Summary of Clinical Study Results

Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of IONIS-MAPT$_{Rx}$ in Patients With Mild Alzheimer's Disease

Protocol #: ISIS 814907-CS1
Study dates: October 2017 to May 2022

Thank you to the participants who took part in the study, “Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of IONIS-MAPT$_{Rx}$ in Patients With Mild Alzheimer’s Disease”.

This study helped researchers find out if a drug called ISIS 814907, also called IONIS-MAPT$_{Rx}$, was safe in participants with mild Alzheimer’s Disease (AD).

Why was this study done?

Alzheimer’s Disease (AD) is a brain condition that causes memory loss. People with AD may have difficulty thinking and performing day-to-day activities. It is more prevalent in people after the age of 65. It is a progressive illness, which means it slowly gets worse over time.

People with AD have an abnormal build-up of proteins in the brain, including tau and amyloid-beta. The neurons in the brain send messages throughout the body and help its function. These proteins support the neurons. However, when tau protein builds up, it can form tangles that disrupt neuron function. Similarly, a build-up of amyloid-beta proteins causes plaques that clump around the neurons. Tau and amyloid protein build-ups lead to the death of neurons. This affects the functioning of the brain.

The progress of AD can be classified into three stages based on the symptoms:

- Preclinical AD: Presence of amyloid plaques and tau tangles without any symptoms or very mild symptoms that do not much affect day-to-day abilities.
- Mild AD: Presence of amyloid plaques and tau tangles with minor symptoms that do affect day-to-day activities.
- Dementia due to AD: Presence of amyloid plaques and tau tangles with more severe symptoms and greater inability to perform day-to-day activities.

Most available treatments that have been around for many years help reduce symptoms. However, they do not slow the progression of the disease in the brain or the damage to neurons. Researchers are looking for treatments that halt or slow the

progression of AD. New treatments are being developed to clear the abnormal clumps of proteins that appear in the brain of AD patients.

In this study, researchers looked at a new medication called ISIS 814907. It is designed to lower the amount of tau protein formed in AD patients. Researchers studied ISIS 814907 in patients with mild AD. They wanted to learn more about its safety and to find out about any side effects that may be caused by ISIS 814907.

When was this study done?

This study started in October 2017 and ended in May 2022.

Who took part in this study?

Participants could take part if they:

- Were 50 to 74 years of age
- Had mild AD
- Had a caregiver who could help them take part in the study

For more information on who could take part in this study, please refer to the website listed at the end of this summary.

How many people took part in this study?

Altogether, 46 participants took part in this study, of whom 23 (50%) were male and 23 (50%) were female. Participants were between 50 and 74 years of age.

The study took place at 12 clinics in Canada, Finland, Germany, Netherlands, Sweden, and the United Kingdom. The list below shows how many participants were enrolled in each country.

- Sweden: 11
- United Kingdom: 10
- Netherlands: 9
- Germany: 8
- Canada: 5
- Finland: 3

What happened during the study?

What did researchers want to know?

Researchers wanted to know more about the safety of ISIS 814907. They recorded all the side effects that the participants had during the study.

Side effects are unwanted medical problems thought to be caused by a medicine or a medical treatment. Researchers determined which side effects they thought were related to ISIS 814907. They also looked at the severity of these side effects.

The main questions researchers wanted to answer was:

What treatments were studied?

- ISIS 814907 10, 30, 60, or 115 milligrams (mg), given as an injection in the space around the spinal cord that is filled with cerebrospinal fluid.
- Placebo, given as an injection into the cerebrospinal fluid

Placebo is a drug that looks like the study medication but doesn't contain any medicine.

How was the study done?

There are many types of clinical studies. This study was a Phase 1 study. In a Phase 1 study, researchers look to see how a new treatment works in the human body for the first time.

Before the study began, all participants were screened to be sure they were a good fit for the study. The screening included laboratory tests and physical and neurological exams. Participants were also checked to get a better idea of their disease state and quality of life.

The study had 2 parts: Part 1 was the multiple ascending dose (MAD) period; Part 2 was the long-term extension (LTE) period.

Part 1 - MAD

This part of the study was:

- Double-blind: Researchers and participants did not know who was getting ISIS 814907 or placebo. Three out of four participants received ISIS 814907 and one participant received placebo.
- Randomized: Who got which study medication was decided randomly by a computer program.
- Placebo-controlled: Researchers used a placebo to learn the effect of ISIS 814907. A placebo is a drug that looks like the study medication but doesn't contain any medicine.

During Part 1, researchers wanted to test multiple doses of ISIS 814907. Participants were placed into 1 of 4 groups.

- Group 1: 10 mg ISIS 814907 or placebo – 4 total doses
- Group 2: 30 mg ISIS 814907 or placebo – 4 total doses

- Group 3: 60 mg ISIS 814907 or placebo – 4 total doses
- Group 4: 115 mg ISIS 814907 or placebo – 2 total doses

Participants in Groups 1 to 3 received treatment on Days 1, 29, 57, and 85. Participants in Group 4 received treatment on Days 1 and 85.

To begin, participants in Group 1 were treated first. Treatment began in the next groups after evaluating the side effects of the previous group.

During Part 1, participants were treated for 13 weeks. Researchers checked participants for 23 weeks after they stopped treatment.

Part 2 – LTE

This part of the study was:

- Open label: Both the researchers and participants knew which study medication the participants received.

After completing Part 1 of the study, participants entered Part 2 of the study. Due to the length of time between the end of Part 1 and the start of Part 2, participants in Groups 1 and 2 were screened again. They were assessed to get a better idea of their disease state before they entered Part 2 of the study.

During Part 2, all the participants received 5 doses of ISIS 814907. There was an interval of 84 days between each dose. Participants received treatment on Days 1, 85, 169, 253, and 337.

Participants were placed into 1 of 6 groups.

- Late Start Groups 1, 2, and 3: Participants who received placebo in Groups 1, 2, or 3 during Part 1 took 60 mg ISIS 814907 in Part 2
- Late Start Group 4: Participants who received placebo in Group 4 during Part 1 received 115 mg ISIS 814907 in Part 2
- Early Start Group 1: Participants who received 10 mg ISIS 814907 in Group 1 during Part 1 received 60 mg ISIS 814907 in Part 2
- Early Start Group 2: Participants who received 30 mg ISIS 814907 in Group 2 during Part 1 received 60 mg ISIS 814907 in Part 2
- Early Start Group 3: Participants who received 60 mg ISIS 814907 in Group 3 during Part 1 continued to receive the same dose in Part 2
- Early Start Group 4: Participants who received 115 mg ISIS 814907 in Group 4 during Part 1 continued to receive the same dose in Part 2

During Part 2, participants were treated for 48 weeks. All participants had check-up visits at the clinic, during and for 16 weeks after the treatment. The participants from the United Kingdom were checked for 23 weeks after they stopped treatment.

Researchers also contacted participants by telephone. Researchers observed participants' health and checked for any side effects.

How often and how severe were drug-related side effects for participants?

The Common Terminology Criteria for Adverse Events (CTCAE) was used to decide the severity of side effects. It classifies side effects based on the impact on day-to-day activities.

- Mild: No impact on the day-to-day activities
- Moderate: More discomfort and impact on the day-to-day activities
- Severe: Major impact on day-to-day activities.
    - A side effect is called severe when it leads to death, is life-threatening, needs hospital care, leads to disability or permanent damage, causes problems with pregnancy, requires medical or surgical intervention, or is thought to be an important medical problem.

What were the results?

The results include all participants who received at least 1 dose of ISIS 814907 or placebo. They include 46 participants from Part 1. A total of 33 participants who completed Part 1 entered Part 2 of the study and 13 participants did not enter Part 2. Most participants who did not enter Part 2 decided to leave the study or to not participate for other reasons including medical issues. One participant did not enter Part 2 due to a side effect of ISIS 814907.

For more information on the study results, refer to the website listed at the end of this summary.

Were there any side effects?

A summary of the side effects that happened during the study are shown below. Not all participants had side effects. The results include all participants who received at least 1 dose of ISIS 814907 or placebo.

Part 1

- Total participants: 46
- 15 out of 34 (44%) participants who received ISIS 814907 had drug-related side effects
    - Group 1: 3 out of 6 (50%) participants had mild side effects
    - Group 2: 1 out of 6 (17%) participants had moderate side effects
    - Group 3: 6 out of 9 (67%) participants had side effects:

        - 5 (56%) participants had mild side effects
        - 1 (11%) participant had moderate side effects
    - Group 4: 5 out of 13 (39%) participants had side effects:
        - 4 (31%) participants had mild side effects
        - 1 (8%) participant had a moderate side effect
- 12 participants who received placebo had no drug-related side effects
- No participants had severe side effects

The most common drug-related side effects that were reported by at least 2 participants in any group are listed below:

- Headache
    - 1 out of 6 (17%) participants from Group 1
    - 2 out of 6 (22%) participants from Group 3
    - 1 out of 13 (8%) participants from Group 4
- Confusion
    - 3 out of 13 (23%) participants from Group 4
- Restlessness
    - 2 out of 13 (15%) participants from Group 4

No participants died or left the study due to side effects.

Part 2

- Total participants: 33
- 14 out of 33 (42%) participants who received ISIS 814907 had drug-related side effects
    - Late Start Groups 1, 2, and 3: 1 out of 4 (25%) participants had a mild side effect
    - Late Start Group 4: 2 out of 4 (50%) participants had moderate side effects
    - Early Start Group 1: 2 out of 3 (67%) participants had side effects:
        - 1 (33%) participant had a mild side effect
        - 1 (33%) participant had a moderate side effect
    - Early Start Group 2: 2 out of 5 (40%) participants had side effects
        - 1 (20%) participant had a mild side effect
        - 1 (20%) participant had a moderate side effect
    - Early Start Group 3: 1 out of 7 (14%) participants had a moderate side effect
    - Early Start Group 4: 6 out of 10 (60%) participants had side effects

- 2 (20%) participants had mild side effects
- 3 (30%) participants had moderate side effects
- 1 (10%) participant had a severe side effect

The most common drug-related side effects that were reported by at least 2 participants in any group are listed below:

- Confusion
  - 1 out of 4 (25%) participants from Late Start Group 4
  - 1 out of 3 (33%) participants from Early Start Group 1
  - 2 out of 10 (20%) participants from Early Start Group 4
- Anxiety
  - 2 out of 10 (20%) participants from Early Start Group 4
- Reduced ability to focus
  - 2 out of 10 (20%) participants from Early Start Group 4
- Restlessness
  - 2 out of 10 (20%) participants from Early Start Group 4
- Increased level of proteins in the CSF
  - 1 out of 5 (20%) participants from Early Start Group 2
  - 2 out of 10 (20%) participants from Early Start Group 4
- Increased level of albumin protein in the CSF
  - 1 out of 5 (20%) participants from Early Start Group 2
  - 2 out of 10 (20%) participants from Early Start Group 4
- Headache
  - 2 out of 10 (20%) participants from Early Start Group 4

No participants died due to side effects. One participant left the study due to a side effect.

How has this study helped patients and researchers?

Researchers look at the results of many studies to decide which medicines work and are safe for patients. This is the first study for ISIS 814907 that was done in patients with AD. This summary gives the results of 46 participants in a single study. Other studies may have more participants and may give different results.

Researchers found no serious safety concerns with ISIS 814907.

Findings from this study may be used in other studies to learn more about the use of ISIS 814907 in participants with mild AD.

Are there plans for further studies?

Further clinical studies with ISIS 814907, now known as Biogen-sponsored BIIB080, are underway. Details of the Phase 2 study of BIIB080 can be found here: https://clinicaltrials.gov/ct2/show/NCT05399888.

Where can I find out more about this study?

- Title of this Study: A Randomized, Double-Blind, Placebo-Controlled Study, Followed by an Open-Label Extension, to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 814907 in Patients With Mild Alzheimer's Disease
- Protocol Number: ISIS 814907-CS1
- Mummery, C. J., et al. (2023). "Tau-targeting antisense oligonucleotide MAPT(Rx) in mild Alzheimer's disease: a phase 1b, randomized, placebo-controlled trial." *Nat Med* 29(6): 1437-1447.
- US Study Number: NCT03186989

  https://clinicaltrials.gov/ct2/show/NCT03186989