What is AN-1792?
AN-1792 is the name for a drug that was under investigation for its potential to stimulate the immune system to “recognize” and attack the amyloid plaques that are one hallmark Alzheimer brain abnormality. The drug, commonly known as the “Alzheimer vaccine,” was a form of beta-amyloid, the protein fragment that makes up most of the amyloid plaques. Scientists at Elan Corporation developed the treatment based on the theory that administration of beta-amyloid might activate the immune system to produce its own anti-amyloid antibodies. Research and development of AN-1792 were carried out collaboratively by Elan and Wyeth-Ayerst Laboratories, the pharmaceutical division of American Home Products. The vaccine was the first drug targeting beta-amyloid to reach clinical trials.

What happened to AN-1792 in clinical trials?
Elan reported its first promising preclinical animal studies in July 1999 in the journal *Nature*. These studies showed that injections of AN-1792 prevented formation of plaques in the brains of young mice genetically engineered to produce human beta-amyloid. Inoculation also reduced numbers of existing plaques in older mice with the same genetic alteration. Later studies by an independent laboratory showed that AN-1792 also improved the performance of these mice in memory tests involving mazes.

Based on these preclinical results, both the U.S. Food and Drug Administration (FDA) and the U.K. Medicines Control Agency permitted Phase I human trials of AN-1792 to assess its safety and tolerability in people with mild to moderate Alzheimer’s. The U.K. trial enrolled about 80 participants and the U.S. trial enrolled about 24.

Results from these Phase I trials, announced in 2000, suggested that the vaccine was well tolerated in human recipients. Tests also showed that some participants developed anti-amyloid antibodies. Based on these outcomes, Elan late in 2001 began a small Phase IIA trial in the United States and Europe enrolling about 370 people with mild to moderate Alzheimer’s disease. Approximately 300 participants were randomly assigned to receive AN-1792 and the rest received a placebo (inactive treatment).

In January 2002, Elan and Wyeth-Ayerst Laboratories suspended administration of medication in the Phase IIA trial after four participants who had received multiple doses of AN-1792 developed symptoms of inflammation of the brain and spinal cord. When an additional 11 participants developed these symptoms by the end of February 2002, scientists on the independent Safety Monitoring Committee concluded that no one should be given further doses of AN-1792.

Eighteen vaccine recipients (six percent) eventually developed brain inflammation. Scientists followed all trial participants for a year after drug treatment stopped to monitor their health, provide any needed treatment and gain additional information about the vaccine’s safety. The researchers also tracked the drug’s effects on memory, thinking and overall function.

Final analysis of Phase II results
Final reports analyzing AN-1792 Phase II data appeared in the May 2005 issue of *Neurology*. Although there was no dramatic benefit on any single benchmark, there were enough small positive signs to sustain interest in immunization therapies targeting beta-amyloid as well as general anti-amyloid strategies.

Key Phase II findings include the following:
- About 20 percent of those who received the vaccine developed high levels of antibodies to beta-amyloid.
Vaccine recipients did not fare any better than those who took the placebo on the trial’s chief tests of memory, thinking and overall function. However, vaccine recipients who developed the highest levels of antibodies to beta-amyloid declined less in their average performance on an additional battery of nine tests of mental function, and their scores actually improved slightly on a few of the specific tests.

Brain autopsies of a few participants who died since receiving the vaccine showed lower-than-expected levels of plaques, the abnormal deposits formed by beta-amyloid.

Some study participants agreed to undergo spinal taps in exchange for a slightly greater chance of getting the vaccine rather than the placebo. In those who developed the highest levels of antibodies, these spinal taps detected reduced levels of a protein called tau (pronounced to rhyme with “wow.”) Tau is involved in tangles, a pathological structure considered the other hallmark Alzheimer abnormality along with amyloid plaques. Plaques and tangles are widely believed to be related to one another, although the nature of the relationship is not known. The fact that AN-1792 also lowers tau by targeting beta-amyloid could be another signal of its effectiveness.

Scientists are not yet certain how to interpret the brain imaging data. Magnetic resonance imaging (MRI) studies showed that vaccine recipients with high antibody levels experienced significantly more brain shrinkage than those with lower levels. This finding was unexpected because over time, the brain of an individual with Alzheimer’s shrinks dramatically. An effective Alzheimer treatment would be expected to prevent or reduce shrinkage rather than increase it. A further puzzle is that the higher level of shrinkage was not accompanied by the greater decline in function that would normally be expected as Alzheimer’s disease progresses.

Where can I get more information?
For more information about clinical trials of experimental drugs or other issues in Alzheimer research, treatment and care, please contact the Alzheimer’s Association.

The Alzheimer’s Association, the world leader in Alzheimer research, care and support, is dedicated to finding prevention methods, treatments and an eventual cure for Alzheimer’s.

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