PHOENIX, AZ (August 23, 2016)—Researchers from the Banner Alzheimer’s Institute (BAI) today announced they have begun enrolling the first participants in a multi-site study to determine whether two investigational anti-amyloid compounds—an active immunotherapy and an oral medication—can prevent or delay the emergence of symptoms of Alzheimer’s in people identified by genetic markers as being at particularly high risk for developing the disease at older ages.

The five-year Alzheimer’s Prevention Initiative (API) Generation Study will involve more than 1,300 cognitively healthy older adults, ages 60 to 75, who are at high risk of developing symptoms of Alzheimer’s because they inherited two copies of the e4 type of the apolipoprotein (APOE) gene—one from each parent. Roughly one in four people carry a single copy of the e4 type of the APOE gene, which is strongly linked to late-onset Alzheimer’s, and about two percent of the world’s population carries two copies.

“Enrolling the first participants into the Generation Study marks a major milestone for the trial and for Alzheimer’s prevention research in general,” said Pierre N. Tariot, MD, one of the API leaders and director of BAI, a division of Banner Health, one of the largest nonprofit healthcare systems in the United States. “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.”

The study is sponsored by Novartis, a Swiss pharmaceutical company, and Amgen, a biotechnology company based in Thousand Oaks, CA, in collaboration with BAI, with funding from the National Institute on Aging, part of the National Institutes of Health (NIH), as well as the Alzheimer’s Association, FBRI, GHR Foundation and Banner Alzheimer’s Foundation.

The Generation Study is part of the API, an international collaborative led by BAI to accelerate the evaluation of promising treatments. It will enroll at about 90 sites across North America, Europe and Australia, including BAI’s headquarters in Phoenix. Since some participants in the study will not yet have brain amyloid deposits at the time they are enrolled, the study can address whether treating before or after this event occurs may be more advantageous.

Study participants will receive either the active immunotherapy (CAD106) developed by Novartis, or the oral medication (CNP520), subject to regulatory approval, developed by
Novartis, in collaboration with Amgen, or a placebo. The two drugs will be tested separately and are intended to stop the accumulation of amyloid.

In addition to testing these two investigational treatments in individuals at especially high risk for Alzheimer’s, the Generation Study is among the API efforts intended to help find faster ways to test the range of promising treatments in other individuals who, based on their genetic background or biological features, are at increased risk for Alzheimer’s, and to provide a public resource of data and biological samples to advance scientific research against this disease.

“We are excited to extend our approach to the evaluation of prevention therapies to individuals at the highest known risk for developing the common form of Alzheimer’s that strikes at older ages,” said Eric M. Reiman, MD, the other API leader and executive director of BAI. “And, we are excited about the chance to work with our collaborators from Novartis and Amgen, our academic colleagues, and our valued research participants in the effort to find effective prevention therapies as soon as possible.”

The API Generation Study 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. Only those who learn they have two copies will be invited to participate in the study. The API Generation Study will be providing genetic counseling in person, by phone or through video-conferencing.

“We understand that learning one’s genetic risk for Alzheimer’s disease may be emotionally impactful,” said Jessica Langbaum, PhD, principal scientist at BAI, associate director of API, and principal investigator of GeneMatch. “To support study participants, we will provide them access to trained professionals who specialize in helping people better understand the results of genetic testing.”

Participants will be recruited via multiple venues, including the Alzheimer’s Prevention Registry’s GeneMatch program (www.endALZnow.org/GeneMatch). GeneMatch is a first-of-its-kind program designed to identify a large group of people interested in volunteering for Alzheimer’s research studies, based in part on their APOE genetic information.

The API Generation Study is an important complement to the ongoing API Autosomal Dominant Alzheimer’s Disease (ADAD) trial in Colombia, South America, which focuses on cognitively unimpaired members of extended families affected by a rare genetic mutation that makes carriers virtually certain to develop Alzheimer’s symptoms by their 40s or 50s.

Alzheimer’s is a debilitating and incurable disease that is estimated to affect as many as 5.1 million Americans age 65 and older, and more than 46 million people worldwide.

For more information on the API Generation Study visit www.generationstudy.com.

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About Banner Alzheimer’s Institute
Banner Alzheimer’s Institute (BAI) is a nonprofit organization dedicated to the goal of ending Alzheimer’s disease without losing another generation. It is helping to launch a new era of Alzheimer’s research—detection, treatment and prevention at the pre-symptomatic stage—and to establish a comprehensive model of care that can be the national standard. BAI was founded in 2006 by Phoenix-based Banner Health, one of the country’s largest nonprofit healthcare systems. For more information, go to www.banneralz.org.

About Alzheimer’s Prevention Initiative
The Alzheimer’s Prevention Initiative (API) is an international collaborative formed to launch a new era of Alzheimer’s prevention research. Led by the Banner Alzheimer’s Institute, the API will conduct prevention trials in cognitively healthy people at increased genetic risk for Alzheimer’s disease. It will continue to establish the brain imaging, biological and cognitive measurements needed to rapidly test promising prevention therapies and provide registries to support enrollment in future prevention trials. API is intended to provide the scientific means, accelerated approval pathway and enrollment resources needed to evaluate the range of promising Alzheimer’s prevention therapies and find ones that work without losing another generation. For more information, go to www.banneralz.org.

About GeneMatch
GeneMatch is a research program of the Alzheimer’s Prevention Registry to help identify individuals who are willing to participate in research studies based in part on their APOE genetic information, the major genetic risk factor for late-onset Alzheimer’s disease. The program is optional for people who are enrolled in the Alzheimer’s Prevention Registry. It will enroll people who are between 55 and 75 years of age, reside in the U.S. and do not have a diagnosis of dementia or other cognitive impairment syndrome. For more information, go to https://www.endalznow.org/genematch.

Generation Study FAQs

What is the Generation Study?
The Alzheimer’s Prevention Initiative (API) Generation Study is seeking to determine whether either or both of two investigational compounds—an active immunotherapy and an oral 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 treatments 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 status. Eligible participants may be enrolled in the study and be randomized to one of the two investigational study medications or placebo.

What phase is the Generation Study?
The Generation Study is a phase 2 study.
What are the primary outcome measures for the Generation Study?
The primary outcome measures for the Generation Study are time to diagnosis of mild cognitive impairment (MCI) due to Alzheimer’s disease or dementia due to Alzheimer’s disease and change in the Alzheimer’s Prevention Initiative Composite Cognitive (APCC) Test Score.

Is the Generation Study registration enabling?
The Generation Study is designed to enable registration if the results are positive.

When do you expect the primary analysis?
The estimated completion date of the Generation Study is the second half of 2023. The results from the primary analysis will be made available soon thereafter.

Is there an interim efficacy analysis?
There will be an interim analysis for futility during the trial.

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 two copies of the gene – one from each parent – are at particularly high risk for developing the disease.

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. 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.

How does the API Generation Study relate to the API study in Colombia?
This is an important complement to the Alzheimer’s Prevention Initiative’s ongoing study in Colombia, South America, which focuses on cognitively unimpaired carriers of a rare genetic mutation that makes them virtually certain to develop early-onset Alzheimer’s at ages as young as 45.

Does a person have to learn their genetic status to participate in the Generation Study?
The API Generation Study 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. Only those who learn they have two copies may be eligible to participate in the study.

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 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 have to have brain amyloid deposits in order to be eligible?**
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 information will remain confidential.

**How many people will need to get screened in order to fill the Generation Study?**
Researchers estimate that they will need to screen approximately 100,000 people to obtain the 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.

**Where will the Generation Study be conducted?**
The study will take place at approximately 90 selected sites in North America, Europe and Australia.

**How does someone go about participating in the Generation Study?**
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 studies 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 research studies based in part on their genetic information.

Through GeneMatch, interested individuals will submit a genetic sample. 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 APOE4 homozygotes and non-homozygotes will be invited into the study.

More information about recruitment in study sites outside of the U.S. will become available in the coming months.

**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 must 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.
• An individual must decide if they are prepared to know the results, given that there is no current cure.
• A person must 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?
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 Study?
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, so in locations in the U.S., the counseling may take place via phone or video conferencing. 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.

Who is funding the Generation Study?
The Generation Study was initially funded with a $33.2 million grant from the National Institutes of Health in 2013. 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.

**Where can people go for more information?**
Interested individuals can visit [www.endALZnow.org/GeneMatch](http://www.endALZnow.org/GeneMatch) to learn more and be considered for participation in GeneMatch and the Generation Study. They may also visit [www.generationstudy.com](http://www.generationstudy.com) for more information.