

**Auditory Insight®**

# Gene Therapy for Hearing Loss

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Interpreting Preliminary Clinical Trial Results

## Introduction from Nancy M. Williams, Founder and President

Gene therapy has transformed hearing for seven profoundly deaf children with mutations in a gene called otoferlin, in three investigational trials around the globe.

**I have been involved with hearing restoration for over a decade**, starting with my board role with the Hearing Health Foundation. As founder of Auditory Insight, the preeminent strategy firm focused exclusively on hearing healthcare, I have advised gene therapy companies. I am also a **person with a genetic, progressive hearing loss**.

Given my roles, I am pleased to report that early results from these trials fared well in **Auditory Insight's rigorous analysis**. They provide the first validation of pharmacological treatments for hearing loss.

Our independent analysis of the clinical trial's published data yields the following insights on gene therapy for hearing loss from otoferlin mutations:

- **The therapy was efficacious with children ranging in age from 10 months to 11 years**
- **The gene expression has a time-release pattern, with patients showing an improvement in hearing over time and the time to full results at least 26 weeks**
- **The therapy generally restores hearing from profoundly deaf to moderate hearing loss, the treated ears consequently indicated only for hearing aids, not cochlear implants**

This research note interprets the clinical trial results in some detail. We look forward to discussing this Auditory Insight research note with our valued clients.



## Three Clinical Trials Have Published Preliminary Results

The three clinical trials treating deafness with gene therapy who have published preliminary results as of February 2024 are summarized in the chart below. All three of these trials target mutations in a gene called otoferlin.

To receive gene therapy, the patient undergoes surgery under general anesthesia. The surgeon injects the therapy into a tiny entrance of the inner ear called the round window. Containing working copies of the otoferlin gene, the therapy sparks production of the otoferlin protein, a necessary ingredient in the complicated recipe for hearing. The inner ear is now able to transmit sound to the auditory nerve in the brain.

The trials treated eight children in the U.S., the U.K., and China. Fully seven of them have regained much of their hearing. The DB-OTO and AAV1-hOTOF trials have reported no major safety concerns at this point, while the AK-OTOF-101 trial has yet to comment on safety.

### AUDITORY INSIGHT SUMMARY OF GENE THERAPY CLINICAL TRIALS FOR OTOFERLIN MUTATIONS, FEB 2024

Gene Therapy Name	# Patients with Results (Ages)	Clinical Trial Site	Primary Investigator	Sponsoring Company
DB-OTO	1 (10 months)	Cambridge University Hospital, UK	Professor Manohar Bance, M.B.	Regeneron (acquired Decibel Therapeutics)
AAV1-hOTOF	6 (Ranging from 1 to 6 years)	Fudan University's Eye & ENT Hospital, China	Professor Yilai Shu, M.D.	Shanghai Refreshgene Therapeutics
AK-OTOF-101	1 (11 years)	Children's Hospital of Philadelphia, US	Professor John Germiller, M.D., Ph.D.	Eli Lilly (acquired Akouos)



## Auditory Insight's Independent, Expert Analysis Relies On Published Data

Auditory Insight conducted an independent analysis of data published by the three clinical trials. We relied on **published audiograms** and summarized results. An audiogram charts the softest tone that a patient can hear, in a measure of loudness called decibels, as the tones increase in pitch, or frequency.

In the case of the Refreshgene trial, we also analyzed **published results for a test called an Auditory Brainstem Response (ABR)**. The ABR, essential for children too young to complete a pure tone audiogram, records brainwave activity in response to soundwaves. Like the audiogram, ABRs measure hearing in decibels for each frequency level.

To categorize levels of hearing loss, we used the **World Health Organization's hearing impairment grades**. Our **sources** appear at the end of this research note.

Our experience interviewing caregivers and parents indicates that many would be ecstatic for their profoundly deaf child to regain hearing. However, members of the **Deaf community** believe that deafness is part of a person's identity, not to be fixed.

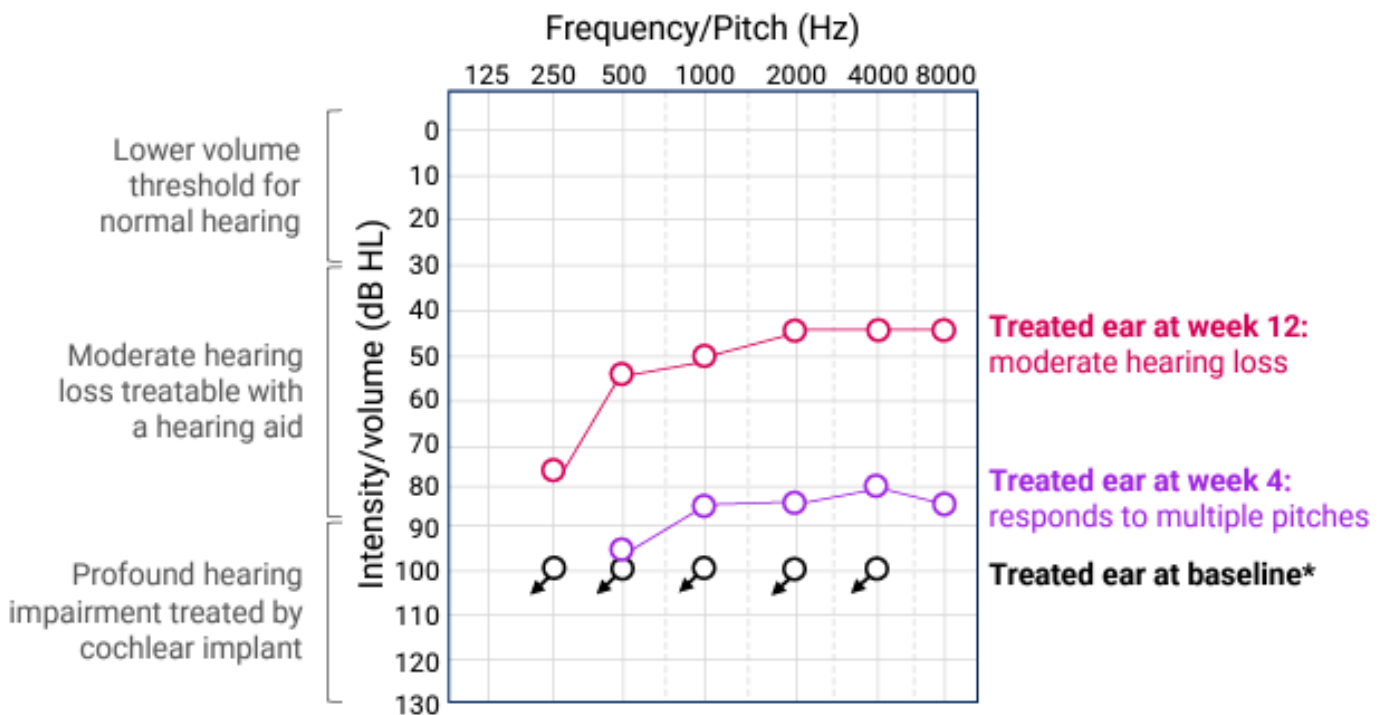


## Auditory Insight's Analysis of Regeneron's Reported Data

Regeneron shared an audiogram (shown below) of its first patient treated with DB-OTO at the JP Morgan Healthcare Conference in January 2024. The patient's hearing in the treated ear at baseline was profoundly deaf, meaning the patient could not hear a shouted voice in that ear. At four weeks, the patient showed some improvement.

Marked gains in hearing, however, occurred within the next two months, such that the patient's hearing in the treated ear at week 12 corresponded to a moderate hearing loss (although close to the border of moderately-severe). A hearing impairment level of moderate translates to a person struggling to hear a soft voice about three feet away. The patient is now indicated for a hearing aid in the treated ear, rather than a cochlear implant, according to Auditory Insight's analysis.

### Regeneron's Audiogram for First Patient Treated with DB-OTO Gene Therapy



Behavioral pure tone audiogram – a plot of softest sounds a patient can hear in an individual ear

\*Arrows indicate no response at maximum level tested

**REGENERON\***

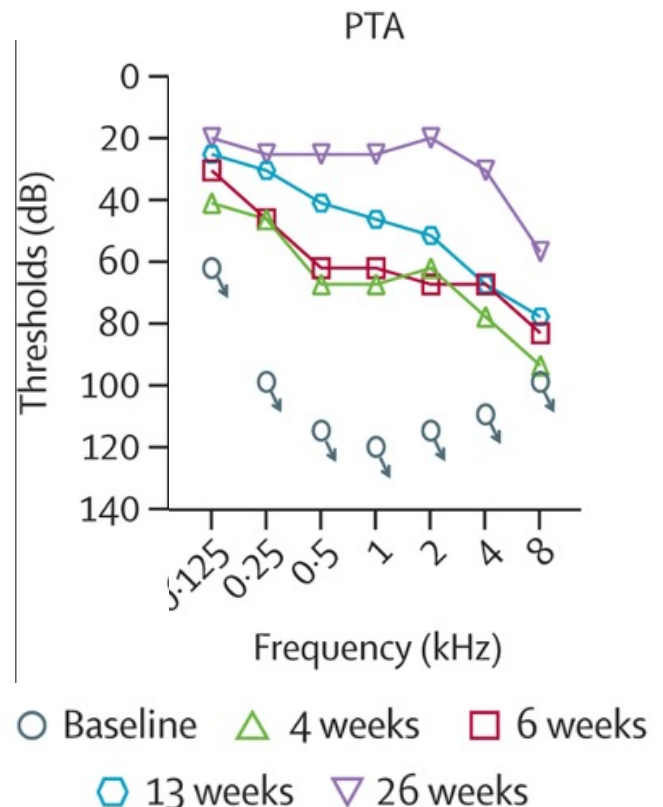
## Auditory Insight's Interpretation of Refreshgene Therapeutics Clinical Trial Results

As in the Regeneron trial, the six patients in this trial were profoundly deaf in the targeted ear before undergoing treatment. The three children old enough to undergo an audiogram, for example, could not hear a sound at 100 decibels, roughly equivalent to the noise level while driving a motorcycle.

Post treatment of AAV1-hOTOF, five of the six children experienced a significant improvement in their treated ears. According to Auditory Insight's analysis, four of them exhibited a moderate hearing loss and one a moderately-severe loss at six months. All these children are now indicated for a hearing aid in the treated ear.

These five patients generally demonstrated significant improvement in the treated ear between 13 weeks and 26 weeks, particularly so for Participant 1, whose audiogram is at right. This finding suggests that Regeneron's patient could continue to register improvements in hearing beyond the 12-week data shown to date.

**Shanghai Refreshgene Therapeutics' Audiogram for Participant 1 Treated with AAV1-hOTOF Gene Therapy**



Source: Lv J, Wang H, Cheng X, Chen Y, Wang D, Zhang L, Cao Q, Tang H, Hu S, Gao K, Xun M, Wang J, Wang Z, Zhu B, Cui C, Gao Z, Guo L, Yu S, Jiang L, Yin Y, Zhang J, Chen B, Wang W, Chai R, Chen ZY, Li H, Shu Y. AAV1-hOTOF gene therapy for autosomal recessive deafness 9: a single-arm trial. *Lancet*. 2024 Jan 24:S0140-6736(23)02874-X. doi: 10.1016/S0140-6736(23)02874-X. Epub ahead of print. PMID: 38280389.

## Auditory Insight's Analysis of Akouos' Preliminary Results for First Patient

As of February 2024, Akouos had not released an audiogram for its first patient undergoing the AK-OTOF-101 gene therapy for otoferlin mutations. However, the company noted in a press release that the patient was profoundly deaf in the treated ear before undergoing treatment, as in the case of the other trials.

The release also shared that 30 days after treatment, the softest sound the patient could hear in the treated ear ranged from 65 to 20 decibels, with some of the frequencies, or pitches, in the normal range. Based on our analysis of this partial data, the patient may very well have moderate hearing loss in the treated ear and be indicated for a hearing aid once his hearing stabilizes.

The patient, an 11-year-old boy at the time of treatment, communicates with sign language. Born profoundly deaf and never fitted with a cochlear implant, he had never learned to speak. In his case, the therapy enables him to hear sounds in his environment and people's voices. Most likely, however, he will not learn how to speak, since brain connections crucial for speaking generally form in children by age three.

## Auditory Insight's Summary Interpretation of Clinical Trial Results

Auditory Insight has four key observations about the clinical trial data to date for the seven patients who achieved positive results:



**TARGET POPULATION.** The gene therapy has partially restored hearing in children with otoferlin mutations **ranging in age from less than one year to 11 years**. The 11-year-old gaining hearing is particularly of note, since he had lived over a decade without sound stimulating his brain.



**TIME TO RESULTS.** **The gene expression has a time-release pattern.** Although patients experience significant improvements in hearing as early as four weeks, the subjects of the Refreshgene Therapeutics trial were still showing hearing gains at 26 weeks. So, **the time to full results appears to be at least six months**. The Refreshgene trial investigators noted in *The Lancet* that they will continue to follow up with patients to understand the “temporal pattern.”



**EFFICACY.** At this point, all three of the trials appear to have restored hearing in the treated ear **from profoundly deaf to moderate (or moderately-severe in one case)**. Hearing levels transformed from an inability to hear a shouted voice in the ear to difficulty only hearing a soft voice three feet away (or a normal voice for moderately-severe). Efficacy may continue to improve over time.



**DEVICE INDICATIONS.** The experimental gene therapy has transformed device indications for the treated ears from cochlear implants to hearing aids. Restoring hearing to the point where only a hearing aid is needed has tremendous benefits. Hearing outcomes with hearing aids are usually better than with cochlear implants, particularly with the patient's ability to hear in noisy places, appreciate music's qualities, and locate the origins of sounds.



## **Auditory Insight Helps Create Value for Clients in Their Mission to Address Hearing Loss**

Auditory Insight partners with senior leaders of device and pharma companies to develop successful market development and commercialization strategies. The firm also advises growth equity and private equity firms to create portfolio value in hearing healthcare.

Auditory Insight helps fuel growth by bringing clarity to market opportunities. The firm's strategic advice has contributed to its clients raising \$750M in funding rounds and IPOs in the last five years.

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# Auditory Insight®

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