This AHEAD Study Guide explains the purpose and design of the AHEAD clinical trials (AHEAD-3 and AHEAD-45). This guide will cover the research and science behind the study, Eligibility requirements for participants, and the procedures involved in trial participation.

The purpose of the AHEAD Study is to test whether an investigational treatment (sometimes referred to as “study drug”) can slow the earliest brain changes associated with Alzheimer’s disease and help to prevent the associated memory loss.

About the AHEAD Study

The AHEAD Study consists of two clinical trials: the AHEAD-3 trial (or A-3) and the AHEAD-45 trial (or A-45). Both trials enroll healthy adults (55-80 years of age) who are thought to be at increased risk for brain changes and memory loss associated with Alzheimer’s disease (AD).

The studies will use an investigational treatment called BAN2401. An investigational treatment is an intervention that is studied in a clinical trial. The AHEAD clinical trials will compare BAN2401 (an anti-amyloid antibody) to a placebo (an inactive substance designed to mimic the appearance of the treatment). BAN2401 may slow accumulation (build up) of, or remove a protein known as “amyloid” or “beta amyloid” that forms amyloid plaques in the brain. Clinicians and researchers believe that accumulation of amyloid plaques in the brain may play a key role in the development of Alzheimer’s disease symptoms, such as memory loss and problems with thinking.

The AHEAD Study is testing this investigational anti-amyloid treatment (BAN2401) in people who have evidence of amyloid build up in their brain but who do not show symptoms of Alzheimer’s disease. As the early brain changes and memory decline associated with Alzheimer’s disease occur over many years, the AHEAD Study requires participation for four and a half years with study visits occurring once or twice a month. We realize this is a major time commitment, but we hope this study will provide critical information to help us one day stop Alzheimer’s disease before symptoms begin.

The Goals of the AHEAD Study

The overall goal of the AHEAD Study is to determine whether intervention with an investigational anti-amyloid treatment (BAN2401), if started, before symptoms are clinically apparent, can slow
the progression of Alzheimer’s disease changes in the brain and delay memory loss.

The AHEAD Study will also help us understand what early Alzheimer’s disease changes in the brain, such as specific levels of amyloid, are associated with cognitive decline.

The AHEAD Study may help us both understand why some groups are at increased risk of Alzheimer’s disease and find the most appropriate treatment for all individuals.

What is the Rationale for Early Intervention Against Amyloid?

Studies have shown that changes caused by Alzheimer’s disease occur in the brain many years before a person shows symptoms of Alzheimer’s disease.

We know that the amyloid protein forms plaques in the brain. This buildup of amyloid is thought to be toxic and have negative effects on brain function. The amyloid plaques are also associated with the spreading of another toxic protein in the brain, known as tau, which forms “tangles” in the brain which are thought to be closely related to memory loss.

Early intervention against amyloid might help prevent amyloid buildup or the spread of tau tangles and slow the problems with memory and thinking seen in persons with AD dementia. Studies in other diseases, like cancer and heart disease, strongly suggest that early intervention is important. Treating amyloid early may reduce the risk of later memory decline, just as reducing cholesterol can reduce the risk of heart attack.

The AHEAD Study will test an investigational treatment (BAN2401) that binds to amyloid to discover if it can lower amyloid plaque levels and slow decline in memory and thinking if started before a person develops symptoms of memory loss due to Alzheimer’s disease.

Alzheimer’s Disease

Alzheimer’s disease is a progressive brain disease, sometimes referred to as a “neurodegenerative disease,” that can cause dementia. Alzheimer’s disease is the most common cause of dementia. “Dementia” describes the progressive loss of thinking, memory, and other cognitive abilities that impair daily function. The most common symptom of dementia caused by Alzheimer’s disease is a gradual worsening of memory, but other cognitive abilities, such as orientation, planning, and the use of language, are affected as well.

Researchers now realize that Alzheimer’s disease is a continuum or process that evolves over several decades. Changes such as amyloid plaque build-up begin in the brain many years prior to the stage of mild cognitive impairment (MCI) and AD dementia.
Alzheimer’s disease brain changes are detectable using biomarkers and PET imaging, prior to any clinical symptoms of Alzheimer’s disease. This asymptomatic stage of Alzheimer’s disease is sometimes referred to as “preclinical” Alzheimer’s disease and is the stage of AD at which we are testing the investigational study drug, an anti-amyloid antibody (BAN2401), in the AHEAD Study.

Risk factors for developing Alzheimer’s disease dementia:

› **Age** – The greatest risk factor for Alzheimer’s disease dementia is advancing age. However, Alzheimer’s disease is not a normal part of aging. People with Alzheimer’s disease dementia show a buildup of amyloid plaques and tau tangles in their brains. The estimated lifetime risk of AD is more than one in five (21.1%) for women, and more than one in 10 (11.6%) for men. The risk of developing Alzheimer’s disease dementia doubles every decade after the age of 60.

› **Family history** – Individuals who have a parent or sibling with Alzheimer’s disease are more likely to develop Alzheimer’s disease.

› **Genetic risk** – Individuals with certain genes are at increased risk. These genes are discussed later in this guide in greater detail.

› **Other health problems** – Cardiovascular disease risk factors, such as physical inactivity, high cholesterol, diabetes, smoking, and obesity, are associated with a higher risk of dementia, particularly if Alzheimer’s disease pathology is present in the brain. Research shows that certain habits and healthy lifestyle decisions may help reduce the risk of cognitive decline. These include participating in regular physical activity, staying socially and mentally engaged, and maintaining good heart health. Maintaining good heart health includes eating a heart-healthy diet and preventing or treating conditions such as obesity, high blood pressure, and diabetes. You can also take care of your brain by managing stress, getting a good amount of sleep, not smoking, and seeking medical treatment if you’re experiencing symptoms of depression or anxiety.

› **Gender** – Women are at increased risk for AD dementia, partially because women live longer. Women and men are equally likely to have elevated amyloid in the brain. However, women with elevated amyloid have shown somewhat faster rates of cognitive decline and higher rates of further brain changes.
Race/ethnicity – African Americans and Latinos are at a higher risk of developing Alzheimer’s disease and other causes of dementia than non-Hispanic white Americans. This risk may be related to several factors that can interact with Alzheimer’s disease pathology to increase memory and thinking decline.

Amyloid – Amyloid plaque build-up in the brain is one of the key brain changes that defines Alzheimer’s disease. Studies using biomarkers and imaging can detect amyloid build-up in the brain many years prior to the stage of AD dementia. Not all people with amyloid build-up will progress to AD dementia within their lifetimes, but some recent studies that followed people over a long period of time suggest that 60–80% of people with elevated levels of amyloid plaque will progress to showing symptoms of Alzheimer’s disease over the next decade.

The AHEAD Investigational Treatment

The AHEAD Study will test whether BAN2401, an investigational treatment, can lower brain amyloid levels and prevent cognitive decline in people with amyloid buildup in the brain but show no symptoms of memory problems. BAN2401 is a “monoclonal antibody.” It was developed to bind to specific forms of amyloid that build up in the brain. In a recent study of people who already had symptoms of Alzheimer’s disease, BAN2401 had been shown to reduce the amount of amyloid plaque buildup in the brain and also may have slowed the decline in cognition in some people. Studies with BAN2401 are ongoing in people with mild cognitive impairment (MCI) and dementia due to AD.

The AHEAD Study is testing BAN2401 in patients up to a decade or more before the diagnosis of MCI or dementia to discover whether BAN2401 can help slow Alzheimer’s disease changes in the brain and delay decline in memory and thinking.

The investigational treatment (BAN2401) or the placebo are each given by an intravenous (IV) infusion. IV infusion means the treatment or placebo will enter the patient’s body through a vein in their arm or hand.

People who pass screening evaluations of their general health will be randomly assigned to receive either BAN2401 or a placebo. A “placebo” is an inactive substance designed to mimic the appearance of the treatment.

“Randomly assigned” means that it will be determined by chance, like the flip of a coin, whether a participant receives either the active investigational treatment (antibody) or a placebo. To ensure the integrity of the trial, neither the participant nor the study team can choose whether the participant is receiving the investigational treatment or the placebo.
Enrolling in the AHEAD Study

The first step in enrolling in the AHEAD Study involves your informed consent at an AHEAD Study site for an amyloid PET scan and other screening tests. If your screening results indicate that you are a good fit for the AHEAD-3 or AHEAD-4S trial, you will be asked to sign another consent form in order to participate in the interventional trial for approximately four years. You have the right to withdraw your consent for screening or participation in the study at any time.

Potential participants in the AHEAD Study will receive an amyloid brain scan called a Positron Emission Tomography (PET) scan. The amyloid PET scan measures brain amyloid plaque levels. **Only individuals with “intermediate” or “elevated” amyloid plaque levels are eligible for the AHEAD Study.** People who are eligible for the study will learn only the range of amyloid in their PET scan (intermediate or elevated), but will not be given a specific “number” or exact

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### Screening Stages

**STAGE 01**
Tests to determine health status and cognitive thinking

**STAGE 02**
PET scan to determine amyloid levels

**STAGE 03**
Discussion of amyloid levels
- **INTERMEDIATE AMYLOID LEVELS**: Eligible for A-3 Study
- **ELEVATED AMYLOID LEVELS**: Eligible for A-45 Study
- **NO AMYLOID DETECTED**: Ineligible

**STAGE 04**
Participant undergoes MRI

**STAGE 05**
PET scan to determine tau levels (another protein associated with Alzheimer’s disease)

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**What is a PET scan?**
Study researchers will use a Positron Emission Tomography (PET) scan to see what your brain looks like—specifically, how much amyloid and tau is present in your brain. It’s a non-invasive imaging test that can detect things other tests cannot.
level of amyloid detected in the brain, or whether their brain amyloid is going up or down over the course of the study, as one of the goals of the AHEAD Study is to learn more about whether specific levels of amyloid are associated with greater risk of cognitive decline. Information about how and what people learn about their amyloid PET scan is explained in more detail below.

**Measuring Amyloid**

The PET scan, also referred to as “amyloid PET scan” or “brain amyloid scan” was developed over the past 20 years and allows clinicians to “see” amyloid plaques in the brain. Before the PET scan was available, amyloid was measured after a person died, or indirectly through examination of spinal fluid.

People with Alzheimer’s disease dementia have elevated levels of amyloid plaque. About 30% of people over the age of 65 with normal memory and thinking abilities also have elevated levels of amyloid. We will test anti-amyloid investigational treatments in people with intermediate or elevated levels of amyloid.

**Amyloid PET Scan Procedures**

The PET scan is performed by a skilled technician at an approved Study Site Center and takes about two hours, including preparation time. Before the scan, the technician will inject a radiotracer dye through a vein in your arm, and then you will be asked to rest quietly in a private room while the dye is absorbed for about an hour. You may be given a warm blanket to help you relax, and you can use the restroom if needed. About an hour later, the technician will bring you to the room with the PET scanner, help you lie down comfortably, and then run the scan from another room for about 20 minutes. Unlike MRI machines, PET scanners are very quiet.

The amyloid PET scan is similar to scans that are used routinely for other medical reasons. All PET scans involve a small amount of radiation exposure. The risk associated with the amount of radiation exposure is considered low, and comparable to everyday risks.

The radiotracer used in this study has not yet been approved by the Food and Drug Administration (FDA). Similar radiotracers have been given to thousands of people, and the FDA has approved using some of these for detecting amyloid in people who have mild cognitive impairment or dementia. The radiotracer used in this study appears to work at least as well if not better than those that are FDA-approved.

During the PET scan, the radiotracer dye “lights up” where amyloid plaques are located. The PET scan turns this information into images. The PET images are sent to a central AHEAD Study PET analysis center where a computer program uses these images to measure the amyloid plaque on a quantitative scale.
The central AHEAD Study PET analysis center will send the amyloid PET scan result to the study team at the AHEAD Study local site.

The PET scan measures the levels of amyloid plaque detectable in your brain. The PET scan does not measure whether you have Alzheimer’s disease dementia. The PET scan also does not predict whether you will develop Alzheimer’s disease dementia in the future.

**Amyloid in the Brain**

In some older individuals, amyloid builds up slowly in the brain over decades. A subset (about 30%) of older individuals who do not show symptoms of Alzheimer’s disease have reached a level of amyloid that we call “elevated.” These people have a higher likelihood of developing memory loss and cognitive impairment due to Alzheimer’s disease.

The AHEAD-45 Study will test whether the investigational treatment can slow the progression of Alzheimer’s pathology in the brain and prevent the development of cognitive impairment in people who have “elevated amyloid” on screening PET scan but who do not yet show any symptoms of cognitive impairment.

Amyloid builds up slowly in the brain, going through a transitional stage we call “intermediate” amyloid. “Intermediate” amyloid plaque is associated with an increased risk of developing an “elevated” level of amyloid plaque. Less is known about the risk of cognitive decline over a longer period of time in people with “intermediate amyloid,” but some recent studies suggest that very subtle changes occur in memory and thinking as amyloid is building up in the brain. The AHEAD-3 study will test whether the investigational treatment can prevent the amyloid increase expected in people with “intermediate amyloid.”

Studies suggest the relationship between elevated amyloid and developing Alzheimer’s disease dementia may be similar to the relationship between cholesterol and heart disease. Having high cholesterol increases the risk of having a heart disease, but having high cholesterol does not mean that a person will definitely have a heart attack. Similarly, having an intermediate or elevated level of amyloid plaque may increase the risk of developing memory problems and Alzheimer’s disease dementia, but it does not mean a person will definitely develop Alzheimer’s disease dementia.

Researchers and clinicians cannot calculate the personal risk of dementia for an individual with elevated amyloid. Why? Research involving thousands of people enabled us to calculate a person’s risk of heart disease, using many pieces of information. There is not yet enough research to do the same with an individual’s amyloid PET scan result. There are likely several other factors that influence the rate of cognitive decline associated with specific amyloid levels. At this point, we know that on average, elevated levels of amyloid are associated with higher chances of cognitive decline and future impairment, but this does not mean that a future diagnosis of mild cognitive impairment or dementia is certain.
The “Amyloid Continuum” and Amyloid Level Thresholds for Eligibility

The PET scan screening for the AHEAD Study will classify people into 3 groups:

1. **Elevated**, where the PET scan shows clearly abnormal levels of amyloid that are associated with increased risk for future memory and thinking decline in cognitively unimpaired people.

2. **Intermediate**, where the PET scan shows amyloid that is detectable but not yet at the elevated level.

3. **Not detected**, where the PET scan shows that elevated and intermediate levels of amyloid plaque are not detected. A “not detected” level means that the scan did not show evidence of amyloid build up. People with a “not detected” result on their PET scan are not eligible to participate in the AHEAD Study Studies. It is possible that very low amounts of amyloid plaque may be present but below the level at which we can reliably detect them. A “not detected” level does not mean that you will not have an “intermediate” or “elevated” result at a future PET scan or that you will never develop Alzheimer’s disease dementia.

Researchers are still learning about whether specific levels of amyloid plaque can help predict an individual's risk of cognitive decline. Amyloid plaque levels in the brain of older people who are cognitively healthy are measured along a continuum with a range of levels. The AHEAD Study researchers have selected “thresholds” (cutpoints or dividing marks to define groups) along this continuum. The threshold range will be used to assign eligible participants to the A-3 or A-45 trials. Specifically, we hope participants in the A-3 and A-45 groups will help us to develop interventions to reduce risk of AD progression based on lower and higher amounts of amyloid plaque in the brain.

The threshold for “elevated” amyloid was chosen to define clearly abnormal levels of amyloid that are closer to that of those seen in people who already have Alzheimer's disease dementia. This elevated level of amyloid in cognitively normal older individuals is associated with an increased risk of experiencing cognitive decline in the next few years. The goal of the AHEAD-45 trial is to test whether we can reduce participants' elevated brain amyloid by providing the investigational treatment every 2 weeks for the first 96 weeks of the study, and then maintain that lower level of amyloid with treatment every 4 weeks can delay memory problems. As a result of BAN2401 (or placebo) being given every 2 weeks for the first 96 weeks of the study, in the AHEAD-45 study, people with elevated amyloid will receive a higher overall “dosage” of the interventional treatment than those with intermediate amyloid enrolled in the AHEAD-3 study.

The threshold for “intermediate” amyloid was selected to define a group of people with lower levels of amyloid who are at an increased risk for further amyloid buildup in subsequent years.
The goal of the AHEAD-3 Trial is to test whether administering study treatment every 4 weeks in those with intermediate levels of amyloid can slow or prevent further amyloid accumulation.

As new data becomes available – such as data from this study – the cutpoints for the levels of amyloid plaque called “elevated” or “intermediate” could change. This is similar to the changes made in cutpoints for the levels of cholesterol and blood pressure considered “high” over the past few decades. The names given to these levels may change as well.

**Amyloid and Genetic Risk Factors**

**THE APOE GENE**

Everyone has two copies of the APOE gene: one copy is inherited from your mother and one copy from your father. These genes do not change with age. Each APOE gene is one of three types: APOE ε2, APOE ε3, or APOE ε4.

Because we all have two copies of the APOE gene, this means each of us has one of six possible APOE combinations, or genotypes:

- ε2/ε2
- ε2/ε3
- ε3/ε3
- ε2/ε4
- ε3/ε4
- ε4/ε4

**APOE & RISK FOR ALZHEIMER’S DISEASE DEMENTIA**

The ε4 type of the APOE gene is a risk factor for developing Alzheimer’s disease dementia, but it cannot predict who will or will not develop symptoms of Alzheimer’s disease, and over what time frame. Some studies suggest that the influence of APOE ε4 on risk of developing symptoms of AD may differ by sex and race. Ongoing research, including the results from the AHEAD Study, will help researchers understand how APOE affects risk of cognitive decline and response to anti-amyloid treatments.

For example:

- Someone can have no copies of ε4 and still develop Alzheimer’s disease dementia
- Someone can have one or two copies of ε4 and NOT develop Alzheimer’s disease dementia

Approximately one of every four people (25%) in the general population has at least one copy of the APOE ε4 gene. Someone who has one copy of the APOE ε4 gene is at higher risk for developing memory and thinking problems due to Alzheimer's disease than someone who has no copies of ε4. If an individual has two copies of APOE ε4, their risk is further increased.

People who have one or two copies of the APOE ε4 gene are more likely to have elevated amyloid than people with no copies of the gene. There is also evidence that, among persons with elevated amyloid, those who have one or two copies of the APOE ε4 gene are more likely to experience memory and thinking problems than those who have no copies of the gene. The likelihood of
having elevated amyloid and the likelihood of memory and thinking problems are higher for those with two copies of the APOE ε4 gene than those with one copy.

The ε2 gene variant is rare but is associated with a lower risk of Alzheimer's disease. The ε3 gene variant is most common and is not associated with an increased risk for developing symptoms of Alzheimer's disease.

APOE & THE RISK OF ARIA

Amyloid-Related Imaging Abnormalities (ARIA) is a possible side effect from the investigational treatment BAN2401. The risk of ARIA is higher for people who have one copy of the APOE ε4 gene than people who do not have APOE ε4, and increases with two copies of APOE ε4. ARIA is explained in more detail later in this Study Guide.

Amyloid & APOE in the AHEAD Study

To participate in the AHEAD Study you are required to learn your amyloid PET result, as this result determines your eligibility for the A-3 or A-45 Trial. You will have the option to learn your APOE result. The amyloid PET result will be disclosed to you a few weeks after your PET scan visit. You may also choose to learn your APOE result at that time.

What Will I Learn by Participating?

- Your Amyloid PET scan* result: Elevated, Intermediate, or Not Detected
- Option to learn if you have a gene that is a risk factor for dementia caused by Alzheimer's disease.

* The PET scan takes pictures of participants' brains, allowing researchers to see and track any changes that may occur.

Learning your Amyloid Result

An experienced member of the Study Site clinical team will discuss your amyloid PET result with you a few weeks after your PET scan in a screening visit. You may choose to bring a friend or family member with you to this visit to learn whether you have “not detected,” “intermediate amyloid,” or “elevated amyloid” in your brain. You will be asked to fill out questionnaires about your feelings when learning your result to help us better understand how to share and explain these results and support our participants. You will have a phone call a few days after learning your results to follow up with any needed support and to answer any further questions that you may have.

While recent studies suggest that most people learn screening results such as APOE genes and amyloid levels without a high level of distress or concern, each person's response is valid. Some
people who learn an “amyloid not detected” result may feel relief; others may be disappointed they cannot participate in the AHEAD Study. Some people who learn an “intermediate” or “elevated” result may feel sad or worried, or frustrated with the lack of clear predictions for their future. After learning their result, some people choose to make lifestyle changes that may help maintain or improve their overall health and brain function. We encourage you to understand that ALL these feelings, and others, are valid. They may also change over time as you talk with others or think about how to respond to these results.

Learning their amyloid result causes some people to reflect upon their plans for the future and the areas of their life that could be impacted in the event of development of cognitive impairment or a diagnosis of Alzheimer’s disease dementia. Some people may find this type of planning uncomfortable or upsetting, but it may also allow individuals and their families to feel prepared and may reduce the likelihood of future stress and conflict. Specific topics that may be relevant range from financial and legal planning, to decisions about living situations, employment, and leisure time, as well as possible changes in family and social relationships.

**Your study partner will learn your amyloid result if you enroll in the AHEAD Study, since they will attend certain visits during the four-year study.** Some people also share their result with other friends or family members. You may want to think about how sharing this information will change your relationships with others. The decision with whom to share this with is totally within your control.

**Learning your APOE Results**

You will have the option to learn your APOE result. The decision whether or not to learn your APOE result is personal. There are many factors to consider, and there is no right or wrong answer. To help you with your decision, we encourage you to think about the different possible results and how you might feel about each. You may also want to consider how learning this information might impact your family members. APOE is a gene, and so blood relatives of persons who have the ε4 gene may have that gene as well.

**APOE & Insurance Considerations**

In the United States, the Genetic Information Nondiscrimination Act (GINA) is a U.S. federal law that protects against genetic discrimination for health insurance and employment, but does not cover life insurance, long-term care/disability policies, or small workplaces. GINA sets a minimum standard for protection against discrimination based on a genetic test result. Some states also have laws that provide additional protections. Information on state laws in the United States may be found through the National Conference of State Legislatures (www.ncsl.org).

**APOE & Family**

Learning your APOE result has implications for family members. Some individuals may have feelings of worry or guilt when thinking about children or siblings who may have inherited the APOE ε4 gene.
If someone has two copies of APOE ε4, this means that all of their biological children must have at least one copy of the APOE ε4 gene. If someone has one copy of APOE ε4, there is a 50% chance of passing this to each of their children. For example, for someone with an APOE ε3/ε4 result, there is a 50% chance of passing the ε4 copy to a child, and an equal 50% chance of passing the ε3 copy.

Keep in mind that your APOE result is determined by inheriting one copy from your mother and one from your father. Your results could also indicate a possible risk for APOE ε4 in your parents and siblings. For these reasons, you may want to consider discussing your decision to learn your APOE result with family members.

**APOE & the AHEAD Study**

Some individuals may wish to know their APOE result to aid in their decision making about whether to join the AHEAD Study, as it is possible that the risks and benefits of the AHEAD trials could differ between people who have the APOE ε4 gene and people who do not.

Whether someone has the APOE ε4 gene may provide information about two types of risk. One is the increased risk of future cognitive decline in people who have both APOE ε4 and elevated amyloid. The other risk associated with APOE ε4 is the potential treatment side effect of Amyloid-Related Imaging Abnormalities (ARIA – [see more information below](#)) from the BAN2401 investigational treatment. Some people may weigh the risk of future cognitive decline against the risk of ARIA from the treatment to delay or prevent cognitive decline. It is not currently possible to give a precise prediction of either of these risks, but the Study Site Team can help you to better understand our current general risk assessments to aid in your own decision. It is also possible that there will be different responses to the investigational treatment between people who have the APOE ε4 gene and those who do not. If new information relevant to the AHEAD Study risks and benefits becomes available, we will share it with you.

**Risks of Participation**

The informed consent form details the AHEAD Study's risks. Here, we focus on four:

1. Participant study information is not released to personal physicians without the participant’s permission, and we code participant study information to protect confidentiality. However, it is possible information about a participant could be entered into an individual's medical record, particularly if the individual experiences an adverse event (side effect) requiring medical treatment.

2. Although we will do everything possible to protect your confidentiality, information about amyloid status or participation in this study could potentially influence the ability to obtain life insurance, health insurance, or long-term care insurance. If you are thinking about purchasing any of these policies, you might do it before enrolling.
3. Information about amyloid status could also affect your employability.

4. All drugs have risks. For investigational drugs, one of the goals of the study is to identify and understand the risks. One of the risks associated with amyloid-clearing antibodies such as BAN2401 is Amyloid Related Imaging Abnormalities, or ARIA.

**Amyloid Related Imaging Abnormalities**

Amyloid-Related Imaging Abnormalities, or ARIA, refers to changes seen on MRI in a small percentage of people treated with the investigational treatment and similar antibodies that help clear amyloid from the brain.

There are two types of ARIA. One we call ARIA-H (for hemorrhage), which refers to small areas of bleeding in the brain.

The other is ARIA-E (for edema), which refers to swelling or buildup of fluid outside the brain on the lining of the brain.

Both types of ARIA are often detected on MRI without any associated symptoms felt by the individual. ARIA-E usually goes away on the MRI without treatment within weeks or months. Evidence of ARIA-H remains stable on the MRI for many years.
Symptoms associated with ARIA can occur in some cases and may include headache, vision changes, confusion, and problems with walking. Often no treatment is required for ARIA, but additional MRI follow-up may be recommended. If severe symptoms are present, your study physician may ask you to undergo additional tests or treatment.

ARIA has been associated with increased amyloid plaque removal in some studies. We do not yet know whether there are any long-term effects of ARIA, positive or negative, and will learn more about this during the AHEAD Study.

The risk of both types of ARIA is higher for people who have the APOE ε4 gene. People who have the APOE ε4 gene and experience ARIA-E have a higher risk of experiencing symptoms than those without the APOE ε4 gene who experience ARIA-E.

### Additional Topics to Think About

#### What Happens During Study Visits?

A number of assessments will be performed during each study visit. A description of some of the assessments is given below:

- You will be asked questions about your memory and thinking abilities, your emotional and psychological state, and how well you can carry out everyday activities.
- Your study partner will also be asked a number of questions about how you carry out everyday activities. Your study partner may answer these questions by phone once a year.
- You’ll be asked about any medications you’re taking (including non-prescription medicines, supplements, and herbal remedies). In general, you will be allowed to continue to take any of these medications, supplements, and herbal remedies as long as they are not likely to affect the investigational treatment. You will also be asked about any medications you may have taken in between study visits (ex. cold/allergy or pain medications).
- You’ll be asked about your general health, including any illnesses or complaints you’ve had or have.

#### Study Partner

**What is a study partner?** All clinical trials focused on reducing cognitive decline due to Alzheimer’s disease require participants to enroll with a family member or friend who can answer questions about the participant’s memory and thinking skills and daily function. This person is called a study partner.

**Why is a study partner required?** Research shows that, over time, at least some people enrolled in trials like AHEAD will develop cognitive impairment, and some of these people may have trouble judging their own memory performance. Study partners may therefore be a good additional source of information. Many people in trials like AHEAD say they want a study partner to be with them for support when they learn their gene and biomarker results.
What are a study partner’s responsibilities? Study partners must attend a yearly study visit, in person or by phone. To participate, they must sign an informed consent form and complete study questionnaires and will be compensated for their time and travel.

Who can be a study partner? Your study partner should have regular contact (weekly) with you, either in person, by phone, or electronically, and should be someone who knows you well and who you trust to care about you.

Blood tests
Routine blood tests will be conducted to ensure there are no medical conditions that may interfere with your participation in the study or that could be responsible for any changes in your well-being throughout the study period. If any of the blood tests are abnormal, we will share the information with you so that you may discuss them with your doctor.

Some blood will be taken at the beginning to allow us to check genetic markers that may be related to amyloid buildup in the brain. As described earlier, you will have the option to learn your APOE genotype result.

Electrocardiogram (ECG)
This procedure will help us check your heart’s electrical activity.

Magnetic Resonance Imaging (MRI)
An MRI helps us look at your brain using a large magnet. During this process, you will lie still on a narrow table that slides into an MRI scanner. There are periodic MRIs over the course of the study. Most MRIs are done at a separate appointment from the study visits. People who find MRIs noisy or claustrophobic may take medication prior to the MRI, if the MRI staff and study team are notified.

Tau PET scan
You will also have a tau PET scan. This scan uses an experimental PET “tracer” to look for evidence of tau tangles in your brain. Tau is another key abnormal protein that builds up in the brain of people with AD dementia (in addition to amyloid). Because the ability to “see” tau in the brain in very new, we hope the data collected in the AHEAD Study, and other studies too, will help us
learn more about how to measure tau, how tau scan results can be used to predict the risk of developing symptomatic Alzheimer’s disease, and whether tau PET changes over time in response to treatment. You will not receive information about your tau PET scan results during the AHEAD Study, but researchers hope to learn enough about tau PET to be able to provide more information at the end of the study.

**Lumbar puncture (Optional)**

During a lumbar puncture (optional), a small amount of spinal fluid will be taken via a needle from your lower spine and analyzed. This test gives us additional information on changes in the brain proteins related to Alzheimer’s disease.

At various points in the study, participants will undergo the following activities:

- **MEDICATION HISTORY AND ADVERSE EVENTS**: Routine discussion of participant’s medication history and any changes to it (including vitamins and/or herbal substances) and any recent changes to the participant’s health status.

- **ELECTROCARDIOGRAMS**: Measurement of heart activity, which can identify any abnormalities.

- **PHYSICAL HEALTH ASSESSMENTS**: Measurement of weight and vital signs (blood pressure, heart rate, breathing rate, and temperature) and brief physical and neurological exams.

- **MEMORY AND THINKING TESTS**: Combination of written, verbal, and computerized tests, including remembering information, naming and drawing pictures, and connecting symbols.

- **BLOOD AND URINE TESTS**: Samples taken will help researchers track your health status and measure study drug levels and biomarkers in your blood.

- **PET SCANS**: Scan capturing images of participant’s brain to detect protein (amyloid and tau) levels.

- **MRI SCANS**: Scan capturing images of participant’s brain.

- **INFUSIONS**: IV infusions of study drug (BAN2401) or the placebo.
Intravenous Infusion

You’ll receive an intravenous infusion of the investigational medication or placebo. Both the investigational treatment and the placebo (a substance that looks like the investigational treatment but doesn’t contain any active ingredient) will be given as an intravenous infusion. The infusion takes about 60 minutes to administer, plus extra time for set-up and finish.

Participants in the A-3 trial will receive infusions every four weeks throughout the entire four years.

Those in the A-45 trial will receive infusions every two weeks for the first 96 weeks (about two years) and then will receive infusions every four weeks for the remainder of the four years.

Adverse Event Monitoring

Whenever you receive a procedure or have an infusion, your Study Team will carefully monitor you for any unexpected response.

Length of the AHEAD Study Participation

The AHEAD studies require a commitment of about four and a half years to complete the screening process and all infusions and assessments.

Initial and on-going participation in the AHEAD Study is entirely voluntary.

What Happens at the End of the AHEAD Studies?

Researchers will analyze the findings from the studies, comparing the results from the group taking the investigational treatment to the group who received the placebo. This information will be presented to participants and the scientific Alzheimer’s field. The coded data from the screening process, and eventually the treatment data, will be made available to researchers around the world. New findings that may help us predict increased risk of cognitive decline, such as blood tests, tau PET, genetics, and other factors, will also be made available to help researchers figure out who may benefit from treatment and what time is optimal to initiate treatment. If you are able to participate through the completion of the AHEAD Study, you may be asked if you would like to participate in another long-term study in which all participants will be able to receive the investigational treatment.
The AHEAD Study is funded by the National Institutes of Health and several non-profit organizations, as well as Eisai, the company that makes the investigational treatment used in the study. The study is coordinated by the University of Southern California’s Alzheimer’s Therapeutic Research Institute, Brigham and Women’s Hospital, Massachusetts General Hospital, and Harvard Medical School.