A Randomized, Two-Period, Double-Blind Placebo-Controlled and Open-Label, Multicenter Extension Study to Determine the Long-Term Safety and Tolerability of JNJ-54861911 in Subjects in the Early Alzheimer*s Disease Spectrum

Published: 04-08-2015
Last updated: 19-04-2024

The primary objective of this study is to evaluate the long-term safety and tolerability of JNJ-54861911 in subjects in the early AD spectrum that have completed a Phase 1b or Phase 2 clinical trial with JNJ 54861911 (e.g., Study 54861911ALZ2002),...

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

Summary

ID

NL-OMON44804

Source
ToetsingOnline

Brief title
A follow-up trial of JNJ-54861911 in the Early Alzheimer*s Disease Spectrum

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

SAFETY EVALUATIONS

The primary objective of this study is to assess the long-term safety and tolerability of JNJ-54861911 in subjects in the early AD spectrum. As such, regular safety assessments will be performed as listed in the Time and Events schedule. These safety assessments include but are not limited to: vital signs, ECG, physical and neurological examination, adverse events, safety labs, suicidality risks (Columbia Suicide Severity Rating Scale [C-SSRS]), dermatologic and ophthalmologic examinations, and MRI.

Specific dermatologic and ophthalmologic examinations have been implemented in this study as potential BACE1- or BACE2-linked toxicities (e.g. melanin deposition changes and retinal abnormalities) have been described in the literature (e.g., BACE1- or BACE2 knock-out mice). With the exception of fur discoloration resulting in progressive lightening of the fur from normal dark brown to paler cream or grey, which was seen in one species only (Tg mice in the 6 month carcinogenicity study), however, these toxicities have not been observed in nonclinical chronic studies with JNJ-54861911.

In addition to the (safety) MRI assessments performed under the parent protocol (if applicable), safety MRIs will be collected in the extension study in Treatment Period 1 and 2, as indicated in the Time and Events schedule, to monitor for amyloid related imaging abnormalities (ARIA)-edema or effusion (E) and ARIA-hemosiderin (H). In case of any safety related changes observed (e.g., ARIA-E or H), additional safety MRIs may be collected at a frequency as recommended by the DRC.

Any changes observed in any of the safety measures performed that are considered not clinically significant or do not have a direct clinical symptomatology as assessed by the investigator, should be closely monitored, with a potential increased safety monitoring frequency as deemed appropriate by the investigator. In addition, these findings will be presented to the DRC, who will make recommendations regarding the safety and continuation of the study as per its charter.

Secondary outcome

PHARMACOKINETIC EVALUATIONS

Venous blood samples for analysis of JNJ-54861911 will be collected at the time points indicated in the Time and Events schedule.

CSF samples for analysis of JNJ-54861911 concentrations will be obtained at the time points indicated in the Time and Events schedule.

COGNITION, FUNCTION AND CLINICAL STATUS

Cognitive evaluations (RBANS, MMSE and CVLT-II) and functional outcome measures (Cognitive Function Index [CFI]) will be applied in this study at different

time points as indicated in the Time and Events schedule to explore the subject*s cognitive performance/progression and function over time.
In addition during course of the study the subject*s clinical status will be assessed regularly by means of the Clinical Dementia Rating Scale as indicated in the Time and Events schedule.

BIOMARKER EVALUATIONS
Fluid (CSF and plasma samples) biomarkers samples and imaging biomarker assessments (MRI) will be performed as listed in the Time and Events schedule to assess the potential and continuous effects of JNJ 54861911 on the pathological and pathophysiological processes of AD. In addition, these biomarkers assessments will be performed to assess if potential treatment effects of JNJ 54861911 are consistent with the putative effects of BACE inhibition.
During the course of the study the continuous effects of JNJ 54861911 on the pathophysiological processes of AD will be monitored by the DRC.
All subjects will receive an MRI in the extension study at the time points indicated in the Time and Events schedule for primarily safety reasons.
However, potential treatment effects may be assessed with MRI as well.

Study description

Background summary

JNJ-54861911 is a BACE inhibitor (BACEi) being developed by Janssen Research and Development (JRD) for the treatment of early Alzheimer*s disease (AD) by

reducing production of amyloid-beta (A*) fragments.
This phase 2 study is an extension study for subjects in the early AD spectrum, i.e., subjects described under the parent protocol as asymptomatic at risk for Alzheimer*s dementia as well as subjects with prodromal Alzheimer*s disease (pAD), who have completed a Phase 1b or Phase 2 clinical trial with JNJ-54861911. This phase 2 extension study is performed to investigate primarily the longer term safety and tolerability of JNJ-54861911, beyond initial clinical trials, supporting longer term treatment with JNJ 54861911.
This extension study will continue to run until registration of JNJ-54861911 or until emerging safety issues arise as defined by the Data Review Committee (DRC) that would warrant termination of the study. Due to its potentially long treatment duration in comparison to the parent protocols, subjects enrolled in this extension study may be more likely to experience clinical benefit.

Study objective

The primary objective of this study is to evaluate the long-term safety and tolerability of JNJ-54861911 in subjects in the early AD spectrum that have completed a Phase 1b or Phase 2 clinical trial with JNJ 54861911 (e.g., Study 54861911ALZ2002), who are willing to continue their assigned treatment.

The secondary objectives of this study in subjects in the early AD spectrum are:
* To assess the maintenance of JNJ 54861911 effects on markers of A* processing (A*1-37, A*1-38, A*1-40, A*1-42) in cerebrospinal fluid (CSF) and plasma.
* To assess the relationship of changes in CSF and plasma A* species (A*1-37, A*1-38, A*1-40, A*1-42) with safety.
* To assess changes in CSF p-tau, t-tau and/or additional alternate biomarkers of neurodegeneration following long term treatment with JNJ-54861911.
* To assess the plasma and CSF pharmacokinetics of JNJ-54861911 in a patient population using a population PK approach and explore its relationship with efficacy and safety parameters.
* To provide ongoing access to JNJ-54861911.

The exploratory objectives are:
* To explore if JNJ 54861911 will slow the rate of cognitive decline, the perceived cognitive function and performance of everyday activities.
* To assess the annual conversion rate of subjects treated with JNJ-54861911 to the different stages/phases of the AD spectrum.
* To explore the potential relationship of markers of neurodegeneration (volumetric magnetic resonance imaging [MRI], CSF t-tau or p-tau) with cognitive decline and/or response to treatment with JNJ 54861911

Study design

This is a randomized, two-period, double-blind placebo controlled and open-label, multi-center, parallel-group study assessing primarily the

long-term safety and tolerability of JNJ-54861911 in subjects in the early AD spectrum that have completed a phase 1b or phase 2 clinical study with JNJ-54861911.
This extension study will be an outpatient study. The Time and Events schedule provides an overview on the visit frequency and assessments to be performed each visit.
For subjects enrolled in this extension study, the study will consist of a screening phase, 2 sequential treatment periods i.e., a 12-Month blinded treatment phases (Treatment Period 1 [placebo-controlled]) and an open-label treatment phase (Treatment Period 2 [active]), followed by an End-of-Treatment visit. Treatment in Period 2 will continue until registration of JNJ-54861911; unless safety issues emerge as determined by the DRC that would warrant termination of the study.
Subjects in the early AD spectrum, enrolled in ongoing or future clinical trials with JNJ-54861911 (Phase 1b or Phase 2 studies) will be provided the opportunity to participate in this extension study upon completion of their treatment period under the parent protocol. Subjects participating in this extension study do not have to complete the End-of-Treatment visit (follow-up) visit under the parent protocol.
Enrollment in the extension study should be completed (Day 1 Treatment Period 1) as soon as possible, but within 6 weeks, following completion of their treatment period under the parent protocol of currently ongoing or any future phase 1b or phase 2 studies with JNJ-54861911.
As a consequence no maximal number of subjects in the early AD spectrum to be enrolled is currently defined.
Subjects will sign the informed consent and be screened for eligibility during the Screening Phase. Eligibility in this study requires that subjects have recently completed their treatment period as described under the parent protocol in study 54861911ALZ2002 or any future phase 1b or phase 2 JNJ-54861911 clinical studies.
Eligible subjects enrolled in this extension study will receive either JNJ-54861911 (10mg or 25 mg q.d.) or placebo (q.d.). Subjects will continue with their current treatment regimen established in the parent JNJ-54861911 study (e.g. for 54861911ALZ2002 placebo or JNJ-54861911) for a period of 52 Weeks (12 Months)(Treatment Period 1; placebo-controlled). Subjects who have received under the parent an active dose different from 10-mg or 25-mg JNJ-54861911 will be receiving the closest dose available in Treatment Period 1 (10-mg or 25-mg JNJ-54861911; i.e. subjects receiving 50 mg in study 54861911ALZ2002 will be assigned to 25 mg JNJ-54861911).
Following the initial 52-Week (12-Month) treatment period (Treatment Period 1) in the extension study, subjects receiving placebo in Treatment Period 1 will be randomized with equal chance to one of two active JNJ-54861911 dose levels (i.e., 5-mg q.d. JNJ-54861911 or 25-mg q.d. JNJ-54861911) for continuous treatment in Treatment Period 2. As such during Treatment Period 2 all subjects will receive active (JNJ-54861911) treatment (open-label).
In addition, subjects who were receiving 10 mg q.d. JNJ-54861911 will have their dose reduced to 5 mg q.d. in order to harmonize the dosage with that of

the Phase 2b/3 program, while subjects who were receiving 25 mg q.d. will continue to receive that dosage.

During the Treatment Phases (Treatment Period 1 and Treatment Period 2), primarily safety and tolerability will be monitored at regular intervals (e.g. MRI, physical and neurological examination, suicidality risk assessment, vital signs, 12-lead electrocardiogram (ECG), safety labs, dermatologic and ophthalmologic examinations, etc.). Pharmacokinetics (CSF and plasma), and pharmacodynamics (PD) effects by means of biomarkers (fluid [CSF and plasma samples] and imaging [volumetric MRI]) will be explored at the time points listed in the Time and Events schedule. In addition, effects of JNJ-54861911 on cognition (e.g., Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Mini Mental State Examination (MMSE) and California Verbal Learning Test * Second Edition [CVLT-II]) will be assessed at regular intervals. The subject*s clinical status will be assessed during the study by means of the Clinical Dementia Rating Scale (CDR). Investigators will monitor and assess subjects for disease progression. Subjects in the early AD spectrum who develop dementia due to AD during enrollment in this extension study will be allowed to continue participation in the study, except if emerging data would show continued treatment could potentially be harmful.
An End-of-Treatment visit (or phone call) for a safety assessment should take place approximately 30 days after the last dose of study drug. The study is considered completed with the last End-of-Treatment safety assessment for the last subject participating in the study or upon a decision by the sponsor to terminate the study.
The Time and Events schedule provides an overview on the visit frequency and assessments to be performed for each treatment period.
Any serious adverse event (SAE) must be reported to the sponsor by study site personnel within 24 hours of their knowledge of the event as outlined in the protocol.
A DRC will be established to review the safety and tolerability data or any other relevant data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study.
In addition an interim review of blinded or unblinded data by an Interim Analysis Committee may be performed at any time as described in Section 11.6, Interim Analysis.

Intervention

Study medication will be provided as JNJ-54861911 tablets, strengths 5-mg, 25-mg and matching placebo, blister packed. All tablets (JNJ-54861911/placebo) are physically identical.
Eligible subjects enrolled in this extension study will participate in 2 sequential treatment phases/periods as described above, i.e.,
* Treatment Period 1: a 52-week (12 Months) placebo-controlled double-blind treatment period. Eligible subjects enrolled in this extension study will receive either JNJ-54861911 (10-mg or 25-mg q.d.) or placebo (q.d.). Subjects

will continue on their current treatment regimen assigned under the parent protocol (placebo, 10-mg or 25-mg q.d. JNJ-54861911). Subjects who received an active dose different from 10-mg or 25-mg JNJ-54861911 under the parent protocol will be receiving the closest dose available in Treatment Period 1 (i.e. subjects receiving 50 mg in study 54861911ALZ2002 will be assigned to 25 mg JNJ-54861911).
* Treatment Period 2: an open label treatment period during which subjects who received placebo in Period 1will be randomized with equal chance to one of two JNJ-54861911 dose levels i.e. 5-mg q.d. JNJ-54861911; or 25-mg q.d. JNJ-54861911. Subjects receiving JNJ-54861911 in Treatment Period 1 will continue their treatment open-label in Treatment Period 2.
During the entire study (Treatment Period 1 and Treatment Period 2) subjects will self-administer once daily (q.d.) study drug (JNJ-54861911/placebo) with a glass of non-carbonated water, after completion of breakfast or a light snack, during the morning hours, according to the instructions provided by the investigator. During scheduled visits subjects will self-administer their study medication on site as described above. On Day 1 study drug administration will be administered following completion of all predose assessment and will not be limited to morning hours.
If a subject realizes before 2:00 PM that he/she forgot to take their daily dose, he/she will be instructed to take the daily dose even if late (before 2:00 PM).
If a subject realizes after 2:00 PM he/she forgot to take his/her daily dose, he/she will be instructed not to take any dose during that day, but resume dosing the following day.
Subjects who are no longer capable of ensuring treatment compliance in the judgment of the investigator (e.g., due to progression to dementia) have to be supported in study drug handling and administration (e.g., care giver or nurse practitioner). In cases where support cannot be provided subjects should be discontinued from treatment and withdrawn from the study.

Study burden and risks

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 infrequent, 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.

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

* Lightening of hair and skin
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. Sometimes during a study the sponsor may learn new facts about the study drug. It is possible that this information might make you change your mind about being in the study. If new information is discovered, your study doctor will tell you about it right away.

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.
* 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.

Contacts

Public
Janssen-Cilag

Graaf Engelbertlaan 75
Breda 4837 DS
NL
Scientific
Janssen-Cilag

Graaf Engelbertlaan 75
Breda 4837 DS
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Participants in the early Alzheimer*s disease (AD) spectrum at time of enrollment under the parent protocol and according to its inclusion and exclusion criteria, must have very recently completed their treatment in a phase 1b or phase 2 JNJ-54861911 clinical study (e.g., 54861911ALZ2002) under the parent protocol. Enrollment in the extension study should be completed (Day 1 Treatment Period 1) as soon as possible, but within 6 weeks, following completion of their treatment period under the parent protocol. If not defined under the parent protocol, completion of the treatment period is defined as having completed all study related procedures of the last visit of the treatment period under the parent protocol. A screening phase of up to 12 weeks may be allowed following written approval of the Sponsor
- Participant must be willing and able to adhere to the prohibitions and restrictions specified in this protocol
- Each Participants must sign an informed consent form (ICF) indicating that he or she

understands the purpose of and procedures required for the study and are willing to participate in the study
- Participants 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 participant (contact can be in-person, via telephone or other audio/visual communication). The informant must have sufficient contact such that the Investigator feels he/she can provide meaningful information about the participant*s daily function. If possible, an alternate informant meeting these criteria who can replace the primary informant should be identified prior to randomization

Exclusion criteria

- Any condition or situation which, in the opinion of the Investigator, may put the subject at significant risk, may confound the study results, or may interfere significantly with subject*s participation in the study
- The use of concomitant medications known to prolong the QT/QTc interval

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-12-2015
Enrollment:	5
Type:	Actual

Ethics review

Approved WMO Date:	04-08-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-11-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-11-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-05-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-05-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-08-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-11-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	05-12-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-04-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-04-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-06-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-07-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-07-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-07-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	22-02-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-03-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-06-2018
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	EUCTR2014-004274-41-NL
CCMO	NL53955.056.15