DIAN-TU-001 A Phase II/III Randomized, Double-Blind, Placebo-Controlled, Cognitive Endpoint, Multicenter Study of Potential Disease Modifying Therapies in Individuals at Risk for and with Dominantly Inherited Alzheimer*s Disease

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To assess the safety, tolerability, biomarker and cognitive efficacy of investigational products in subjects who are known to have an Alzheimer*s disease-causing mutation by determining if treatment with the study drug slows the rate of progression...

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

Summary

ID

NL-OMON44417

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: Quintiles
Source(s) of monetary or material Support: University (abroad)

Intervention

Keyword: Alzheimer□s disease (AD), and JNJ-54861911, Disease modifying therapies, Gantenerumab (RO4909832), reducing amyloid plaque formation, Solanezumab (LY2062430)

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. The cognitive composite score is determined from its components using a simple z-score method (Bateman et al., 2016). Each of the four component scores is divided by the baseline standard deviation of that component to form standardized z-scores. These z scores are averaged to form

the composite. Comparisons will be made between each active drug and pooled placebo but not between the active drugs.

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 following clinical and cognitive measures:

* 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 CDR Sum of Boxes (CDR SB) and clinician*s diagnostic assessment

o Geriatric Depression Scale (GDS)

o Neuropsychiatric Inventory Questionnaire (NPI-Q)

o Functional Assessment Questionnaire (FAQ)

o Mini Mental State Examination (MMSE)

* 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 Trails 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)

* A subset of these 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 Trails A & B

o WMS-R Digit Span

o WAIS-R Digit-Symbol Substitution Test

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

o Additional tests for the JNJ-54861911 arm only

* Mini Mental State Examination (MMSE)

* Category Fluency (Animals & Vegetables)

Other drug-specific secondary endpoints may be listed in each drug-specific

appendix.

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, and families identified by the sites.
As part of the DIAN-TU-001 protocol, subjects undergo longitudinal assessments that include clinical assessment, cognitive testing, 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 (Ryman, Acosta-Baena et al. 2014), 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.
Gantenerumab (RO4909832): is a recombinant human anti-amyloid beta peptide (A*) monoclonal antibody of the immunoglobulin subclass G1 (IgG1) that binds specifically to aggregated forms of A* peptide. In a Phase 1 multiple ascending dose (MAD) study, subjects treated with gantenerumab for up to 6 months had a dose dependent reduction in brain amyloid, as measured by a reduction in [11C]-Pittsburgh Compound B ([11C]PiB) binding, using a volume-weighted average from 6 cortical areas (Ostrowitzki, Deptula et al. 2012).
Solanezumab (LY2062430): is humanized anti-A* peptide immunoglobulin G-1 (IgG1); solanezumab recognizes an epitope in the middle of the A* peptide and binds to soluble A*. In a Phase 2 trial, treatment with solanezumab resulted in a dose-dependent increase in levels of A*40 and A*42 in both CSF and plasma (Siemers, Friedrich et al. 2010).
Drugs that target amyloid beta peptide may be associated with amyloid-related imaging abnormalities (ARIA), including both vasogenic edema (ARIA-E) and hemorrhages (ARIA-H), which are typically microhemorrhages, but larger hemorrhages and frank infarction have also been reported (Sperling, Salloway et al. 2012). Subjects will undergo MRI scans to monitor for ARIA. The schedule is drug arm specific and the frequency reflects the likely risk, based on available safety studies and the mechanism of action of the treatment.
BACE Inhibitor (JNJ-54861911): is a *-site amyloid precursor protein cleaving enzyme (*-secretase, BACE) inhibitor being developed for the treatment of Alzheimer*s disease (AD). The hallmark pathologic features of AD patients are neurofibrillary tangles, which consist of hyperphosphorylated tau protein and amyloid plaques (AP), the main constituent of which is beta-amyloid (A*). BACE Inhibitor reduces production of A* fragments by inhibiting BACE-1 processing of amyloid precursor protein (APP) with the aim of reducing AP formation.

Study objective

To assess the safety, tolerability, biomarker and cognitive efficacy of investigational products in subjects who are known to have an Alzheimer*s disease-causing mutation by determining if treatment with the study drug slows the rate of progression of cognitive impairment and improves disease related biomarkers.

Study design

This study is an adaptive platform based study which allows flexibility to add

a new compound to the same protocol, allowing new subjects to be randomized to study drug arms open to enrollment. This study has 3 study drug arms (gantenerumab, solanezumab and JNJ-54861911), each enrolling subject is to receive active drug or the corresponding placebo. All subjects will be treated with active drug or placebo with biomarker (e.g., PET imaging, volumetric brain MRI, CSF, and plasma measures), cognitive, and safety assessments (including safety MRI scans, vital signs, ECG, clinical chemistry, and hematology) throughout the study period.
The primary efficacy hypothesis 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 biomarker and cognitive endpoints may be used to conduct interim analyses in any of the study drug arms; a study drug arm may be stopped early or revised (e.g., dose adjustment or treatment duration) based upon the results of the interim analyses or information from other clinical trials for the same drug, as outlined in each drug-specific appendix.

Mutation positive subjects will be randomized in a 3:1 ratio for active drug:placebo. Groups enrolled simultaneously will be balanced by a minimization algorithm including clinical state and stage of disease measures (CDR-SB, years from onset) and other factors (gene type [APP, PSEN1, PSEN2), years of education, age, presence of an APOE *4 allele, region, study site and gender). Subjects who are mutation negative will be assigned to one of the placebo groups.
Mutation negative subjects are included to maintain blinding as to genetic status for those who do not wish to know their genetic status. Mutation negative subjects will not be included in the primary efficacy or futility analyses.
At the request of participants, mutation negative subjects participate in the trial to maintain blinding of their genetic status. Data from mutation negative subjects will be used to develop models for longitudinal changes in biomarkers and cognition in healthy adult controls.

Intervention

- PET scan and a lumbar puncture * at four visits.
- MRI * at eight visits
- ECG - at eighteen visits
- Vital signs (blood pressure, breathing rate, temperature and heartbeat) * at each in-person visit
- Body weight * approximately every three months
- Blood draw - at most visits.
- Urine samples * at all visits.
- Physical and neurological examination * at 8 visits
- Dermatologic evaluation (eye and skin examination) * at two visits.

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 (Bateman et al., 2012). 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 (Sperling et al., 2012). 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

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Know they have an AD-causing mutation OR be unaware of their genetic status and have a 50% chance of having an AD-causing mutation (e.g., parent or biological sibling clinically affected with known AD-causing mutation in family)
* Are 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
* Are able to undergo MRI, LP, PET, and complete all study related testing and evaluations.

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:	15
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	JNJ-54861911
Generic name:	JNJ-54861911
Product type:	Medicine
Brand name:	LY2062430
Generic name:	Solanezumab
Product type:	Medicine
Brand name:	RO4909832
Generic name:	Gantenerumab

Ethics review

Not approved

Date:	07-12-2017
Application type:	First submission
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	EUCTR2013-000307-17-NL
ClinicalTrials.gov	NCT01760005
CCMO	NL63885.056.17