A Phase 2b/3 Randomized, Double-blind, Placebo-Controlled, Parallel Group, Multicenter
Study Investigating the Efficacy and Safety of JNJ-54861911 in Subjects who are
Asymptomatic At Risk for Developing Alzheimer*s Dementia

Published: 30-09-2015
Last updated: 19-04-2024

Primary Objective:The primary objective of this study is to determine whether treatment with JNJ-54861911 slows cognitive decline compared with placebo treatment, as measured by a composite cognitive measure, the Preclinical Alzheimer Cognitive...

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

Summary

ID

NL-OMON43995

Source
ToetsingOnline

Brief title
ALZ2003

Condition

- Dementia and amnestic conditions

Synonym
Alzheimer's Dementia

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: Alzheimer's disease (AD), BACE inhibitor (BACEi), JNJ-54861911, reducing amyloid plaque formation

Outcome measures

Primary outcome

The primary efficacy endpoint is the change in the PACC score from baseline at

Month 54. The

PACC score is the sum of the transformed z-scores for each of the 4 components

of this measure

(Free and Cued Selective Reminding Test; Delayed Paragraph Recall score on

Logical Memory from

Wechsler Memory Scale; Coding Subtest from the Wechsler Adult Intelligence

Scale IV; and Mini-

Mental State Examination Total score).

Secondary outcome

The key secondary efficacy endpoint is the change from baseline at Month 54 on

CFI (total score). Other secondary efficacy endpoints include the following:

the change from baseline in the ADCS-ADL-PI total score at Month 54; the change

from baseline in the RBANS total scale score at

Month 51; the change from baseline in the NAB-DLTs for Memory and Attention at

Month 54; and the change from baseline in the CDR-Sum of Boxes (CDR-SB) at

Month 54.

Study description

Background summary

Alzheimer*s disease (AD) is a fatal neurodegenerative disease that is manifested by progressive cognitive deficits and memory loss, as well as by behavioral problems such as anxiety. With the increasing number of elderly in the population, AD is a growing medical concern. No treatment is currently available that targets the underlying cause of these symptoms.

The hallmark pathologic features of AD are neurofibrillary tangles, which consist of hyperphosphorylated tau protein and amyloid plaques, whose main constituent is amyloid-beta (Aβ). In amyloid plaques, Aβ1-42 peptide is overrepresented relative to other forms of Aβ (eg, Aβ1-40). Aβ1-42 has a high tendency to aggregate, forming oligomers and fibrils as well as amyloid plaques. The oligomers and fibrils of Aβ formed immediately after amyloid precursor protein (APP) cleavage have been demonstrated to be neurotoxic. Aβ accumulation and amyloid deposition are thought to be early, potentially initiating events in the pathogenesis of AD, formulated as the amyloid cascade hypothesis.

Convergent data from positron emission tomography (PET) amyloid imaging and cerebrospinal fluid (CSF) markers in both genetic and sporadic forms of AD suggest that the pathophysiological process begins many years prior to the onset of dementia. The accumulation of Aβ in particular is thought to be a very early event that may trigger and accelerate neurodegeneration and lead to cognitive decline. Thus, very early intervention with an anti-amyloid agent may hold the greatest promise for slowing the inexorable disease progression of AD.

Agents that prevent the formation of Aβ overall, or Aβ1-42 specifically, have been proposed as potentially disease-modifying agents for the treatment of AD. Aβ is generated from the APP as mentioned above. The N-terminus of Aβ is cleaved by the β-site amyloid precursor protein cleaving enzyme 1 (BACE-1), and then γ-secretase cleaves the C-terminal end. BACE-1 cleavage is the first and rate-limiting step. As such, it is hypothesized that BACE-1 inhibition can reduce the production of toxic amyloid forms and impact the progression of AD. The observed correlation between the catalytic efficiency of BACE-1 for its substrate APP and the occurrence of AD

supports this hypothesis. The Swedish APP mutant (KM670/671NL), which is a more efficient substrate for BACE-1 (±10x), causes a rare familial form of AD that is inherited
in a dominant Mendelian fashion. At the other end of the spectrum, an allelic variant of APP (A673T), which is a less efficient substrate for BACE-1 (± 0.5x), is protective against sporadic AD in the wider population.

JNJ-54861911 is an orally administered BACE inhibitor (BACEi) being developed for the treatment of AD. JNJ-54861911 reduces production of Aβ fragments by inhibiting BACE-1 processing of APP, with the aim of reducing amyloid plaque formation.

Study objective

Primary Objective:
The primary objective of this study is to determine whether treatment with JNJ-54861911 slows cognitive decline compared with placebo treatment, as measured by a composite cognitive measure, the Preclinical Alzheimer Cognitive Composite (PACC), in amyloid-positive subjects who are asymptomatic at risk for developing Alzheimer*s dementia.

Secondary Objectives:
- Change from Baseline in Cognitive Function Index (CFI) to Month 54
- Change from Baseline in Alzheimer*s Disease Cooperative Study Activities of Daily Living - Prevention Instrument (ADCS-ADL-PI) Total Score to Month 54
- Change from Baseline in Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Total Scale Score to Month 51
- Change from Baseline in Clinical dementia Rating Sum of Boxes (CDR-SB) Score to Month 54
- Change from Baseline in Neuropsychological Assessment Battery Daily Living Tests (NAB-DLTs) Score to Month 54
- Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)
- Trough Plasma Concentration (Ctrough) of JNJ54861911
- Area Under the Plasma Concentration Time Curve from 0 to tau Hours After Dosing (ACUCtau)
- Change in mean Cerebral Fibrillar Amyloid Accumulation
- Change from Baseline of Neurodegeneration by Assessing Changes in imaging Biomarkers

Study design

This is a multicenter, double-blind, placebo-controlled, randomized, parallel-group study assessing the efficacy and safety of JNJ-54861911 over approximately 4.5 years of treatment in subjects (60 to 85 years of age) who are asymptomatic and at risk for developing Alzheimer*s dementia due to

evidence of elevated amyloid accumulation based on CSF or amyloid PET imaging. The study will be conducted in an outpatient setting, with a planned recruitment of approximately 1,650 randomized subjects (550 per treatment group). It is planned that a total of 1,155 subjects (38 5per group) will complete the Month 54 (Year 4.5) assessments, assuming a 30% attrition rate. The number of subjects randomized can be increased based on blinded sample size re-estimation, but the study enrollement will be capped at 2400 subjects. Some design elements of this Phase 2b/3 study can be modified during the study based on emerging external data. The potential changes include optimization of the primary endpoint and the timing of the primary analysis. Sample size may be adjusted using blinded aggregated study data. Unblinded interim analyses (IAs) may be performed to assess futility.

The study will consist of 3 phases: a screening phase of approximately 90 days in which subject eligibility will be assessed; a double-blind treatment phase during which eligible subjects will receive a fixed dose of randomly assigned study drug once daily for up to 4.5 years; and a follow-up phase to be conducted 7 to 28 days after the last dose of study drug (ie, after the last visit of the double-blind treatment phase). In addition to the longitudinal follow-up of subjects* screening biomarker(s) (ie, amyloid PET and/or CSF), subjects will have the opportunity to participate in 1 or more longitudinal pharmacodynamic (PD) substudies: CSF for biomarkers and drug exposure, amyloid PET imaging, and tau PET imaging. When sufficient longitudinal biomarker data has been collected, further collection of biomarker data can be terminated to reduce patient and site burden.

Following screening and baseline evaluations, subjects who meet all of the study inclusion criteria and none of the study exclusion criteria will be assigned randomly to 1 of 2 doses of JNJ-54861911 or placebo in a 1:1:1 ratio. Randomization will be stratified by country and by apolipoprotein E (APOE) *4 carrier status (carrier vs noncarrier). The dose levels of JNJ-54861911 selected are in the dose range expected to be well tolerated and to achieve a substantial reduction in CSF Aβ at steady state based on results of single and multiple ascending dose studies in healthy elderly subjects and preliminary results in a population with predementia Alzheimer*s disease.

An independent Data Monitoring Committee (DMC) will be commissioned for this study to review safety and other relevant data on an ongoing basis, and to review findings from the potential IAs and make recommendations based on prespecified decision rules.

Intervention

During the double-blind treatment phase, the randomly assigned investigational product will consist of JNJ-54861911 5 mg (administered as one tablet JNJ-54861911 of 5 mg), JNJ-54861911 25 mg (administered as a single tablet JNJ-54861911 of 25 mg) or placebo (administered as 1 corresponding placebo

tablet). All study medication tablets will be identical in appearance. Study medication should be self-administered by subjects orally once daily with a glass of noncarbonated water, preferably between
07:00 and 11:00 hours (7:00-11:00 AM).
The first dose of study drug should be self-administered by the subject at the site as described above, and at all subsequent scheduled visits, subjects should self-administer their study medication on site. Subjects having difficulties reaching the site during morning hours will be permitted to administer drug later during the day (eg, with lunch), but every attempt should be made to ensure consistency in the time of study drug administration during the course of the study. Subjects who forget to take their daily dose in the morning as directed will be instructed to take
their daily dose later that day, as long as it is before 1600 hours (4:00 PM). Subjects who forget to take their morning dose of study drug and cannot take their daily dose of study drug before 1600 hours (4:00 PM) will be instructed not to take any dose during that day and to resume
dosing the following day. Subjects who are no longer capable of ensuring compliance with their daily medication schedule,
in the judgment of the investigator (eg, due to progression to dementia), will be required to have support in the handling and administration of study drug (eg, study informant, partner, caregiver, or nurse practitioner).

For some blood tests it is aksked if feasible not to eat or drink before. This applies for the visits Screening visit GH, M0, M1, M2, M3, M4, M5, M6, M8, M10, M12, M15, M18, M21, M24, M27, M30, M33, M36, M39, M42, M45, M48, M51, M54, ET and follow-up visit.

Study burden and risks

Participation of the subject will be approximately 5 years. During the double-blind treatment phase, subjects will be asked to orally self-administer once daily JNJ-54861911 5 mg (as one 5-mg tablet of JNJ-54861911), JNJ-54861911 25 mg (administered as one 25-mg tablet of JNJ-54861911), or placebo (administered as 1 matching placebo tablet) with a glass of noncarbonated water, preferably between 0700 and 1100 hours (7:00-11:00 AM).

Subjects who participate will visit the site approximately 32 times. Every month for the first 3 months, at months 8,9,10 and 12, and then every 3 months afterwards. The subject will return to the study clinic for a follow-up exam 1-4 weeks after the last dose of study drug, or the end of the treatment period in the study.
After the end of the study, the subject will be contacted by the study team of the site by telephone approximately every 6 months for up to 5 years.

The screening phase consists of 4 primary screening steps as shown below. In addition, part of the
baseline cognitive, functional, and medical resource utilization/health

outcomes measures will be
performed during the screening phase, as described further below. Assessments for Step III (MRI) and
Step IV (Elevated Amyloid Accumulation) may only be performed after the subject is determined to be
still eligible for the study after review of results from Step I (General Health) and Step II (Clinical
Scales).

There may be risks associated with taking investigational product (for adverse events see section E9) which have (not) been identified in the studies completed to date. Participation in this study does not guarantee that the patient will receive any medical benefit. During the investigation, his / her condition may remain the same or deteriorate, regardless of the treatment group to which he / she has been assigned. It is possible that the patient has been allocated to the placebo arm and may receive no active investigational product.

Contacts

Public
Janssen-Cilag

Turnhoutseweg 30
Beerse 2340
BE
Scientific
Janssen-Cilag

Turnhoutseweg 30
Beerse 2340
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subject must be a man or woman 60 to 85 years of age, inclusive, at time of informed consent. Subjects 60 to 64 years of age must also have 1 of the following 3 conditions:
a. A positive family history for dementia (minimum of 1 first degree relative)
b. A previously known APOE *4 genotype
c. A previously known biomarker status demonstrating elevated amyloid accumulation in CSF or PET
2. Subjects must have a global CDR score of 0 at screening.
3. Subjects must be able to read and write and must have adequate hearing and visual acuity to complete the psychometric tests. The legally acceptable representative must also be able to read and write.
4. Subjects must have evidence of elevated amyloid accumulation by means of either:
a. Low CSF Aβ1-42 levels at screening
b. A positive amyloid PET scan at screening (depending on the site's PET capability)
Note: The cut off value for CSF Aβ1-42 will be based on the value established by the central CSF screening laboratory and specified in a separate laboratory manual. Screening amyloid PET scans will be assessed centrally by a qualified reader for inclusion based on predefined criteria as documented in the imaging manual.

Exclusion criteria

1. Subject is receiving an acetylcholinesterase (AChE) inhibitor and/or memantine at any time during screening or Day 1 predose.
2. Subject has evidence of any brain disease other than potential very early signs of AD (eg, mild hippocampal atrophy) or typical age-related changes (eg, mild white matter hyperintensity on MRI). The screening MRI scan shall be interpreted by a local radiologist and a central radiologist for exclusionary findings prior to enrolling the subject. Both local and central interpretations shall be reviewed by the investigator; in case of disagreement, the central radiology report will be used to determine subject eligibility in consultation with the sponsor*s medical monitor.
3. Subject has any other abnormality that could cause a possible cognitive deficit (including, but not limited to, vascular encephalopathy or large strokes [as imaged by cerebral MRI]).
4. Subject has any contraindications for MRI (eg, prostheses, implants, claustrophobia,

pacemaker)
5. Subject has met criteria for dementia or has a brain disorder that can cause dementia.
6. Subject has evidence of familial autosomal dominant AD (mutation identified in the family and/or subject prior to randomization).
7. Subject has a history of or current thyroid disease or thyroid dysfunction, which is currently uncontrolled, unevaluated, or untreated. Subjects treated for thyroid disease may be enrolled following review of their diagnostic and treatment history records by the investigator and with written concurrence by the sponsor*s medical monitor to ensure disease/treatment stability and compliance.
8. Subject has a vitamin B12 or folic acid deficiency. A low vitamin B12 level is exclusionary unless follow-up labs (homocysteine and methylmalonic acid) indicate that the value is not physiologically significant. Subjects treated with vitamin B12 or folic acid may be enrolled following review of their diagnostic and treatment history records by the investigator and with written concurrence by the sponsor's medical monitor to ensure disease/treatment stability and compliance.
9. Subject has chromosome 21 trisomy (Down syndrome).
10. Subject has a history within the past 2 years or current diagnosis of significant psychiatric illness, per the most current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM) (including but not limited to major depressive disorders and anxiety disorders) (subjects who are symptom free or with minimal limited symptoms may be included); or the subject has a current diagnosis or history of schizophrenia or bipolar disorder.

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:	Pending
Start date (anticipated):	04-02-2016

Enrollment:	46
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	JNJ-54861911
Generic name:	JNJ-54861911

Ethics review

Approved WMO Date:	30-09-2015
Application type:	First submission
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	14-03-2016
Application type:	First submission
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	25-07-2016
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	20-10-2016
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	21-10-2016
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	16-12-2016

Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	21-12-2016
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	08-03-2017
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	27-03-2017
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	12-04-2017
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	21-04-2017
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	24-04-2017
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	09-08-2017
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)

Approved WMO Date:	08-09-2017
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	13-12-2017
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Not approved Date:	31-01-2018
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	27-03-2018
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	03-05-2018
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	09-07-2018
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	16-10-2018
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)

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	EUCTR2015-000948-42-NL
CCMO	NL54739.072.15