Early Results On Alzheimer's Vaccine Trial In People With Down Syndrome Promising, Researchers Say

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Retirement

Though often underrepresented and overlooked, they actually make up the world's largest population of individuals predisposed to getting Alzheimer's disease. Because of this, researchers say people with Down syndrome offer unique opportunities for clinicians exploring effective treatments for Alzheimer's that could benefit both the Down syndrome and the general populations.

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Interim results of a clinical trial on an Alzheimer's vaccine being tested on Down syndrome individuals are promising, say researchers at the Swiss clinical-stage

biopharmaceutical company AC Immune. The company's liposomal therapeutic anti Abeta vaccine, dubbed ACI-24, is also being evaluated in mild to moderate Alzheimer's patients in a Phase 2 study.

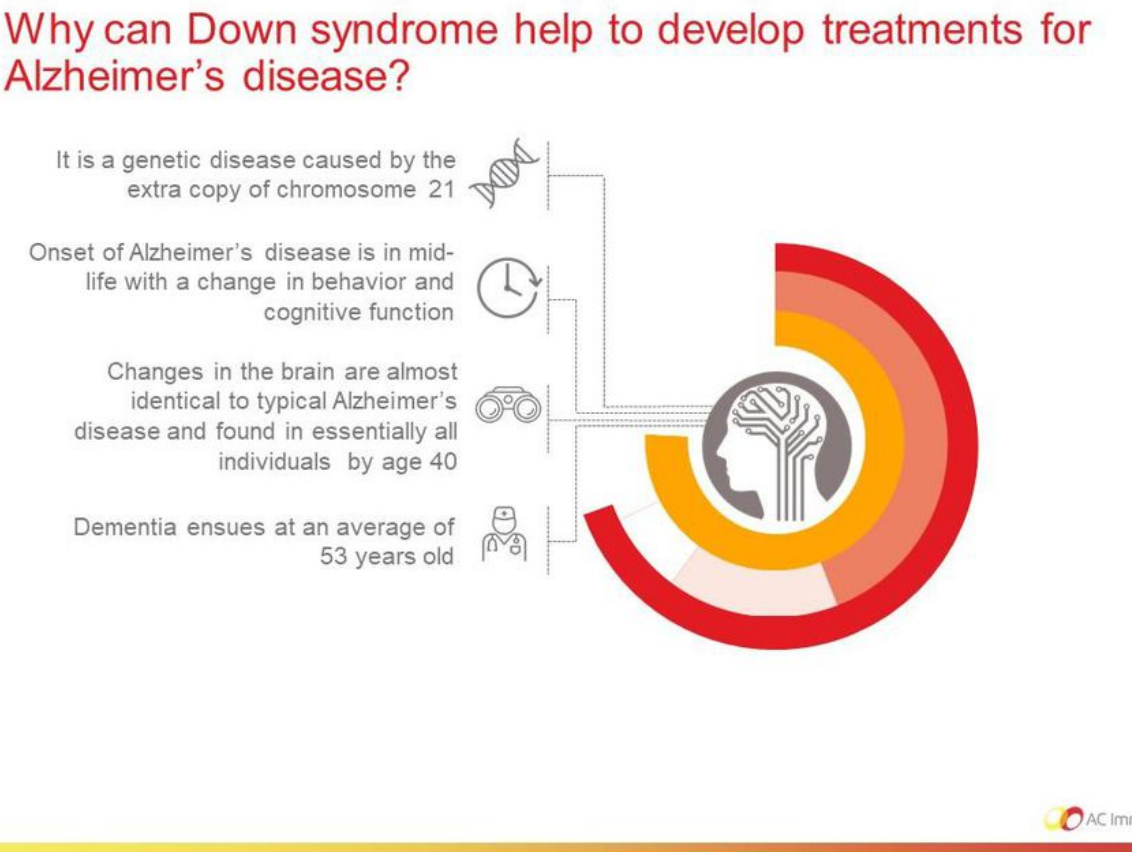
The company announced this month early clinical results of an ongoing Phase 1b study of an anti-beta-amyloid (Abeta) therapeutic vaccine in people with Down syndrome. The vaccine is being tested for safety, tolerability and its ability to provok an immune response, or immunogenicity, in adults with Down syndrome. The vaccine is designed to stimulate a patient's immune system to produce antibodies th specifically target Abeta proteins to prevent beta amyloid plaque accumulation and t boost plaque clearance.

Preclinical data have already demonstrated the vaccine's safety as well as efficacy, as significant amount of plaque reduction and memory restoration was achieved, said Prof. Andrea Pfeifer, CEO of AC Immune. "This is the first vaccine targeting Abeta that has been tested in the Down syndrome population," she said, adding that she believes studying the Down syndrome population is critical for developing successfu treatments for everyone with Alzheimer's, since it permits testing potential Alzheimer's disease therapeutics in a more homogeneous group, earlier in the cours of development of Alzheimer's symptoms than would otherwise be possible.

Pfeifer said the Phase 2 study has now begun, "assessing the vaccine's safety, tolerability, immunogenicity, target engagement, biomarkers and clinical efficacy in people with mild to moderate Alzheimer's disease." The company reported in its Phase 1b clinical study that ACI-24 was "well tolerated in subjects with Down syndrome, demonstrating a favorable safety profile at all doses tested, mirroring previous clinical trial results," Pfiefer said. Pending final outcomes of the 1b study, the Phase 2 study of the vaccine in subjects with Down syndrome will likely focus on disease prevention and will include biomarker and PET imaging to monitor disease progression, she said.

Because their bodies produce extra amyloid, most people with Down syndrome develop problems with thinking and memory early on. "The reason we are using Down syndrome individuals is that they have very defined genetics," Pfeifer said. "Basically since birth they have beta-amyloid, which leads to plaques in Alzheimer's disease. By the time they are 20, they develop Alzheimer's like symptoms. By the tim they are 40, they all have such symptoms. At the age of 60, the probability is almost

100% that they will have Alzheimer's disease." (Beta-amyloid is a sticky compound o microscopic brain protein fragment that accumulates in the brain, disrupting communication between brain cells and eventually killing them.)



(PHOTO COURTESY OF ACIMMUNE)

Most babies are born with 46 chromosomes. But individuals with Down syndrome have an extra copy of one of these chromosomes, chromosome 21—a condition referred to as Trisomy 21. Approximately 40 percent of people with Down syndrome develop Alzheimer's-like symptoms by age 40, and 50 percent develop symptoms by the age of 50. It used to be rare because the medical problems associated with Down syndrome meant people with the disorder rarely lived long enough to develop dementia. But today, better medical treatments mean people with the disorder often live into their 60s.

"The reason the study focuses on individuals with Down syndrome is that they have very defined genetics," Pfeifer said. There are 212,000 people living with Down syndrome in the US and 359,000 in Europe. The neuropathological changes in Down syndrome subjects are very similar but not identical to typical Alzheimer's disease, Pfeifer said. "People with Down syndrome have an extra copy of chromosome 21, which houses the gene that codes for amyloid precursor protein (APP)," she said.

“APP is the parent protein of Abeta, a protein fragment that accumulates into amylo plaques, a key feature of Alzheimer’s disease.” (Beta-amyloid is a sticky compound o microscopic brain protein fragment that accumulates in the brain, disrupting communication between brain cells and eventually killing them.)

One of the challenges in Alzheimer’s research, Pfeifer said, is that the disease is typically diagnosed once symptoms are already clinically present. “For Alzheimer’s disease in people with Down syndrome, the disease mechanism and approximate timing of onset are known; readily detectable pathological changes occur prior to Alzheimer-like symptoms, enabling treatment prior to disease onset,” Pfeifer continued. “That’s why the Down syndrome population is so important, because it can be an entry point which allows us to test treatments in a more homogenous, genetically defined situation to potentially help people with Down syndrome and a much wider Alzheimer’s population.”

Pfeifer said studying Alzheimer-like symptoms in people with Down syndrome addresses many of the key dilemmas that hinder the discovery of new treatments fo everyone, including:

- Uncertain mechanisms and timing of disease-induced brain changes.
- Difficulty offering treatment before disease onset, genetic and age-related variability.
- The risk of including subjects with other forms of age-related dementia.

Pfeifer said studying people with Down syndrome in hopes of making new discoveri about Alzheimer’s disease is not new. In fact, William Mobley, Ph.D., executive director of University of California San Diego’s (UCSD) Down Syndrome Center for Research and Treatment, said in a 2014 *NPR* article that finding a drug that prevents Alzheimer's in people with Down syndrome could help millions of people who don't have the disorder. "This approach to treating Alzheimer's disease might apply to all us," he told *NPR*. "Imagine someday a drug that we all start taking when we're 25 so we never get Alzheimer's disease." Mobley is now conducting the first clinical trial of the vaccine against Abeta in individuals with Down syndrome.

“The new attention given to people with Down syndrome now impacting society *is* new,” Pfeifer said. “Now, a lot of people with Down syndrome reach 60 years and older. They are independent and have relationships and are working. It has been

completely overlooked. Their specialized genetics may give us hope to develop therapies for the wider population."

AC Immune clinical pipeline currently includes nine therapeutic and three diagnosti product candidates, with five currently in clinical trials and has collaborations with major pharmaceutical companies including Roche/Genentech, Eli Lilly and Janssen

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