A Phase Ib/IIa Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety, Tolerability and Immunogenicity of Different Doses, Regimens and Combinations of Tau Targeted Vaccines in Subjects with Early Alzheimer*s Disease

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

Summary

ID

NL-OMON55583

Source
ToetsingOnline

Brief title
ACI-35-1802

Condition

- Neurological disorders NEC

Synonym
Alzheimer's Disease, form of Dementia

Research involving
Human

Sponsors and support

Primary sponsor: AC Immune SA
Source(s) of monetary or material Support: AC Immune SA

Intervention

Keyword: Early Alzheimer's Disease, Placebo, Tau Targetted Vaccines

Outcome measures

Primary outcome

Primary Endpoints

Safety and tolerability: Adverse events, immediate and delayed reactogenicity (e.g. anaphylaxis, local and systemic reactogenicity, including immune-complex disease); suicidal ideation (C-SSRS); behavior (NPI); cognitive and functional assessments (RBANS, CDR-SB) to assess safety; vital signs; MRI imaging; electrocardiogram; routine hematology and biochemistry evaluation in blood and urine; evaluation of autoimmune antibodies including anti-dsDNA antibodies in blood; inflammatory markers in blood and CSF

Immune response (i.e. immunogenicity): Anti-pTau IgG titers in serum (geometric mean, change from baseline, responder rate, peak and area under the curve)

Secondary outcome

Secondary Endpoints

Immune response (i.e. immunogenicity): Anti-Tau IgG, anti-pTau and anti-Tau IgM titers in serum (geometric mean, change from baseline, responder rate, peak and area under the curve), determination of the IgG response profile by avidity testing

Exploratory Endpoints

Change from baseline of putative AD biomarker titers in blood and/or CSF (e.g. total Tau, pTau), change from baseline in T-cell activation levels as measured in blood, change from baseline of inflammatory cytokine titers in blood, change from baseline in antibody titers in blood, change from baseline in behavior (NPI), cognitive (including the proportion of subjects maintaining their decisional capacity during the study using the MacCAT-CR interview in the Netherlands) and functional performance (RBANS, CDR-SB) scores

Study description

Background summary

A first generation of the vaccine called ACI-35 has been studied in animals as well as in 24 subjects with mild to moderate Alzheimer*s disease and was safe and well tolerated.
Subsequently, second generation vaccines have been developed to increase further the production of antibodies against the abnormal Tau proteins. These second generation vaccines, which include ACI-35.030 and JACI-35.054, have been studied in animals. Both ACI-35.030 and JACI-35.054 have already been given to the patients who participated earlier in this study.

Study objective

The purpose of this research study is to evaluate the safety and tolerability of two study vaccines, ACI-35.030 and JACI-35.054 in subjects with a mild form of Alzheimer*s disease who are 50-75 years-old. Both study vaccines have been designed to stimulate the body*s immune system to make proteins called antibodies which remove an abnormal form of the Tau protein which accumulates in the brain in Alzheimer*s Disease. It is hoped that the reduction of the buildup of the abnormal Tau proteins will slow down the progression of Alzheimer*s disease.
The aim of this research study is to find out if these new vaccines:
• are safe and tolerated by patients with early Alzheimer*s Disease
• increase the immune response against the abnormal form of the Tau protein

Study design

The study consists of 3 periods - screening period (up to 42 days); treatment period (50 weeks) and safety follow-up period (24 weeks) and post-injection period extension which is optional.

Your participation in the study will last up to 80 weeks (around 1.5 years) in total. This should involve 18 visits to your study doctor in hospital. During the 50-week treatment period you will receive 4 administrations of the study vaccine. At the end of this time the study doctor will continue to monitor you for 24 weeks. If the follow-up period is extended in a given sub-cohort by another 24 weeks (6 months), the overall duration will be up to around 104 weeks.

All subjects will be kept under clinical observation for 24 hours after the first administration of study vaccine and for 4 hours after subsequent administrations of study vaccine. If the follow-up period is extended in a given sub-cohort by another 24 weeks (6 months), the overall duration will be up to around 104 weeks.I

Group 1 will receive either ACI-35.030 or a placebo. Group 2 will receive either JACI-35.054 or a placebo. The placebo looks like ACI-35.030 or JACI-30.054 but contains no medication and so it is not expected to have any effect. This will allow the Sponsor to see if ACI-35.030 and JACI-30.054 work as well as or better than the placebo. The administration schedule will be the same in both groups, i.e. the study vaccine or placebo will be administered 4 times with an interval of 8, 16 and 24 weeks respectively between each dose. Group 3 will receive ACI-35.030 and JACI-35.054 in sequential administration.

In group 1 and 2, the dose will be increased successively based on the observations made during the study, as long as the treatment is considered safe. At each dose level, the data obtained will be thoroughly assessed, for example possible adverse reactions observed and results from tests performed, before the decision is made whether to elevate the dose or not. In group 3 both vaccines ACI-35.030 and JACI-35.054 will be administered in a sequence based on non-human primate immunogenicity data and on data reviewed during the previous sub-cohort interim analyses. Prior to starting any of the sub-cohorts 3.1, 3.2 and/or 3.3 the selected dosages will have been evaluated in cohorts 1 and 2 and safety monitored for at least 10 weeks.

Due to the Covid-19 pandemic, local travel restrictions in Finland effective as of 18 March 2020, and the need to preserve the safety of study participants, modifications are made to the schedule of immunizations of sub-cohort 1.1 subjects not having received the 3rd injection at month 6 already: immunizations at month 6 (week 24) will not be performed in 7 of 8 sub-cohort 1.1 subjects for whom the planned Visit 5 does not allow all assessments to be done according to the protocol. In addition, Visits 5 (week 24), 6 (week 26) and 7 (week 36) are replaced by remote visits in case these fall during the at-risk period. Due to the resurgence of the Covid-19 pandemic in multiple

participating countries since September 2020, additional adjustments related to the mode of administration of study assessments including study vaccine administration may apply in Finland and other participating countries after the above measures were implemented in Finland.

Intervention

Group 1 (with ACI-35.030 or placebo) will have three sub-groups with different doses of the vaccine:
• Sub-group 1.1: The participants of this sub-group have already been enrolled and received 300 µg ACI-35.030 or placebo per administration.
• Sub-group 1.2: The participants of this subgroup have already been enrolled and received 900 µg ACI-35.030 or placebo per administration.
• Sub-group 1.3: The participants of this subgroup have already been enrolled and received 1800 µg ACI-35.030 or placebo per administration.
Group 2 (with JACI-35.054 or placebo) will have three sub-groups with different doses of the vaccine:
• Sub-group 2.1: The participants have already been enrolled been enrolled and received 15 µg JACI-35.054 or placebo per administration.
• Sub-group 2.2: The participants will receive up to 60 µg JACI-35.054 or placebo per administration. This sub-group may or may not be opened dependent on the assessment of results from the first sub-group.
• Sub-group 2.3: The participants will receive up to 150 µg JACI-35.054 or placebo per administration. This sub-group may or may not be opened dependent on the assessment of results from the second sub-group.
Group 3 with ACI-35.030 and JACI-35.054 in sequential administration:
• Sub-group 3.1: ACI-35.030 at 900 µg/dose and JACI-35.054 at a dose previously evaluated in cohort 2 and found to be safe after a study treatment period of at least 10 weeks will be administered sequentially
• Sub-group 3.2: This optional sub-cohort may include a different sequence of administration than in sub-cohort 3.1 and/or different dosages of ACI-35.030 and/or JACI-35.054 based on available safety, tolerability and immunogenicity data from previous sub-cohort interim analyses. Dosages of ACI-35.030 and of JACI-35.054 will have been previously evaluated in cohorts 1, 2 and/or 3 without significant safety or tolerability concerns.
• Sub-group 3.3: This optional sub-cohort may include a different sequence of administration than in sub-cohorts 3.1 and 3.2 and/or different dosages of ACI-35.030 and/or JACI-35.054 based on available safety, tolerability and immunogenicity data from previous sub-cohort interim analyses. Dosages of ACI-35.030 and of JACI-35.054 will have been previously evaluated in cohorts 1, 2 and/or 3 without significant safety or tolerability concerns.

Study burden and risks

The study vaccine is in a research stage, so it may have adverse effects that are not known in advance. As with any new drug there is a risk that rare or

unexpected adverse effects may occur.

Reaction at the Injection Site

It is possible that redness, pain, itching or swelling might be observed at the site of the injection.

Meningoencephalitis (brain inflammation)

There is a small theoretical risk that ACI-35.030 and JACI-35.054 might lead to inflammation in the brain, so-called meningoencephalitis. This was observed in 6% of subjects in a previous study with another vaccine targeting a different protein, so-called beta-amyloid. No signs of meningoencephalitis have been observed to date in animal studies with ACI-35.030 and JACI-35.054 or in the study of the previous formulation in 24 subjects. The study physician will look for any signs of this by examining you at the study visits. In addition, the brain MRI and lumbar puncture will help to identify the cause and/or exclude such an inflammation of the brain.

Placebo Risks

If you are in the group that is assigned to placebo (the medically inactive substance), you will not be able to benefit from potential effect of the vaccine.

Allergic or Other Immune Reactions

As with taking any drug, there is a risk of allergic reaction. You will be asked to stay at least 24 hours in the clinic after receiving the first injection of the study vaccine, and for 4 hours following each subsequent injection to monitor any occurrence of acute reactions during this timeframe. Please inform your study doctor if you notice any allergic reactions after the visit. You will also be monitored with blood tests for any other unwanted reactions of the immune system to the study vaccine.

Blood Sampling

The risks of taking blood include fainting and pain, bruising, swelling, or rarely, infection where the needle was inserted. These discomforts are brief and transient.

Electrocardiogram

Skin irritation from the ECG electrode pads or pain when removing the pads are possible adverse effects.

Lumbar Puncture (spinal tap)

Lumbar puncture (also called spinal tap) involves insertion of a needle at the bottom of the spinal canal to collect a cerebrospinal fluid. For most people, spinal tap does not cause any serious problems; the most common side effect is headache after the procedure which occurs in about 1-2% of people over 50 years of age. This is usually short lasting (1-2 days), and you will be asked to lie down and drink caffeinated fluids and then contact the study doctor. On rare occasions if it continues (for up to 7 days) you may need to be treated with a *blood patch* (a small amount of your blood injected into the puncture site). Less common adverse effects include pain at the place where the needle was inserted or a very brief sensation in the leg or in the buttocks, if the needle has hit a nerve. These symptoms can be treated and usually improve over time. Other complications such as low blood pressure, dizziness, bleeding into the spinal canal or an infection in the brain are very uncommon and may require

hospital treatment.

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

Inclusion criteria
1. Male or female with age from 50 and up to 75 years old inclusive.
2. Mild Cognitive Impairment (MCI) due to AD or Mild AD according to NIA-AA criteria and a Clinical Dementia Rating scale (CDR) global score of 0.5 or 1 respectively.
3. Mini Mental State Examination (MMSE) score of 22 or above.
4. Abnormal level of CSF Abeta amyloid 42 (Aß42) consistent with AD pathology at screening.
• In borderline cases for CSF Aß42 levels, other results may be considered to

help determine amyloid positivity e.g. the Aß42/Aß40 ratio and, on a case by case basis, a history of positive amyloid PET scan or positive CSF Aß42 level.
• Results from CSF sampling performed within 6 months prior to screening are acceptable on a case by case basis provided that they are consistent with the presence of amyloid pathology and that the corresponding CSF sample can be used in the study for testing.
5. Subjects either not taking any marketed treatment for AD or receiving a stable dose of an acetylcholinesterase inhibitor and/or memantine for at least 3 months prior to baseline.
6. Subjects cared for by a reliable informant or caregiver to assure compliance, assist with clinical assessments and report safety issues.
7. Women must be post-menopausal for at least one year and/or surgically sterilized. Women of childbearing potential or not post-menopausal must have a negative blood pregnancy test at screening (blood draw between day -14 and day -3 prior to baseline) and be willing to use highly effective methods of contraception from the screening visit until the end of their participation. Urine pregnancy testing will be performed throughout the treatment period to determine if the subject can continue receiving the study vaccine. Male participants in the trial with female partners of child bearing potential are required to use barrier methods of contraception (condoms with spermicide) in addition to contraceptive measures used by female partners during the whole study duration.
8. Subjects who in the opinion of the investigator are able to understand and provide written informed consent. In the Netherlands, the subjects* decisional capacity will be also assessed and must be consistent with the ability to provide informed consent using the MacArthur Competency Tool for Clinical Research in order to evaluate their abilities in the areas of understanding, reasoning, appreciation and choice.
9. Both subject and informant or caregiver must be fluent in one of the languages of the study and able to comply with all study procedures, including lumbar punctures.

Exclusion criteria

Exclusion criteria
1. Participation in previous clinical trials for AD and/or for neurological disorders using active immunization unless there is documented evidence that the subject was treated with placebo only and the placebo vaccine is not expected to induce any specific immune response.
2. Participation in previous clinical trials for AD and/or for neurological disorders using any passive immunization within the past 6 months (or 5 half-lives of the investigational antibody, whichever is longer) prior to screening unless there is documented evidence that the subject was treated with placebo only and the placebo is not expected to induce any specific immune response.

3. Participation in previous clinical trials for AD and/or for neurological disorders using any small molecule drug including BACE-1 inhibitors within the past 3 months prior to screening.
4. Concomitant participation in any other clinical trial using experimental or approved medications or therapies.
5. Presence of positive Anti-nuclear Antibody (ANA) titers at a dilution of at least 1:160 in subjects without clinical symptoms of auto-immune disease.
6. Current or past history of auto-immune disease, or clinical symptoms consistent with the presence of auto-immune disease.
7. Immune suppression including but not limited to the use of immunosuppressive drugs or systemic steroids unless they have been prescribed transiently more than 3 months prior to screening.
8. History of severe allergic reaction (e.g., anaphylaxis) including but not limited to severe allergic reaction to previous vaccines and/or medications.
9. Prior history of clinically significant hypoglycaemic episodes.
10. Clinically significant deviations from normal values for hematologic parameters, liver function tests, and other biochemical measures

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):	09-09-2019
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	ACI-35.030
Product type:	Medicine
Brand name:	JACI-35.054

Ethics review

Approved WMO Date:	18-04-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-08-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-11-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-03-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-08-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-08-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	10-08-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-12-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-01-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-03-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-06-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-08-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-12-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-01-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	25-02-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-03-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-03-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-04-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2018-004573-27-NL

Register	ID
CCMO	NL69383.000.19