A Phase 2a Randomized, Double-blind, Placebo-Controlled, Parallel-Group, Multi-center Study Investigating the Safety and Tolerability of JNJ-54861911 in Subjects in the Early (Predementia) Alzheimer*s Disease Spectrum

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This safety study in subjects in the early (predementia) AD spectrum is performed to investigate primarily the safety and tolerability of JNJ-54861911 during 6 months of treatment.

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

Summary

ID

NL-OMON44318

Source
ToetsingOnline

Brief title
Phase 2A: JNJ-54861911 in Early Alzheimer*s Disease

Condition

- Neurological disorders NEC

Synonym
cognitive impairment, Early Alzheimer□s Disease

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 objective of this study is to investigate the longer-term safety and tolerability of JNJ 54861911 during 6 months of treatment in subjects in the early (predementia) AD spectrum.

Secondary outcome

Secondary Objectives

The secondary objectives of this study are:

• To assess the relationship of dose and exposure of JNJ-54861911 with safety in subjects in the early AD spectrum.

• To evaluate the pharmacokinetics over time of JNJ-54861911 in subjects in the early AD spectrum.

• To assess changes in cerebrospinal fluid (CSF) Aβ species (Aβ1-37, Aβ1-38, Aβ1-40, Aβ1-42) and soluble amyloid precursor protein (sAPP) fragments (sAPPα, sAPPβ, total sAPP) at 6 months of treatment with JNJ-54861911 compared to placebo in subjects in the early AD spectrum.

• To assess changes in plasma Aβ1-40 and sAPP fragments (sAPPα, sAPPβ, total sAPP) at 6 months of treatment with JNJ-54861911 compared to placebo in

subjects in the early AD spectrum.

• To assess the relationship of changes in CSF and plasma Aβ species and sAPP fragments with safety in subjects in the early AD spectrum.

Exploratory Objectives

• To assess changes in brain volumes and cortical thickness (regional and global) from baseline to Month 6 by volumetric magnetic resonance imaging (MRI) during treatment with JNJ-54861911 compared to placebo in subjects in the early AD spectrum.

• To explore changes in CSF p-tau, t-tau and additional downstream biomarkers of neuroinflammation, neurodegeneration, and neuronal injury at 6 months of treatment with JNJ 54861911 compared to placebo in subjects in the early AD spectrum.

• To explore the relationship of dose and exposure at 6 months of JNJ-54861911 with changes in CSF p-tau, t-tau or additional downstream biomarkers of neuroinflammation, neurodegeneration, and neuronal injury in subjects in the early AD spectrum.

• To explore the relationship of dose and exposure at 6 months of JNJ-54861911 with changes in CSF and plasma Aβ species (Aβ1-37, Aβ1-38, Aβ1-40, Aβ1-42) and sAPP fragments (sAPPα, sAPPβ, total sAPP) in subjects in the early AD spectrum.

• To explore changes in cognitive measures at 6 months of treatment with JNJ-54861911 compared to placebo in subjects in the early AD spectrum.

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 early AD by reducing production of Aβ fragments. This will be the second study with JNJ-54861911 in subjects in the early (predementia) AD spectrum, including subjects described as asymptomatic at risk for AD as well as subjects with prodromal Alzheimer*s disease (pAD).

Study objective

This safety study in subjects in the early (predementia) AD spectrum is performed to investigate primarily the safety and tolerability of JNJ-54861911 during 6 months of treatment.

Study design

This is a multi-center, double-blind, placebo-controlled, randomized, parallel-group study assessing the safety and tolerability of JNJ-54861911 over a 6-month treatment period in subjects in the early (predementia) AD spectrum. Approximately one-hundred (100) subjects in the early (predementia) AD spectrum will be enrolled.

Subjects enrolled in this study will be stratified by early (predementia) AD spectrum status (i.e. asymptomatic at risk [CDR = 0] vs. prodromal [CDR = 0.5]) to avoid imbalances between treatment arms. No minimum number of subjects per strata is defined.
For all enrolled subjects this study will consist of an eligibility screening period of at most 90 days, a 6-month double-blind treatment period and a follow-up examination. The study duration for each subject will be approximately 10 months.

It is intended that subjects who previously participated in study 54861911ALZ1005 will be allowed to be enrolled in this study, receiving the

same treatment as in study 54861911ALZ1005, (i.e., placebo, 10 mg or 50 mg once daily [q.d.] JNJ-54861911), provided they are still eligible based on the inclusion and exclusion criteria defined.

Eligible subjects, who did not previously participate in study 54861911ALZ1005, will be assigned randomly to 1 of 3 treatment groups i.e. placebo or one of 2 dose levels of JNJ-54861911 (i.e. 5 and 25 mg q.d.) at an approximate ratio of 1:1:1.

Intervention

Subjects will receive either JNJ-54861911 (tablets) or placebo during 6 months. There are 3 treatment groups in this study:
• Group 1: 5 mg JNJ-54861911
• Group 2: 25 mg JNJ-54861911
• Group 3: placebo

Study burden and risks

A medicine can always cause unwanted effects called side effects. In 12 previous clinical trials with JNJ-54861911 in humans, the dosing ranged from a single dose to up to 1 month of daily dosing. In these studies no specific risks were identified. Even the most common side effects were uncommon, in the range of 2-4% (constipation, diarrhea, vomiting, fatigue, nasopharyngitis, muscle stiffness, and sleepiness), and these were considered as either not related or doubtfully related to JNJ-54861911. Headache was seen in up to 20-30% of participants, but most likely related to CSF sampling procedures, as a known side effect of this procedure. Overall, the conclusion of these studies is that JNJ-54861911 was safe and well tolerated for the treatment durations studied. One trial that investigated the potential for a heart rhythm disorder, demonstrated that doses of 150mg per day have the potential to cause a clinically relevant heart rhythm disorder. Lower doses, e.g. 25mg, are not expected to have a relevant effect on the heart rhythm. Furthermore, ECGs will be monitored during all parts of the study to identify any potential risks.
In this ongoing clinical study where JNJ-54861911 is being administered for 6 months, the blood values of certain liver tests in some patients were increased, indicating potential for liver injury. Importantly, there were no symptoms clearly related to these elevations, and upon discontinuation of the drug, the liver tests have decreased toward normal, and there were no lasting effects. The further investigation of this signal is continuing, but there is potential that JNJ-54861911 can cause injury to the liver and therefore frequent monitoring of these liver tests will be included in ongoing clinical studies.
Based on animal studies in mice, rats, and dogs, additional possible side effects of JNJ-54861911 in humans might include, but are not limited to epileptic seizure and lightening of hair and skin. These side effects are only

seen at higher doses. In a 1-month dog toxicology study, short-lasting convulsions and tremors were reported within 2 hours after dosing. The highest dose in this study will be 25 mg/day. Plasma drug concentrations in human subjects dosed 25 mg/day were shown in a previous experiment to be approximately 30 times lower than the concentration that caused convulsions in the dog. The lightening of body hair has not been seen in all experiments and as well only at very high doses. It has not been observed in earlier studies in humans with JNJ-54861911. Detailed skin exams and a photo of your face, including your hair are included in this study to understand if any discoloration is seen related to JNJ-54861911.
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: A very small needle used to draw the CSF is never in contact with the spinal cord. Irritation of nerve roots may be caused upon insertion of the needle. This may cause a sensation of tickling, tingling, burning, pricking, or numbness to the skin area. Withdrawal of the needle results in relaxation of the nerve root and end of the symptoms.
* There may be slight discomfort or bruising of the skin where the needle was inserted, similar to what may occur when one gives blood.
* In less than 10% of cases individuals report a headache which usually responds to treatment with over-the-counter pain relievers. In very rare instances, more severe headache may occur. All precautions are taken to anticipate potential problems and minimize any risks.
• MRI Risk: There are no known risks or side effects with having an MRI. For this study no use of contrast material is planned. Tell your study doctor if you have a metal implants, including joint replacements or a pacemaker.
• OCT Risk: There are no known risks or side effects with having an OCT exam. If dilating eye drops are used during the OCT testing, those can interfere with your ability to drive or work for a few hours after the OCT procedure.
• PET: The amount of radiation used in a PET scan is low. It is about the same amount of radiation as in most CT scans. Also, the radiation doesn't last for very long in your body.
• Risk of Information on biomarker test: During the screening process biomarker testing will be performed. The result may indicate a higher risk to develop Alzheimer Disease. Only biomarker positive subjects 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. If you decide, that you don*t want to know this information, you may reconsider your study participation.

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;
1. Subjects in the early AD spectrum must have a global CDR score of 0 (asymptomatic at risk for AD) to 0.5 (pAD) inclusive;
2. Subjects with pAD: Subject must be a man or woman between 50 and 85 years of age, inclusive;
Subjects who are asymptomatic at risk for AD: Subject must be a man or woman between 65 and 85 years of age, inclusive; if rolling over from study 54861911ALZ1005, subjects aged 60 to 64 may be included
3. Subjects must have had sufficient education or work experience to exclude mental retardation and must be able to read and write;
4. Subjects must have evidence of amyloid pathology by means of either;
a) low CSF Aß1-42 levels at screening;

b) a positive amyloid PET scan at screening (depending on the site*s PET capability) by visual read;
5. Subjects must have a body mass index (BMI=weight/height²) between 18 and 35 kg/m2, inclusive, at screening;
6. Before randomization, a woman must be not of childbearing potential: 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. In case of questionable status qualified personal of the sponsor should be consulted to decide on the potential for inclusion of the subject;
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, if of childbearing potential, should also use an appropriate method of birth control for at least the same duration. Effective methods of contraception include prescription oral contraceptives, contraceptive injections, intrauterine device, double barrier method, contraceptive patch;
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 and not a potential cause of cognitive impairment, with written concurrence with the sponsor's medical monitor;
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, to be appropriate and reasonable for the population under study and not to be a potential cause of cognitive impairment, with written concurrence with the sponsor's medical monitor. 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, or friend). The informant must be willing to participate as a source of information and has at least weekly contact with the subject (contact can be in-person, via telephone or electronic communication). The informant must have sufficient contact such that the investigator feels he/she can provide meaningful information about the subject*s daily function;
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;
1. Subject has evidence of any brain disease, other than potential very early signs of AD or typical age-related changes or any other abnormality that could explain a possible cognitive deficit;
2. Subject has met criteria for dementia or has a degenerative brain disorder that can cause dementia;
3. Subject has evidence of familial autosomal dominant AD;
4. Subject has a history of or current thyroid disease, thyroid dysfunction and is currently untreated for it;
5. Subject has a vitamin B12 or folic acid deficiency;
6. History or presence of significant depression as defined by the most current DSM criteria.
7. Subject has chromosome 21 trisomy (Down Syndrome);
8. Subject has a history of or current evidence of neurosyphilis;
9. Subject has any contra-indications for MR;
10. Subject has a clinically significant abnormal physical- or neurological examination, vital signs at screening or baseline;
11. Subject has, in the opinion of the investigator, a clinically significant 12-lead ECG at screening or baseline;
12. Subject has a relevant history of or current neurological disease which in the opinion of the investigator may make interpretation of possible new neurological signs or symptoms difficult;In case of triplicate ECG recordings, 2 out of 3 individual recordings must have a QTc below 450
msec
13. Subject has a history of or current liver or renal insufficiency; clinically significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, hematologic, rheumatologic, psychiatric, or metabolic disturbances;
14. 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 is considered cured with minimal risk of recurrence);
15. Subject has a history of epilepsy or fits or unexplained black-outs other than vasovagal collapse within 10 years before screening;
16. Subject has current anemia;
17. Subject has a history of positive tests for hepatitis B surface antigen or hepatitis C antibody, or other clinically active liver disease;
18. Subject has a history of human immunodeficiency virus (HIV) antibody positive;
19. Subject has a history of drug or alcohol abuse according to most current DSM criteria within 6 months before Screening or positive test result(s) for alcohol or other drugs of abuse at Screening (except if related to current treatment e.g., benzodiazepines);
20. Subject has taken any disallowed therapies;
21. Subject has a clinically significant acute illness within 7 days prior to study drug administration;
22. Subject has known allergies, hypersensitivity, or intolerance to JNJ-54861911 or its excipients;
23. Subject has received an investigational drug (excluding the use of JNJ-54861911 in previous studies);

24. Subject is a man who plans to father a child while enrolled in this study or within 3 months after the last dose of study drug;
25. Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject or that could prevent, limit, or confound the protocol-specified assessments;
26. Subject has had major surgery, (e.g., requiring general anesthesia) within 8 weeks before screening, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 4 weeks after the last dose of study drug administration;
27. Subject has a history of spontaneous, prolonged or severe bleeding;
28. Subject has donated one or more units of blood or acute loss of an equivalent amount of blood within 90 days prior to study drug administration;
29. Subject has a topical infection or local dermatological condition at the puncture site prior to puncture that may compromise the lumbar puncture;
30. Subject has a pigmentation abnormality of the skin such as vitiligo;
31. Subject has signs of increased intracranial pressure;
32. Subject has a current or recent history of clinically significant suicidal ideation within the past 6 months, or a history of suicidal behavior within the past year;
33. Subject is an employee of the investigator or study site, as well as family members of the employees or the investigator;
34. Subject has any condition that would compromise the well-being of the subject or the study or prevent the subject from meeting or performing study requirements;
35. Only for subjects who will have an optional PET scan performed at screening: Subject has past or planned exposure to ionizing radiation that in combination with the planned administration with study amyloid PET ligand would result in a cumulative exposure that exceeds local recommended exposure limits;
36. Subject is unable to comply with the study-specific requirements.

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):	09-03-2015
Enrollment:	5
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	07-10-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-11-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-02-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-02-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-04-2015

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-04-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-02-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-02-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-04-2016
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	EUCTR2014-002159-24-NL
ClinicalTrials.gov	NCT02260674
CCMO	NL50421.056.14