A Double-blind, Placebo-Controlled, Randomized, 4-Week, Multiple-Dose, Proof-of-Mechanism Study in Subjects with Early Alzheimer*s Disease Investigating the Effects of JNJ-54861911 on Aß Processing in CSF and Plasma

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This proof-of-mechanism (POM) study in subjects with early AD, being subjects asymptomatic at risk for AD and subjects with pAD, is performed to confirm a drug interaction with the intended enzyme (BACE) at the intended target location (brain) by...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neurological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON40301

Source
ToetsingOnline

Brief title
Phase 1 B: JNJ-54861911 in Subjects with Early Alzheimer*s Disease

Condition

- Neurological disorders NEC

Synonym
Early Alzheimer□s disease; cognitive impairment

Research involving

Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: BACE inhibitor, Early Alzheimer□s Disease, JNJ-54861911

Outcome measures

Primary outcome

The primary objectives of this study are:

• To determine the effect of JNJ-54861911 on the level of Aβ1-40 in CSF following 4 weeks of treatment in subjects with early AD, i.e., asymptomatic subjects at risk for AD and subjects with pAD at the intended target dose range;

• To determine the effect of JNJ-54861911 on level of Aβ1-40 in plasma following 4 weeks of treatment in subjects with early AD at the intended target dose range.

• To investigate the plasma PK and metabolism of JNJ-54861911 following 4 weeks of treatment in subjects with early AD;

• To investigate the CSF exposure of JNJ-54861911 following 4 weeks of treatment in subjects with early AD;

• To investigate the safety and tolerability of JNJ-54861911 after multiple-dose administration in the anticipated target dose range in subjects with early AD.

Secondary outcome

The secondary objectives of this study are:

• To determine the effect of JNJ-54861911 on levels of Aβ fragments (Aβ1-37, Aβ1-38, and Aβ1-42) in CSF following 4 weeks of treatment in subjects with early AD at the intended target dose range;

•To determine the effect of JNJ-54861911 on levels of Aβ fragments (Aβ1-37, Aβ1-38, and Aβ1-42) in plasma following 4 weeks of treatment in subjects with early AD at the intended target dose range;

• To evaluate the effect of JNJ-54861911 on APP fragments in CSF (sAPPα, sAPPβ, totalAPP) in subjects with early AD following 4 weeks of treatment at the intended target dose range.

• To evaluate the relationship between central and peripheral effects on Aβ1-40 of JNJ-54861911 in subjects with early AD following 4 weeks of treatment at the intended dose range.

The exploratory objectives of this study are:

• To explore effect of baseline BACE levels in CSF on reduction of CSF Aβ fragments (Aβ1-37, Aβ1-38, Aβ1-40 and Aβ1-42) following 4 weeks of treatment with JNJ-54861911 in subjects with early AD at the intended target dose range.

• To explore the change in BACE levels in CSF following 4 weeks of treatment with JNJ-54861911 in subjects with early AD at the intended target dose range.

• To explore the effect of JNJ-54861911 on exploratory biomarkers downstream of the Aβ cascade/pathway in CSF (e.g., p-Tau/tau) in subjects with early AD following 4 weeks of treatment at the intended target dose range.

• To explore the effect of JNJ-54861911 on amyloid precursor protein (APP) fragments in plasma (sAPPα, sAPPβ, totalAPP) following 4 weeks of treatment at

the intended target dose range.

• To explore the effect of JNJ-54861911 on cognition in subjects with early AD

following 4 weeks of treatment at the intended target dose range.

Study description

Background summary

Alzheimer's disease (AD) is a neurodegenerative disease associated with aging. With the increasing number of elderly in the population, AD is a growing medical concern. Currently available therapies for AD merely treat the symptoms of the disease and include acetylcholinesterase inhibitors to improve cognitive properties as well as anxiolytics and antipsychotics to control the behavioral problems frequently associated with AD. Agents that prevent the formation of Aβ overall or Aβ1-42 specific have been proposed to be disease-modifying agents for the treatment of AD. Inhibitors of BACE1 prevent the formation of Aβ1-42 as well as Aβ1-40, Aβ1-38 and Aβ1-43 and would be potential therapeutic agents in the treatment of AD. JNJ-54861911 is a BACE inhibitor (BACEi) being developed by Janssen Research and Development (JRD) for the treatment of (prodromal) AD by reducing production of Aβ fragments.This will be the first study with JNJ-54861911 in the intended target population i.e, early Alzheimer*s disease patients, following prior studies in healthy young and older subjects.

Study objective

This proof-of-mechanism (POM) study in subjects with early AD, being subjects asymptomatic at risk for AD and subjects with pAD, is performed to confirm a drug interaction with the intended enzyme (BACE) at the intended target location (brain) by showing a potential drug effect on cell biology in the desired manner and direction based on a biomarker read out (Aβ) in cerebrospinal fluid (CSF) at the intended target dose range. The inhibition of BACE in the brain can be directly assessed by measuring Aβ lowering in CSF.

Study design

This is a multi-center, double-blind, placebo-controlled, randomized multiple dose, proof-of-mechanism (POM) study in subjects with early AD i.e., subjects asymptomatic at risk for AD and subjects with prodromal AD. This 4 week study will include a total of approximately 48 subjects, diagnosed as asymptomatic at risk for AD (n=24) or prodromal AD (n=24). For all enrolled subjects this study will consist of an 8-week eligibility screening period, a 4-week double-blind treatment period and a follow-upexamination. The study will be an outpatient

study.
The maximal study duration for a subject will be 14 weeks.
Within each study population group, subjects will be assigned randomly to 1 of 3 treatment groups i.e. placebo or one of 2 dose levels of JNJ-54861911 at a ratio of 1:1:1. As such each treatment group will consist of 8 subjects asymptomatic at risk for AD and 8 subjects with pAD.
After giving written informed consent, subjects may be screened over a period of up to 56 days to assess their eligibility for the study according to the inclusion and exclusion criteria defined for this study. All subjects with early AD participating in this study being subjects asymptomatic at risk for AD or subjects with prodromal AD will follow the same study procedures unless otherwise indicated.
A 4-step screening process will be performed. During Step I, the subject*s general health will be assessed. Note that all subjects having a contraindication to a lumbar puncture are not eligible for the study. In Step II the subject*s cognitive status will be graded using the Clinical Dementia Rating Scale (CDR) (baseline assessment). In order to perform the CDR the subjects need to be accompanied by their informant (e.g., partner, relative or friend). Subjects with a CDR of 0 are clinically asymptomatic (in relation to cognitive deficits/dementia) and subjects with a CDR of 0.5 are expected to be consistent with prodromal AD (pAD). Subjects with a CDR global rating score higher than 0.5 will be excluded from further participation. Evidence of any brain disease, other than potential very early signs of AD (e.g., mild hippocampal atrophy) or typical age related changes (e.g., mild white matter hyperintensity on MRI) will be assessed in Step III. Finally in Step IV, amyloid deposition in the intended target patient group (early AD) will be assessed by either 1) baseline CSF Biomarkers (A*1-42) at screening, or 2) an amyloid positron emission tomography (PET) scan (optional) or both depending on a site*s PET capability and practical challenges. A CSF sample (12 mL) may be collected by single lumbar puncture to assess eligibility between Day -28 to Day -10 inclusive.

Intervention

Subjects will receive either JNJ-54861911 (tablets) or placebo from Day1 to Day28. There are 3 treatment groups in this study:
• Group 1: 10 mg JNJ-54861911
• Group 2: 50 mg JNJ-54861911
• Group 3: placebo

Study burden and risks

A medicine can always cause unwanted effects called side effects. Since this is the fourth time that JNJ-54861911 is being given to humans there are currently no data on risks in a human population.
Based on animal studies in mice, rats and dogs, some possible side effects of

JNJ-54861911 in humans might include, but are not limited to, the following:
• QT prolongation: a heart rhythm disorder.
• Epileptic seizure.

These side effects are only seen at higher doses. ECGs will be monitored during all parts of the study to identify potential risks early. Regarding the epileptic seizures, it has been agreed that the exposure in human studies will stay lower than the exposure that resulted in seizures in dogs.
There may be risks with the use of JNJ-54861911 that are not yet known.

Side effects from tests:
• Blood draw: Taking blood may cause bruising at the place where the needle goes into the skin. Fainting, and in rare cases infection, may occur.
• ECG: There is generally no risk with having an ECG. The sticky patches may pull your skin or cause redness or itching.
• CSF Sampling: Possible theoretical risks associated with the spinal punctures include: procedural pain during insertion of needle, spinal headache, also called post-dural puncture headache (a complication of puncture of the dura mater (one of the meninges that surround the brain and spinal cord)), epidural (outside of the spinal cord) infection, spinal cord trauma / nerve root trauma, spinal/epidural hematoma and cerebral herniation (very high pressure that occurs inside the brain). Post-dural puncture headache is the most common and most important complication inherent to the spinal puncture. The possible introduction of an infection into the CSF (e.g. resulting in meningitis) is a rare complication. To avoid this, the lumbar puncture is performed under strict sterile conditions. Prior to the puncture, you will be examined thoroughly for (possible) topical infections or local dermatological condition at the puncture site, of which their presence will lead to exclusion participation in the study. All CSF collections will be performed under aseptic conditions. Irritation of nerve roots may be caused upon insertion of the needle, thereby inducing paraesthesia (a sensation of tickling, tingling, burning, pricking, or numbness) in the affected skin area. This is usually benign and self-limiting: withdrawal of the needle results in relaxation of the nerve root and resolution of the symptoms. Cerebral herniation (due to pre-existing intracranial hypertension) and a spinal epidural haematoma are very rare complications.
• MRI Risk: There are no known risks or side effects with having an MRI. If a contrast material is used, your study doctor will tell you about possible side effects or allergic reaction.
• Risk of Information on measurement of the concentration of amyloid-beta in cerebrospinal fluid: During the screening, the concentration of amyloid-beta in cerebrospinal fluid will be measured. The result may indicate a higher risk to develop Alzheimer Disease. Only subjects with different concentration of amyloid-beta in cerebrospinal fluid will participate in the study. Your physician can inform you on the implications and you can discuss if you want to know this information or not.
Other

During the study the condition of the subject may remain the same or get worse.

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

Each potential subject must satisfy all of the following criteria to be enrolled in the study unless otherwise specified:;1. Criterion Modified per amendment;1.1 Subjects with prodromal AD: Subject must be a man or woman between 50 and 90 years of age, inclusive.;Subjects who are asymptomatic at risk for AD: Subject must be a man or woman between 60 and 85 years of age, inclusive.;2. Criterion modified per amendment;2.1 Subjects must have had sufficient education or work experience to exclude mental retardation and must be able to read and write.;3. Criterion Modified per amendment;3.1 Subjects with prodromal AD: Subjects must have a CDR score of 0.5 consistent with MCI.;Subjects who are asymptomatic at risk for AD: Subjects must have a CDR score of 0 and as such rated as normal.;4. Criterion

modified per amendment;4.1 Subjects must have evidence of amyloid deposition by means of either:;a) low CSF Aß1-42 levels at screening;b) a positive amyloid positron emission tomography (PET) amyloid scan at screening (optional depending on the site*s PET capability);;5. Subjects must have a body mass index (BMI=weight/height^2) between 18 and 35 kg/m2, inclusive, at screening.;6. Before randomization, a woman must be not of childbearing potential: premenarchal; postmenopausal (>=50 years of age with amenorrhea for at least 12 months; permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy); or otherwise be incapable of pregnancy,;7. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control e.g., either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also agree not to donate sperm during the study and for 3 months after receiving the last dose of study drug. In addition, their female partners should also use an appropriate method of birth control for at least the same duration.;8. Subjects must be otherwise healthy for their age group or medically stable with or without medication on the basis of physical examination, medical history, vital signs, and 12-lead ECG performed at screening or at baseline. If there are abnormalities, they must be consistent with the underlying illness in the study population.;9. Subjects must be otherwise healthy or medically stable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel [including liver enzymes, other specific tests], hematology, or urinalysis are outside the normal reference ranges, the subject may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the subject*s source documents and initialed by the investigator.;10. Subjects must have a reliable informant (relative, partner, friend, *);11. Subject must be able to be compliant with self-administration of medication;12. Subject must be able to swallow drug as a whole.;13. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.;14. Subject must sign an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.

Exclusion criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study unless otherwise specified:;1. Criterion modified per amendment;1.1 Subject has evidence of any brain disease, other than potential very early signs of AD (e.g. mild hippocampal atrophy) or typical age related changes (e.g. mild white matter hyperintensity on MRI) or any other abnormality (e.g. folic acid/Vitamin B12 deficiency) that could explain a possible cognitive deficit (including, but not limited to vascular encephalopathy or strokes, as imaged by cerebral MRI and Major Depression, as defined by DSM-IV criteria).;2. Subject has been diagnosed with dementia due to AD, due to other diseases, or with AD and contribution of other disorders (mixed dementia):;Degenerative dementia such as: frontal lobe dementia, cortical basal dementia, progressive supranuclear palsy and primary progressive aphasia; dementia associated with significant Parkinsonism, e.g. Parkinson*s Disease, diffuse Lewy body disease; multi infarct

dementia (vascular dementia,); primary and secondary brain tumor; genetic disorder associated with dementia (Huntington*s disease, Pick*s disease, fronto-temporal dementia, hereditary ataxias, early-onset familial AD); dementia due to sporadic or familiar forms of prion diseases , e.g. Creutzfeldt-Jakob disease; diffuse white matter disease; normal-pressure hydrocephalus; head injury leading to cognitive decline; recently diagnosed or untreated thyroid disease; vitamin B12 or folic acid deficiency; drug and medication intoxication; severe depression (pseudo dementia); chromosome 21 trisomy (Down Syndrome); neurosyphilis; HIV dementia;;3. Subject has evidence of familial autosomal dominant Alzheimer*s Disease;4. Subject has any contra-indications for MRI (prostheses, implants, claustrophobia, pacemakers, etc.);5. Subject has a clinically significant abnormal physical- or neurological examination, vital signs or 12-lead ECG (incl. QTc>450msec for males and females, Left Bundle Branch Block, AV Block second degree or higher, permanent pacemaker or implantable cardioverter defibrillator (ICD)) at screening or baseline (Day 1 predose), which in the opinion of the investigator is not appropriate and reasonable for the population under study.;6. Criteria modified per amendment;6.1. Subject has a relevant history of or current neurological disease other than asymptomatic at risk for AD/pAD/MCI (including any history of post-lumbar puncture headache), which in the opinion of the investigator may make interpretation of possible new neurological signs or symptoms difficult.;7. Criteria modified per amendment;7.1.Subject has a history of or current liver or renal insufficiency; clinically significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, hematologic, rheumatologic, psychiatric, or metabolic disturbances (e.g. instable situation needing monitoring or regular dose adaptations).;8. Subject has a history of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence).;9. Subject has a history of spontaneous, prolonged or severe bleeding of unclear origin.;10. Criterion modified per amendment.;10.1. Subject has a history of epilepsy or fits or unexplained black-outs other than vasovagal collapse within 10 years before screening.;11. Criterion deleted per amendment.;12. Subject has current anemia.;13. Subject has a history of positive tests for hepatitis B surface antigen (HBsAg) or hepatitis C antibody (anti-HCV) positive, or other clinically active liver disease, or tests positive for HBsAg or anti-HCV at Screening.;14. Subject has a history of human immunodeficiency virus (HIV) antibody positive, or tests positive for HIV at Screening;15. Subject has a history of drug or alcohol abuse according to Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-IV) criteria within 6 months before Screening or positive test result(s) for alcohol and/or drugs of abuse (including barbiturates, opiates, cocaine, cannabinoids, amphetamines and benzodiazepines) at Screening or baseline (Day 1 predose) (except if related to current treatment e.g. benzodiazepines).;16. Subject has taken any disallowed therapies as noted in Section 8, Concomitant Therapy before the planned first dose of study drug.;17. Subject has a clinically significant acute illness within 7 days prior to study drug administration.;18. Subject has known allergies, hypersensitivity, or intolerance to JNJ-54861911 or its excipients (refer to Investigator's Brochure and its addenda);For more please refer protocol page no. 58-62

Study design

Design

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):	06-03-2014
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NAP
Generic name:	NAP

Ethics review

Approved WMO Date:	13-11-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-12-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	12-05-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-06-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-03-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-04-2016
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	EUCTR2013-003036-69-NL
ClinicalTrials.gov	NCT01978548

Register	ID
CCMO	NL46452.056.13