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

Published: 21-12-2017
Last updated: 12-04-2024

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…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Dementia and amnestic conditions
Study type	Interventional

Summary

ID

NL-OMON48730

Source
ToetsingOnline

Brief title
TAURIEL

Condition

- Dementia and amnestic conditions

Synonym
Alzheimer's disease, Appearance of initial symptoms to a mild form of dementia

Research involving
Human

Sponsors and support

Primary sponsor: Genentech
Source(s) of monetary or material Support: Genentech

Intervention

Keyword: Mild Alzheimer's Disease, MTAU9937A, Prodromal Alzheimer's Disease

Outcome measures

Primary outcome

Efficacy endpoint: Change from baseline to Week 73 on the CDR-SB.

Safety endpoints: The 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 outcome

Efficacy endpoints: Change from baseline to Week 73 on the RBANS Total Score. Change from baseline to Week 73 on the ADAS-Cog 13. Change from baseline to Week 73 on the Amsterdam iADL questionnaire. Change from baseline to Week 73 on the ADCS-ADL.

Pharmacokinetic endpoint: Serum concentrations of MTAU9937A at specified timepoints.

Immunogenicity endpoint: Presence of anti-drug antibodies during the study

relative to the presence of ADAs at baseline.

Study description

Background summary

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. The disease is characterized pathologically by the accumulation in the brain neocortex of extracellular *-amyloid (A*) 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).
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. 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.
MTAU9937A represents a novel potential therapeutic for the treatment of AD. 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.

Study objective

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). The efficacy objective is to evaluate the efficacy of MTAU9937A compared with placebo. The safety objective is to evaluate the safety and tolerability
of MTAU9937A compared with placebo.

Study design

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 ([18F] 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 cerebrospinal fluid (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.
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 RatingScale (C-SSRS), and abnormalities in standard safety blood tests, ECG, 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. 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. All patients must have baseline and longitudinal tau-related biomarker evaluation. If [18F]GTP1 PET imaging is available to a patient, based on site availability of [18F]GTP1 PET imaging and lack of local restriction to such imaging, the patient must undergo [18F]GTP1 PET imaging for tau-related biomarker evaluation. [18F]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 [18F]GTP1 PET imaging performed at Week 169. In addition, for patients undergoing [18F]GTP1 PET imaging, optional CSF collection at baseline and postbaseline time points is also encouraged. For sites where [18F]GTP1 PET imaging is not available, or where local restrictions preclude [18F]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).

Intervention

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. [18F]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.

Study burden and risks

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.

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. Study sites will be prepared to manage any hypersensitivity or hypersensitivity-like events. The occurrence of neuroimaging abnormalities believed to represent cerebral vasogenic edema and microhemorrhage have been reported in association with the investigational use of immunotherapy targeting the A*peptide, possibly by interacting with A*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.
Anti-Drug Antibodies (ADA) 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.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Age between 50 and 80 years
- National Institute on Aging/Alzheimer*s Association core clinical criteria for probable AD dementia or mild cognitive impairment (prodromal AD)
- Evidence of the AD pathological process, by a positive amyloid assessment either on cerebrospinal fluid A*1*42 OR amyloid positron emission tomography (PET) scan. Historical amyloid PET scans may be accepted in some cases
- Mild AD symptomatology, as defined by a screening Mini-Mental State Examination score of >< = 20 points and Clinical Dementia Rating (CDR) *Global Score of 0.5 or 1
- Abnormal memory function at screening
- Availability of a person with sufficient contact with the patient to be able to provide accurate information on the patient*s cognitive and functional ability

Exclusion criteria

- Pregnant or breastfeeding
- Inability to tolerate magnetic resonance imaging (MRI) procedures or contraindication to MRI
- Able to undergo either PET imaging or lumbar dural puncture, or both, and

patients with contraindications to both procedures are ineligible
- Residence in a skilled nursing facility
- 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
- Any evidence of a condition other than AD that may affect cognition
- 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
- Use of any experimental therapy within 90 days or 5 half-lives prior to screening, whichever is greater and any passive immunotherapy (immunoglobulin) against tau, except use of RO7105705 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 A*, unless the last dose was at least 1 year prior to screening and 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
- Systemic immunosuppressive therapy within 12 months of screening through the entire study period
- Typical antipsychotic or neuroleptic medication within 6 months of screening
- 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 such as atypical antipsychotics, Opiates or opioids ,Benzodiazepines, barbiturates, or hyponotics and any medication with centrally-acting antihistamine or anticholinergic activity
- Stimulant medications, unless the dose has been stable within the 6 months prior to screening and is expected to be stable throughout the study

Study design

Design

Study phase: 2

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-06-2018
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	Fluorine-18 Genentech tau probe 1 ([18F]GTP1)
Product type:	Medicine
Brand name:	-
Generic name:	MTAU9937A

Ethics review

Approved WMO

Date:	21-12-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	04-06-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	27-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-08-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-11-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-11-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-02-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-07-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-07-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	27-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-09-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-02-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-001800-31-NL
ClinicalTrials.gov	NCT03289143
CCMO	NL63541.056.17