group, the Sponsor may operationally manage the proportion of pAD and mAD patients in the study (e.g., no more than approximately 80% of one category).

Patients will be selected on the basis of clinical diagnosis of probable AD (according to the National Institute on Aging/Alzheimer's Association [NIA-AA] Diagnostic Criteria and Guidelines for AD; see Appendix 3; McKhann et al. 2011) or pAD (according to the NIA-AA Diagnostic Criteria and Guidelines for AD; see Appendix 4; Albert et al. 2011). pAD is defined in this protocol as a clinical diagnosis of mild cognitive impairment (MCI) due to AD (see Appendix 4; Albert et al. 2011) coupled with evidence of cerebral amyloidosis (see below). Clinical diagnosis for each patient must be supported by information provided on a Diagnostic Verification Form (DVF), which must be reviewed

and approved by the Sponsor or Sponsor delegate. For more details on the DVF approval process, see the description of the screening period in Section 3.1.1.1.

Eligible patients must be 50–80 years old at the beginning of screening, meet diagnostic criteria for MCI (Albert et al. 2011) or probable AD dementia (McKhann et al. 2011), and have evidence of cerebral amyloidosis as indicated by CSF analysis (i.e., CSF-enrolled patients) *or* positive amyloid PET scan by qualitative read (i.e., PET-enrolled patients). The choice between CSF versus PET for determination of cerebral amyloidosis should be made on the basis of the capability of an individual site and/or the preference of an individual patient. If a patient is amyloid negative based on one of the two modalities (CSF assessment or amyloid PET), then the patient may undergo assessment with the other modality during screening; amyloid positivity by either modality is sufficient for eligibility. Under certain circumstances, a previously acquired amyloid PET scan may be used for study inclusion (see Section 4.5.8). If the previously acquired amyloid PET scan is read as amyloid negative by the core/central PET vendor, the patient may undergo CSF assessment to determine eligibility, but the patient may not undergo an additional amyloid PET scan for enrollment.

At the time of screening, patients must have a MMSE score of ≥ 20 points and a Clinical Dementia Rating–Global Score (CDR-GS) of 0.5 or 1.0. To confirm objective memory impairment, patients must also have a Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Delayed Recall Index of ≤ 85 at the time of screening. Patients will be eligible for the study whether or not they are receiving standard-of-care symptomatic medications for AD (e.g., cholinesterase inhibitors, memantine, and/or the medical food supplement Souvenaid®). These medications must have been stable for ≥ 2 months prior to screening, and there should be no a priori planned initiation, discontinuation, or dose changes for these medications during the study (including during the double-blind treatment and OLE treatment periods). However, following the initiation of study drug, standard-of-care symptomatic medications for AD may be initiated, dose adjusted, or discontinued as deemed clinically appropriate.

See Section 4.1 for further details of the inclusion and exclusion criteria.

To monitor patients for safety, the incidence and nature of adverse events, serious adverse events, adverse events of special interest, responses on the Columbia-Suicide Severity Rating Scale (C-SSRS), and abnormalities in standard safety blood *and urine* tests, ECG, *vital signs, physical examination,* and MRI will be assessed on a regular basis by the Sponsor and an unblinded iDMC. Blood samples will be obtained from all patients for the assessment of pharmacokinetics and for the measurement of antibodies directed against MTAU9937A and other components of the drug product.

Baseline measures of COAs (for clinical efficacy) and tau biomarkers (for PD activity) will be obtained prior to the initiation of study drug, either during the screening period

(e.g., Clinical Dementia Rating–Sum of Boxes [CDR-SB]) or during the post-randomization baseline visit (e.g., the Amsterdam Instrumental Activity of Daily Living [iADL] or [^{18}F]GTP1 PET imaging) (see Appendix 1 for details). Assessment of clinical efficacy will be determined by changes from baseline to Week 73 on a number of COAs. Changes from baseline to Week 73 on a number of biomarker measurements (e.g., tau burden as measured by [^{18}F]GTP1 PET, plasma/CSF analytes) will be used to assess PD activity in this study. Assessment of COAs and biomarkers will continue into the OLE period, for those patients continuing into the optional OLE period.

All patients must have baseline and longitudinal tau-related biomarker evaluation. If [^{18}F]GTP1 PET imaging is available to a patient, based on site availability of [^{18}F]GTP1 PET imaging and lack of local restriction to such imaging, the patient must undergo [^{18}F]GTP1 PET imaging for tau-related biomarker evaluation. [^{18}F]GTP1 PET imaging will be performed at the baseline visit (after randomization), Week 49, and Week 73 during the double-blind treatment period; those patients continuing into the optional OLE period must also have [^{18}F]GTP1 PET imaging performed at Week 169. In addition, for patients undergoing [^{18}F]GTP1 PET imaging, optional CSF collection at baseline and postbaseline time points is also encouraged.

For sites where [^{18}F]GTP1 PET imaging is not available, or where local restrictions preclude [^{18}F]GTP1 PET imaging, patients must have CSF collected via lumbar puncture (LP) at baseline, Week 49, and Week 73 during the double-blind treatment period; those patients continuing into the optional OLE period are encouraged to have an LP performed at Week 169. If an LP was performed during screening for the assessment of amyloid positivity, CSF from this LP will be used for the baseline measurement; otherwise, an LP must be performed during the baseline visit (after randomization).

[^{18}F]GTP1 PET, amyloid PET, and MRI evaluation will use a standard protocol, provided in the imaging technical operations manuals. Screening amyloid PET and MRIs will be read by a central reader to determine eligibility (see Section 4.1.2). Screening amyloid CSF analysis will be performed by a central laboratory.

PET scans should be performed only if the investigator has determined that the total past and planned annual radiation exposure does not exceed local guidelines. Radiation exposure for [^{18}F]GTP1 doses can be found in the [^{18}F]GTP1 Investigator's Brochure. Radiation exposure for doses of the amyloid radioligands can be found in the local labeling instructions *or, depending on locality, in the Investigator's Brochures.*

3.1.1.1 Study Periods

A schedule of activities is provided in Appendix 1 and Appendix 2, describing in detail the procedures and assessments of the various study periods.

Screening

After signing the Informed Consent Form, patients enter a screening period of up to 8 weeks to determine eligibility. Extensions to this 8-week period (e.g., to complete an assessment of cerebral amyloidosis) may be granted on a case-by-case basis by the Medical Monitor. Initial screening procedures may be staged; for instance, in accordance to site and/or patient preference, an initial Mini-Informed Consent Form may be signed that covers only medical history, MMSE, and RBANS, and if a patient remains potentially eligible for the study on the basis of these results, then the full, main Informed Consent Form may be signed to cover the remainder of the screening and study procedures. Staging of consent and screening in this manner is not required, and patients may sign the full, main Informed Consent Form at the beginning of screening.

On the basis of any initial screening procedures, provided that the patient remains eligible, a DVF must be completed by the investigator and submitted to the Sponsor or Sponsor delegate. The DVF must contain results from the MMSE, RBANS, and CDR, along with information supportive of a pAD or mAD diagnosis. The DVF must be reviewed and approved by the Sponsor or Sponsor delegate prior to performing MRI, [^{18}F]GTP1 or amyloid PET scans, or LP. If the DVF is not approved by the Sponsor or Sponsor delegate, the patient is not eligible for the study. Patients who are determined to be not eligible for the study, by the DVF or other screening procedures, may be rescreened at a later date, at the discretion of the Sponsor, if changes occur to the patient's condition or situation that might render the patient eligible to participate. See Appendix 1 for details regarding screening activities. On a case-by-case basis, the Medical Monitor may advise whether any specific screening procedures need to be repeated at the time of a rescreening.

Double-Blind Treatment Period

The double-blind treatment period of the study includes a baseline visit (of up to 15 days; extensions to the 15-day baseline visit period [e.g., to complete [^{18}F]GTP1 PET imaging] may be granted on a case-by-case basis by the Medical Monitor), a 68-week treatment period (Weeks 1–69), and an efficacy assessment period (baseline to Week 73). Treatment with study drug will occur Q2W for the first three doses (i.e., doses at Weeks 1, 3, and 5) and Q4W thereafter, up to and including the Week 69 dose (for a total of 19 doses). There will be no administration of study drug at the Week 73 visit. Safety, efficacy, PK, and biomarker assessments will be performed at baseline (during screening, the baseline visit, or at the Week 1 visit, prior to initiation of study drug) and at several postbaseline visits, including the Week 73 visit. See Appendix 1 for details regarding study activities during the double-blind treatment period.

Open-Label Extension Period

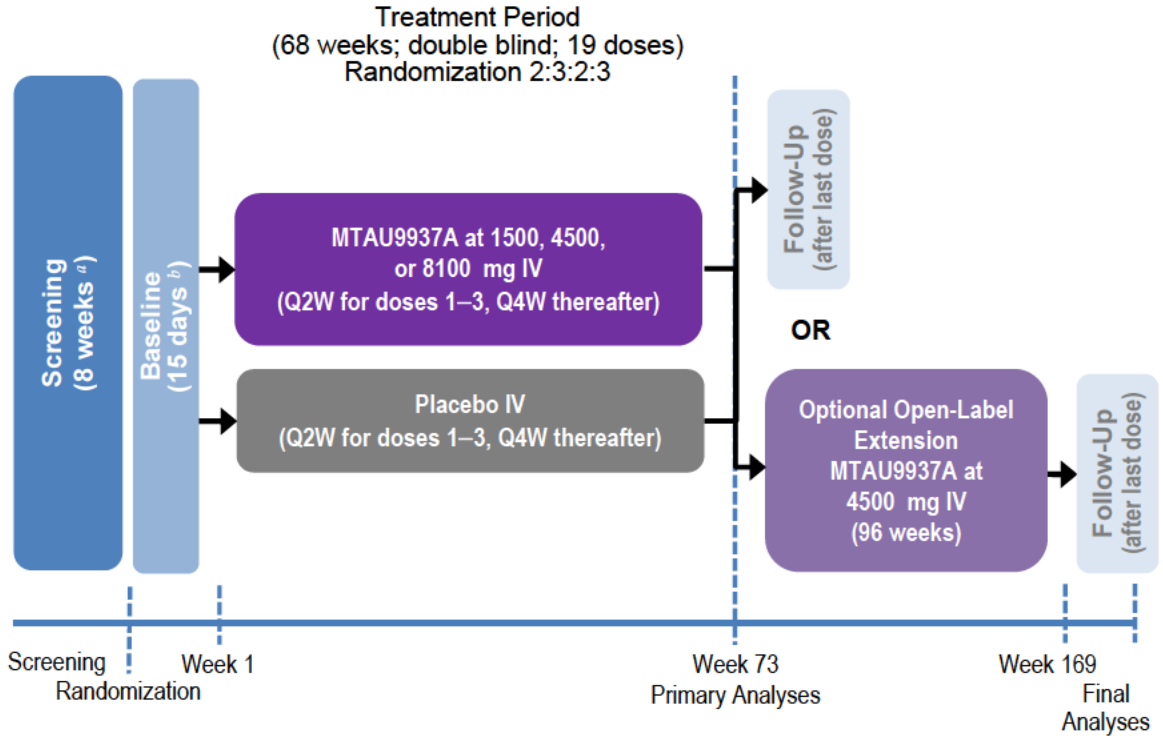
An optional 96-week OLE period is available to patients who complete the double-blind treatment period and who, in the judgment of the investigator, would potentially benefit from open-label MTAU9937A treatment. For the OLE period, all patients will receive MTAU9937A 4500 mg IV. Safety and efficacy assessments during the OLE period will

be performed at a schedule similar to that of the double-blind treatment period. The procedure(s) performed for tau-based biomarker evaluation during the OLE period ([^{18}F]GTP1 PET imaging and/or LP) should match the procedure(s) performed during the double-blind treatment period; LP will remain optional, but encouraged, for any patient who continues with longitudinal [^{18}F]GTP1 PET imaging and had a screening or baseline LP. See Appendix 2 for details regarding study activities during the OLE period.

Safety Follow-Up Period

All patients must be followed for safety after their final dose of study drug. Patients not entering the OLE period will have a safety follow-up visit 12 weeks after the last dose of study drug (i.e., at Week 81). Patients entering the OLE period will have a safety follow-up visit 12 weeks after the last dose of open-label treatment (i.e., at Week 181). Patients who discontinue from treatment *early*, in either the double-blind treatment period or in the OLE period, will have a *treatment discontinuation* visit 12 weeks following their last treatment dose. See Appendix 1 and Appendix 2 for details regarding study activities during the safety follow-up period.

Figure 1 Study Schema



Q2W=every 2 weeks; Q4W=every 4 weeks; W=week.

[a] Extensions to the 8-week screening period may be granted on a case-by-case basis by contacting the Medical Monitor.

[b] Extensions to the 15-day baseline visit period may be granted on a case-by-case basis by contacting the Medical Monitor.

3.1.2 Independent Data Monitoring Committee

To monitor patients for safety, the incidence and nature of adverse events, serious adverse events, and adverse events of special interest, responses on the C-SSRS, and abnormalities in standard safety blood and urine tests, ECG, vital signs, physical examination, and MRI will be assessed on a regular basis, approximately every 3–4 months, by an unblinded iDMC. The unblinded iDMC may also receive select summary statistics of COA endpoints.

At each safety review meeting, the iDMC will meet in a closed session to recommend whether the study should continue without modification, continue with minor modification, continue with substantial modification, suspend enrollment or treatment, or be terminated. There are currently no planned interim analyses to stop the trial early for either futility or clear signs of efficacy. Details of the iDMC will be provided in the iDMC Charter.

The Sponsor will also monitor all safety data continuously on a blinded basis.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit occurs or the date at which safety follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur 43 months after the last patient is enrolled.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 63 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for MTAU9937A Dose and Schedule

The potentially efficacious dose of MTAU9937A is not known. Due to the lack of a fully translatable animal model of AD, preclinical experiments do not provide guidance for human efficacious dose selection. In addition, the exploratory PD and efficacy data collected in the Phase I study (GN39058) were not intended to guide dose selection. Therefore, this study will evaluate three doses of MTAU9937A in order to explore dose/exposure-response relationships for efficacy, pharmacodynamics, safety, and tolerability.

The rationale for the three proposed dosing regimens of 1500, 4500, and 8100 mg Q4W in this study take into account the safety profiles from the nonclinical toxicology studies, safety and PK profiles from the Phase I study (GN39058), and results from the target engagement modeling exercise. The 8100-mg IV Q4W dose, the highest dose level of MTAU9937A, is justified on the basis of a 1.3- to 1.4-fold safety margin between the highest mean exposure (based on both C_{max} and AUC) in the multiple-dose portion of the Phase I study and the predicted steady-state exposure in this study at the 8100-mg dose. The favorable safety profile of MTAU9937A to date in Study GN39058 supports

doses up to 8100 mg IV (see Section 1.2.2). In addition, simulations incorporating model-based PK variability predict that these three doses will have minimal overlap with regard to PK exposure.

In the target engagement modeling analysis, simulations were conducted to predict percent target (i.e., tau) engagement by MTAU9937A in the interstitial fluid of the brain. Results demonstrated that high target engagement (i.e., > 80%) is predicted for the three doses under various scenarios (e.g., several plasma:brain partitioning ratios and MTAU9937A binding affinities). It should be noted that the extent of target engagement required for clinical efficacy is unknown.

The dosing frequency will be Q4W, except during the first month, when a dose of MTAU9937A will also be administered to patients on Week 3 to rapidly increase the serum concentrations to those achieved at steady state.

3.3.2 Rationale for Patient Population

The patient selection approach is consistent with the NIA-AA research diagnostic criteria and guidelines for AD as well as with the Qualification Opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use on the use of CSF biomarkers and/or PET-amyloid imaging for enrichment of trials in mild to moderate AD dementia (2012), and U.S. Food and Drug Administration (FDA) draft guidance for early AD (2013). Although the FDA guidance refers to the early stage of AD in which individuals present with MCI, biomarkers of amyloid pathology are expected to add value to patient selection in mAD studies (see Section 3.3.3).

Patients in this study are also required to meet standard research criteria for mAD (according to the NIA-AA research criteria and guidelines for AD; Appendix 3) or pAD (according to the NIA-AA research criteria and guidelines for MCI; Appendix 4). Patients with pAD will present with documented objective evidence of deficit in at least one cognitive domain. Patients with mAD will present with documented deficits in at least two cognitive domains and in functional decline. Overall, the population will have an MMSE of $\geq$20 points and a CDR-GS of between 0.5 and 1.0. The MMSE score provides evidence of mild disease severity, and the CDR-GS score indicates that the patients have noticeable amnestic (pAD) or cognitive and functional deficits (mAD).

To ensure that the patients selected are likely to decline over the length of the study, two approaches have been included. The first is that all patients have to demonstrate amnestic deficits as measured by the Delayed Recall index of the RBANS (see Section 4.5.7.3). The Delayed Recall index of $\leq$85 has been selected, corresponding to one standard deviation below population-based normative data.

The second approach to ensure decline is to verify that there is evidence of prior decline through observations made by clinician or caregiver and recorded on the DVF. Enrollment into this study is subject to adjudication of diagnosis by the Sponsor or

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

3.3.3 Rationale for Amyloid Enrichment

The rationale for selecting amyloid-positive patients in this study is consistent with recently proposed revised diagnostic criteria for AD (McKhann et al. 2011; Dubois et al. 2014). Such biomarker enrichment is important for clinical trials in AD patients because recent results have demonstrated that approximately 20% of patients enrolled in trials on the basis of a clinical diagnosis of AD may not have underlying amyloid pathology as assessed by amyloid PET (Doody et al. 2014). Cerebral amyloid pathology is a required component of AD pathology, and biomarker evidence against such pathology makes an underlying neuropathological diagnosis of AD highly unlikely (Clark et al. 2012).

For enrollment, biomarker evidence of Aβ deposition will be assessed either by decreased CSF $A\beta_{1-42}$ levels (using a pre-specified cutoff point and the Roche Diagnostics Elecsys® β amyloid [1–42] immunoassay) or a centralized visual assessment of the brain by amyloid PET imaging. The Sponsor is proposing to enroll patients on the basis of a positive CSF test or PET scan, because both approaches have been shown to correlate with the "gold standard" of Aβ pathology at autopsy (Shaw et al. 2009; Clark et al. 2011; Le Bastard et al. 2013). Both methods have been widely used in the research community, and patients or physicians in the study and in clinical practice generally may not have access to both methods.

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

3.3.4 Rationale for Requiring Caregiver Participation

Patients with AD generally require supervision or assistance in their daily activities and may lack the insight necessary to provide accurate reports of their functioning. For this reason, caregivers provide essential information for the endpoints evaluated in AD trials.

A caregiver is defined as a non-paid (i.e., non-health care professional) individual who has frequent and sufficient contact with the patient to be able to provide accurate information as to the patient's cognitive and functional abilities.

3.3.5 Rationale for Control Group

A placebo dose group will be used as a concurrent control in the double-blind treatment period of this study. The placebo-control group will help to establish a baseline safety profile, help to identify any adverse events that may be non–study drug related, and serve as a comparison group for efficacy measures in the double-blind treatment period of the study.

3.3.6 Rationale for Pharmacokinetic Sampling

A sparse sampling schedule is being used to minimize patient burden and yet provide an adequate characterization of the population PK profile of MTAU9937A. The PK data may be compared with available data from other MTAU9937A studies and may be used to assess exposure-response relationships for relevant imaging, CSF, plasma PD biomarkers, ECG, and efficacy and safety outcomes in patients with pAD to mAD, as appropriate.

3.3.7 Rationale for Use of Clinician and Observer Reported Outcome Assessments

COAs provide an understanding of the effect a treatment has on a patient. A variety of observer (caregiver) and clinician reported outcomes will be collected to characterize the efficacy and clinical profile of study treatment. The primary outcome, CDR-SB, is a validated instrument that has been widely used in assessing AD. Additional observer (caregiver) and clinician reported outcomes will be used to evaluate patient cognition, function, and behavior, as well as health resource usage during the course of the study. Site staff will be provided with a standardized rater-training program to certify them to administer the COAs identified in this protocol.

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

3.3.8 Rationale for Use of Investigational Tau Radioligand [^{18}F]GTP1

Tau pathology is a required finding in autopsy-confirmed AD. Patients in this study will have the option of biomarker measurements of tau in CSF or measurement of tau with the investigational PET radioligand [^{18}F]GTP1 (or both). Tau measurements will be collected at baseline but will not serve as an eligibility criterion for patient enrichment because correlations between these measurements and underlying pathology are not yet sufficiently understood. Tau imaging using the investigational [^{18}F]GTP1 PET radioligand has been incorporated in this study because it provides an opportunity to

evaluate the relationship between baseline levels and distribution of tau pathology, and response to the investigational anti-tau therapy. Use of [^{18}F]GTP1 PET has unique advantages, a favorable safety profile to date (see Section 1.3.1), and the potential to inform the relationship between spatial distribution of tau pathology, cognitive function, and disease progression.

3.3.9 Rationale for Biomarker Assessments

Biomarker assessments will be used to verify amyloid-positivity for enrichment (see Section 3.3.3), demonstrate evidence of the biologic activity of MTAU9937A in patients, identify biomarkers that may be predictive of response to MTAU9937A, define PK and PD relationships, advance the understanding of the mechanism of action of MTAU9937A in patients, support selection of a recommended dosing regimen, and increase the knowledge and understanding of disease biology.

Blood samples will be collected at baseline for DNA extraction to enable analysis using methods such as whole genome sequencing (WGS) to identify common and rare genetic variants that may be predictive of response to study drug, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, or can increase the knowledge and understanding of disease biology.

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

4. MATERIALS AND METHODS

4.1 PATIENTS

This study has enrolled 457 male and female patients with pAD to mAD, between the ages of 50 and 80 years, at *97* investigative sites located in North America, Europe, and the Asia-Pacific region.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form by the patient (co-signed by the patient's legally authorized representative, if required by the local regulations, guidelines, and independent ethics committee [EC] or Institutional Review Board [IRB])

  Patients should be judged by the investigator to be lucid and oriented when giving the informed consent.
- Age between 50 and 80 years, inclusive, at time of signing Informed Consent Form

- NIA-AA core clinical criteria for probable AD dementia (see Appendix 3; McKhann et al. 2011) or pAD (consistent with the NIA-AA diagnostic criteria and guidelines for MCI; Appendix 4; Albert et al. 2011)
- Evidence of the AD pathological process, by a positive amyloid assessment either on CSF $A\beta_{1-42}$ as measured on Elecsys β-Amyloid(1–42) Test System OR amyloid PET scan by visual read by the core/central PET vendor as specified in the Imaging Review Charter

  If a patient is amyloid negative based on CSF assessment, they may undergo an amyloid PET scan during screening to potentially be enrolled. The patient may undergo an LP for CSF assessment or an amyloid PET scan only one time each during screening.

  If a patient is amyloid negative based on an amyloid PET scan, they may undergo an LP for CSF assessment during screening to potentially be enrolled. The patient may undergo an LP for CSF assessment or an amyloid PET scan only one time each during screening.

  Under certain circumstances, a previously acquired amyloid PET scan may be used for study inclusion (see Section 4.5.8). If the previously acquired amyloid PET scan is considered valid and is read negative by the core/central PET vendor, the patient may undergo CSF assessment to potentially enrollment, but the patient may not undergo an additional amyloid PET scan for enrollment.
- mAD symptomatology, as defined by a screening MMSE score of $\geq$20 points and CDR-GS of 0.5 or 1
- Abnormal memory function at screening as demonstrated by an RBANS Delayed Recall Index $\leq$ 85
- If the patient is receiving non-investigational AD medications, the dosing regimen must have been stable for 2 months prior to *the start of* screening. There should be no a priori intent to initiate, discontinue, or alter the dose of any AD therapy for the duration of the study. However, following the initiation of study drug, standard-of-care symptomatic medications for AD may be initiated, dose adjusted, or discontinued as deemed clinically appropriate.
- Inclusion is subject to review of clinical criteria at screening (via the DVF)
- Availability of a person (referred to as the “caregiver” throughout this protocol) who in the investigator's judgment:

  Has frequent and sufficient contact with the patient to be able to provide accurate information regarding the patient’s cognitive and functional abilities, agrees to provide information at clinic visits (which require partner input for scale completion), signs the necessary consent form, and has sufficient cognitive capacity to accurately report upon the patient’s behavior and cognitive and functional abilities

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

Every effort should be made to have the same caregiver participate throughout the duration of the study for completing the designated caregiver COAs

- Fluency in the language of the tests administered at the study site
- Completion of at least 6 years of formal education after the age of 5 years
- Willingness and ability to complete all aspects of the study (including MRI, LP [if applicable], clinical genotyping, and PET imaging [if applicable])

  The patient should be capable of completing study procedures either alone or with the help of caregiver(s).

- Adequate visual and auditory acuity, in the investigator's judgment, to perform the neuropsychological testing (eye glasses and hearing aids are permitted)
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use of contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for 9 weeks after the last dose of study drug or 4 days after the last dose of [^{18}F]GTP1 or an amyloid radioligand, whichever is longer

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

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

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

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

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 9 weeks after the last dose of study drug or 4 days after the last dose of [^{18}F]GTP1 or an amyloid radioligand, whichever is longer, to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

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

4.1.2 Exclusion Criteria

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

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 9 weeks after the last dose of study drug or 4 days after the last dose of [^{18}F]GTP1 or an amyloid radioligand, whichever is longer

  Women of childbearing potential must have a negative serum pregnancy test result during screening and a negative urine pregnancy test result each day of dosing or of PET imaging prior to administration of study drug or radioligand.

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

- A patient must be able to undergo either PET imaging or lumbar dural puncture, or both, and patients with contraindications to both procedures are ineligible.

  For patients undergoing PET imaging: Planned, or recent (within 12 months prior to screening) exposure to ionizing radiation that in combination with the planned administrations of [^{18}F]GTP1 or an amyloid radioligand would result in a cumulative exposure that exceeds recommended local guidelines

  For patients undergoing LP: Contraindication to lumbar dural puncture, including coagulopathy, concomitant anticoagulation (except for a platelet inhibitor such as aspirin or clopidogrel), thrombocytopenia, prior lumbar spinal surgery, significant deformity of the lumbosacral region, or other factor that precludes safe LP in the opinion of the investigator

- Body mass index >40

- Hospitalization during the 4 weeks prior to screening

  In regions where hospitalization status can be classified as observational or an inpatient admission, this exclusion criterion specifically refers to an inpatient admission.

- Planned procedure or surgery during the study that in the investigator's opinion would affect cognitive assessments or otherwise interfere with compliance with the protocol

- Residence in a skilled nursing facility such as a convalescent home or long-term care facility, except if current residence is in a section of the facility where no assistance is provided for basic activities of daily living (ADL)

  Patients who subsequently 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 caregiver who meets the minimum requirement.

- Blood transfusion within 8 weeks prior to screening or planned transfusion during the study

- Poor peripheral venous access
- Any serious medical condition or abnormality in clinical laboratory tests that remains abnormal on retest and, in the investigator's judgment, precludes the patient's safe participation in and completion of the study, or bias the assessment of the clinical or mental status of the participant to a significant degree. Including, but not limited to:

    Severe chronic kidney disease (Stage 4 or 5, according to National Kidney Foundation guidelines)

    Hypertension not stably controlled by current medication (e.g., sustained systolic blood pressure > 160 mmHg or diastolic blood pressure > 95 mmHg)

    Diabetes not stably controlled by current medication (e.g., hemoglobin A1c $>$ 8%, or any history of clinically significant hypoglycemia, hyperosmolar syndrome, ketoacidosis, or other significant complication of diabetes within 2 years before screening)

    Heart failure (e.g., New York Heart Association Class II or higher)

    Clinically significant, abnormal ECG at screening (e.g., evidence of significant conduction blockade, or evidence of prior myocardial infarction, unless associated with a known myocardial infarction more than 2 years before screening)
- History of cancer, except as follows:

    If considered to be cured

    An appropriately treated carcinoma in situ of the cervix or Stage I uterine cancer

    If there has been no significant clinical progression during the past 5 years, with no active anti-cancer therapy or radiotherapy and, in the opinion of the investigator, is not likely to progress or require treatment in the ensuing 5 years

    Prostate cancer or basal cell carcinoma, where there has been no significant progression over the previous 2 years
- QT interval corrected using Fridericia's formula (QTcF) $>$ 470 ms in females and > 450 ms in males, demonstrated by at least two ECGs $>$ 30 minutes apart
- Abnormal screening thyroid function tests or tests that remain abnormal on retest or require a new treatment or an adjustment of current treatment

    Abnormal screening thyroid function tests are defined as a thyroid-stimulating hormone (TSH) level outside the normal range and either a free thyroxine (T4) or a total T4 level outside the normal range.

    A patient may be rescreened if there is no improvement in cognition in the investigator's judgment after 2 months of adequate treatment for thyroid function.

- Screening folic acid or vitamin B12 levels that are sufficiently low or remain low on retest such that deficiency requires initiation or alteration of treatment and/or may be contributing to cognitive impairment

    A patient may be rescreened if there is no improvement in cognition after 2 months of adequate treatment for folic acid or vitamin B12 deficiency.

Cerebrovascular/Neurologic/Psychiatric

Patients who meet any of the following cerebrovascular/neurologic/psychiatric criteria will be excluded from study entry:

- History of seizures, with the exception of childhood febrile seizures or other remote, non-recurrent seizure
- History of prior traumatic brain injury graded as moderate or severe, defined as a head injury resulting in loss of consciousness lasting 30 minutes or longer, an initial Glasgow Coma Scale of 12 or worse at presentation, posttraumatic amnesia or confusion lasting 24 hours or longer, or any associated abnormal brain imaging finding at presentation
- Any evidence of a condition other than AD that may affect cognition, including but not limited to, dementia with Lewy bodies, vascular dementia, Parkinson's disease, corticobasal degeneration, Creutzfeldt-Jakob disease, progressive supranuclear palsy, frontotemporal degeneration, Huntington's disease, normal pressure hydrocephalus, hypoxia, severe sleep apnea or other chronic sleep disturbance, or baseline intellectual disability
- History of schizophrenia, schizoaffective disorder, major depression, or bipolar disorder

    A history of major depression is acceptable if patient has had no episode within the past year, is considered in remission, or depression is controlled by treatment.

- At risk of suicide in the opinion of the investigator
- Substance abuse meeting criteria for alcohol, cannabis, phencyclidine, other hallucinogen, inhalant, opioid, sedative, hypnotic, anxiolytic, or stimulant use disorder of any severity (per the Diagnostic and Statistical Manual of Mental Disorders, Version 5) within the past 2 years

    Investigators may elect to obtain a urine drug screen if clinically indicated.

- History or presence of clinically evident vascular disease potentially affecting the brain (e.g., clinically significant carotid, vertebral stenosis, or plaque; aortic aneurysm; intracranial aneurysm; cerebral hemorrhage; arteriovenous malformation) that, in the opinion of the investigator, has the potential to affect cognitive function
- History or presence of any stroke with clinical symptoms within the past 2 years, or documented history within the last 6 months of an acute event consistent, in the opinion of the investigator, with a transient ischemic attack

- History of cerebral amyloid angiopathy or MRI evidence of > 6 microhemorrhages, any macrohemorrhage, or superficial siderosis comprising more than one region or a single region > 1 cm
- History or presence of intracranial tumor that is clinically relevant (e.g., glioma, cerebral metastasis) in the opinion of the investigator
- Presence of infections that affect brain function or history of infections that resulted in neurologic sequelae (e.g., HIV, syphilis, neuroborreliosis, viral or bacterial meningitis/encephalitis)
- History or presence of central nervous system or systemic autoimmune disorders potentially causing progressive neurologic disease with associated cognitive deficits (e.g., multiple sclerosis, lupus erythematosus, antiphospholipid antibody syndrome, Behçet disease)
- MRI evidence of 1) more than two lacunar infarcts, 2) any territorial infarct > 1 cm^3, or 3) significant fluid attenuated inversion recovery hyperintense lesions in the cerebral deep white matter corresponding to a Fazekas deep white matter score of 3 or that otherwise may, in the investigator's opinion, contribute to cognitive dysfunction

Infections and Immune Disorders

Patients who meet any of the following infections and immune disorders criteria will be excluded from study entry:

- Systemically, clinically significantly immunocompromised patients, owing to continuing effects of immune-suppressing medication
- Positive for hepatitis C virus (HCV) antibody at screening
- Positive for hepatitis B surface antigen (HBsAg) at screening
- Positive for HIV antibody at screening
- Serious infection requiring oral or IV antibiotics within 30 days prior to screening
- Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins

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

- Use of any experimental therapy within 90 days or 5 half-lives prior to screening, whichever is greater
- Use of any passive immunotherapy (immunoglobulin) against tau, except use of MTAU9937A in Genentech Study GN39058, as long as the last dose was at least 90 days prior to screening.
- Use of any passive immunotherapy (immunoglobulin) against Aβ, unless the last dose was at least 1 year prior to screening.

- Use of any active immunotherapy (vaccine) that is under evaluation to prevent or postpone cognitive decline
- *Investigational* biologic therapy *(e.g., therapeutic proteins, monoclonal antibodies, or other* active or passive immunotherapy*)* within 1 year of screening*,* or any expectation to require *additional investigational* biologic therapy for the duration of the trial
- Any previous treatment with medications specifically intended to treat Parkinsonian symptoms or any other neurodegenerative disorder within 1 year of screening

  Certain medications are acceptable if the patient is taking the medicine for a non-neurodegenerative disorder, such as restless leg disorder (e.g., pramipexole).
- Systemic immunosuppressive therapy within 12 months of screening through the entire study period

  Short courses (≤2 weeks) of high-dose corticosteroid therapy are permitted. Chronic corticosteroid therapy (>2 weeks) is permitted as long as the dose is <7.5 mg/day prednisolone equivalent and the condition being treated is not expected to deteriorate significantly during the study period.
- Typical antipsychotic or neuroleptic medication within 6 months of screening, except as brief treatment for a non-psychiatric indication (e.g., emesis)
- Daily treatment with any of the following classes of medication, except for intermittent short-term use, which is permitted except within 2 days or 5 half-lives (whichever is longer) prior to any COA. The investigator should contact the Medical Monitor if there are questions regarding permitted medications.

  Atypical antipsychotics

  Opiates or opioids (including long-acting opioid medication)

  Benzodiazepines, barbiturates, or hypnotics

  Any medication with clinically significant centrally-acting antihistamine or anticholinergic activity (i.e., those medications with significant levels of blood-brain barrier penetration that are likely to affect cognition and/or behavior)
- Stimulant medications (amphetamine, methylphenidate preparations, or modafinil), unless the dose has been stable within the 6 months prior to screening and is expected to be stable throughout the study

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Patients will be randomly assigned to one of three active, IV dose arms (1500, 4500, or 8100 mg MTAU9937A) or to an IV placebo dose arm in a 2:3:2:3 (1500mg:4500 mg: 8100 mg:placebo) ratio. Randomization of patients will be managed by a central interactive voice or Web-based response system (IxRS) vendor using stratified permuted block randomization. The randomization will be stratified by dementia status (pAD vs. mAD) and *APOE* status (ApoE4+ vs. ApoE4−).

Patients, study site personnel who will evaluate patient status, contract research organization (CRO) personnel who will review CRFs, other Sponsor agents (with the exception of the IxRS vendor), and the Sponsor will remain blinded to treatment assignment. The unblinded site pharmacist and the unblinded CRO monitor will be unblinded to treatment assignment.

The iDMC and independent data coordinating center vendor will be unblinded to treatment assignment.

Although PK samples must be collected from participants assigned to placebo to maintain the blinding of treatment assignment, PK assay results for the placebo participants are generally not needed for the safe conduct or proper interpretation of this trial. Laboratory personnel responsible for performing PK assays will be unblinded to participants' treatment assignments to identify appropriate PK samples to be analyzed. Samples from participants assigned to the placebo arm will not be analyzed except by request (e.g., to evaluate a possible error in dosing).

If unblinding is necessary for immediate patient management (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations. If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any non-emergency unblinding. The investigator will be able to break the treatment code by contacting the IxRS.

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 5.7) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

4.3 STUDY TREATMENTS RELEVANT TO THE STUDY DESIGN

MTAU9937A is an investigational medicinal product (IMP) in this study. Depending on local classification, the [^{18}F]GTP1 tau PET radioligand and/or the amyloid PET radioligand(s) may be considered non-investigational medicinal products (NIMPs) or IMPs. Refer to the Amyloid Imaging Technical Operations Manual for a list of amyloid PET radioligands allowed in this study.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 MTAU9937A and Placebo

MTAU9937A will be supplied by the Sponsor as a sterile liquid in 20-mL glass vials. For information on the formulation and handling of MTAU9937A, see the pharmacy manual and the MTAU9937A Investigator's Brochure.

4.3.1.2 [^{18}F]GTP1 Tau PET Radioligand

[^{18}F]GTP1 will be provided under contract with a PET imaging vendor in accordance with approved national and/or local standards. [^{18}F]GTP1 will be supplied as a sterile non-pyrogenic solution in sterile borosilicate glass vials with gray butyl septa and aluminum ring seals. The vial is contained within an outer lead or tungsten shield ("pig") to protect from gamma radiation. The final product bears a label with the following items: total activity (mCi), volume (mL), strength (mCi/mL), calibration date and time, batch number, study identification, and shelf life. For information on the formulation and handling of [^{18}F]GTP1, see the [^{18}F]GTP1 Investigator's Brochure and the [^{18}F]GTP1 PET Imaging Technical Operations Manual.

4.3.1.3 Amyloid PET Radioligands

Appropriate amyloid PET radioligands will be provided under contract with a PET imaging vendor and/or PET radioligand producers in accordance with approved national and/or local standards. Refer to the local labeling instructions or, depending on locality, the Investigator's Brochures, for details on packaging, formulation, and handling of the amyloid PET radioligands. Depending on locality, additional information may also be found in the local labeling information or the Investigator's Brochure for the particular amyloid PET radioligand being used.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.1.

Any overdose or incorrect administration of MTAU9937A or [^{18}F]GTP1 or an amyloid radioligand (if they are considered IMPs) should be noted on the Study Drug Administration eCRF. Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.3.

4.3.2.1 MTAU9937A and Placebo

MTAU9937A will be prepared and diluted into 100-mL IV bags according to the pharmacy manual, and infusions will be administered per the instructions outlined in Table 2 and the pharmacy manual.

Table 2 Administration of First and Subsequent Infusions of MTAU9937A

First Infusion	Subsequent Infusions
• Begin infusion at an initial rate of 0.5 mL/min (30 mL/hr). • If no infusion-related or hypersensitivity reaction occurs during the first 30 minutes, then increase the rate to 1.0 mL/min (60 mL/hr). • If no infusion-related or hypersensitivity reaction occurs during the subsequent 30 minutes, then increase the rate to 3.0 mL/min (180 mL/hr) • If a reaction develops, stop or slow the infusion. Administer medications and supportive care in accordance with institutional guidelines. The patient should be monitored until all infusion-related adverse events are Grade 1 or are resolved. If the reaction resolves, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time that the reaction occurred). If the reaction recurs after resumption of the infusion, then stop the infusion. For patients who experience serious or severe hypersensitivity or hypersensitivity-like reactions (e.g., hypotension, mucosal involvement), the investigator must discuss with the Medical Monitor whether to continue study drug treatment.	• If the participant experienced an infusion-related or hypersensitivity reaction during the prior infusion, begin infusion at an initial rate of 0.5 mL/min and follow instructions for first infusion. • If the participant tolerated the prior infusion well (defined by an absence of Grade 2 reactions during a final infusion rate of 3.0 mL/min), begin infusion at a rate of 3.0 mL/min. • If a reaction develops, stop or slow the infusion. Administer medications and supportive care in accordance with institutional guidelines. The patient should be monitored until all infusion-related adverse events are Grade 1 or are resolved. If the reaction resolves, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time that the reaction occurred). If the reaction recurs after resumption of the infusion, then stop the infusion. For patients who experience serious or severe hypersensitivity or hypersensitivity-like reactions (e.g., hypotension, mucosal involvement), the investigator must discuss with the Medical Monitor whether to continue study drug treatment.

4.3.2.2 [^{18}F]GTP1 Tau PET Radioligand

Patients who undergo tau PET imaging will receive [^{18}F]GTP1 and undergo a PET scan on multiple occasions as described in the schedule of activities in Appendix 1 and Appendix 2. Refer to the [^{18}F]GTP1 PET Imaging Technical Operations Manual for details on the use of [^{18}F]GTP1.

4.3.2.3 Amyloid PET Radioligands

All patients enrolled using amyloid PET evaluation will be assessed by PET imaging using an appropriate amyloid PET radioligand. Refer to the Amyloid Imaging Technical Operations Manual for details on the use of the amyloid PET radioligands.

4.3.3 Investigational Medicinal Product Accountability

IMPs required for completion of this study (MTAU9937A or placebo) and radiotracers (which may be IMPs or NIMPs) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs, using the

appropriate documentation mechanism (system or paper form), to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or will be returned to the Sponsor with the appropriate documentation. The site's method of MTAU9937A/placebo destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any MTAU9937A/placebo is destroyed, and MTAU9937A/placebo destruction must be documented on the appropriate form. Radioligands will be disposed of or returned according to instructions provided by the PET imaging vendor.

Accurate records of all study treatments (received at, dispensed from, returned to, and disposed of by the study site should be recorded on the applicable Drug Inventory or Dispensing Logs.

4.3.4 Continued Access to MTAU9937A

Currently, the Sponsor (Genentech, a member of the Roche Group) does not have any plans to provide Sponsor study drug (MTAU9937A) or any other study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing MTAU9937A in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:

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

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from *3 months* prior to *the start of* screening until the final study visit. However, any agent that targets Aβ used by the patient at any time during their life is also considered to be a concomitant therapy. All such medications should be reported to the investigator and recorded on the appropriate Concomitant Medications eCRF.

4.4.1 Permitted Therapy

All participants who use concomitant therapies should continue to use those therapies, unless they conflict with the inclusion or exclusion criteria as stated in Sections 4.1.1 and 4.1.2.

Non-investigational therapies for AD are permissible, provided that the dosing regimen has been stable for 2 months prior to screening. At the time of enrollment, there should be no a priori intent to initiate, discontinue, or alter the dose of any AD therapy for the duration of the study. However, following the initiation of study drug, standard-of-care symptomatic medications for AD may be initiated, dose adjusted, or discontinued as deemed clinically appropriate.

4.4.2 Cautionary Therapy

4.4.2.1 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies may be used during the study at the discretion of the investigator.

4.4.3 Prohibited Therapy

Refer to the exclusion criteria (Section 4.1.2) for a list of prohibited therapies and exceptions.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1 and Appendix 2. All activities must be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and *available* local laboratory test values are acceptable.

4.5.1 Informed Consent Forms and Screening Log

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

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

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures); reproductive status; smoking history; and use of alcohol and drugs of abuse; and recent history (5 years) of non-elective hospitalizations, pneumonia or cardiovascular events, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within *3 months* prior to initiation of screening until the final study visit will be recorded. Any agent that targets Aβ used by the patient at any time during their life (any time before initiation of screening and while on study) will also be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, self-reported race/ethnicity, and years of education. Demographic data will be collected for both the patient and the caregiver.

As this study is being conducted in multiple geographic regions, it is likely that patients of different ethnic origins will be enrolled in the study. Although there is currently no indication that MTAU9937A is metabolized or eliminated differently or that the treatment effect would be different in patients with different ethnic origins, collecting this information (where permitted by local regulations) is essential to adequately evaluate the results of this study (e.g., possible differences in PK exposure [concentration of the drug in the blood] or treatment effect).

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, respiratory, and gastrointestinal systems. In addition, the musculoskeletal and genitourinary systems should be examined as clinically indicated. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Neurological Examinations

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

4.5.5 Lumbar Puncture

For patients consenting to LP, the LP procedure should be performed according to standard procedures at the study site using sterile technique and an atraumatic needle. See the laboratory manual for details regarding the collection, processing, and storage of CSF.

4.5.6 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

The same arm should be used for all blood pressure measurements. Pulse rate and blood pressure should not be measured unless 15 minutes have passed since the last blood draw. Vital sign assessments should be performed just prior to study drug administration.

4.5.7 Clinical Outcome Assessments

The COAs listed in Table 3 will be administered to all patients and/or caregivers enrolled in this study. Clinicians/raters (but not caregivers or patients) will use an electronic device to capture COA data. COA data from the electronic device will be transmitted to a centralized database maintained by the electronic device vendor. The C-SSRS will be used to monitor safety (as described below). All other COAs will only be used as assessments of treatment efficacy.

Table 3 Clinical Outcome Assessments

Clinical Outcome Assessments	Concept
Mini-Mental State Examination (MMSE)	Cognition
Clinical Dementia Rating Scale (CDR)	Cognition and Function
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)	Cognition
Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog 13)	Cognition
Amsterdam Instrumental Activity of Daily Living Questionnaire (iADL)	Function
Alzheimer's Disease Cooperative Study Group–Activities of Daily Living Inventory (ADCS-ADL)	Function
Alzheimer's Disease Event Inventory (ADEI)	Significant events
Resource Utilization in Dementia–Lite (RUD-lite)	Resource utilization
Columbia-Suicide Severity Rating Scale (C-SSRS)	Suicidality
Diagnostic Classification	Diagnosis
Caregiver Global Impression of Change Scales for Alzheimer's disease (CaGI-Alz)	Cognition and Function

The questionnaires, translated into the local language as required, will be completed in their entirety at specified timepoints during the study. To ensure instrument validity and that data standards meet health authority requirements, questionnaires will be administered before the patient, clinician, or caregiver receives any information regarding disease status, prior to the performance of non-COA assessments and administration of study drug or radioligand, unless otherwise specified.

The COA scales and assessments for this study will be provided unless otherwise specified. Whenever possible, there should be consistency in the rater and caregiver

who complete the scales for each patient throughout the duration of the study. Potential raters should be designated at each site and will receive training and be approved by the rating-scale vendor prior to being allowed to administer any cognitive assessments/ rating scales in the study. Administration of cognitive assessments/rating scales (i.e., the COAs) will be done in accordance with instructions provided in the GN39763 COA Manual and the training/documentation provided by the rating-scale vendor.

In addition, given that the primary outcome measure in this study involves subjective judgment, the adequacy of patient interviews and ratings will be monitored by an endpoint reliability program administered by the rating-scale vendor; this is considered to be an essential part of good research methodology. Prior studies have clearly demonstrated that the failure to adequately monitor such ratings can substantially increase the risks of failed trials (Becker and Greig 2008; Kobak 2010).

Please see the GN39763 COA Manual for instructions on COA administration order, specification of list versions to use at each visit, rater roles, restrictions on raters, and additional details on COA administration and the endpoint reliability program.

4.5.7.1 Mini-Mental State Examination

The MMSE is a brief clinical cognitive examination commonly used to screen for dementia and other cognitive deficits (Folstein et al. 1975), which has a total score of 0–30. The MMSE will be administered to patients at screening to determine eligibility for the trial and at other timepoints postbaseline.

4.5.7.2 Clinical Dementia Rating Scale

The CDR (Morris 1993) instrument is a semi-structured interview that yields five degrees of impairment in performance for each of six categories of cognitively based functioning: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The CDR interview is administered to both the patient with AD and their caregiver informant. The ratings of degree of impairment obtained for each of the six categories of function (the six “boxes”) are synthesized into one global rating of dementia (range, 0–3). A more refined measure of impairment is available by using the Sum of Boxes (CDR-SB). Reliability and validity have been established, as has high inter-rater reliability. This will be used as a global assessment of severity of dementia.

4.5.7.3 Repeatable Battery for the Assessment of Neuropsychological Status

The RBANS is a validated neuropsychological assessment has been shown to be a useful tool in both clinical and research settings. The RBANS consists of ten subtests that are combined to provide five indices, one for each of the five domains tested (immediate memory, visuospatial/constructional, language, attention, and delayed memory) (Randolph et al. 1998). Extensive normative values are provided in the testing manuals.

The RBANS was initially developed as an assessment tool for dementia and has been validated in a number of studies of dementia and MCI (Kotani et al. 2006). The RBANS has also been related to functional limitations in patients with dementia and MCI (Freilich and Hyer 2007; Badenes Guia et al. 2008; Hobson et al, 2010). More recently, the diagnostic accuracy of the RBANS has been shown to adequately detect cognitive impairment associated with AD (Duff et al. 2008). Although several studies have used the RBANS as a tool to examine cognitive dysfunction, there remains little information regarding the diagnostic accuracy of the RBANS and its ability to detect milder deficits in cognition in the elderly. The RBANS is administered to the patients.

4.5.7.4 Alzheimer's Disease Assessment Scale–Cognitive Subscale

The Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) is the most frequently used scale to assess cognition in clinical trials for mild to moderate AD (Rozzini et al. 2007; Connor and Sabbagh 2008; Ihl et al. 2012). The modified version will be used; which has 13 items (ADAS-Cog 13). This version includes the addition of delayed word recall and number cancellation, as well as use of only 1 trial for word recognition. This is the version used in the Alzheimer's Disease Neuroimaging Initiative protocol (2013). The ADAS-Cog13 is administered to the patient. Equivalent alternate forms of the word recall, word recognition, and number cancellation subtests will be used in successive test administrations.

4.5.7.5 Amsterdam Instrumental Activity of Daily Living Questionnaire

The Amsterdam iADL questionnaire (Sikkes et al. 2013) is an informant-based instrument for measuring iADL problems in patients with dementia. This instrument consists of 70 items, scored on a 5-point scale, that uses item response theory for scoring. Items presented to the informant are tailored to responses to earlier items; thus each administration of the Amsterdam iADL may consist of less than the total of 70 items. The Amsterdam iADL has been shown to possess good content validity, high internal consistency, good test-retest reliability, and good construct validity (Sikkes et al. 2013).

4.5.7.6 Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory

The Alzheimer's Disease Cooperative Study Group–Activities of Daily Living Inventory (ADCS-ADL; Galasko et al. 1997) is the scale most widely used to assess functional outcome in patients with AD (Vellas et al. 2008). The ADCS-ADL is administered to caregivers and covers both basic ADL (e.g., eating and toileting) and more complex ADL or instrumental ADL (e.g., using the telephone, managing finances, preparing a meal).

4.5.7.7 Alzheimer's Disease Event Inventory

The Alzheimer's Disease Event Inventory is an informant-based instrument for collecting information on important events that occur in the lives of a patient and their caregivers during a clinical trial. The Event Inventory was developed at Genentech.

4.5.7.8 Resource Utilization in Dementia–Lite Questionnaire

The Resource Utilization in Dementia (RUD)-Lite is an instrument administered to caregivers to assess health resource use by patients (Wimo and Winblad 2008). The RUD-Lite comprises 26 questions that evaluate informal time a caregiver spends caring for a patient and patient's work status and use of social and health services including respite care, day care, nursing facility use, and hospitalization (Wimo and Winblad 2008).

4.5.7.9 Columbia-Suicide Severity Rating Scale

The C-SSRS is an interview-based instrument used to assess baseline incidence of suicidal ideation and behavior and to prospectively assess suicidal ideation and behavior at postbaseline visits. Postbaseline assessments will assess suicidal ideation and behavior since the previous visit. The C-SSRS will be used to monitor safety. It is administered to the patient and measures five subtypes of suicidal ideation and behavior thought by the FDA to be important to capture in a prospective assessment of suicidality (FDA 2012). If any C-SSRS responses are suggestive of an adverse event, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

Patients who are suicidal on the basis of C-SSRS will be referred for appropriate psychiatric evaluation and management as per local clinical practice.

4.5.7.10 Diagnostic Classification

At specified visits, a diagnostic classification should be made using the forms provided by the electronic device vendor.

4.5.7.11 Caregiver Global Impression of Change Scales

The Caregiver Global Impression of Change Scales for Alzheimer's disease (CaGI-Alz) include four items assessing caregivers' perceptions of change in the patient *disease severity*. Caregivers will be asked to rate the *patient's* change *in memory and ADL* since study treatment started and since the previous CaGI-Alz assessment *(e.g., the prior 6 months)*. All items are rated on a 7-point Likert-type scale from 1 (very much improved since treatment started/previous CaGI-Alz assessment) to 7 (very much worsened since treatment started/previous CaGI-Alz assessment). These items will be used as anchors to determine meaningful change on other clinical outcome assessments.

4.5.8 Amyloid and Tau Positron Emission Tomography

Patients who are enrolled using amyloid PET evaluation will be assessed by PET imaging at screening and must have a positive amyloid PET scan by central visual read (see Section 4.1.1). Refer to the study overview (Section 3.1.1) and the inclusion criteria (Section 4.1.1) for details regarding amyloid PET evaluation.

If a prospective participant has received an amyloid PET scan within 12 months before the start of screening as part of their prior medical care, and they have not received prior amyloid immunotherapy, this prior scan may be used to determine eligibility if all of the following requirements are met:

- The prior amyloid PET scan must have been conducted in accordance to the specifications outlined in the appropriate local reference documentation and must pass the quality control procedures established by the core/central PET vendor. If the prior scan does not pass the quality control procedures or cannot be reliably read by the core/central PET vendor, the prior scan is not considered valid.
- Relevant prior data must be the original, raw scan images themselves, not the resulting clinical reading. Images need to be sent to the imaging vendor for central review (see instructions for transferring in the Amyloid Imaging Technical Operations Manual).
- Images must be presented to the study reader(s) in the same format and undifferentiated in any way from images that would result from a newly acquired scan in this study.

The study reader(s) must conduct a new, independent reading of the prior amyloid scan, following the same process as for a newly acquired scan (see the Amyloid Imaging Technical Operations Manual), to determine eligibility. The study reader(s) should not reference any prior reading of a previously acquired scan.

Patients who undergo tau PET imaging will receive [^{18}F]GTP1 and undergo a PET scan on multiple occasions as described in the Schedule of Activities in Appendix 1 and Appendix 2. Refer to the study overview (Section 3.1.1) for details regarding the circumstances when [^{18}F]GTP1 PET scans must be performed. Appendix 1 and Appendix 2 specify when a final [^{18}F]GTP1 PET scan should be performed if a patient discontinues from the study, provided that local radiation limits have not been exceeded.

If occurring at the same visit, amyloid PET or [^{18}F]GTP1 PET scans must be performed after administration of COAs. Only one PET scan should be performed on a given day.

Positron Emission Tomography Imaging Procedures

The Sponsor in conjunction with the CRO will prepare and distribute detailed imaging technical operations manuals for image acquisition, reconstruction procedures, and parameters for each center prior to the start of the study. All imaging data will be transferred to the imaging CRO for quality control and image analysis as documented in the PET Technical Operations Manual or other image transfer instructions.

Detailed methodology, including scanning procedures, is included in the [^{18}F]GTP1 PET Imaging Technical Operations Manual.

4.5.9 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening (performed by a central laboratory). Urine pregnancy tests will be performed at specified subsequent visits (by the study site's local laboratory). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test (performed by a central laboratory).

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (absolute counts of neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): sodium, potassium, chloride, magnesium, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, LDH, gamma glutamyl transpeptidase, lactate dehydrogenase, and creatine kinase. Glomerular filtration rate should also be calculated from creatinine using the Cockcroft-Gault formula.
- Coagulation: INR, aPTT, and PT
- Lipids: cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood). Microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria) should be performed if the dipstick is abnormal.
- Viral serology (at screening only): HIV, HBsAg, total hepatitis B core antibody, and HCV antibody
- Additional analytes (at screening only): glycosylated hemoglobin, B12, *folic acid, TSH*, thyroxine

The following samples will be sent to the Sponsor or a designee for analysis:

- CSF samples for PK analysis (MTAU9937A)
- Serum samples for PK analysis (MTAU9937A)
- Serum samples for immunogenicity analysis (ADAs)
- Blood sample for determination of *APOE4* status
- Blood and CSF samples for exploratory research on biomarkers (see Table 4)
- Blood samples for DNA extraction for WGS and analyses of single nucleotide polymorphisms (SNPs) (see Section 4.5.11)

Exploratory biomarker research may include, but will not be limited to, the biomarkers listed in Table 4.

Table 4 Exploratory Biomarkers

Sample Type	Proposed Biomarkers
Plasma	Markers include, but are not limited to, soluble tau and neurofilament light chain
Cerebrospinal fluid	Markers include, but are not limited to, soluble tau and neurofilament light chain

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

Exploratory biomarker research may include, but will not be limited to, analysis of fluid biomarkers and genetic markers associated with AD, neurodegeneration, and neuro-inflammation. These samples will be used to further the Sponsor's understanding of AD and the response to treatment and may also be used to support the development of biomarker and diagnostic assays.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.12), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Serum samples collected for PK analysis and/or immunogenicity analysis may be used for additional PK and ADA assay development and validation, and additional immunogenicity characterization; these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood samples collected for WGS and SNP (see Section 4.5.11)
- Whole blood, plasma, and CSF samples collected for exploratory biomarker research will be stored 20 years after the study results have been reported

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

Data arising from sample analysis, including data on germline mutations, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of the analyses, data derived from SNP or WGS specimens will generally not be provided to study investigators or patients unless

required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.10 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the Schedule of Activities (see Appendix 1 and Appendix 2), and may be obtained at unscheduled timepoints as indicated.

Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and a large and/or rich meal should be avoided within 3 hours before the ECG recording (a snack or light meal is acceptable). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

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

If at a particular postdose timepoint the mean QTcF is $>$500 ms and/or $>$60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision regarding study drug discontinuation should be made, as described in Section 5.1.3.3. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.5.11 Mandatory Samples for Genetic Analysis

At participating sites, blood samples will be collected for DNA extraction to enable WGS and analysis of SNPs that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, or can increase the knowledge and understanding of disease biology. The blood samples may be sent to one or more laboratories for analysis.

Collection and submission of WGS and SNP samples is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for SNP sampling, this section of the protocol (Section 4.5.11) will not be applicable at that site.

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

Blood samples collected for WGS and SNP analyses 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 Informed Consent Form and applicable laws (e.g., health authority requirements).

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

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

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

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

4.5.12 Optional Samples for Research Biosample Repository

4.5.12.1 Overview of the Research Biosample Repository

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

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

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

4.5.12.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.12) will not be applicable at that site.

4.5.12.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to MTAU9937A, tau, or diseases:

- Leftover whole blood samples
- Leftover plasma samples
- Leftover CSF samples
- Leftover blood sample for DNA extraction

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via WGS, whole exome sequencing (WES), next-generation sequencing, or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS 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. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

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

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

4.5.12.4 Confidentiality

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

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

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

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

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

4.5.12.5 Consent to Participate in the Research Biosample Repository

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

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

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

4.5.12.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their consent at any time for any reason. *After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient.* However, if RBR specimens have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study GN39763 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study GN39763.

If a patient wishes to withdraw consent to the testing of his or her specimens after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

4.5.12.7 Monitoring and Oversight

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

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient’s safety if he or she continues to receive study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Pregnancy

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

Patients will return to the clinic for a treatment discontinuation visit 12 weeks (±7 days) after the last dose of study drug (see Appendix 1 and Appendix 2 for additional details).

4.6.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF, as well as in the site source document. Patients who withdraw from the study will not be replaced.

4.6.3 Study Discontinuation

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

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

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

4.6.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

MTAU9937A is not approved, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with MTAU9937A in completed and ongoing studies. Important potential safety risks for patients receiving MTAU9937A are outlined below. Refer to the MTAU9937A Investigator's Brochure for a complete summary of safety information.

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

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. Ongoing review of unblinded safety will be performed by an iDMC (see Section 3.1.2). External experts may be consulted. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1.1 Potential Risks Associated with MTAU9937A

5.1.1.1 Infusion-Related Reactions or Hypersensitivity

Monoclonal antibodies such as MTAU9937A may be associated with a potential immune response in clinical trials, such as hypersensitivity or hypersensitivity-like reactions, including severe, anaphylactic reactions (see Appendix 5 for precautions). Study sites will be prepared to manage any hypersensitivity or hypersensitivity-like events.

All participants will be monitored for infusion reactions, hypersensitivity, or hypersensitivity-like reactions during the infusion and immediately afterwards (see Section 5.1.3.2 for additional instructions on monitoring and management of infusion reactions).

5.1.1.2 Neuroimaging Abnormalities

The occurrence of imaging abnormalities believed to represent cerebral vasogenic edema and microhemorrhage have been reported in association with the investigational use of immunotherapy targeting the Aβ peptide, possibly by interacting with Aβ deposited in or around blood vessels and eliciting an immune response. Symptoms, when present in association with such imaging abnormalities, have been reported to include headache, worsening cognitive function, alteration of consciousness, seizures, unsteadiness, and vomiting (Salloway et al. 2009; Sperling et al. 2012).

Tau pathology occurs primarily intracellularly in the cytoplasm of diseased neurons (Braak et al. 2006), and soluble extracellular tau is found in the CSF (Blennow and Zetterberg 2009). Unlike Aβ, tau is not known to deposit in vascular structures, and administration of an antibody against the tau protein is not anticipated to cause vasogenic edema or microhemorrhage. Moreover, MTAU9937A has an IgG4 backbone, which is associated with reduced effector function. Nevertheless, in this study, the following will be performed to monitor for potential neuroimaging abnormalities:

- All patients will have an MRI at screening and at several postbaseline timepoints (see Appendix 1 and Appendix 2). *MRI must be performed prior to any dosing on the corresponding study visit and must be read locally in real time for the evaluation of any new, clinically significant abnormality prior to the dose being given. However, if no such abnormalities are identified in the local MRI interpretation, the dose may be given prior to the receipt of the central MRI report. In case of an abnormality identified by the central MRI reading, the investigator should assess the clinical significance of it and proceed as described below.*
- Regardless of severity, all events of a clinically significant *new or worsening* MRI abnormality that occur at any time after receiving study drug are considered to be adverse events of special interest and *must* be reported in an expedited manner.
- All patients will regularly undergo neurologic examinations to evaluate for any neurologic signs or symptoms. In case of findings suggestive of a new, clinically significant central nervous system disturbance or lesion, patients must undergo an MRI examination *as soon as possible*.
- All MRIs will be read *locally* in real time for the evaluation of any clinically significant *new or worsening* abnormality. Study drug will be withheld *at the corresponding study visit* if*, in the investigator's judgment, any clinically significant new or worsening MRI abnormalit*y *(e.g., symptomatic or asymptomatic intracranial tumor, cerebral infarct [lacunar or territorial], cerebral hemorrhage [macrohemorrhage, microhemorrhage, superficial siderosis], vasogenic edema, sulcal effusion) is observed.* Restarting study drug treatment can occur only after discussion with the Medical Monitor.

5.1.1.3 Immunogenicity

MTAU9937A is a pan-tau IgG4 monoclonal antibody engineered to contain Fc mutations (YTE) that enhance binding to FcRn and have been shown to slow peripheral antibody clearance in humans. ADAs to MTAU9937A in humans may be associated with changes in MTAU9937A exposure, reductions in treatment efficacy, or safety findings such as hypersensitivity reactions. There was no evidence of treatment emergent ADA in the ongoing Phase I study (GN39058). Immunogenicity in humans will be evaluated using validated immunoassays and by assessing the incidence of ADAs after treatment relative to their prevalence at baseline. The study site will be prepared to manage any hypersensitivity events.

Refer to Section 5.6 of the MTAU9937A Investigator's Brochure for ADA data from clinical trials.

5.1.2 Potential Risks Associated with [^{18}F]GTP1 and Amyloid PET Radiopharmaceuticals

5.1.2.1 Infusion-Related Reactions

All participants will be monitored for infusion reactions both during the infusion and immediately afterwards. Infusion reactions should be treated as per institutional guidelines. In the event that a participant experiences an infusion-related reaction, the infusion should be halted.

5.1.2.2 Radiation Risk

[^{18}F]GTP1 and amyloid PET radioligands, similar to other radiopharmaceuticals, contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk of cancer. Safe handling of [^{18}F]GTP1 and amyloid PET radioligands should be ensured to protect patients and health care workers from unintentional radiation exposure.

Radiation exposure for [^{18}F]GTP1 doses can be found in the [^{18}F]GTP1 Investigator's Brochure. Radiation exposure for the amyloid tracers can be found in the local labeling instructions or, depending on locality, in the Investigator's Brochures. See the local labeling instructions or, depending on locality, the Investigator's Brochures, in addition to consulting with the local PET imaging center for additional radiation exposure due to potential head CT (attenuation correction) scans acquired in conjunction with PET imaging.

Refer to local guidelines for recommended annual radiation exposure.

5.1.3 Management of Patients Who Experience Specific Adverse Events

5.1.3.1 Treatment Interruption

MTAU9937A or placebo treatment may be temporarily suspended in patients who experience toxicity considered to be related to study drug. If more than two doses of MTAU9937A or placebo have been withheld because of toxicity, the patient should be discontinued from MTAU9937A or placebo, unless resumption of treatment is approved following investigator discussion with the Medical Monitor. MTAU9937A or placebo treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

5.1.3.2 Management Guidelines for Infusion-Related Reactions

In the event that a participant experiences a mild infusion-related reaction, the infusion may be halted. Once the reaction has resolved, the infusion rate will be resumed at half of the most recently used rate (e.g., from 60 mL/hr [1.0 mL/min] to 30 mL/hr [0.5 mL/min]; see Section 4.3.2.1). Patients who experience a moderate-to-severe infusion-related reaction (e.g., fever or chills) should have their infusion stopped immediately and should receive aggressive symptomatic treatment. The patient should be monitored until all

infusion-related adverse events are Grade 1 or are resolved. The infusion should not be restarted before all symptoms have disappeared, and then it should be restarted at half the initial rate. The infusion should not be resumed if there is a second occurrence at the same visit or if the patient experiences any of the following: mucosal tissue involvement, airway compromise, or symptomatic hypotension with systolic blood pressure <90 measured in the supine position. In the case of any serious or severe infusion-related reaction, the investigator must discuss with the Medical Monitor whether to continue study drug treatment (see Section 4.3.2.1 for further details).

For patients who experience a serious or severe hypersensitivity or hypersensitivity-like reaction (e.g., hypotension, mucosal involvement), the investigator must discuss with the Medical Monitor whether to continue study drug treatment (see Section 4.3.2.1 for further details).

5.1.3.3 Management of Increases in QT Interval

Study drug should be discontinued in patients who develop any of the following, unless there is a clear alternative cause for the changes:

- Sustained (at least two ECG measurements >30 minutes apart) QTcF that is >500 ms and >60 ms longer than the baseline value
- Sustained absolute QTcF that is >515 ms
- An episode of torsades de pointes or a new ECG finding of clinical concern

Of note, if there is a new intraventricular conduction block, the increase in QRS complex duration should be subtracted from the QTcF change, because this represents an increase in QTcF unrelated to alterations in repolarization. Also of note, it is not uncommon to record arrhythmias such as non-sustained ventricular tachycardia, supraventricular tachycardia, pauses, or atrial fibrillation in HVs receiving placebo during periods of extended ECG monitoring. Therefore, it is critical that expert cardiology advice be sought to confirm any ECG changes and to ascertain the likelihood of a drug-induced arrhythmia versus the background occurrence of this arrhythmia. In such a situation, saving all available ECG data is highly suggested.

Management of patients with sustained QTcF prolongation should include close monitoring, with ECGs repeated at least hourly until two successive ECGs show resolution of the findings, correction of any electrolyte abnormalities, and possible discontinuation of other concomitant medications that are known to prolong the QT interval. Consultation with a cardiologist or electrophysiologist is recommended, to help in the management of such patients.

In rare circumstances, it may be acceptable to resume study drug, at a lower dose, provided that any ECG abnormalities have resolved and the patient is appropriately monitored. Clinical judgment should be applied.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and Section 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug or [^{18}F]GTP1 or an amyloid radioligand (if considered to be an IMP)
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug or [^{18}F]GTP1 or an amyloid radioligand (if considered to be an IMP)
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

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

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

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

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

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study 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 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug or [^{18}F]GTP1, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug or [^{18}F]GTP1 is suspected.
- Clinically significant MRI abnormalities (see Section 5.1.1.2)
- Severe (Grade $\geq$3) infusion-related reactions

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

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

After informed consent has been obtained but prior to initiation of study drug (MTAU9937A or placebo) or [^{18}F]GTP1 or an amyloid radioligand, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug or [^{18}F]GTP1 or an amyloid radioligand, all adverse events will be reported until 12 weeks after the last dose of study drug or 4 days after the last dose of [^{18}F]GTP1 or an amyloid radioligand, whichever is longer.

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The WHO toxicity grading scale (see Appendix 6) will be used for assessing adverse event severity. Table 5 will be used for assessing severity for adverse events that are not specifically listed in the WHO toxicity grading scale.

Table 5 Adverse Event Severity Grading Scale for Events Not Specifically Listed in WHO Toxicity Grading Scale

Grade	Severity
1	Mild; transient or mild discomfort (<48 hours); no medical intervention or therapy require
2	Moderate; mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required
3	Severe; marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible
4	Life-threatening; extreme limitation in activity; significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

Notes: Developed by the Division of Microbiology and Infectious Diseases.
Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug or [^{18}F]GTP1 or an amyloid radioligand (if [^{18}F]GTP1 or the amyloid radioligand is considered to be an IMP), indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 6):

- Temporal relationship of event onset to the initiation of study drug or [^{18}F]GTP1 or an amyloid radioligand
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug or reintroduction of study drug (as applicable)
- Known association of the event with the study drug, [^{18}F]GTP1 or an amyloid radioligand, or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 6 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug or [^{18}F]GTP1 or an amyloid radioligand on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug or [^{18}F]GTP1 or an amyloid radioligand, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug or [^{18}F]GTP1 or an amyloid radioligand; and/or the adverse event abates or resolves upon discontinuation of the study drug or [^{18}F]GTP1 or an amyloid radioligand or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug or [^{18}F]GTP1 or an amyloid radioligand (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug or [^{18}F]GTP1 or an amyloid radioligand (e.g., cancer diagnosed 2 days after first dose of study drug or [^{18}F]GTP1 or an amyloid radioligand).

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after administration of study drug or [18F]GTP1 or an amyloid radioligand and are judged to be related to study drug infusion or [18F]GTP1 or an amyloid radioligand should be captured as a specific diagnosis (e.g., "infusion-related reaction," "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and a systemic reaction to the same dose of study drug, [18F]GTP1, or an amyloid radioligand infusion, each reaction should be recorded separately on the Adverse Event eCRF with signs and symptoms recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 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, asterixis, and elevated transaminases). However, if a constellation of signs

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

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

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

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

5.3.5.5 Abnormal Laboratory Values

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

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

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

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

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

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

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

5.3.5.6 Abnormal Vital Sign Values

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

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

- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

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

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

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

5.3.5.7 Abnormal Liver Function Tests

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

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

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

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug or [^{18}F]GTP1 or an amyloid radioligand, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of AD.

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

be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

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

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

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of Alzheimer's Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on decline in clinical efficacy measures. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for respite care

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

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

  The patient has not experienced an adverse event

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

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

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

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug or [^{18}F]GTP1 or an amyloid radioligand (if considered to be an IMP) should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

No safety data related to overdosing of MTAU9937A are available.

5.3.5.13 Clinical Outcome Assessment Data

Adverse event reports will not be derived from COA data by the Sponsor, and safety analyses will not be performed using COA data, except for the C-SSRS. However, if any COA responses suggestive of a possible adverse event are identified during site review of the COA data (including the C-SSRS), the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug or [^{18}F]GTP1 or an amyloid radioligand:

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

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

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

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor contact information:

Primary Medical Monitor:	[redacted] M.D. (IQVIA North and Latin America)
Telephone Nos.:	United States: [redacted] International: [redacted]
Secondary Medical Monitor:	[redacted] M.D., Ph.D. (Genentech North America)
Telephone No.:	[redacted]

IQVIA Emergency Medical Contact Telephone Nos.:

+1 973-659-6677 or [redacted] (United States)

Alternate Medical Monitor contact information:

Medical Monitor supporting E.U. sites: [redacted] M.D. (*IQVIA Slovakia*)

Telephone Nos.: *Office:* [redacted]
Mobile: [redacted]

Medical Monitor supporting APAC sites: [redacted], M.D. (*IQVIA* India)

Telephone Nos.: *Office:* [redacted]
Mobile: [redacted]

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

5.4.2.1 Events That Occur prior to Initiation of Study Drug or [^{18}F]GTP1 or an amyloid radioligand

After informed consent has been obtained but prior to initiation of study drug or [^{18}F]GTP1 or an amyloid radioligand, 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), by scanning and emailing the form using the email address provided below:

Email address: *GenentechEDC@IQVIA.com*

5.4.2.2 Events That Occur after Initiation of Study Drug or [^{18}F]GTP1 or an Amyloid Radioligand

After initiation of study drug or [^{18}F]GTP1 or an amyloid radioligand, serious adverse events and adverse events of special interest will be reported until 12 weeks after the last dose of study drug or 4 days after the last dose of [^{18}F]GTP1 or an amyloid radioligand, whichever is longer. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), by scanning and emailing the form using the email address provided in Section 5.4.2.1. 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 > 12 weeks after the last dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 9 weeks after the last dose of study drug or 4 days after the last dose of [^{18}F]GTP1 or an amyloid radioligand, whichever is longer. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), by scanning and emailing the form using the email address provided in Section 5.4.2.1. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a paper Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 9 weeks after the last dose of study drug or 4 days after the last dose of [^{18}F]GTP1 or an amyloid radioligand, whichever is longer. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), by scanning and emailing the form using the email address provided in Section 5.4.2.1. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a paper Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Congenital Anomalies/Birth Defects and Abortions

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or [^{18}F]GTP1 or an amyloid radioligand or the female partner of a male patient exposed to study drug or [^{18}F]GTP1 or an amyloid radioligand should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the

Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). Any abortion should be reported in the same fashion (as the Sponsor considers abortions to be medically significant).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or [^{18}F]GTP1 or an amyloid radioligand or trial-related procedures until a final outcome can be reported.

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

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

5.5.2 Sponsor Follow Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 12 weeks after the last dose of study drug or 4 days after the last dose of [^{18}F]GTP1 or an amyloid radioligand, whichever is longer), if the event is believed to be related to prior study drug or [^{18}F]GTP1 or an amyloid radioligand treatment. *If a patient discontinues the study due to an adverse event after 12 weeks after the final dose of study drug or after 4 days after the final dose of [^{18}F]GTP1 radioligand or an amyloid radioligand, whichever is longer, the adverse event(s) leading to study discontinuation should be reported.* These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

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

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

- MTAU9937A Investigator's Brochure
- GTP1 Investigator's Brochure
- Investigator’s Brochure or Summary of Product Characteristics or US Package Insert for amyloid ligand used, depending on whether the amyloid ligand is considered to be an IMP in the local jurisdiction

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 iDMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The efficacy analyses will be based on the modified intent-to-treat population, which is defined as all randomized patients who receive at least one dose of study drug and have at least one postbaseline primary efficacy CDR-SB measurement. For the efficacy analysis, patients will be grouped according to the treatment assigned at randomization.

The safety analysis will be based on all randomized patients who receive at least one dose of either MTAU9937A or placebo, or GTP1. Patients will be grouped according to MTAU9937A treatment actually received.

- A primary analysis will occur after the last patient has completed the Week 73 assessment.
- A final analysis will occur after the last patient has finished the OLE and completed the Week 169 assessment.

6.1 DETERMINATION OF SAMPLE SIZE

This study *was designed to* enroll approximately 360 patients randomized to one of three active, IV dose arms or to an IV placebo dose arm in a 2:3:2:3 ratio. This sample size provides reasonable precision for estimating a clinically significant treatment effect on CDR-SB scores when MTAU9937A is compared with placebo. Assuming an observed 0.6-point difference in mean CDR-SB decline between the 4500 mg MTAU9937A arm and placebo at Week 73, a standard deviation across patients of 2, and a 25% dropout rate, a 90% confidence interval on the population treatment effect point estimate for the CDR-SB is approximately 0.08–1.12.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue (early discontinuation of treatment or early termination from the study), complete the study (through Week 73), and continue into the OLE will be tabulated by treatment group. Reasons for early discontinuation of treatment or early termination from the study will be listed and summarized by treatment group. Any eligibility criteria exceptions and other major protocol deviations will also be summarized by treatment group.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics such as age, sex, race, *ApoE4* status, and baseline MMSE score will be summarized with means, standard deviations, medians, and ranges for continuous variables and with frequencies and proportions for categorical variables, as appropriate. Summaries will be presented by treatment arm and overall.

6.4 EFFICACY ANALYSES

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is change in CDR-SB score from baseline to Week 73. The difference in mean change from baseline to Week 73 between MTAU9937A- and placebo-treated patients will be estimated using an analysis of covariance model adjusting for *ApoE4* status and baseline clinical status (i.e., prodromal AD vs. mild AD dementia). Confidence intervals as well as least squares estimates will be used to aid in interpretation of study results. Detailed statistical methods will be outlined in the Statistical Analysis Plan (SAP).

6.4.2 Secondary Efficacy Endpoints

The secondary endpoints include the RBANS total score, ADAS-Cog (13-item), Amsterdam iADL, and ADCS-ADL. Secondary efficacy endpoints will be analyzed in the same manner as the primary endpoint.

6.5 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least one dose of either MTAU9937A or placebo, or GTP1, with patients grouped according to treatment arm. Patients will be analyzed according to actual MTAU9937A treatment received.

All adverse events that occur after informed consent is given will be summarized by mapped term, appropriate thesaurus level, and toxicity grade. In addition, all serious adverse events, including deaths and events leading to discontinuation, will be listed separately and summarized.

Laboratory data will be summarized by descriptive statistics by treatment group. In addition, all laboratory abnormalities will be summarized by grade using the WHO grading scale.

Dose-limiting adverse events and adverse events of special interest will be listed and summarized by treatment group.

Vital signs (pulse rate, blood pressure, body temperature, and respiratory rate), weight, and other disease-specific data will be summarized by descriptive statistics by treatment group. Changes from baseline will be summarized by treatment group.

6.6 PHARMACOKINETIC ANALYSES

Individual and mean serum MTAU9937A concentration–time data will be tabulated and plotted by cohort/dose level, and C_{max} and minimal concentration will be reported. Estimates for PK parameters will be tabulated and summarized by descriptive statistics (e.g., mean, standard deviation, minimum, and maximum). Individual and mean MTAU9937A CSF concentration–time data will be tabulated by cohort/dose level. Additional PK analyses will be conducted as appropriate.

6.7 IMMUNOGENICITY ANALYSES

Baseline prevalence and postbaseline incidence of ADA to MTAU9937A will be summarized. ADA response and potential effect of ADA response to relevant clinical safety and activity endpoints will be assessed for evaluable patients.

The immunogenicity analyses will include patients with at least one predose and one postdose ADA assessment, with patients grouped according to treatment arm.

The number and proportion of ADA-positive patients and ADA-negative patients during both the treatment and follow-up period will be summarized by treatment group. Patients are considered to have treatment-emergent ADAs if they are ADA negative at baseline but develop an ADA response following study drug administration, or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 4-fold greater (i.e., $\geq$0.60 titer units) than the titer of the baseline sample. Patients are

considered to be ADA negative if they are ADA negative at baseline and all postbaseline samples are negative or treatment unaffected if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample

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

6.8 BIOMARKER ANALYSES

Exploratory analyses will be conducted to evaluate the effect of MTAU9937A on exploratory biomarkers such as those listed in the Exploratory Biomarker Objective of Section 1.3. Exploratory biomarkers may be analyzed before and after dosing with MTAU9937A to determine the relationship between PK exposure and exploratory biomarker levels. In addition, relationships amongst biomarkers may be assessed.

WGS data will be analyzed in the context of this study and explored in aggregate with data from other studies to increase researcher's understanding of disease pathobiology and guide the development of new therapeutic approaches.

6.9 INTERIM ANALYSES

6.9.1 Optional Interim Analysis

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct an interim efficacy analysis. The rationale for conducting an interim analysis will be on the basis of factors and information external to this study such as new, emergent data from other clinical trials. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

If an interim analysis is conducted, the Sponsor will remain blinded. The interim analysis will be conducted by an external statistical group and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC charter.

The decision to conduct an optional interim analysis, along with the rationale and timing, will be documented in the protocol. Statistical details for the interim analysis will be contained within the Statistical Analysis Plan (SAP). A substantial protocol amendment (in the European Union) or the SAP (other jurisdictions) will be submitted to relevant health authorities, as appropriate, prior to the conduct of the interim analysis. The iDMC charter will also be updated to document potential recommendations the iDMC can make to the Sponsor as a result of this analysis and the iDMC charter will be submitted to relevant health authorities. All documents submitted to health authorities would be simultaneously submitted to the study master file to further document this information appropriately. The Clinical Study Report will also document that such an interim analysis occurred.

If the interim analysis plan allows for early assessment of efficacy, the type I error rate will be controlled to ensure statistical validity is maintained. Specifically, the Lan-DeMets α-spending function that approximates the O'Brien-Fleming boundary will be applied to determine the critical value for stopping for positive efficacy at the interim analysis (DeMets and Lan 1994). Additional criteria for recommending that the study be stopped for positive efficacy may be added to the iDMC charter. If the study continues beyond the interim analysis, the critical value at the final analysis would be adjusted accordingly to maintain the overall type I error rate, per standard Lan-DeMets methodology. The select efficacy endpoints provided to the iDMC as part of ongoing safety review do not enable and are not considered sufficient for a formal interim analysis to assess early efficacy or futility.

If the interim analysis plan allows for early assessment for futility, the threshold for declaring futility will include an assessment of the predictive probability that the primary endpoint will achieve statistical significance. An interim analysis that might lead to stopping the study for futility will not occur before at least 50% of the information has been accumulated for the primary endpoint.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data, imaging data, sample information, and sample analysis data as well as COA data listed in Table 3 (see Section 4.5.7), using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 ELECTRONIC CLINICIAN-REPORTED OUTCOME DATA

Clinicians will use an electronic device to capture ClinRO data. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with FDA regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

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

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in a password-protected, machine-readable format. Sites should extract the data soon as possible after receiving it.

7.4 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.5 USE OF COMPUTERIZED SYSTEMS

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

7.6 RETENTION OF RECORDS

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

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

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

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

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

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

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

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

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

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

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

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures,

prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

This study will be sponsored and managed by Genentech, Inc., a member of the Roche group. The Sponsor will provide clinical operations management, data management, and medical monitoring oversight. A CRO will provide study and site management, medical and site monitoring, along with safety reporting support. Overall procedures for quality assurance of clinical study data are described in the Roche and CRO standard operating procedures.

Globally, 97 sites *have enrolled 457* patients. Randomization and drug distribution will occur through an IxRS system. EDC will be used for data collection.

Central facilities will be used for certain study assessments throughout the study (e.g., COAs, imaging, LP, specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5.

An iDMC will be employed to monitor and evaluate patient safety throughout the study.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

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

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of

the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

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

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

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

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

9.6 PROTOCOL AMENDMENTS

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

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

Assessment	Screening Days −56 to −1 [ii]	Baseline [a]	Double-Blind Treatment Period																				Unplanned Visit [b]	Tx Completion [c]	Tx D/C [c]
Week			1 [a]	3 [d]	5 [d]	9	13	17	21	25	29	33	37	41	45	49	53	57	61	65	69	73			
Dose			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19				
Informed consent	x [e]																								
Medical history, AD history, personal status, and demographics [f]	x																								
Diagnostic verification	x																								
Diagnostic classification							x			x			x			x			x			x			x [g]
MMSE [h]	x	x					x			x			x			x			x			x			x [g]
Event inventory [h]		x					x			x			x			x			x			x			x [g]
CDR [h]	x	x								x						x					x	x			x [i]
RBANS [h]	x	x								x						x						x			x [i]
ADAS-Cog 13 [h]		x								x						x						x			x [i]
Amsterdam iADL [h]		x								x						x						x			x [i]
ADCS-ADL [h]		x								x						x						x			x [i]
RUD-lite [h]		x					x			x			x			x			x			x			x [g]
C-SSRS		x			x		x			x			x			x			x			x		x	x
CaGI-Alz [jj]										*x*						*x*						*x*			
Vital signs [j]	x	x [k]	x	x	x	x	x	x	x	x	x	x	x	x	x	x [k]	x	x	x	x	x	x [k]	x	x	x [k]
Weight	x		x							x						x						x		x	x
Height	x																								
Complete physical examination [l]	x									x						x						x		x	x

Appendix 1
Schedule of Activities (cont.)

Assessment	Screening Days −56 to −1 [ii]	Baseline [a]	Double-Blind Treatment Period																				Unplanned Visit [b]	Tx Completion [f]	Tx D/C [c]
Week			1 [a]	3 [d]	5 [d]	9	13	17	21	25	29	33	37	41	45	49	53	57	61	65	69	73			
Dose			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19				
Limited physical examination [m]			x		x		x						x						x				x		
Neurological examination	x		x		x		x			x			x			x			x			x	x	x	x
MRI [kk]	x					x										x						x			x [i]
Amyloid PET	x [n]																								
[^{18}F]GTP1 PET [o]		x														x						x			x [p]
ECG	x [q]		x [r]		x [r]																	x			x [s]
Hematology [t]	x [q]		x		x					x						x						x			x
Chemistry, lipids, coagulation [u]	x [q]		x		x					x						x						x			x
HbA_{1c}, B12, *folic acid,* TSH thyroxine	x [q]																								
Viral serology [v]	x [q]																								
Pregnancy test [w]	x	x [x]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Urinalysis [y]	x [q]		x							x						x						x			x
Study drug administration			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Serum PK sample [z]			x [aa]	x [bb]	x [bb]	x [bb]	x [bb]	x [bb]				x [bb]				x [bb]				x [bb]		x		x [i]	x [i]
Serum ADA sample [z]			x					x				x				x				x				x [i]	x [i]
Blood sample for *APOE*	x																								
Blood sample for SNPs [cc]		x																							
Blood sample for WGS [dd]		x																							
Blood sample for biomarkers [ee]		x	x [bb]	x	x	x	x	x [bb]				x				x				x		x		x	x [i]

Appendix 1
Schedule of Activities (cont.)

Assessment	Screening Days −56 to −1[ii]	Baseline[a]	Double-Blind Treatment Period																				Unplanned Visit[b]	Tx Completion[c]	Tx D/C[c]
Week			1[a]	3[d]	5[d]	9	13	17	21	25	29	33	37	41	45	49	53	57	61	65	69	73			
Dose			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19				
LP for CSF sample for PK and biomarkers[ff]	x	x														x						x			x[i]
Concomitant medications[gg]	x[hh]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[hh]	x[hh]
Adverse events[hh]	x[hh]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[hh]	x[hh]

[^{18}F]GTP1 = fluorine-18 Genentech tau probe 1; AD=Alzheimer's disease; ADA=anti-drug antibody; ADAS-Cog=Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS-ADL=Alzheimer's Disease Cooperative Study Group–Activities of Daily Living Inventory; CaGI-Alz = Caregiver Global Impression of Change Scales for Alzheimer's disease; C-SSRS=Columbia-Suicide Severity Rating Scale; CDR=Clinical Dementia Rating; COA=clinical outcome assessment; CSF=cerebrospinal fluid; D/C=discontinuation; DVF = Diagnostic Verification Form; eCRF=electronic Case Report Form; HbA_{1c} = glycosylated hemoglobin; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; iADL=Instrumental Activity of Daily Living; LP=lumbar puncture; MMSE=Min-Mental State Examination; MRI=magnetic resonance imaging; OLE=open-label extension; PET=positron emission tomography; PK=pharmacokinetic; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; RUD=Resource Utilization in Dementia; SNP=single nucleotide polymorphism; TSH = thyroid-stimulating hormone; Tx=treatment; WGS=whole genome sequencing.

Notes: All postbaseline study visits must be scheduled in reference to the first dosing day (Week 1/Dose 1 visit). All activities/assessments in a given study visit must be performed within ±5 days of the scheduled visit, unless otherwise specified *(e.g., [^{18}F]GTP1 PET scans)*. On study drug administration visits that span multiple days, study drug administration must occur on the last day. On study drug administration days, all assessments must be performed prior to dosing, unless otherwise specified.

On study drug administration days, pre-infusion laboratory samples should be drawn 0–4 hours before the start of infusion, and post-infusion laboratory samples should be drawn 0–30 minutes after the end of infusion, unless otherwise specified.

Appendix 1
Schedule of Activities (cont.)

[a] The baseline visit must occur after enrollment (randomization) and may be split over multiple visit days; the first and last visit days of the baseline visit must be separated by no more than 14 days from each other (e.g., the baseline visit may start on a Monday and end on the Monday 2 weeks forward). All COA assessments at the baseline visit should be performed as close to the last visit day of the baseline visit as possible. COA assessments, [^{18}F]GTP1 PET scans, and LP from the baseline visit may be performed on the same day that study drug is first administered (on the Week 1 visit), but they must be performed prior to dosing. All activities specified for the Week 1 visit (the first dosing visit) must be performed on the same day and must occur no later than 15 days after the first baseline assessment (e.g., if the first baseline visit day is a Monday, then the first dosing of study drug must occur no later than the Tuesday two weeks later). Extensions to the 15-day baseline visit period (e.g., to complete [18F]GTP1 PET imaging) may be granted on a case-by-case basis by the Medical Monitor.

[b] Visit not specified by the protocol. Assessments (possibly including PK sample collection) should be performed as clinically indicated.

[c] Patients who complete the double-blind treatment period and who do not enroll into the OLE treatment period will return to the clinic for a treatment completion visit (safety follow-up) at Week 81 $(\pm 7\ days)$. Patients who complete the OLE treatment period will return to the clinic for a treatment completion visit (safety follow-up) at Week 181 $(\pm 7\ days)$. Patients who discontinue study drug prematurely either in the double-blind treatment period or in the OLE treatment period will return to the clinic for a treatment discontinuation visit 12 weeks ($\pm$7 days) after the last dose of study drug.

[d] At these visits, all activities/assessments must be performed within $\pm$3 days of the scheduled visit.

[e] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained up to 56 days before initiation of study treatment.

[f] Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures); reproductive status; smoking history; use of alcohol and drugs of abuse; recent history (5 years) of non-elective hospitalizations, pneumonia or cardiovascular events; and all medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the patient within 3 months prior to the screening visit. Demographics include age, sex, self-reported race/ethnicity, and years of education. Demographics of caregiver will also be collected.

[g] Only perform assessment if discontinuation visit is $\geq$8 weeks after last assessment for this instrument or procedure.

[h] Please see the GN39763 COA Manual for instructions on COA administration order, specification of list versions to use at each visit, rater roles, restrictions on raters, and additional details on COA administration and the endpoint reliability program. At all visits, all COA questionnaires/scales (excluding the DVF and diagnostic classification form will be rater-administered before the patient or rater or caregiver receives any information on disease status, prior to LPs scheduled in the visit, and prior to the administration of study drug. In addition, on any given day when COAs are performed, all COAs (with the exception of the DVF/diagnostic classification form and the C-SSRS) must be completed prior to blood draws or imaging performed on the same day. For details on permitted concomitant medication use prior to COA assessments, see Section 4.1.2.

Appendix 1
Schedule of Activities (cont.)

[i] Only perform assessment if discontinuation visit is ≥16 weeks after last assessment for this instrument or procedure. However, if the patient discontinues study drug because of an infusion-related reaction, concurrent ADA and PK samples will also be collected at 12 weeks after the last administration of study drug.

[j] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. 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. On study drug treatment visits, vital signs should be collected 0–4 hours prior to infusion and 60–90 minutes after completion of infusion.

[k] Vital signs should be assessed on the same day(s) that the [^{18}F]GTP1 PET scan and/or LP are performed. Vital signs should be assessed just prior to injection of [^{18}F]GTP1 or initiation of the LP procedure, but no earlier than 1 hour prior to injection of [^{18}F]GTP1 or initiation of the LP procedure. Vital signs should also be assessed just after injection of [^{18}F]GTP1 or conclusion of the LP procedure, but no later than 1 hour after injection of [^{18}F]GTP1 or conclusion of the LP procedure.

[l] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, respiratory, and gastrointestinal systems. In addition, the musculoskeletal and genitourinary systems should be examined as clinically indicated. 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.

[m] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[n] If amyloid PET is used to confirm amyloid positive eligibility, an LP will not be performed as part of screening. If amyloid PET result suggests a patient is amyloid negative, an LP may be performed as part of screening to re-assess amyloid positivity eligibility on the basis of CSF.

[o] If a [^{18}F]GTP1 PET scan is performed at the baseline visit, [^{18}F]GTP1 PET scans must be performed at all indicated postbaseline visits. [^{18}F]GTP1 PET scans must be performed if [^{18}F]GTP1 is available at the PET imaging center through the [^{18}F]GTP1 distribution network, unless local restrictions preclude [^{18}F]GTP1 PET imaging. If a [^{18}F]GTP1 PET scan is not performed at the baseline visit, [^{18}F]GTP1 PET scans become optional at any of the indicated *postbaseline* visits. *Postbaseline* [^{18}F]GTP1 PET scans *may* be performed *prior to or after study treatment administration at the corresponding visit. Postbaseline [^{18}F]GTP1 PET scans should be performed within ±14* days of the scheduled visit. *Further extensions to the Week 73 visit [^{18}F]GTP1 PET scan window may be granted on a case-by-case basis by the Medical Monitor. The Week 49 and treatment discontinuation visit [^{18}F]GTP1 PET scan dates may be coordinated by the [^{18}F]GTP1 distribution network on the basis of tracer availability and may be scheduled outside the ±14 day window around the scheduled visit if appropriate extenuating circumstances arise.* If*, at any time,* local restrictions for radiation exposure disallow performing a [^{18}F]GTP1 PET scan, the site should contact the Sponsor to discuss alternative timing.

[p] A [^{18}F]GTP1 tau PET scan should only be performed if the following has been met: at least 24 weeks have elapsed since any previous [^{18}F]GTP1 tau PET scan and local annual radiation limits have not been exceeded.

[q] Results obtained up to 90 days prior to obtaining informed consent may be used to determine eligibility; such tests do not need to be repeated during screening.

[r] On the day of the first administration of study drug, ECG should be performed 0–4 hours before the start of infusion and 0–30 minutes after the end of infusion. On the Week 5 visit and all following visits, ECG should be performed 0–30 minutes after the end of infusion.

[s] Only perform assessment if clinically indicated.

[t] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (absolute counts of neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[u] Chemistry panel (serum or plasma) includes sodium, potassium, chloride, magnesium, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, LDH, gamma glutamyl transpeptidase, lactate dehydrogenase, creatine kinase. Glomerular filtration rate should also be calculated from creatinine using the Cockcroft-Gault formula. Lipid panel includes cholesterol, LDL cholesterol, HDL cholesterol, triglycerides. Coagulation panel includes INR, aPTT, and PT; the coagulation panel should be measured at screening and *within 90 days prior to any LP or within an interval consistent with the local standard of care, whichever is shorter. If required per local standard of care, additional coagulation panel tests may be performed at central laboratory or at a local laboratory. For patients taking multiple anti-platelet medications, the investigator should determine (per local standards of care) whether the temporary discontinuation of one or more anti-platelet medications prior to LP is warranted (e.g., continuing aspirin and discontinuing thienopyridine derivatives for 1–2 weeks prior to LP).*

[v] Viral serology panel includes: HIV, HBsAg, total hepatitis B core antibody, HCV antibody.

[w] For women of childbearing potential only: A serum pregnancy test must be performed at screening. Urine pregnancy tests will be performed at specified subsequent visits, prior to dosing of study drug, [^{18}F]GTP1 or an amyloid radioligand. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Pregnancy tests must be negative prior to dosing with MTAU9937A (or placebo) or [^{18}F]GTP1 or an amyloid radioligand.

[x] Only perform if a [^{18}F]GTP1 PET scan is being performed.

[y] Includes dipstick (pH, specific gravity, glucose, protein, ketones, blood). Microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria) should be performed if the dipstick is abnormal.

[z] At all indicated visits, serum ADA sample should be taken 0–4 hours before the start of infusion. In addition, concurrent ADA and PK samples should also be collected in patients with signs and symptoms of an infusion-related reaction at the time of the infusion-related event, for analyses of antibodies to MTAU9937A and/or other components of the drug product. Concurrent ADA and PK samples should also be collected in all patients at the treatment completion or treatment discontinuation visit (see footnote i, above for more details).

[aa] Serum PK samples should be taken 0–4 hours before the start of infusion and 1 hour (±15 minutes), 2 hours (±20 minutes), and 4 hours (±30 minutes) after the end of infusion.

[bb] Serum PK and blood biomarker samples should be taken 0–4 hours before the start of infusion and 0–30 minutes after the end of infusion.

[cc] Not applicable for a site that has not been granted approval for blood collection for SNP.

[dd] Not applicable for a site that has not been granted approval for WGS.

[ee] Blood biomarker samples should be taken 0–4 hours before the start of infusion unless otherwise noted.

[ff] When an LP is performed, it should be performed only once during either screening or the baseline visit, and may be used for assessment of amyloid positivity (if performed at screening) and/or for assessing tau or other biomarkers. If a [^{18}F]GTP1 PET scan is not performed at the baseline visit, an LP at the baseline visit is mandatory for collection of CSF (unless performed during screening) to enable the assessment of tau biomarkers. Follow-up LPs must also be performed at postbaseline visits if a [^{18}F]GTP1 PET scan is not performed at the baseline visit. If [^{18}F]GTP1 PET is performed at baseline and LP is performed at the screening or baseline visit, then follow-up LPs are optional.

[gg] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 3 months prior to screening until the final study visit.

[hh] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 12 weeks after the last dose of study drug. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug or [^{18}F]GTP1 or amyloid radioligand treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or [^{18}F]GTP1 or amyloid radioligand or trial-related procedures until a final outcome can be reported.

[ii] Extensions to this 8-week screening period may be granted by contacting the Medical Monitor on a case-by-case basis.

[jj] At the Week 25 visit, only CaGI-Alz assessments referring to changes relative to start of study should be administered. At subsequent administrations, both CaGI-Alz assessments referring to changes relative to start of study and relative to the prior assessment should be administered.

[kk] *The MRI must be performed and assessed locally and in real time prior to any study drug dosing at the corresponding study visit. Study drug should be withheld if there are clinically significant new or clinically significant worsened MRI abnormalities identified in the local MRI interpretation. However, if no such abnormalities are identified, the dose may be given prior to receipt of the central MRI report (see Section 5.1.1.2).*

Appendix 2
Schedule of Activities (Open-Label Extension)

	Open-label Treatment Period																								Unplanned Visit[a]	Tx Completio[b]	Tx D/C[b]
Week	77	81	85	89	93	97	101	105	109	113	117	121	125	129	133	137	141	145	149	153	157	161	165	169			
Diagnostic classification			x			x			x			x			x			x			x			x			x[c]
MMSE[d]			x			x			x			x			x			x			x			x			x[c]
CDR[d]												x												x			x[e]
RBANS[d]												x												x			x[e]
ADAS-Cog 13[d]												x												x			x[e]
Amsterdam iADL[d]												x												x			x[e]
ADCS-ADL[d]												x												x			x[e]
C-SSRS			x			x			x			x			x			x			x			x	x	x	x
CaGI-Alz[z]												*x*												*x*			*x*
Vital signs[f]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[g]	x	x	x[g]
Weight						x						x						x						x	x	x	x
Complete physical examination[h]						x						x						x						x		x	x
Limited physical examination[i]			x						x						x						x				x		
Neurological examination			x			x			x			x			x			x			x			x	x	x	x
MRI *j*				x																				x			x[e]
[^{18}F]GTP1 PET *k*																								x			x[l]
ECG																											x[m]
Hematology[n]												x													x	x	x
Chemistry *and* lipids[o]												x													x	x	x

Appendix 2
Schedule of Activities (Open-Label Extension) (cont.)

	Open-label Treatment Period																								Unplanned Visit[a]	Tx Completion[b]	Tx D/C[b]
Week	77	81	85	89	93	97	101	105	109	113	117	121	125	129	133	137	141	145	149	153	157	161	165	169			
Coagulation[p]												x												x			
Pregnancy test[q]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Urinalysis[r]												x													x	x	x
Study drug administration	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Serum PK sample	x[s]				x[t]				x[t]				x[t]				x[t]				x[t]			x[t]		x[e]	x[e]
Serum ADA sample[u]	x				x				x				x				x				x			x		x[e]	x[e]
Blood sample for biomarkers[v]	x												x											x		x	x[e]
LP for CSF sample for PK and biomarkers[w]																								x			x
Concomitant medications[x]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[x]	x[x]
Adverse events[y]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[y]	x[y]

[^{18}F]GTP1 = fluorine-18 Genentech tau probe 1; ADA=anti-drug antibody; ADAS-Cog=Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS-ADL=Alzheimer's Disease Cooperative Study Group–Activities of Daily Living Inventory; CaGI-Alz = Caregiver Global Impression of Change Scales for Alzheimer's disease; C-SSRS=Columbia-Suicide Severity Rating Scale; CDR=Clinical Dementia Rating; COA=clinical outcome assessment; CSF=cerebrospinal fluid; D/C=discontinuation; eCRF=electronic Case Report Form; iADL=Instrumental Activity of Daily Living; LP=lumbar puncture; MMSE=Mini-Mental State Examination; MRI=magnetic resonance imaging; OLE=open-label extension; PET=positron emission tomography; PK=pharmacokinetic; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; Tx=treatment.

Notes: All postbaseline study visits must be scheduled in reference to the first dosing day (Week 1 visit). All activities/assessments in a given study visit must be performed within ±5 days of the scheduled visit, unless otherwise specified *(e.g., [^{18}F]GTP1 PET scans)*. On study drug administration visits that span multiple days, study drug administration must occur on the last day. On study drug administration days, all assessments must be performed prior to dosing, unless otherwise specified.

On study drug administration days, pre-infusion laboratory samples should be drawn 0–4 hours before the start of infusion, and post-infusion laboratory samples should be drawn 0–30 minutes after the end of infusion, unless otherwise specified.

Appendix 2
Schedule of Activities (Open-Label Extension) (cont.)

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[a] Visit not specified by the protocol. Assessments (possibly including PK sample collection) should be performed as clinically indicated.

[b] Patients who complete the OLE treatment period will return to the clinic for a treatment completion visit (safety follow-up) at Week 181 $(\pm 7\ days)$. Patients who discontinue study drug prematurely in the OLE treatment period will return to the clinic for a treatment discontinuation visit 12 weeks (±7 days) after the last dose of study drug.

[c] Only perform assessment if discontinuation visit is ≥8 weeks after last assessment for this instrument.

[d] Please see the GN39763 COA Manual for instructions on COA administration order, specification of list versions to use at each visit, rater roles, restrictions on raters, and additional details on COA administration and the endpoint reliability program. At all visits, all COA questionnaires/scales (excluding the diagnostic classification form) will be rater administered before the patient or rater or caregiver receives any information on disease status, prior to LP scheduled in the visit, and prior to the administration of study drug. In addition, on any given day when COAs are performed, all COAs (with the exception of the diagnostic classification form and the C-SSRS) must be completed prior to blood draws or imaging performed on the same day. For details on permitted concomitant medication use prior to COA assessments, see Section 4.1.2.

[e] Only perform assessment if discontinuation visit is ≥16 weeks after last assessment for this instrument or procedure. However, if the patient discontinues study drug because of an infusion-related reaction, concurrent ADA and PK samples will also be collected at 12 weeks after the last administration of study drug.

[f] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. 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. On study drug treatment visits, vital signs should be collected 0–4 hours prior to infusion and 60–90 minutes after completion of infusion.

[g] Vital signs should be assessed on the same day(s) that the [^{18}F]GTP1 PET scan and/or LP are performed. Vital signs should be assessed just prior to injection of [^{18}F]GTP1 or initiation of the LP procedure, but no earlier than 1 hour prior to injection of [^{18}F]GTP1 or initiation of the LP procedure. Vital signs should also be assessed just after injection of [^{18}F]GTP1 or conclusion of the LP procedure, but no later than 1 hour after injection of [^{18}F]GTP1 or conclusion of the LP procedure.

[h] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, respiratory, and gastrointestinal systems. In addition, the musculoskeletal and genitourinary systems should be examined as clinically indicated. 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.

[i] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[j] *The MRI must be performed and assessed locally and in real time prior to any study drug dosing at the corresponding study visit. Study drug should be withheld if there are clinically significant new or clinically significant worsened MRI abnormalities identified in the local interpretation. However, if no such abnormalities are identified, the dose may be given prior to receipt of the central MRI report (see Section 5.1.1.2).*

[k] If a [^{18}F]GTP1 PET scan is performed at the baseline visit, [^{18}F]GTP1 PET scans must be performed at all indicated postbaseline visits. [^{18}F]GTP1 PET scans must be performed if [^{18}F]GTP1 is available at the PET imaging center through the [^{18}F]GTP1 distribution network, unless local restrictions preclude [^{18}F]GTP1 PET imaging. If a [^{18}F]GTP1 PET scan is not performed at the baseline visit, [^{18}F]GTP1 PET scans *become optional* at any of the indicated postbaseline visits. *Postbaseline* [^{18}F]GTP1 PET scans *may* be performed *prior to or after study treatment administration at* the *corresponding* visit. *The Week 169 and treatment discontinuation visit [^{18}F]GTP1 PET scan dates may be coordinated by the [^{18}F]GTP1 distribution network on the basis of tracer availability and may be scheduled outside the ±14 day window around the scheduled visit should appropriate extenuating circumstances arise.* If*, at any time,* local restrictions for radiation exposure disallow performing a [^{18}F]GTP1 PET scan, the site should contact the Sponsor to discuss alternative timing.

[l] A [^{18}F]GTP1 tau PET scan should only be performed if the following has been met: informed consent has been obtained, at least 24 weeks have elapsed since any previous [^{18}F]GTP1 tau PET scan, and local annual radiation limits have not exceeded.

[m] Only perform assessment if clinically indicated.

[n] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (absolute counts of neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[o] Chemistry panel (serum or plasma) includes sodium, potassium, chloride, magnesium, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, LDH, gamma glutamyl transpeptidase, lactate dehydrogenase, creatine kinase. Glomerular filtration rate should also be calculated from creatinine using the Cockcroft-Gault formula. Lipid panel includes cholesterol, LDL cholesterol, HDL cholesterol, triglycerides.

[p] Coagulation panel includes INR, aPTT, and PT; the coagulation panel should be measured *within 90 days prior to any LP or within an interval consistent with the local standard of care, whichever is shorter. If required per local standard of care, additional coagulation panel tests may be performed at central laboratory or at a local laboratory. For patients taking multiple anti-platelet medications, the investigator should determine (per local standards of care) whether the temporary discontinuation of one or more anti-platelet medications prior to LP is warranted (e.g., continuing aspirin and discontinuing thienopyridine derivatives for 1–2 weeks prior to LP). The Week 169 coagulation laboratory tests are only applicable to patients participating in the optional CSF collection (lumbar puncture).*

[q] For women of childbearing potential, urine pregnancy tests will be performed at specified subsequent visits, prior to dosing. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Pregnancy tests must be negative prior to dosing with MTAU9937A (or placebo) or [^{18}F]GTP1 or an amyloid radioligand.

Appendix 2
Schedule of Activities (Open-Label Extension) (cont.)

[r] Includes dipstick (pH, specific gravity, glucose, protein, ketones, blood). Microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria) should be performed if the dipstick is abnormal.

[s] Serum PK samples should be taken 0–4 hours before the start of infusion and 1 hour (± 15 minutes), 2 hours ± 20 minutes), and 4 hours (± 30 minutes) after the end of infusion.

[t] Serum PK samples should be taken 0–4 hours before the start of infusion and 0–30 minutes after the end of infusion.

[u] At all indicated visits, serum ADA sample should be taken 0–4 hours before the start of infusion. In addition, concurrent ADA and PK samples should also be collected in patients with signs and symptoms of an infusion-related reaction at the time of the infusion-related event, for analyses of antibodies to MTAU9937A and/or other components of the drug product. Concurrent ADA and PK samples should also be collected in all patients at the treatment completion or treatment discontinuation visit (see footnote e, above, for more details).

[v] Blood biomarker samples should be taken 0–4 hours before the start of infusion.

[w] LPs are optional during the OLE period.

[x] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment until the final study visit.

[y] All adverse events will be reported until 12 weeks after the last dose of study drug. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug or [^{18}F]GTP1 or amyloid radioligand treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or [^{18}F]GTP1 or amyloid radioligand or trial-related procedures until a final outcome can be reported.

[z] Both CaGI-Alz assessments referring to changes relative to start of study and relative to the prior assessment *(e.g., the prior 6 months)* should be administered.

Appendix 3
National Institute on Aging/Alzheimer's Association Criteria for Mild Alzheimer's Disease

NIA-AA category	Description
Probable Dementia: core Clinical Criteria Meets criteria for dementia described earlier in the text, and in addition, has the following characteristics:	A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days; B. Clear-cut history of worsening of cognition by report or observation; and C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories. a. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text. b. Non-amnestic presentations: Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present. Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present. Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present. D. The diagnosis of probable AD dementia should not be applied when there is evidence of (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) core features of Dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

Appendix 3
National Institute on Aging/Alzheimer's Association Criteria for Mild Alzheimer's Disease (cont.)

NIA-AA category	Description
Probable AD dementia with increased level of certainty	Probable AD dementia with documented decline In persons who meet the core clinical criteria for probable AD dementia, documented cognitive decline increases the certainty that the condition represents an active, evolving pathologic process, but it does not specifically increase the certainty that the process is that of AD pathophysiology. Probable AD dementia with documented decline is defined as follows: evidence of progressive cognitive decline on subsequent evaluations based on information from informants and cognitive testing in the context of either formal neuropsychological evaluation or standardized mental status examinations. Probable AD dementia in a carrier of a causative AD genetic mutation In persons who meet the core clinical criteria for probable AD dementia, evidence of a causative genetic mutation (in *APP, PSEN1, or PSEN2*), increases the certainty that the condition is caused by AD pathology. The workgroup noted that carriage of the ε4 allele of the *apolipoprotein E* gene was not sufficiently specific to be considered in this category.
Probable AD dementia with evidence of the AD pathophysiological process	AD dementia is part of a continuum of clinical and biological phenomena. AD dementia is fundamentally a clinical diagnosis. To make a diagnosis of AD dementia with biomarker support, the core clinical diagnosis of AD dementia must first be satisfied. Relevant biomarkers include amyloid-β(CSF or PET); tau (CSF or PET)

AD=Alzheimer's disease; CSF=cerebrospinal fluid; NIA-AA=National Institute on Aging/Alzheimer's Association; PET=positron emission tomography.

Reference: 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. Alzheimers Dement 2011;7:263–9.

Appendix 4
National Institute on Aging/Alzheimer's Association Criteria for Prodromal Alzheimer's Disease (Mild Cognitive Impairment due to Alzheimer's Disease)

NIA-AA category	Clinical and Cognitive Criteria
Clinical Criteria	Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time) Objective evidence of Impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains) Preservation of independence in functional abilities Not demented
Etiology of MCI consistent with AD pathophysiological process	Rule out vascular, traumatic, medical causes of cognitive decline, where possible. Provide evidence of longitudinal decline in cognition, when feasible Report history consistent with AD genetic factors, where relevant
pAD dementia with evidence of the AD pathophysiological process	pAD is part of a continuum of clinical and biological phenomena. pAD is fundamentally a clinical diagnosis. To make a diagnosis of pAD with biomarker support, the core clinical diagnosis of pAD must first be satisfied. Relevant biomarkers include amyloid-β(CSF or PET); tau (CSF or PET)

AD=Alzheimer's disease; CSF=cerebrospinal fluid; MCI=mild cognitive impairment; NIA-AA=National Institute on Aging/Alzheimer's Association; pAD=prodromal AD; PET=positron emission tomography.

Reference: Albert MS, DeKosky ST, Dickson B, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:270–79.

Appendix 5
Anaphylaxis Precautions

The following equipment is needed in the event of a suspected anaphylactic reaction during study drug infusion:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intravenous, intramuscular, and endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

The following are the procedures to follow in the event of a suspected anaphylactic reaction during study drug infusion:

- Stop the study drug infusion.
- Call for additional medical assistance.
- Maintain an adequate airway.
- Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring, if possible.
- Administer antihistamines, epinephrine, or other medications as required by participant status and as directed by the physician in charge.
- Continue to observe the participant and document observations.
- Draw serum samples for immunogenicity testing.
- Ask participant to return for washout immunogenicity sample (12 weeks after last dose) if appropriate.

Appendix 6
World Health Organization Toxicity Grading Scale

Appendix: WHO TOXICITY GRADING SCALE FOR DETERMINING THE SEVERITY OF ADVERSE EVENTS

HEMATOLOGY				
ITEM	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
Hemoglobin	9.5 - 10.5 gm/Dl	8.0 - 9.4 gm/Dl	6.5 - 7.9 gm/Dl	< 6.5 gm/Dl
Absolute Neutrophil Count	1000-1500/mm^3	750-999/mm^3	500-749/mm^3	500-749/mm^3
Platelets	75000-99000/mm^3	50000-74999/mm^3	20000-49000/mm^3	<20000/mm^3
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 -1.66 x ULN	1.67 - 2.33 x ULN	2.34 - 3 x ULN	3 x ULN
Fibrinogen	0.75 - 0.99 X LLN	0.50 - 0.74 x LLN	0.25 - 0.49 x LLN	< 0.25 x LLN
Fibrin Spilt Product	20-40 mcg/ml	41-50 mcg/ml	51-60 mcg/ml	> 60 mcg/ml
Methemoglobin	5 - 9.9 %	10.0 - 14.9 %	15.0 - 19.9%	> 20 %
LIVER ENZYMES				
AST (SGOT)	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	10 x ULN
ALT (SGPT)	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	10 x ULN
GGT	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	10 x ULN
Alkaline Phosphatase	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	10 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN
CHEMISTRIES				
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 or mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement Rx required or hospitalization required	< 2.0 mEq/L or paresis or ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/l	> 7.0 mEq/L or life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or mental status changes or coma

Appendix 6
World Health Organization Toxicity Grading Scale (cont.)

Appendix: WHO TOXICITY GRADING SCALE FOR DETERMINING THE SEVERITY OF ADVERSE EVENTS

CHEMISTRIES (continued)				
Hyperglycemia (note if fasting)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or life threatening arrhythmia or tetany
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL life-threatening arrhythmia
Hypomagnesemia	1.4 - 1.2 mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0 -1.4 mg/dL intensive Rx or hospitalization required	< 1.0 mg/dL or life-threatening arrhythmia
Hyperbilirubinemia	1.1 - 1.5 x ULN	1.6 - 2.5 x ULN	2.6 - 5 x ULN	> 5 x ULN
BUN	1.25 - 2.5 x ULN	2.6 - 5 x ULN	5.1 - 10 x ULN	> 10 x ULN
Creatinine	1.1 x 1.5 x ULN	1.6 - 3.0 x ULN	3.1 - 6 x ULN	> 6 x ULN or required dialysis
URINALYSIS				
Proteinuria	1+ or < 0.3% or <3g/L or 200 mg - 1 gm loss/day	2 -3 + or 0.3 - 1.0% or 3-10 g/L 1- 2 gm loss/day	4+ or > 1.0% or > 10 g/L 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day
Hematuria	microscopic only	gross, no clots	gross+ clots	obstructive or required transfusion
CARDIAC DYSFUNCTION				
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; No Rx required	requires treatment
Hypertension	transient inc. > 20 mm; no Rx	recurrent, chronic, > 20 mm, Rx required	requires acute Rx; No hospitalization	requires hospitalization
Hypotension	transient orthostatic hypotension, No Rx	symptoms correctable with oral fluids Rx	requires IV fluids; no hospitalization required	requires hospitalization
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no Rx	symptomatic effusion; pain; EKG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused

Appendix 6
World Health Organization Toxicity Grading Scale (cont.)

Appendix: WHO TOXICITY GRADING SCALE FOR DETERMINING THE SEVERITY OF ADVERSE EVENTS

RESPIRATORY				
Cough	transient- no Rx	treatment associated cough local Rx	uncontrolled	
Bronchospasm, Acute	transient; no Rx < 80% - 70% FEV_1 (or peak flow)	requires Rx normalizes with bronchodilator; FEV_1 50% - 70% (or peak Flow)	no normalization with bronchodilator; FEV_1 25% - 50% (or peak flow retractions)	cyanosis: FEV_1 < 25% (or peak flow) or intubated
GASTROINTESTINAL				
Stomatitis	mild discomfort; no limits on activity	some limits on eating/drinking	eating/talking very limited	requires IV fluids
Nausea	mild discomfort; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	severe discomfort; no significant intake; activities limited	minimal fluid intake
Vomiting	transient emesis	occasional/moderate vomiting	orthostatic hypotension or IV fluids required	hypotensive shock or hospitalization required for IV fluid therapy
Constipation	mild	moderate	severe	distensions w/vomiting
Diarrhea	transient 3-4 loose stools/day	5-7 loose stools/day	orthostatic hypotension or > 7 loose stools/day or required IV fluids	hypotensive shock or hospitalization for IV fluid therapy required
NEURO & NEUROMUSCULAR				
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Mood	mild anxiety or depression	moderate anxiety or depression and therapy required	severe anxiety or depression or mania; needs assistance	acute psychosis; incapacitated, requires hospitalization
Neuro Control (ADL = activities of daily living)	mild difficulty concentrating; no Rx; mild confusion/agitation; ADL unaffected	moderate confusion/agitation some limitation of ADL; minimal Rx	severe confusion/agitation needs assistance for ADL; therapy required	toxic psychosis; hospitalization
Muscle Strength	subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis

Appendix 6
World Health Organization Toxicity Grading Scale (cont.)

Appendix: **WHO TOXICITY GRADING SCALE FOR DETERMINING THE SEVERITY OF ADVERSE EVENTS**

OTHER PARAMETERS				
Fever: oral, > 12 hours	37.7 - 38.5 C or 100.0 - 101.5 F	38.6 - 39.5 C or 101.6 - 102.9 F	39.6 - 40.5 C or 103 - 105 F	> 40 C or > 105 F
Headache	mild, no Rx therapy	transient, moderate; Rx required	severe; responds to initial narcotic therapy	intractable; required repeated narcotic therapy
Fatigue	no decrease in ADL	normal activity decreased 25- 50%	normal activity decreased > 50% can't work	unable to care for self
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Local Reaction	tenderness or erythema	induration < 10 cm or phlebitis or inflammation	induration > 10 cm or ulceration	necrosis
Mucocutaneous	erythema; pruritus	diffuse, maculo papular rash, dry desquamation	vesiculation, moist desquamation, or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery