Positive Phase 1/2 Clinical Trial Data for an Investigational Gene Therapy for Genetic Hearing Loss to be Presented at the Association for Research in Otolaryngology 2024 MidWinter Meeting

January 23, 2024

Hearing restoration was observed within 30 days of a single administration of AK-OTOF in the initial AK-OTOF-101 study participant, the first to receive gene therapy in the United States for a genetic form of hearing loss

*AK-OTOF is a gene therapy being developed for the treatment of sensorineural hearing loss due to mutations in the otoferlin gene (*OTOF*)*

INDIANAPOLIS, Jan. 23, 2024 /PRNewswire/ -- Akouos, Inc., a wholly owned subsidiary of Eli Lilly and Company (NYSE: LLY), today announced positive initial clinical results from the Phase 1/2 AK-OTOF-101 study, which demonstrated pharmacologic hearing restoration within 30 days of AK-OTOF administration in the first participant, an individual with a decade-plus history of profound hearing loss. Results, including initial data from a second participant to receive AK-OTOF, will be presented during the Late Breaking Presidential Symposium at the 2024 Association for Research in Otolaryngology (ARO) MidWinter Meeting.

Details of the presentation are listed below:
Title: Clinical development of AK-OTOF gene therapy for *OTOF*-mediated hearing loss
Session: Late Breaking Presidential Symposium
Date/Time: Saturday, February 3, 10:00 a.m. PT
Location: Anaheim Marriott, Anaheim, California

The first participant to receive AK-OTOF in the study, an 11-year-old at the time of AK-OTOF administration with profound hearing loss from birth, experienced restored hearing within 30 days of AK-OTOF administration. In this individual, hearing was restored across all tested frequencies, achieving thresholds of 65 to 20 dB HL, and within the normal hearing range at some frequencies at the Day 30 visit. Both the surgical administration procedure and the investigational therapy were well tolerated, and no serious adverse events were reported.

"Gene therapy for hearing loss is something physicians and scientists around the world have been working toward for over 20 years," said Professor John Germiller, M.D., Ph.D., attending surgeon and Director of Clinical Research in the Division of Otolaryngology at Children's Hospital of Philadelphia, and a principal investigator of the AK-OTOF-101 Clinical Trial who administered AK-OTOF to this participant. "These initial results show that it may restore hearing better than many thought possible."

In the AK-OTOF-101 trial, eligible participants receive a single, unilateral intracochlear administration of AK-OTOF, with hearing restoration assessed by behavioral audiometry and auditory brainstem response (ABR), a clinically accepted and objective measure of hearing sensitivity. Participants in cohort 1 receive AK-OTOF at a dose of 4.1E11 total vector genomes.

"Children with *OTOF*-mediated hearing loss are often born with profound hearing loss, yet only a small fraction have undergone genetic testing to receive a definitive diagnosis," said Dr. Oliver Haag, pediatric otolaryngologist, Head of Otolaryngology at Sant Joan de Deu Hospital in Barcelona, and an investigator in Akouos's AK-OTOF-NHS-002 Natural History Study in which the first individual to receive AK-OTOF was participating. "The AK-OTOF-101 Clinical Trial and AK-OTOF-NHS-002 Natural History Study demonstrate the power of international collaboration in the development of new medicines for rare genetic conditions. It is gratifying to see this collaborative effort provide benefit to the first participant to receive AK-OTOF."

Hearing loss is the most common sensory condition, and with no approved pharmacologic treatments to restore hearing, represents a significant area of unmet need in medicine. Millions of individuals worldwide have disabling hearing loss because one of their genes generates an incorrect or incomplete version of a protein the ear requires for hearing. In many of these cases – including for some of the estimated 200,000 individuals worldwide who live with *OTOF*-mediated hearing loss – delivering a healthy version of the gene to a target cell within the inner ear has the potential to restore auditory function and enable high-acuity physiologic hearing. *OTOF*-mediated hearing loss is the first monogenic form of hearing loss to be investigated as part of a gene therapy clinical trial.

"We are grateful to the participants, their families, the investigators and other collaborators who are working together with us on this pioneering trial," said Emmanuel Simons, Ph.D., M.B.A., CEO of Akouos and SVP, Gene Therapy at Lilly. "These initial results highlight the potential impact genetic medicines could have on individuals with *OTOF*-mediated hearing loss and reinforce our mission to make healthy hearing available to all."

AK-OTOF has been granted Orphan Drug Designation and Rare Pediatric Disease Designation by the FDA and has received a positive opinion on orphan drug designation by the EMA Committee for Orphan Medicinal Products.

About AK-OTOF and the AK-OTOF-101 Clinical Trial
AK-OTOF (AAVAnc80-hOTOF) is a dual adeno-associated viral (AAV) vector-based gene therapy designed to restore auditory function by gene transfer and durable expression of normal, functional otoferlin protein to the inner hair cells of the cochlea. AK-OTOF utilizes AAVAnc80, a capsid with high transduction efficiency for inner hair cells, together with a strong ubiquitous promoter to achieve expression of otoferlin, observed only in the target inner hair cells, at levels that have the potential to restore high acuity physiologic hearing. The Akouos delivery device, being developed in parallel specifically for intracochlear administration, enables a minimally invasive surgical approach to deliver AK-OTOF throughout the cochlea. The AK-OTOF-101 Clinical Trial (NCT05821959) is a Phase 1/2 trial that is assessing the safety, tolerability, and bioactivity of escalating doses of AK-OTOF delivered via the Akouos delivery device. More information about the trial can be found at https://www.clinicaltrials.gov/study/NCT05821959.

About the OTOF-mediated Hearing Loss Natural History Study

The AK-OTOF-NHS-002 Natural History Study (NCT05572073) is designed to characterize the natural history of *OTOF*-mediated hearing loss, including progression of physiologic responses and audiologic outcomes over time, potential genotype-phenotype relationships, and longitudinal assessment of clinical outcomes. More information about the study can be found at https://www.clinicaltrials.gov/ct2/show/NCT05572073.

About Lilly
Lilly unites caring with discovery to create medicines that make life better for people around the world. We've been pioneering life-changing discoveries for nearly 150 years, and today our medicines help more than 51 million people across the globe. Harnessing the power of biotechnology, chemistry and genetic medicine, our scientists are urgently advancing new discoveries to solve some of the world's most significant health challenges, redefining diabetes care, treating obesity and curtailing its most devastating long-term effects, advancing the fight against Alzheimer's disease, providing solutions to some of the most debilitating immune system disorders, and transforming the most difficult-to-treat cancers into manageable diseases. With each step toward a healthier world, we're motivated by one thing: making life better for millions more people. That includes delivering innovative clinical trials that reflect the diversity of our world and working to ensure our medicines are accessible and affordable. To learn more, visit Lilly.com and Lilly.com/news or follow us on Facebook, Instagram and LinkedIn. C-LLY

Cautionary Statement Regarding Forward-Looking Statements
This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about AK-OTOF as a potential treatment for sensorineural hearing loss due to mutations in the otoferlin gene (*OTOF*) and reflects Lilly's current beliefs and expectations. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of drug research, development, and commercialization. Among other things, there is no guarantee that planned or ongoing studies will be completed as planned, that future study results will be consistent with study results to date, or that AK-OTOF will receive regulatory approvals, or be commercially successful. For further discussion of risks and uncertainties relevant to Lilly's business that could cause actual results to differ from Lilly's expectations, see Lilly's Form 10-K and Form 10-Q filings with the United States Securities and Exchange Commission. Except as required by law, Lilly undertakes no duty to update forward-looking statements to reflect events after the date of this release.

Refer to: Stefanie Prodouz; stefanie.prodouz@lilly.com; +1-317-287-9899 (Media)
Joe Fletcher; jfletcher@lilly.com; +1-317-296-2884 (Investors)

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