THERAPEUTICS

ACI-24

SEARCH THERAPEUTICS | THERAPEUTICS HOME

OVERVIEW

Name: ACI-24
Synonyms: Pal1-15 acetate salt
Therapy Type: Immunotherapy (active) (timeline)
Target Type: Amyloid-Related (timeline)
Condition(s): Alzheimer's Disease, Down's Syndrome
U.S. FDA Status: Alzheimer's Disease (Phase 2), Down's Syndrome (Phase 2)
Company: AC Immune SA

BACKGROUND

ACI-24 is a liposome vaccine designed to elicit an antibody response against aggregated Aβ peptides without concomitant pro-inflammatory T cell activation. This vaccine grew out of work with tetrapalmitoylated preparations of N-terminal Aβ fragments, which rapidly stimulated anti-Aβ antibodies that dissolve amyloid fibers in vitro and in vivo. ACI-24 is based on the truncated Aβ-15 sequence, which is devoid of T-cell epitopes located closer to the peptide's C-terminus. An array of Aβ1-15 sequences, sandwiched between palmitoylated lysines at either end, is anchored into the surface of liposomes in such a way that the peptides adopt an aggregated β-sheet structure, forming a conformational epitope (Feb 2002 news story).

In preclinical studies, repeated subcutaneous injection of ACI-24 into APPxPS-1 transgenic mice and into cynomolgus monkeys was reported to generate high titers of anti-Aβ IgG1 and IgG2b antibodies, which involve a non-inflammatory Th2 helper cell response. In a three-month treatment study in APPxPS-1 mice, ACI-24 reportedly decreased the concentration of insoluble Aβ40 and 42 and of soluble Aβ42; it also improved novel object recognition while prompting neither gliosis nor increases in measures of pro-inflammatory cytokines. Antisera from immunized monkeys stain human Alzheimer's disease brain (Muhs et al., 2007; Hickman et al., 2011). This vaccine uses the lipid adjuvant MPLA.

In a mouse model of Down's syndrome, immunization at 5 months of age elicited anti-Aβ IgG,

and led to a modest reduction in brain Aβ at 8 months. Vaccination improved memory deficits, and reduced cholinergic neuron atrophy, with no signs of inflammation or hemorrhage (Belinchenko et al., 2016).

More recently, AC Immune tested an optimized version of ACI-24 in mice and nonhuman primates (Vukicevic et al., 2022; Mar 2022 conference news). This vaccine contains additional non-Aβ peptides (e.,g. tetanus) to boost helper T cell responses. The vaccine was well-tolerated. It induced high titers of IgG reactive to pyroGlu-Aβ, an N-terminally truncated and modified form of Aβ that is highly amyloidogenic and toxic. PyroGlu-Aβ is also the target of donanemab, a monoclonal antibody currently in Phase 3.

FINDINGS

In 2009, AC Immune began a Phase 1/2 trial of ACI-24 to evaluate safety, immunogenicity, and efficacy. Five sites in Finland, Sweden, and Denmark planned to enroll up to 198 participants age 40 and older with mild to moderate Alzheimer's disease with a positive amyloid PET scan and on stable acetylcholinesterase inhibitor therapy. This adaptive study compared doses of 10, 100, 300, and 1,000 µg to placebo, delivered subcutaneously. Patients were treated for one year and followed for one or two more. Some received a booster shot 2.5 to 3.5 years after their last dose. Primary outcomes included safety and tolerability measures, as well as serum titers of anti-Aβ42 IgG antibodies and one-year change from baseline of total cognitive score on the neuropsychological test battery. Secondary outcomes include, besides clinical endpoints, amyloid PET scanning with Piramar Imaging's tracer Neuroceq (formerly Bayer's florbetaben), as well as biomarker measures such as MRI volumetry, tau, phospho-tau and Aβ levels in CSF, and measures of T-cell activation.

The trial finished in October 2018; results are posted in the EU Clinical Trials Register. The trial ultimately enrolled only 48 patients. In the responder analysis, anti-Aβ42 antibodies were detected in only one of 36 treated patients, and the planned expansion into a Phase 2 efficacy stage was cancelled.

In August 2018, a Phase 2 trial started testing a new formulation. This study, in Finland, Sweden, and Great Britain, was to enroll 45 people ages 50 to 85 who have mild AD confirmed by amyloid PET. Primary outcomes included safety, tolerability, induction of Aβ antibodies, and changes in brain amyloid assessed by PET. Secondary objectives comprised biomarkers of amyloid and tau in blood and/or CSF, T cell activation, and inflammatory markers in blood, volumetric MRI, and a variety of clinical and cognitive endpoints. The study was completed in March 2021, and AC Immune presented results at the November 2021 CTAD conference. Twenty-one participants received injections of 1,000 µg ACI-24 or placebo, eight times over 18 months, with six months of follow-up. In this study, ACI-24 produced a clear IgM antibody response, but low IgG titers. CSF Aβ40 and Aβ42 were increased from baseline, suggesting target engagement, but there was no change on amyloid-PET. No ARIA or CNS inflammation was reported. Results are posted on the EU Clinical Trials Register.

At the November 2021 CTAD conference, AC immune presented results of a two-year trial in 21 people with mild AD and PET evidence of amyloid. They received injections of 1,000 µg ACI-24 or placebo, eight times over 18 months, with six months of follow-up. In the study, ACI-24 produced a clear IgM antibody response, but low IgG titers. CSF Aβ40 and Aβ42 were increased from baseline, suggesting target engagement, but there was no change on amyloid-PET. No ARIA or CNS inflammation was reported.

In March 2016, ACI-24 became the first anti-Aβ vaccine to be evaluated for the treatment of Alzheimer's disease in Down's syndrome, a genetic condition that leads to brain amyloid deposition, and dementia in midlife. Co-funded by the NIH and the LuMind Research Down Syndrome Foundation, this trial ran at UC San Diego and four other centers in the United States that specialize in treatment and research of Down's. It planned to enroll 24 trisomy 21 patients aged 35 to 55 and treat them with ACI-24 injected subcutaneously for one year, with an additional year of follow-up. Primary endpoints include measures of safety, tolerability, and immunogenicity, i.e., Aβ titers. Effects on biomarkers of AD pathology, as well as cognitive and clinical function, constitute secondary endpoints. The study ended in June 2020.

According to a meeting presentation, the DS trial enrolled 16 participants aged 25 to 45 years who received seven injections of 300 or 1,000 µg versus placebo. In each dose cohort, six received the vaccine, two placebo. Most are Caucasian; the group has a high rate of obesity. Of 12 vaccinated participants, four had increased anti-Aβ IgG antibodies; none of the placebo group did. Plasma Aβ rose after vaccination. Safety and tolerability appeared favorable, with no dropouts, serious adverse events, or MRI abnormalities such as ARIA (May 2021 news). Results were published after peer review (Rafii et al., 2022).

In May 2020, AC Immune registered a Phase 2 trial in people with Down's. Slated to begin in October 2020, the trial was to enroll 72 participants aged 40 to 50 years who had brain amyloid deposition but no dementia. The COVID-19 pandemic delayed the start of this trial, and in October 2021 it was withdrawn before enrollment began. The given reason was a decision to proceed with an optimized study design and vaccine formulation.

For U.S. trial details, see clinicaltrials.gov.

Last Updated: 16 May 2022

COMMENTS

No Available Comments

Make a Comment

To make a comment you must login or register.

REFERENCES

News Citations

In Down's Syndrome, Amyloid Vaccine Opens Door to Trials 20 May 2021

Early-Stage Alternative Vaccine Reported: Better Antibody Response with Liposomes? 22 Nov 2002

Therapeutics Citations

Donanemab

Paper Citations

Rafii MS, Sol O, Mobley WC, Delpretti S, Skotko BG, Burke AD, Sabbagh MN, Yuan SH, Rissman RA, Pulsifer M, Evans C, Evans AC, Beth G, Fournier N, Gray JA, Dos Santos AM, Hliva V, Vukicevic M, Kosco-Vilbois M, Streffer J, Pfeifer A, Feldman HH. Safety, Tolerability, and Immunogenicity of the ACI-24 Vaccine in Adults With Down Syndrome: A Phase 1b Randomized Clinical Trial. *JAMA Neurol*. 2022 Jun 1;79(6):565-574. PubMed.

Muhs A, Hickman DT, Pihlgren M, Chuard N, Giriens V, Meerschman C, van der Auwera I, Van Leuven F, Sugawara M, Weingertner MC, Bechinger B, Greferath R, Kolonko N, Nagel-Steger L, Riesner D, Brady RO, Pfeifer A, Nicolau C. Liposomal vaccines with conformation-specific amyloid peptide antigens define immune response and efficacy in APP transgenic mice. *Proc Natl Acad Sci U S A*. 2007 Jun 5;104(23):9810-5. PubMed.

Hickman DT, López-Deber MP, Ndao DM, Silva AB, Nand D, Pihlgren M, Giriens V, Madani R, St-Pierre A, Karastaneva H, Nagel-Steger L, Willbold D, Riesner D, Nicolau C, Baldus M, Pfeifer A, Muhs A. Sequence-independent control of peptide conformation in liposomal vaccines for targeting protein misfolding diseases. *J Biol Chem*. 2011 Apr 22;286(16):13966-76. PubMed.

Belichenko PV, Madani R, Rey-Bellet L, Pihlgren M, Becker A, Plassard A, Vuillermot S, Giriens V, Nosheny RL, Kleschevnikov AM, Valletta JS, Bengtsson SK, Linke GR, Maloney MT, Hickman DT, Reis P, Granet A, Mlaki D, Lopez-Deber MP, Do L, Singhal N, Masliah E, Pearn ML, Pfeifer A, Muhs A, Mobley WC. An Anti-β-Amyloid Vaccine for Treating Cognitive Deficits in a Mouse Model of Down Syndrome. *PLoS One*. 2016;11(3):e0152471. Epub 2016 Mar 29 PubMed.

Vukicevic M, Fiorini E, Siegert S, Carpintero R, Rincon M, Lopez-Deber P, Piot N, Ayer M, Rentero I, Babolin C, Bravo-Veyrat S, Giriens V, Morici C, Beuzelin M, Gesbert A, Rivot S, Depretti S, Donati P, Streffer J, Pfeifer A, Kosco-Vilbois MH. An Amyloid beta (Abeta) vaccine that safely drives immunity to a key pathological species in Alzheimer's disease: pyroglutamate Abeta. *Brain Communications, Volume 4, Issue 1, 2022, fcac022* Brain Commun.

Other Citations

Mar 2022 conference news

External Citations

EU Clinical Trials Register

clinicaltrials.gov

EU Clinical Trials Register

FURTHER READING

News

Stockholm: New Strategies for Immunotherapy 9 Jun 2012

Crenezumab Disappoints in Phase 2, Researchers Remain Hopeful 22 Jul 2014

Therapies Take Aim at Tau 15 Aug 2014

Three's Company: Florbetaben Approved, Excludes AD Diagnosis 2 May 2014

Papers

Maier M, Seabrook TJ, Lemere CA. Modulation of the humoral and cellular immune response in Abeta immunotherapy by the adjuvants monophosphoryl lipid A (MPL), cholera toxin B subunit (CTB) and E. coli enterotoxin LT(R192G). *Vaccine*. 2005 Oct 25;23(44):5149-59. PubMed.

Pihlgren M, Silva AB, Madani R, Giriens V, Waeckerle-Men Y, Fettelschoss A, Hickman DT, López-Deber MP, Ndao DM, Vukicevic M, Buccarello AL, Gafner V, Chuard N, Reis

P, Piorkowska K, Pfeifer A, Kündig TM, Muhs A, Johansen P. TLR4- and TRIF-dependent stimulation of B lymphocytes by peptide liposomes enables T cell-independent isotype switch in mice. *Blood*. 2013 Jan 3;121(1):85-94. Epub 2012 Nov 8 PubMed.