A 2-Part Randomized, Placebo-Controlled, Double-Blind, Single and Multiple Ascending Dose Study to Investigate Safety and Tolerability, Pharmacokinetics and Pharmacodynamics of JNJ-63733657 in Healthy Subjects and Subjects With Alzheimer*s Disease

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

Summary

ID

NL-OMON48645

Source
ToetsingOnline

Brief title
JNJ-63733657 SAD/MAD FIH study

Condition

- Neurological disorders NEC

Synonym
Alzheimer□s Disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Alzheimer□s Disease, JNJ-63733657, Pharmacodynamics, Pharmacokinetics

Outcome measures

Primary outcome

1. Assess the safety and tolerability of JNJ-63733657 following single

ascending IV dose administration in healthy subjects (Part 1).

2. Assess the safety and tolerability of JNJ-63733657 following multiple

ascending IV dose administrations in subjects with prodromal or mild AD; Part

2).

Secondary outcome

1. Pharmacokinetics of JNJ-63733657 in Serum en CSF (Part 1)

2. Immunogenicity of JNJ-63733657 in Serum (Part 1)

3. Pharmacodynamics of JNJ-63733657 in CSF (Part 1)

4. Pharmacokinetics of JNJ-63733657 in Serum en CSF (Part 2)

5. Immunogenicity of JNJ-63733657 in Serum (Part 2)

6. Pharmacodynamics of JNJ-63733657 in CSF (Part 2)

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 target symptomatic treatment of the disease and include acetylcholinesterase inhibitors to improve cognitive properties and NMDA receptor antagonist (memantine) to control behavioral problems associated with AD.

The current main therapeutic approaches for drug development for the treatment of AD are the prevention of amyloid (plaque) formation and tau aggregation (tangles). Inhibition of the β-site amyloid precursor protein cleaving enzyme (BACE) and anti-amyloid antibodies are already in clinical testing for prevention and clearance of amyloid β aggregation. Tau immunotherapy is currently considered a promising approach to target prevention of tau spread with several clinical programs underway.

JNJ-63733657 is a humanized immunoglobulin G (IgG)1/ monoclonal anti-tau antibody. JNJ-63733657*s proposed mechanism of action is prevention of spreading of tauopathy.

JNJ-63733657 is being developed by Janssen Research and Development for the treatment of AD, namely the prevention or slowing of cognitive decline.

Study objective

This will be the first study with JNJ-63733657 in humans to investigate the safety, tolerability and pharmacokinetics of JNJ-63733657 and to explore potential pharmacodynamic (PD) effects in healthy subjects following single dose administration and in subjects with prodromal or mild AD following multiple dose administration. Results of this study will facilitate the design of a proof-of-concept study in subjects with AD.

Study design

This will be a 2 part, double-blind, placebo-controlled, randomized, single ascending dose study in healthy subjects aged 55 to 75 inclusive (Part 1) and multiple ascending dose study in subjects with prodromal or mild AD aged 55 to 80 inclusive (Part 2). .

The study will consist of 2 parts with approximately 10 cohorts in total and 8 subjects/cohort: Part 1 (Cohorts 1 to 5) is a single ascending dose study in healthy subjects to assess the safety, tolerability, PK, PD (biomarker response

- decrease in free CSF p217+tau), immunogenicity, and isoform levels of JNJ-63733657 (glycoforms; high dose cohort only) of single ascending IV doses of JNJ-63733657; Part 2 (Cohorts A to D) is a multiple ascending dose study to assess the safety, tolerability, PK, and immunogenicity of multiple ascending IV doses of JNJ-63733657 (Day 1, Day 29 and Day 57) as well as assess PD in subjects with prodromal or mild AD and in healthy subjects.

In total, approximately 56 healthy subjects and 24 subjects with prodromal or mild AD will be enrolled in this study. Up to 3 additional cohorts (24 subjects) may be added to either Part of the study to better define the safety/tolerability profile, PK, immunogenicity or PD profile of JNJ-63733657.

For all subjects enrolled, this study will consist of 3 phases: a screening phase (8 weeks), a double-blind treatment phase (13 weeks for Part 1 and 21 weeks for Part 2), and a follow-up phase (2 weeks). The duration of subject participation will be approximately 23 weeks for subjects enrolled in Part 1 and 31 weeks for subjects enrolled in Part 2.

Intervention

JNJ-63733657 of placebo.

Study burden and risks

RISKS ASSOCIATED WITH JNJ-63733657
Potential Discomforts, Side Effects, and Risks Associated with JNJ-63733657
A medicine can always cause unwanted effects called side effects. Problems that are not expected may arise and they may be life-threatening. Most side effects are typically mild to moderate, but some may be serious and/or require treatment including hospitalization or additional testing. At this time, there is limited experience available for JNJ-63733657 in humans. To date, no risks have been identified with JNJ-63733657 in humans.

What are the side effects of JNJ-63733657 in animals?
JNJ-63733657 was given intravenously (directly into a vein, IV) to minipigs over 6 weeks (6 dose administrations) and to rats over 8 weeks (9 dose administrations). Minipigs and rats tolerated JNJ-63733657 well without any clinical findings or findings when tissues were examined.

RISKS ASSOCIATED WITH MONOCLONAL ANTIBODIES IN GENERAL?
Infusion Reactions
The body might have a side effect during or following an infusion of JNJ-63733657 into your vein. This is called an infusion reaction. These reactions are usually mild but they can be serious and/or life threatening.

They are managed by slowing or stopping the infusion and/or by giving the subject medication. The subject will be observed closely during and after treatment with JNJ-63733657.
Symptoms of an infusion reaction may include 1 or more of the following:
• Chills
• Hives or rash
• Itching
• Chest pain or tightness
• Wheezing
• Difficulty breathing or swallowing
• A decrease or increase in blood pressure
• Headache
• Flushing
• Nausea

Allergic Reactions
Allergic reactions have been observed with administration of monoclonal antibodies and may occur at any time during the administration of JNJ-63733657 or within the first few hours after administration. Some reactions may be severe. The following can be signs of an allergic reaction:
• Chills
• Rash or hives
• Nausea
• Flushing
• Light-headedness
• Irregular heartbeats
• Chest tightness or wheezing
• Difficulty breathing or swallowing
• Low blood pressure
• Swelling in face, lips, tongue and/or throat
If the subject has an allergic reaction, the study doctor may give antihistamine (medication used to treat allergic symptoms such as hay fever) or other medications used for treating an allergy. Antihistamines can make the subject sleepy.

Some allergic reactions can be life threatening. The subject should seek immediate medical help if he/she has any of the symptoms listed above. The doctor will treat the subject if this should happen. If the symptoms cannot be managed or become serious or life threatening, the infusion will be stopped and appropriate therapy will be provided.

Reactions due to *antibodies* to JNJ-63733657
Sometimes the body can make *antibodies* (proteins that can react to drugs) that may increase the risk of an allergic reaction to either JNJ-63733657 or other antibody medicines. If the subject has an allergic reaction, the subject may not be able to have these types of medications in the future. The subject should always tell doctors that he/she has been treated with human antibodies

in this study.

Unknown Risks
There may be other side effects, discomforts, or risks with the use of JNJ-63733657 that are not yet known.

RISKS ASSOCIATED WITH SPECIFIC STUDY PROCEDURES
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. Occasionally, blood draws require you to be fasting (no food before blood is taken) and sometimes people get a headache when they don*t eat on their normal schedule.

ECG Risk: There is generally no risk with having an ECG. The sticky patches may pull your skin or cause redness or itching.

Cerebrospinal Fluid (CSF) Sampling Risks: A very thin needle used to remove 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. Withdrawal of the needle typically results in resolution 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 after the lumbar puncture which generally improves when lying down and resolves with time. Over-the-counter pain relievers also may help. In very rare instances, more severe headache may occur. A special type of needle is used to perform the LP in order to minimize the likelihood of developing a post-LP headache.
• Following the LP, you may experience a backache.
• There is the possibility that an infection could develop in the CSF (e.g., resulting in meningitis) To minimize this risk, the lumbar puncture is performed under strict sterile conditions.

MRI Risks: There are no known risks or side effects with having an MRI.

Risk of Information on biomarker test: During the screening process biomarker testing will be performed. Only participants with biomarker findings consistent with prodromal/mild Alzheimer*s disease may participate in the study. It is possible that the CSF study results may suggest that the subject does not have pAD or mild AD. If this is the case, the subject will not be able to participate in the study, and the study doctor will discuss the meaning of the results with the subject.

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. Male or female. Note: equal gender representation is preferred when feasible. ;2. 55 to 75 years of age, inclusive.;3.1. body mass index (BMI) between 18 and 35 kg/m2, inclusive (BMI = weight/height2) and
body weight greater than 40 kg but less than 110 kg at screening.;4.1 otherwise healthy for their age group (Part 1 and Part 2-HS) or medically stable (Part 2 AD) on the basis of physical examination, medical history, vital signs, and 12 lead ECG performed at screening or admission to the clinical unit. If there are abnormalities, they must be consistent with the underlying illness or age of the study population and not deemed clinically unstable. This determination must be recorded in the subject's source documents and initialed by the investigator;5. 1 otherwise healthy for their age group (Part 1 and Part 2-HS) or medically stable (Part 2 AD) on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel (including liver enzymes), hematology, coagulation or urinalysis are outside the normal reference ranges, the subject may be included only if the investigator judges the abnormalities to be not clinically significant. This determination must

be recorded in the subject's source documents and initialed by the investigator.

6. Women must not be of childbearing potential defined as: ;• Postmenopausal: A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level at screening (>40 international units per liter (IU/L) or milli-international units per milliliter [mIU/mL]) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.;• Permanently sterile: Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.;Note: If reproductive status is questionable, additional evaluation will be considered;7. During the study and up to 16 weeks after receiving the last dose of study drug a man:;• who is sexually active with a woman of childbearing potential and has not had vasectomy must agree to use a barrier method of contraception (e.g., 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). In addition, their female partner should also use a highly effective method of birth control (e.g. hormonal contraception) for at least the same duration.;• who is sexually active with a woman who is pregnant must use a condom. ;• must agree not to donate sperm.;8. must be willing to adhere to the prohibitions and restrictions specified in this protocol.;9. must sign an informed consent form (ICF) (or their legally acceptable representative;depending on disease state) indicating that he or she understands the purpose of, and;procedures required for, the study and is willing to participate in the study.;4.1.2 Specific Inclusion Criteria Part 2;Each potential subject enrolled in Part 2-AD must satisfy all of the following specific criteria in addition to the general criteria to be enrolled in the study:;10. Clinical Dementia Rating (CDR) global rating score of 0.5 or 1.0 at screening.;11. must have a reliable informant (e.g., relative, partner, friend).;12. must have CSF finding consistent with AD pathology: abnormal CSF A-β 1-42 levels and elevated CSF p-tau181P or t-tau levels at screening#.;Note: #cut off value for CSF ratio A-β1-42, t-tau and p-tau181P will be based on the value established by the central CSF screening lab and specified in a separate lab manual.;13. 55 to 80 years of age, inclusive
-AD
4.1.3. Specific Inclusion Criteria Part 2-HS
Each potential subject enrolled in Part 2-HS must satisfy all of the following specific criteria in addition to the general criteria to be enrolled in the study:;14. 55 to 80 years of age, inclusive

Exclusion criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:;1.1 history of or current liver or renal insufficiency; significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic (including but not limited to neurodegenerative disease (excluding AD for Part 2-AD) [e.g., Parkinson*s disease], seizure disorders, transient ischemic attacks, etc.), hematologic (including coagulation disorders), rheumatologic, psychiatric, or metabolic disturbances, any inflammatory illness or any other illness that the Investigator considers should exclude the subject.

2.1 relevant history of or current neurological disease (other than prodromal AD or mild AD for Part 2-AD), which in the opinion of the investigator may make interpretation of possible new neurological signs or symptoms difficult
3.1. Positive result on hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis C antibody (anti-HCV), or any other clinically active liver disease at screening (per screening evaluations)
4. History of human immunodeficiency virus (HIV) antibody positive, or tests positive for HIV at Screening (per screening evaluations)
5. Any contra-indications for magnetic resonance imaging (MRI) (prostheses, implants, claustrophobia, pacemakers, etc)
6. 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), that could explain the cognitive deficit (including, but not limited to vascular encephalopathy or strokes, as imaged by cerebral MRI and Major Depression, as defined by DSM (current edition) criteria. The screening MRI scan shall be interpreted by a local radiologist and investigator for exclusionary findings prior to enrolling the subject.
7. 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 written concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence).
8. history of drug or alcohol use disorder according to DSM (latest edition) criteria within 6 months before Screening or has a positive test result(s) for alcohol and/or drugs of abuse (including: opiates (including methadone), cocaine, amphetamines, methamphetamines, cannabinoids, barbiturates, and benzodiazepines) at screening or admission to the clinical unit.
9.1. drinks, on average, more than 8 cups of tea/coffee/cocoa/cola/caffeinated beverages (e.g., energy drink) per day for Part 1 subjects.
10. clinically significant acute illness within 7 days prior to study drug administration.
11.1. smokes cigarettes (or equivalent) and/or has used nicotine based products within 3 months prior to study drug administration for Part 1 subjects.
12. man who plans to father a child while enrolled in this study or within 13 weeks after the last dose of study drug.
13. history of clinically significant drug and/or food allergies.
14. known or suspected intolerance or hypersensitivity to any biologic medication or known allergies or clinically significant reactions to human proteins, monoclonal antibodies or antibody fragments, or any of the excipients of JNJ-63733657 (refer to Investigator's Brochure).2
15. taken any disallowed therapies as noted in Section 8, Prestudy and Concomitant Therapy before the planned first dose of study drug. The use of medication that is considered not to have any impact on the study results may be allowed after agreement between the investigator and the sponsor's medical monitor.
Note: Medication for chronic use except for those medications specifically listed in Section 8, Prestudy and Concomitant Therapy will be allowed after approval by both the investigator and the sponsor's medical monitor. This medication should be kept stable from the screening visit until completion of the double-blind treatment phase.
16. received an investigational drug (including vaccines) or used an investigational medical device within 3 months or 5x T1/2, whichever is longest before the planned start of study

or are currently enrolled in an investigational study.
17. previously participated in a tau vaccine or tau/amyloid antibody study.
18. 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 3 months (>=5 half-lives) after study drug administration.
Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate.
19. donated one or more units (approximately 450 mL) of blood or acute loss of an equivalent amount of blood within 90 days prior to study drug administration.
20. relevant history of lower back pain or scoliosis and/or major (lumbar) back surgery (microdiscectomy is allowed) that could impact the ability to have a LP in the opinion of the investigator.
21. topical infection or local dermatological condition at the puncture site prior to puncture (screening), that may compromise the LP.
22. signs of increased intracranial pressure, e.g., based on clinical or MRI examination.
23. any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
24. employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.
25. vulnerable subjects (e.g., a person kept in detention or a person under guardianship).
NOTE: Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.
4.2.2. Specific Exclusion Criteria Part 1and Part 2-HS
26. MMSE score <=27 at screening.
4.2.3. Specific Exclusion Criteria Part 2-AD
27. evidence of brain disease, other than AD, that could explain the cognitive deficit (including, but not limited to, vascular encephalopathy or strokes, as imaged by cerebral MRI).

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:	Completed
Start date (anticipated):	22-01-2018
Enrollment:	36
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	29-11-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-01-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-03-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-04-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	03-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-08-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-09-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-02-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-02-2019
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	EUCTR2017-003852-21-NL
ClinicalTrials.gov	NCT03375697
CCMO	NL63253.056.17

Study results

Date completed: 05-12-2019

Results posted: 17-05-2022

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File