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Gene Therapy: A Potential Treatment Option for Vestibular Schwannoma

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The standard of care treatment options for vestibular schwannoma/acoustic neuroma—which include observation, radiation, and/or surgery—have remained largely unchanged for more than a decade.

In 2022, Akouos partnered with the Acoustic Neuroma Association to survey ANA members about their care journeys, currently available treatment options, and potential new treatment technologies. The survey results were shared in the **December 2022 ANA newsletter**.

Responses suggested a desire for alternative treatment options for VS, including investigations into potential gene therapies, and an openness to participating in this type of research. This patient community feedback supported the further development of Akouos's AK-antiVEGF-101 gene therapy clinical trial.

Previous clinical trials investigated the effect of bevacizumab (Avastin®) in patients with neurofibromatosis type 2 (NF2), a genetic condition that is associated with development of vestibular schwannomas. Bevacizumab works by blocking a protein called vascular endothelial growth factor (VEGF), and the majority of patients who received bevacizumab in these trials showed stabilization or improvement in VS tumor size and/or hearing. However, bevacizumab was administered systemically, requiring regular infusions, and was associated with side effects that limited its continued use. When bevacizumab treatment stopped, patients' VS tumors tended to grow again. VEGF protein levels are increased in vestibular schwannomas, even in individuals without NF2, suggesting that these individuals may also benefit from anti-VEGF therapy.

In the AK-antiVEGF-101 clinical trial, an investigational gene therapy (AK-antiVEGF) is delivered directly to the inner ear and is designed to provide local, long-term anti-VEGF therapeutic effect in individuals with VS after a single administration. This local approach may potentially provide benefits of anti-VEGF therapy (stabilization or improvement in VS tumor size and/or hearing) while minimizing the side effects associated with systemic anti-VEGF medications.

What's new at Akouos in 2025?

Michael J. McKenna, M.D.: Our goal is to develop genetic medicines for inner ear conditions. We believe that hearing loss is one of the largest unmet needs in medicine. In December 2022, Akouos was acquired by Eli Lilly and Company, which provides resources, global reach, and growing capabilities in gene therapy to help accelerate our mission of healthy hearing available to all.

Akouos received clearance from the U.S. Food and Drug Administration for our Investigational New Drug (IND) application to initiate AK-antiVEGF-101, a Phase 1/2, first-in-human clinical trial of AK-antiVEGF, a gene therapy intended for the treatment of patients with vestibular schwannoma. The AK-antiVEGF-101 clinical trial is currently active and recruiting.

How can I participate in the Akouos-sponsored AK-antiVEGF-101 clinical trial?

Kathleen Reape, M.D.: This multicenter Phase 1/2 trial is designed to assess the safety, tolerability, and bioactivity of escalating doses of the investigational product AK-antiVEGF (AAVAnc80-antiVEGF), delivered once via direct unilateral administration to the cochlea of clinical trial participants using an investigational delivery device.

While additional eligibility criteria apply, participants may be eligible for the trial if they meet the following eligibility criteria:

- At least 18 years old
- Significant hearing loss in one ear caused by vestibular schwannoma
- At least one MRI scan of the head within the past two years
- No prior surgery or radiation to treat the vestibular schwannoma
- Vestibular schwannoma on one side only

INTERESTED IN PARTICIPATING?

If you are interested in participating and want to be evaluated for trial eligibility, you can contact study coordinators at trial sites to find out more information:

Mayo Clinic, Rochester
507-538-5862
Tuchscherer.Amy@mayo.edu

University of Texas Southwestern
214-648-3626
OTOResearch@UTSouthwestern.edu

Vanderbilt University
615-322-4386
Taha.a.jan@vumc.org

Visit **VSclinicaltrial.com** or **clinicaltrials.gov/study/NCT06517888** for the most up to date information on clinical trial sites.

What can I expect if I participate in the clinical trial?

Dr. Reape: Trial participants can expect the following:

Informed consent: Review and sign the Informed Consent Form.

Screening: Receive trial assessments, including an MRI scan of the head, blood tests, and hearing tests to determine if you are eligible for the trial.

Investigational gene therapy administration: If you are eligible for the trial, you will undergo the surgical administration procedure to receive one dose of the investigational gene therapy (using the investigational delivery device) in the ear next to the vestibular schwannoma. You will stay overnight at the trial site for observation.

Follow-up: If you receive the investigational gene therapy, you will visit the trial site approximately nine times over the next year for follow-up visits. After one year, you will be expected to join a separate long-term follow-up study with one visit per year for an additional approximately four years (a total of approximately five years of follow-up after receiving the investigational gene therapy).

The trial will cover travel expenses for eligible participants and a travel companion. The participant is welcome to determine which clinical trial site would be most convenient for them.

How is the investigational gene therapy (AK-antiVEGF) administered?

Dr. McKenna: AK-antiVEGF is delivered using Akouos's investigational delivery device through a one-time, minimally invasive surgical approach through the ear canal to the inner ear, which is in close proximity to the vestibular schwannoma. This delivery approach and investigational delivery device are already in use in another clinical trial sponsored by Akouos. Visit **vimeo.com/1045417566** to view a video illustrating the surgical approach and intracochlear (inner ear) delivery.

What if the investigational gene therapy does not work?

Dr. McKenna: Participants may choose to pursue standard of care treatment options. Visit **anausa.org/learn-about-acoustic-neuroma/treatment-options** for the ANA overview of treatment options.

Where can I find more information about the AK-antiVEGF-101 clinical trial?

Dr. Reape: Please email **AkouosClinicalTrials@lilly.com** or visit **VSclinicaltrial.com** or **clinicaltrials.gov/study/NCT06517888** for additional information about the AK-antiVEGF-101 clinical trial. ❤

Michael J. McKenna, M.D., is co-founder and chief surgical officer of Akouos. He is a world-renowned neurotologist with expertise in translational inner ear drug delivery research. Dr. McKenna led efforts to establish inner ear drug delivery systems to enable the development of hearing restoration therapies. Prior to co-founding Akouos, he held the Joseph B. Nadol, Jr. chair, served as the director of the Division of Otology and Neurotology at Massachusetts Eye and Ear, and was a professor of otolaryngology at Harvard Medical School.

Kathleen Reape, M.D., is chief medical officer at Akouos. Dr. Reape has overseen numerous clinical trials and had a hands-on role in the approvals of more than two dozen products, including small molecules, biologics, biosimilars, and devices spanning a wide range of therapeutic areas. Prior to joining Akouos, she was chief medical officer at Spark Therapeutics where she helped lead the development and approval of the gene therapy Luxturna®.