



Frequently Asked Questions

The following frequently asked questions (FAQs) are meant to serve as background information for your site.

These questions are not to be shared externally, but provide approved responses to questions about the Generation Program. The information can help you prepare for conversations with reporter and answer their questions.

Generation Program

What is the Generation Program?

The Generation Program consists of two pivotal phase 2/3 studies—Generation Study 1 and Generation Study 2. The trials are testing whether investigational anti-amyloid study medications might prevent or delay the emergence of symptoms of Alzheimer's in people at particularly high risk for developing symptoms of Alzheimer's at older ages because of their genetic status.

These trials are part of a collaboration between Banner Alzheimer's Institute (BAI), Amgen, and Novartis and are part of a groundbreaking research effort known as the Alzheimer's Prevention Initiative (API), an international collaboration formed to further Alzheimer's prevention research.

What is the difference between the Generation Study 1 and the Generation Study 2?

The Generation Study 1 is examining whether two investigational anti-amyloid study medications—CAD106, an active immunotherapy, and CNP520, a BACE1 inhibitor given separately—can prevent or delay the diagnosis of Alzheimer's among high-risk cognitively healthy older adults who have two copies of the APOE4 gene, one from each parent.

The Generation Study 2 is examining whether the BACE inhibitor CNP520 can prevent or delay the onset of the symptoms in a broader population of individuals who are at high risk of developing Alzheimer's because of their age and because they carry either one or two copies of the apolipoprotein E (APOE) 4 gene, the major genetic risk factor for late-onset Alzheimer's disease.

What is the e4 type of the apolipoprotein E gene?

The e4 type of the APOE gene is the major genetic risk factor for late-onset Alzheimer's disease. People with one or two copies of the gene—one from each parent—are at particularly high risk for developing the disease.

How does someone go about participating in the Generation Program?

Potential recruitment pathways vary from country to country (e.g. genotype previously known by the participants, existing site-specific registries, access to biobanks, local site-specific campaigns, etc.)

In the U.S., the Alzheimer's Prevention Registry's GeneMatch program is one

of the primary recruitment sources for participating. GeneMatch is a research program designed to identify a large group of people ages 55 to 75 living in the U.S. who agree to be contacted about Alzheimer's prevention research studies based in part on their genetic information. GeneMatch is overseen by an IRB and requires informed consent from participants.

Through GeneMatch, interested individuals will submit a genetic sample via a cheek swab. Once their genetic sample is analyzed they may be notified that they may be eligible to participate in the Generation Study. Upon notification, they will be informed of next steps. Both genetically eligible and non-genetically eligible individuals will be invited into the study.



Generation Program

ALZHEIMER'S PREVENTION INITIATIVE



Generation Study 1

What is Generation Study 1?

The Alzheimer's Prevention Initiative (API) Generation Study 1 is seeking to determine whether either or both of two investigational study medications—an active immunotherapy and an oral study medication—compared to placebo can reduce or eliminate amyloid proteins in the brains of cognitively unimpaired older adults, ages 60-75, who have two copies of the e4 type of the apolipoprotein E (APOE) gene, the major genetic risk factor for late-onset Alzheimer's disease. The study is testing whether the investigational study medications might prevent or delay the emergence of symptoms of Alzheimer's in people at particularly high risk for developing the disease at older ages because of their genetic results. Eligible participants may be enrolled in the study and be randomized to one of the two investigational study medications or placebo.

Why is it important to study people with two copies of the e4 type of APOE gene?

About 2 percent of the world's population has two copies of the e4 type of the APOE gene or APOE4 (Corder et al 1993, Cupples et al 2004, Farrer et al 1997, Ward et al 2012). A person who has two copies of the APOE4 gene is called "an APOE4 homozygote."

Individuals with two copies of APOE4, one from each parent, are at increased risk for developing Alzheimer's disease at older ages. By studying this high-risk population, we hope to assess each treatment's potential to preserve memory and thinking as well as their effects on biological measures of the disease.

Does a person have to learn their genetic status to participate in Generation Study 1?

Generation Study 1 is the first to incorporate genetic testing and counseling into the study screening process. Participants will be required to learn whether they carry none, one or two copies of the e4 type of the APOE gene.

Is this the first Alzheimer's study to employ this strategy? Are other studies currently doing this? If so, how is this different?

While other Alzheimer's studies have used genetic testing and PET scans to examine amyloid buildup in the brain, the Generation Study 1 is unique in being the first to require participants to learn whether they carry none, one or two copies of the e4 type of the APOE gene. To help ensure the overall well-being of each participant, the study will provide genetic counseling. Individuals will speak with a healthcare provider, such as a genetic counselor, to discuss their APOE results and address specific questions and concerns regarding their genetic information.

Does a person need to have brain amyloid deposits in order to be eligible for Generation Study 1?

No. Some participants in the study will not yet have brain amyloid deposits at the time they are enrolled, which means that the study can address whether treating before or after this deposition occurs may be more advantageous.

How will participants' personal information be protected?

Privacy is very important to us. All personal information will remain strictly confidential in accordance with all applicable laws.

How many people will participate in Generation Study 1 and what population will be studied?

Researchers will recruit approximately 1,300 cognitively healthy older adults, ages 60 to 75, who carry two copies of the e4 type of the APOE gene and are eligible for the Generation Study 1. The study will take place at more than 100 selected sites in North America, Europe, and Australia.

What are the investigational study medications being studied?

Study participants will receive either the investigational study medication active immunotherapy (CAD106) developed by Novartis, or the oral investigational study medication (CNP520) co-developed by Novartis and Amgen, or a placebo. The two investigational study medications will be tested separately and are intended to stop the accumulation of amyloid.

Who is funding the Generation Study 1?

The Generation Study was initially funded with a \$33.2 million grant from the National Institutes of Health. Additional funding has been provided by the Alzheimer's Association, FBRI, GHR Foundation and Banner Alzheimer's Foundation. The majority of the cost will be covered by Novartis as the study sponsor, and Amgen as co-development partner for CNP520.





Generation Study 2

What is Generation Study 2?

The Generation Study 2 is a global, randomized, double-blind, placebo-controlled, parallel-group trial, assessing the investigational anti-amyloid compound CNP520, co-developed by Novartis and Amgen.

The trial will enroll cognitively healthy older adults, ages 60-75, at increased risk of developing symptoms of Alzheimer's disease. Participants will carry either one or two copies of the e4 type of the APOE gene; those with one copy will require evidence of elevated brain amyloid, as measured by an amyloid Positron Emission Tomography (PET) or amyloid levels in cerebrospinal fluid.

Eligible participants will be randomized to one of two doses of the investigational study medication (CNP520 15 mg or 50 mg) or placebo.

Why is it important to study people with one or two copies of the e4 copy of the APOE gene?

The e4 type of the APOE gene is strongly linked to late-onset Alzheimer's. Roughly one in four people carry a single copy of the e4 type of the APOE gene, and about two percent of the world's population carries two copies. (Corder et al 1993, Cupples et al 2004, Farrer et al 1997, Ward et al 2012)

Does a person have to learn their genetic status to participate in Generation Study 2?

Generation Study 2 incorporates genetic testing and counseling into the study screening process. Participants will be required to learn whether they carry none, one or two copies of the e4 type of the APOE gene. Only those who learn they have one or two copies may be eligible to participate in the study. In addition, the presence or absence of elevated brain amyloid will be disclosed.

Does a person need to have brain amyloid deposits in order to be eligible for Generation Study 2?

It depends. Participants who carry only one copy of the e4 type of the APOE gene will require evidence of elevated brain amyloid, as measured by an amyloid Positron Emission Tomography (PET) or lumbar puncture. Participants who carry two copies of the e4 type of the APOE gene may be eligible regardless of brain amyloid.

How will participants' personal information be protected?

Privacy is very important to us. All information will remain strictly confidential.

How many people will participate in the Generation Study 2 and what population will be studied?

The Generation Study 2 will be conducted at more than 180 sites in North and South America, Europe, Asia, and Australia. Participants will be enrolled over about a two-year period.

What is the investigational study medication that is being studied in the Generation Study 2?

CNP520 is an oral medication, co-developed by Novartis and Amgen. It is a β -site amyloid precursor protein cleaving enzyme (BACE)1 inhibitor designed to prevent the production of different forms of the amyloid protein.

Early in the course of Alzheimer's disease (AD), amyloid build-up in the brain is evident and is thought to be a key factor in driving the subsequent progressive damage and clinical symptoms in AD. By inhibiting the BACE1 enzyme, CNP520 is hypothesized to reduce the accumulation of different forms of amyloid which accumulates in the brains of individuals with AD.

Can you tell us more about CNP520? Where is it in drug development?

CNP520 is currently in Phase II/III Generation Program being initiated worldwide. CNP520 entered preclinical development in 2013 and was selected for further development at Novartis because of its favorable pharmacodynamic and safety profile in these preclinical studies.

It is an oral medication that entered phase 1 trials in Europe in 2014. To date, more than 400 healthy participants were enrolled in a total of 5 completed human studies (4 Phase I studies and one Phase II study). The toxicological and clinical studies required to support the Generation Program were finished in 2016.

Why is only CNP520 being used as the study medication in the Generation Study 2, while in Generation Study 1 there were two investigational anti-amyloid therapies?

The Generation Program includes two different investigational study medications, each with its own individual development plan. The Generation Study 2 expands the safety database and the targeted population specifically for CNP520. It also provides a second pivotal trial to support the potential filing of CNP520 for Health Authority approval.

As part of its development plan, a second study for CAD106 might be considered in the future.

Who is funding the study?

The cost will be covered by Novartis (the study Sponsor) and Amgen. Additional funding for the study will be provided by the Banner Alzheimer's Foundation.



Generation Program

ALZHEIMER'S PREVENTION INITIATIVE



Genetic Testing/Disclosure

What should a person consider before undergoing genetic testing?

Learning the results of genetic testing can have a significant impact on potential participants and family members. A person should weigh several factors before participating:

- An individual should determine if this is the right time to learn his or her APOE gene results because this information could have psychological impact, such as anxiety or depression, as well as other personal impact, such as difficulty obtaining long-term care insurance in the U.S.
- An individual should decide if they are prepared to know the results, given that there is no current cure.
- A person should also consider the impact that learning this information might have on family members. Learning something about their genetic information will also affect what their family knows about their own genetic information. For example, if a person possesses two copies of the APOE4 gene, this means their child(ren) possess(es) at least one copy.

Are there laws in place to protect individuals who learn their genetic status?

Local regulations apply, but in general such laws are in place.

In the US, in 2008, the Genetic Information Nondiscrimination Act (GINA) was passed to protect Americans against discrimination based on their genetic information in reference to health insurance and employment.

However, the legislation includes several undefined areas and lacks protection for individuals when trying to obtain long-term care, disability or life insurance.

GeneMatch has received a certificate of confidentiality from the National Institutes of Health.

How will people learn their APOE results as part of the Generation Program?

People will meet with a healthcare provider, such as a genetic counselor, to learn their results. Genetic counseling can help address not only what those results mean for a person's risk for developing Alzheimer's disease, but also the emotional reactions that can accompany learning one's genetic status.

Why is genetic counseling an important part of the study?

Genetic counseling is important because it provides participants access to trained professionals who specialize in helping people better understand and adapt to the results of genetic testing. Genetic counseling can help address not only what those results mean for a person's risk for developing Alzheimer's disease, but also the emotional reactions that can accompany genetic testing and disclosure.

Will the counseling take place in person?

Not all study sites will have a genetic counselor on staff.

For Generation Study 1 sites in the U.S., the counseling may take place

via phone or video conferencing. For Generation Study 2 sites in the U.S., remote counseling is only conducted via phone.

For both Generation Studies 1 and 2 in sites outside of the U.S., counseling will either take place face-to-face with a genetic counselor or other health care provider (per local laws and regulations), or via telemedicine if allowed per local laws and regulations.

For Generation Study 1, we will be studying the effectiveness and impact of this remote delivery counseling.

Should participants share this information with their health care provider?

If a person chooses to share their genetic results with their health care provider, that information would become part of their medical record. A person can choose to keep this information private and it would only be seen by the researchers conducting the Generation Study.

Are you collaborating with 23andme?

At specific sites in the US, we are engaged in collaboration with 23andMe to recruit participants for Generation Study 1. The collaboration is overseen by an IRB and requires informed consent from participants.

Can you comment on specifics of the agreement with 23andme?

The terms of the agreement and participant privacy prevent us from disclosing additional specifics.





Call to Action

Where can people go for more information?

Interested individuals in the U.S. should visit **www.endALZnow.org/GeneMatch** to learn more and be considered for participation in GeneMatch and the Generation Program. They may also visit **www.GenerationProgram.com** for more information.

Additionally, **www.clinicaltrials.gov** contains information on both Generation Study 1 and 2.

Interested individuals outside of the U.S. should contact the study site closest to them for more information.

