A Phase II/IIIRandomized, Double-Blind, Placebo-Controlled, Cognitive Endpoint, Multi-centerStudy of Potential Disease Modifying Therapies in Individuals at Risk for and with Dominantly Inherited Alzheimer' s Disease

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Assess cognitive efficacy of gantenerumab, solanezumab in individuals who have mutations causing dominantly inherited Alzheimer's disease as measured by change in the DIAN-TU cognitive composite score between baseline and a minimum of 4 years....

Ethical review	Not approved
Status	Will not start
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON48340

Source
ToetsingOnline

Brief title
DIAN-TU-001

Condition

- Other condition

Synonym
alzheimer, dementia

Health condition

Alzheimer's disease

Research involving
Human

Sponsors and support

Primary sponsor: Washington University
Source(s) of monetary or material Support: Whashington University

Intervention

Keyword: Alzheimer□s disease (AD), CRI-Period, DIAD

Outcome measures

Primary outcome

The primary efficacy hypothesis of the study is that the active drug group will have a slower rate of progression on the cognitive composite endpoint compared to the mutation*carrier placebo group after treatment for a minimum of 4 years. The DIAN*TU cognitive composite score is calculated from four cognitive measures:

1) The Delayed Recall score of the International Shopping List Test,

2) The Delayed Recall score of the Logical Memory IIa subtest from the Wechsler Memory Scale*Revised,

3) The Digit Symbol Substitution Test total score from the Wechsler Adult Intelligence Scale*Revised, and

4) The Mini*Mental State Examination total score.

Secondary outcome

1. Assess safety and tolerability of each study drug in individuals who have mutations causing dominantly inherited Alzheimer*s disease.

2. Biomarker Endpoints used at interim analysis: Assess target engagement of

each study drug in individuals who have mutations causing dominantly inherited Alzheimer*s disease as measured by the change from baseline to interim analysis for the biomarker measure for each drug. The biomarker endpoints are specified for each drug based on mechanism of action. Comparisons between the active drug and pooled placebo will be made at each interim for a study drug arm; however, there will be no

comparisons between active drugs.

3. Comparisons between each drug and placebo for change in values between baseline and endpoint for the clinical and cognitive measures

listed below.

Clinical measures to be obtained at baseline, and annual visits will be administered at the host DIAN*TU site include:

o Clinical Dementia Rating* (CDR), including Clinical Dementia Rating Sum of Boxes* (CDR*SB) and clinician*s diagnostic assessment

o Geriatric Depression Scale (GDS)

o Neuropsychiatric Inventory Questionnaire (NPI*Q)

o Functional Assessment Scale (FAS)

o Mini*Mental State Examination (MMSE)

o Cognitive measures to be obtained at baseline and annual visits will be administered at host DIAN*TU site include:

o International Shopping List Test (12*Item Word List Learning):

3 learning trials, Immediate Recall, 30*min Delayed Recall (Cogstate)

o Groton Maze Learning Test: Timed Chase Task, 5 learning Trials, Immediate Recall, 30*min Delayed/Reversed Recall (Cogstate)

o Cogstate Detection Task

o Cogstate Identification Task

o Cogstate One Card Learning Test

o Cogstate One*Back Task

o Behavioral Pattern Separation Object Task

o Memory Complaint Questionnaire (MAC*Q)

o Trailmaking Test parts A & B

o WMS*R Digit Span

o WAIS*R Digit*Symbol Substitution Test

o Raven*s Progressive Matrices (Set A)

o Category Fluency (Animals & Vegetables)

o WMS*R Logical Memory (Immediate & Delayed Recall)

o A subset of clinical and cognitive measures will be administered by the site

or home health nurse at 24*week intervals when not the

annual visits. This subset includes:

o International Shopping List Test (12*Item Word List Learning):

3 learning trials, Immediate Recall,30*min Delayed Recall (Cogstate)

o Groton Maze Learning Test: Timed Chase Task, 5 learning Trials, Immediate

Recall,30* min Delayed/Reversed Recall (Cogstate)

o Cogstate Detection Task

o Cogstate Identification Task

o Cogstate One Card Learning Test

o Cogstate One*Back Task

o Trailmaking Test parts A & B

o WMS*R Digit Span

o WAIS*R Digit*Symbol Substitution Test

o WMS*R Logical Memory (Immediate & Delayed Recall)

o For the CRI period and drug arms other than gantenerumab and solanezumab:

o Mini*Mental State Examination (MMSE)

o Category Fluency (Animals & Vegetables)

Study description

Background summary

This study will recruit subjects from the Dominantly Inherited Alzheimer Network (DIAN) observational study, a multicenter international study supported by the National Institutes of Health (Grant Number U01*AG032438; RJ Bateman), Dominantly Inherited Alzheimer Network
Trial Units (DIAN*TU) sites, DIAN*TU partner sites, DIAN Expanded Registry (DIAN*EXR), and families identified by the sites. As part of the DIAN*TU*001 protocol, subjects undergo longitudinal assessments that include clinical assessment, cognitive testing, magnetic resonance
imaging (MRI) and amyloid imaging, and analysis of cerebrospinal fluid.

There are DIAN observational study sites located in multiple countries including the USA, Argentina, Australia, Germany, Japan, and the United Kingdom. Subjects in DIAN are recruited from families that have at least one member who has been identified as having a mutation
linked to dominantly inherited Alzheimer*s disease (DIAD). The mutations in presenilin 1 (PSEN1), presenilin 2 (PSEN2) and amyloid precursor protein (APP) that are associated with dominantly inherited Alzheimer*s disease have very high penetrance (near 100%). This study will
target individuals who are either known to have a disease*causing mutation or who are at risk for such a mutation (the child or sibling of a proband with a known mutation) and unaware of their genetic status. Because the age at onset of cognitive changes is relatively consistent within
each family and with each mutation, an age at onset is determined for each affected parent or mutation as part of the DIAN observational study protocol. This study will enroll subjects who are either asymptomatic and are within a specific window of time of expected age at onset for their family and/or mutation or who have symptoms of mild Alzheimer*s disease.

Study objective

Assess cognitive efficacy of gantenerumab, solanezumab in individuals who have mutations causing dominantly inherited Alzheimer's disease as measured by change in the DIAN-TU cognitive composite score between baseline and a minimum of 4 years. Comparisons will be made between each drug and placebo but not between the active drugs.

Study design

This study is an adaptive platform*based study, which allows flexibility to add a new compound to the same protocol, allowing subjects to be randomized to study drug arms open to enrollment, and to maintain a cohort of trial ready subjects with or at risk for DIAD mutations.
Subjects have been enrolled to the gantenerumab and solanezumab study drug arms, with each enrolled subject randomized to active drug or the corresponding placebo. Gantenerumab en solanezumab treatment arms are not applicable in the Netherlands.

Intervention

NA

Study burden and risks

Plaque removal effect was demonstrated in the prodromal study WN25203 with the higher 225 mg dose showing a stronger effect of removal. These results for the first time showed the effect of immunotherapies against A* in early (prodromal) AD. In dominantly inherited Alzheimer*s disease (DIAD), amyloid deposition is present at early stages of the disease when no memory impairment is present. Thus, the current dose and the higher doses to be administered are expected to be effective in DIAD.
The mutations in presenilin 1 (PSEN1), presenilin 2 (PSEN2) and amyloid precursor protein (APP) that are associated with DIAD and which subjects in this study who receive active study drug will have tested positive for, have very high penetrance (near 100%). AD is a progressive and ultimately fatal disease and no disease modifying treatment is available to date.
Besides injection site reactions which, however appear of mild intensity in most subjects and not limiting the maintenance of subjects in the long-term treatment trial, ARIAs represent a side effect of concern in the development of immune-therapeutics targeting A* in the brain. These changes may include micro-hemorrhage, vasogenic edema/effusion and infarction; they are most often asymptomatic, but symptoms have been reported in some cases.
Therefore, dedicated monitoring and action plans for ARIAs are implemented in respective multiple dose clinical trials of gantenerumab including the DIAN-TU-001 study. Given the experiences made with gantenerumab thus far, the

proposed risk minimization plan including frequent MRI monitoring and reads by independent experts together with an ARIA based dose intervention algorithm appears to be effective in preventing clinical sequelae to the subjects treated with gantenerumab.

Contacts

Public
Washington University

South Euclid Ave, Campus Box 8111 660
Saint Louis MO 63110
US
Scientific
Washington University

South Euclid Ave, Campus Box 8111 660
Saint Louis MO 63110
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* *15 to +10 EYO (secondary prevention population): within *15 to +10 years of the estimated age at symptom onset, or, if symptomatic, within 10 years of their age at symptom onset, CDR 0 to 1, inclusive,
known carrier or at 50% risk (affected parent or sibling)
* Younger than *15 EYO (primary prevention population): more than 15 years younger (< *15) than estimated age at symptom onset, CDR 0, known carrier or mutation in their family

pedigree; if the at*risk
parent is deemed a non*carrier at any point, subject will be withdrawn from study
* Are able and willing to complete all study*related testing, evaluations, and procedures

Exclusion criteria

Subjects will be excluded if they have a major or unstable illness or are unable to complete all study related testing. Exclusions include implanted metal that cannot be removed for MR scanning, required anticoagulation therapy and pregnancy.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	LY2062430
Generic name:	Solanezumab

Ethics review

Approved WMO Date:	21-03-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Not approved Date:	21-05-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	EUCTR2013-000307-17-NL
ClinicalTrials.gov	NCT01760005
CCMO	NL69009.029.19