Clinical trial results – summary

A study to look at whether crenezumab works and how safe it is in people with early Alzheimer's disease (CREAD)

About this summary

This is a summary of the results of a clinical trial (called a 'study' in this document) written for:

- Members of the public and
- People who took part in the study.

This study started in March 2016 and finished in May 2019. This summary was written after the study ended and represents the final study results which have been fully analysed.

No single study can tell us everything about the risks and benefits of an investigational treatment (also known as a study medicine). It takes a large number of people in many studies to find out everything we need to know. The results from one study may be different from those of other studies.

- **This means that you should not make decisions based on this one summary – always speak to your doctor before making any decisions about your treatment.**

Contents of this summary

Glossary

- ARIA = Amyloid-Related Imaging Abnormalities; a class of side effect sometimes experienced by people receiving study medications similar to crenezumab, and are visible during a brain scan
- CDR-SB = Clinical Dementia Rating–Sum of Boxes; a test to understand the severity of a patient's dementia symptoms

Thank you to the people who took part in the study

The people who took part in this study, and their families and study partners, have helped research doctors to answer important questions about Alzheimer's disease and crenezumab, such as whether crenezumab was effective and well tolerated when treating people living with Alzheimer's disease.

Key information about the study

- The study (known as the CREAD study) compared an investigational treatment, called crenezumab, with a placebo (a dummy treatment that looked like crenezumab but had no medicine in it) in people with early Alzheimer's disease (from prodromal Alzheimer's disease to mild Alzheimer's disease).
- The CREAD study was done to see if the study medicine called crenezumab was effective and well tolerated. Research doctors compared the study medicine with a placebo in people with early Alzheimer's disease.
- A total of 813 people, aged between 50 and 85 years, living with early Alzheimer's disease, from 30 countries, participated in the CREAD study.
- Out of the 813 people who took part in the CREAD study, 409 people were randomly chosen to receive a placebo and 404 people were randomly chosen to receive crenezumab.
- An analysis of data from the CREAD study was done part way through, before the study was finished, which showed that crenezumab was safe (side effects experienced in people who took crenezumab were similar in those that took the placebo), but also showed that crenezumab was not effective (unlikely to help people with prodromal or mild Alzheimer's disease).
- For this reason, the CREAD study was stopped early (along with several other studies of crenezumab).
    - A study of similar design called CREAD2 was also stopped.
    - A small number of people completed the CREAD study and joined another study called the CREAD open-label extension (OLE) where everyone was given treatment with crenezumab. The CREAD OLE was stopped at the same time as the CREAD study. As only a few people (149 people) had entered into the CREAD OLE, there was not enough data from the CREAD OLE to do any analysis.
- When the CREAD study was stopped, 173 people had completed the study.
    - A total of 88 of 409 people (22%) in the placebo group and 85 of 404 people (21%) in the crenezumab group completed the study.
- A total of 5 out of 405 people (1.2%) taking a placebo and 3 out of 404 people (1%) taking crenezumab had a serious side effect which was considered related to the study. Most side effects were well tolerated (meaning they were mild to moderate in severity) and were similar to those seen in previous crenezumab studies.

1. General information about the study

Why were the CREAD studies carried out?

Studies have shown that people with Alzheimer's disease have abnormal levels of amyloid protein, which gather together to form small clusters (oligomers) and clumps (amyloid plaques) in the brain.

The CREAD study was done to test whether the study medicine, called crenezumab, would be effective and well tolerated in slowing down the build-up of amyloid in the brain and the progression of symptoms.

What was the study medicine?

The study medicine called crenezumab was tested in CREAD.

Crenezumab was compared with a placebo:

- The placebo looked the same as crenezumab; however, the placebo did not contain any active medicine.
- People who received placebo were considered a "control group", to help better understand if the effects seen in people receiving crenezumab were due to crenezumab and not likely to be by chance.

What did research doctors want to find out in CREAD?

Previous studies have suggested that crenezumab was better in treating people with early Alzheimer's disease (from prodromal Alzheimer's disease to mild Alzheimer's disease), rather than those with more advanced disease.

The main questions that research doctors wanted to answer were:

1. How does crenezumab affect the symptoms of people with early Alzheimer's disease when given every month for 2 years?
2. What are the side effects of crenezumab when given to people with early Alzheimer's disease every month for 2 years?

What kind of study was this?

This study was a 'Phase 3' study. This means that crenezumab had been tested in a smaller number of people with Alzheimer's disease before this study. In this study, a larger number of people with Alzheimer's disease either took a placebo or crenezumab – this was to find out how crenezumab affects the symptoms of people with early Alzheimer's disease and about the side effects of crenezumab. This study was done to help understand if crenezumab should be approved for doctors to give to people with early Alzheimer's disease.

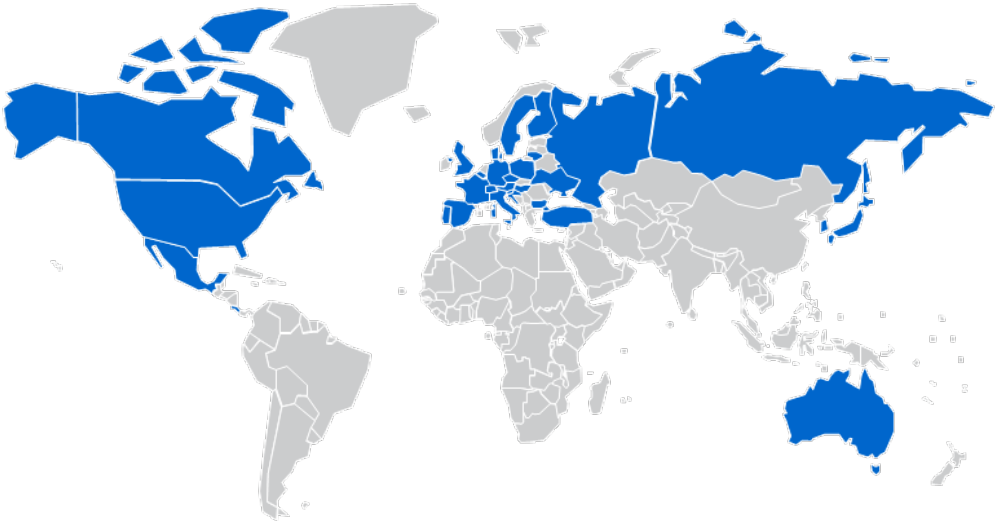
The study was ‘randomised’. This means that it was decided by chance if participants were receiving the placebo or crenezumab – like tossing a coin. Randomly choosing which study medications people take, makes it more likely that the types of people in both groups (for example, age, race) will be a similar mix. Apart from the exact medicines being tested in each group, all other aspects of care were the same between the groups.

This study looked at the results from participants taking a placebo and compared these with the results from participants taking crenezumab.

This study was also ‘double-blinded’. This means that neither participants nor research doctors knew who was given placebo or crenezumab. This was done to make sure that the study results were not influenced in any way.

When and where did the CREAD study take place?

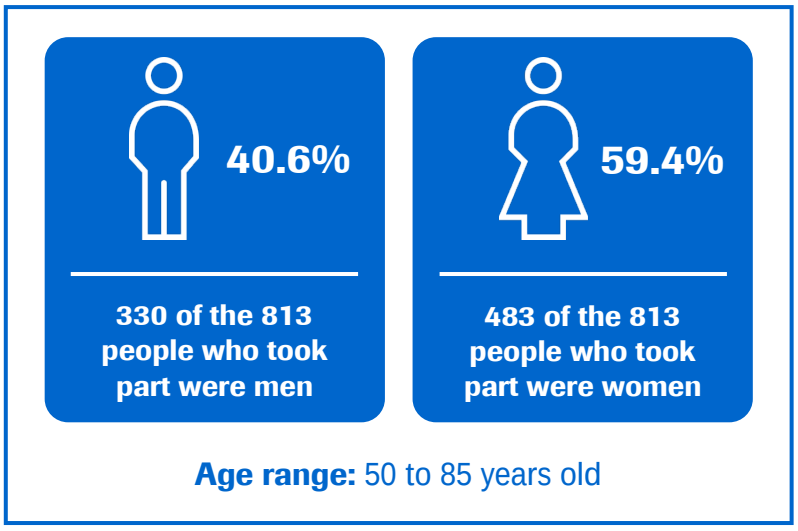
CREAD started in March 2016 and stopped in May 2019. It was conducted in 260 study centres across 30 countries in Asia, Europe, and North America. The following map shows the countries which were included.



Australia	Denmark	Republic of Korea	Sweden
Austria	Finland	Lithuania	Switzerland
Belgium	France	Mexico	Turkey
Bulgaria	Germany	Poland	Ukraine
Canada	Hong Kong	Portugal	UK
Costa Rica	Hungary	Russia	USA
Croatia	Italy	Slovenia	
Czech Republic	Japan	Spain	

2. Who took part in the CREAD study?

A total of 813 adults with early Alzheimer’s disease took part in the CREAD study.



People could take part in the study if they:

- were aged between 50 and 85 years at the beginning of the study
- had memory loss and were diagnosed with early Alzheimer's disease (also known as prodromal or mild Alzheimer's disease)
- had high levels of amyloid in the brain, confirmed by one of the following tests:
    - an analysis of spinal fluid collected from a needle inserted between two spinal bones in the lower back
    - a brain scan
- were in frequent contact with a dedicated study partner who could provide information on the person's progress

People could not take part in the study if they:

- had other diseases caused by abnormal function of their brain, spine, or nerves
- had other diseases such as cancers, as well as heart, liver, immune, and metabolic diseases

3. What happened during the CREAD study?

CREAD study

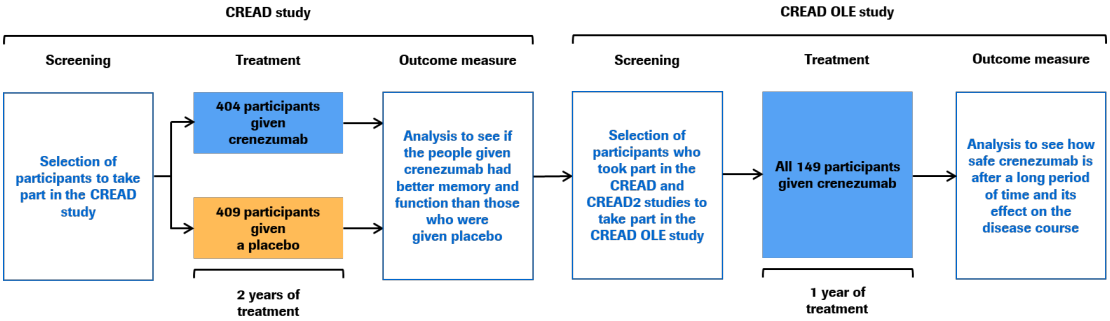
During the CREAD study, people were split randomly into 2 groups and given either placebo or crenezumab. Neither the people taking part in the study nor the research doctors involved knew which group was receiving a placebo and which group was

receiving crenezumab. This was done to make sure that the people participating in the study and research doctors involved could not sway the results of the study.

CREAD OLE study

People who finished the CREAD study were invited to participate in the CREAD OLE study, and everyone who participated in the CREAD OLE study was given crenezumab. The study was done to see if crenezumab would still be safe after a longer period of time and to see how crenezumab affects the disease course of Alzheimer's disease. Both the participants and the research doctors involved in the CREAD OLE study knew all participants were given crenezumab in this part of the study. Data from the CREAD OLE study was not published because the number of participants in the CREAD OLE study was too small when it was stopped early.

The CREAD study was stopped early, in January 2019, before everyone taking part in the study reached 2 years of treatment. This was done following an analysis of the data that had already been collected, called the interim analysis, which showed that crenezumab was unlikely to provide any benefit to people with Alzheimer's disease even if everyone completed 2 years of treatment.



4. What were the results of the CREAD study?

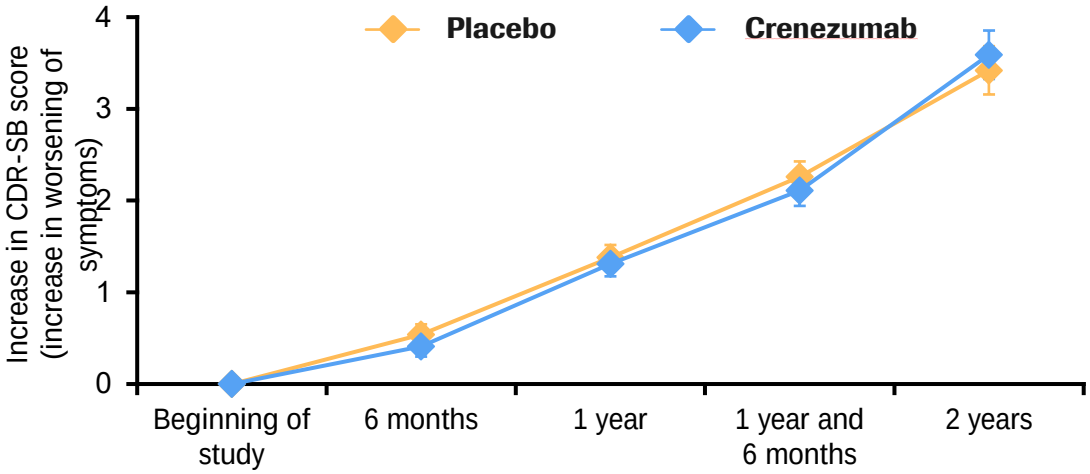
Question: How does crenezumab affect the symptoms of early Alzheimer's disease when given for up to 2 years?

Research doctors used a test called the Clinical Dementia Rating–Sum of Boxes (CDR–SB) test to measure the change in participants' symptoms over 2 years.

The CDR is a questionnaire that looks at symptoms in six categories (memory; orientation; judgement and problem-solving; community affairs; home and hobbies; and personal care). Each domain is scored on a scale from 0 (no symptoms) to 3 (severe symptoms). Scores are added together to give a total out of 18, with higher scores indicating worse symptoms.

The figure below shows the changes in CDR–SB score in people treated with placebo or crenezumab over two years, until the study was stopped in January 2019.

There was no difference in the change in CDR–SB score between the placebo and crenezumab groups for up to 2 years. Everyone participating in the study experienced similar worsening of symptoms.



Research doctors also used a range of other tests combined with information given by caregivers about the memory and thinking skills of people in the study (questionnaires completed during clinic visits) to assess their symptoms. Examples of these tests included the Alzheimer's Disease Assessment Scale and the Activities of Daily Living Scale. Research doctors also looked at smaller specific groups of people to see if there were any differences.

Even when looking at other tests or these smaller groups of people, there were no differences between the placebo and crenezumab groups over time. For example, it did not matter whether someone had prodromal or mild Alzheimer's at the start of the study; the results were the same.

5. What were the side effects in the CREAD study?

The CREAD study investigated the safety of crenezumab by recording the number of side effects (or 'adverse events'), and particularly the number of serious side effects, that people had during the study.

Side effects or 'adverse events' are unwanted medical problems (such as a headache) that may happen to participants receiving study medications or placebo. They are described in this summary because the research doctor believes the side effects were related to the study treatments (study treatment is either a placebo or crenezumab) in the study.

Not all of the people in this study had all of the side effects.

Side effects may be mild to very serious any can be different from person to person. Serious side effects are side effects that are life-threatening or require immediate treatment or hospitalisation.

Side effects and serious side effects are not necessarily related to the use of a specific treatment.

In some cases, side effects may be related to study treatment. These are the ones that occur during the study period and which the research doctors think may have been related to the treatment received.

It is important to be aware that the side effects reported here are from this single study. Therefore, the side effects shown here may be different from those seen in other studies.

Serious side effects related to study treatment

A side effect is considered 'serious' if it is life-threatening, needs hospital care, or causes lasting problems.

During this study, of all the participants who received at least 1 dose of as part of the placebo or crenezumab groups, 5 (1.2%) participants experienced a serious side effect in the placebo group compared with 6 (1.2%) participants in the crenezumab group.

The table below shows all of the serious side effects considered to be related to the study treatment by the research doctors across both placebo and crenezumab groups. Some people had more than one side effect – this means that they are included in more than one row in the table.

Serious side effects related to the study treatment

Serious side effects reported in this study	**People taking the placebo** (405 people total)	**People taking crenezumab** (404 people total)
Pneumonia	Less than 1% (1 out of 405 people in this treatment group)	Less than 1% (2 out of 404 people in this treatment group)
Severe allergic reaction	Less than 1% (1 out of 405)	0% (0 out of 404)
Bleeding of the surface of the brain	Less than 1% (1 out of 405)	0% (0 out of 404)
Lack of blood supply to the brain	0% (0 out of 405)	Less than 1% (1 out of 404)
Build-up of fluid in the brain	0% (0 out of 405)	Less than 1% (1 out of 404)
Low blood pressure	0% (0 out of 405)	Less than 1% (1 out of 404)
Loss of consciousness	Less than 1% (1 out of 405)	0% (0 out of 404)
Seizure	0% (0 out of 405)	Less than 1% (1 out of 404)
Collection of blood in the between the skull and the surface of the brain	Less than 1% (1 out of 405)	0% (0 out of 404)

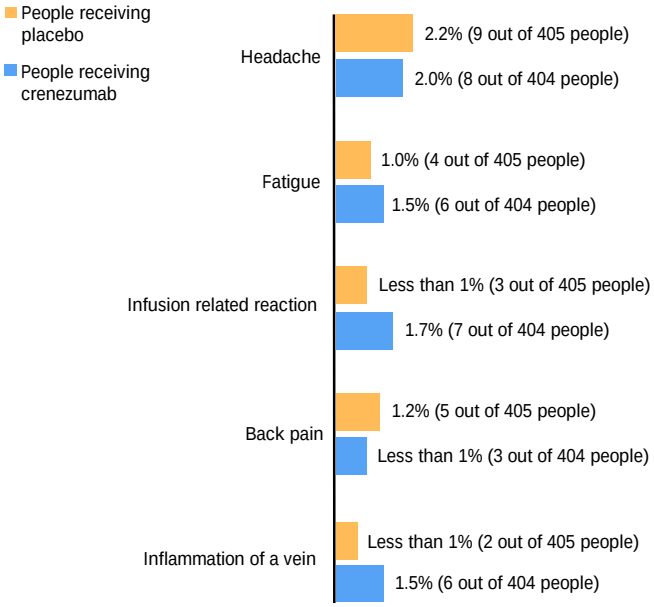
A total of 13 people died during the study. All of the deaths that occurred were considered by research doctors to be caused by reasons other than the treatment with the study drug.

Most common side effects related to the study treatment

During this study, of all the participants who received at least 1 dose of as part of the placebo or crenezumab groups, 72 (17.8%) participants experienced a side effect that was considered related to the study treatment in the placebo group compared with 78 (19.3%) participants in the crenezumab group.

The most common side effects considered related to the study treatment by research doctors are shown in the following graph – these are the 4 most common side effects across both placebo and crenezumab groups which were experienced in 5 or more people. Some people had more than one side effect – this means that they are included in more than one row in the graph.

Most common side effects related to the study treatment



Other side effects

The study showed that crenezumab was well tolerated at the dose studied. All types of side effects reported during this study were similar to those reported in other studies of crenezumab (for example, headaches and falls).

The majority of side effects were mild or moderate (such as headaches or common colds), meaning that they were easy to treat if necessary, and people recovered quickly.

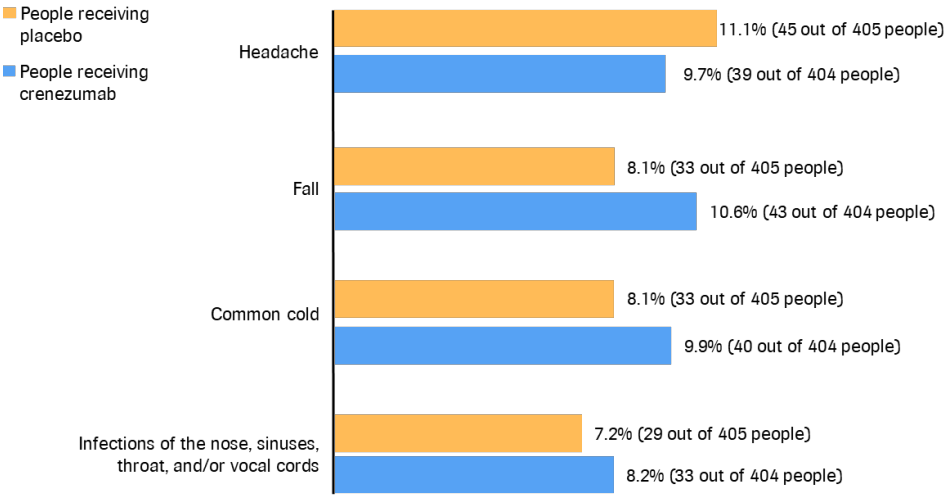
The number of people who had one or more side effect(s) was similar in the placebo and crenezumab groups.

Overall, 337 out of 405 people (83%) who received placebo had at least 1 side effect and 347 out of 404 people (86%) who received crenezumab had at least 1 side effect (see the table and graph below for the number, types of side effects and most common side effects in this study). A total of 1656 side effects occurred in people given the placebo and 1892 side effects occurred in those given crenezumab.

Number of people who had side effects in this study

	People who received placebo	People who received crenezumab
At least 1 side effect	**83.2%** (337 out of 405)	**85.9%** (347 out of 404)
Serious side effects	**15.6%** (63 out of 405)	**16.6%** (67 out of 404)
Side effects considered related to study treatment	**17.8%** (72 out of 405)	**19.3%** (78 out of 404)

Most common side effects in this study



A total of 17 people receiving placebo and 15 people receiving crenezumab experienced side effects that made them stop treatment. The most common side effects that caused people to stop treatment were agitation and loss of consciousness. Agitation was experienced by 1 person receiving placebo and by 2 people receiving crenezumab. Loss of consciousness was experienced by 2 people receiving placebo and no participants receiving crenezumab. Other side effects did not occur in more than one person.

Amyloid-related imaging abnormalities (ARIA) are a class of side effect sometimes experienced by people receiving drugs similar to crenezumab and are visible in the brain during MRI scans. The two types of ARIA are ARIA-E, which is the build-up of fluid in the brain and ARIA-H, which is small bleeding in the brain. One person receiving placebo and 1 person receiving crenezumab experienced a mild ARIA-E which resolved within 1 month. ARIA-H was found in 31 people receiving placebo and in 39 people receiving crenezumab.

You can find information about other side effects (not shown in the sections above) on the websites listed at the end of this summary – see section 8.

6. How has the CREAD study helped research?

Crenezumab had no benefits when given every month for up to 2 years to people with early Alzheimer's disease (from prodromal Alzheimer's disease to mild Alzheimer's disease). Although there was no benefit of crenezumab treatment, this information is important to the research community, and adds to our understanding of Alzheimer's disease and the role of study medications like crenezumab.

7. Are there plans for other studies of crenezumab?

One study continues to test whether crenezumab works, and how safe crenezumab is in people with a genetic mutation that causes Alzheimer's disease earlier in life than other forms of Alzheimer's disease. People in this trial started the trial before any symptoms started to appear. More information on this study can be found on the ClinicalTrials.gov website (ClinicalTrials.gov Identifier: NCT01998841). However, the study is still ongoing so the results and information on how the study was carried out are not available yet.

No other studies of crenezumab are planned at this time.

8. Where can I find more information?

You can find more information about this study on the websites listed below:

- https://clinicaltrials.gov/ct2/show/NCT02670083
- https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-003034-27/results
- https://forpatients.roche.com/en/trials/neurodegenerative-disorder/ad/cread-study--a-study-of-crenezumab-versus-placebo-to-ev-21662.html

For more information regarding the identical CREAD2 study, please refer to the CREAD2 summary available here: https://forpatients.roche.com/en/trials/neurodegenerative-disorder/ad/a-study-of-crenezumab-versus-placebo-to-evaluate-the-efficacy-an.html

The full scientific paper reporting more detailed CREAD and CREAD2 results will be published in a scientific journal.

Who can I contact if I have questions about this study?

If you have any further questions after reading this summary:

- Visit the ForPatients platform and fill out the contact form – https://forpatients.roche.com/en/trials/neurodegenerative-disorder/ad/cread-study--a-study-of-crenezumab-versus-placebo-to-ev-21662.html
- Contact a representative at your local Roche office.

If you took part in the CREAD study and have any questions about the results: speak to the research doctor or staff at the study hospital or clinic.

If you have questions about your own treatment: speak to the doctor in charge of your treatment.

Who organised and paid for the study?

The study was organised and paid for by F. Hoffmann-La Roche Ltd who have their headquarters in Basel, Switzerland.

Full title of the study and other identifying information

The full title of this study is: “A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Efficacy And Safety Study Of Crenezumab In Patients With Prodromal To Mild Alzheimer’s Disease”.

The study is known as ‘CREAD’.

- The protocol number for this study is: BN29552.
- The ClinicalTrials.gov identifier for this study is: NCT02670083.
- The EudraCT number for this study is: 2015-003034-27.