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Gene Therapy to Treat Deafness

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Abstract

This article describes the first FDA-approved gene therapy for genetic deafness, Otarmeni (lunsotogene parvec-cwha), developed for pediatric and adult patients with severe-to-profound sensorineural hearing loss caused by biallelic OTOF mutations. The objective was to restore auditory function by addressing the underlying molecular defect responsible for impaired synaptic transmission in inner hair cells. The therapy is delivered as a one-time intracochlear injection using adeno-associated viral vectors that carry a functional OTOF gene, enabling production of otoferlin and reactivation of signal transmission from the cochlea to the auditory nerve.

Clinical data from the pivotal CHORD trial showed substantial hearing improvement after treatment. Approximately 80% of participants achieved hearing thresholds at or below 70 dB within 24 weeks, 42% reached normal or near-normal hearing levels by 48 weeks, and 70% demonstrated confirmed auditory brainstem responses. Benefits appeared durable, with responders maintaining gains through at least 48 weeks and early evidence suggesting continued stability beyond that period. The strongest outcomes were observed in younger patients, particularly those 18 years and under.

Overall, Otarmeni represents a major advance in precision otologic medicine by targeting the genetic cause of deafness rather than bypassing it. These findings suggest that OTOF gene therapy may offer meaningful, durable restoration of natural hearing in appropriately selected patients, while broader application to other genetic forms of hearing loss remains under investigation.

Key words: OTOF gene, deafness, restoration, reactivation, signal transmission

In a major medical breakthrough, the U.S. Food and Drug Administration (FDA) has officially approved the first-ever gene therapy for treating genetic deafness as of **April 23, 2026**.

This treatment, known as **Otarmeni** (generic name: lunsotogene parvec-cwha), is specifically designed for pediatric and adult patients with severe-to-profound hearing loss caused by mutations in the **OTOF gene**.

How The Therapy Works

- **The Problem**: A mutation in the OTOF gene prevents the production of **otoferlin**, a protein essential for transmitting sound signals from the inner ear's hair cells to the brain.
- **The Solution**: The therapy uses a viral vector (Adeno-associated virus or AAV) to deliver a functional copy of the human OTOF gene directly into the **cochlea** via a one-time injection.
- **Restoration**: Once the gene is inside the hair cells, they begin producing the otoferlin protein, enabling the ear to "fire" signals to the auditory nerve and allowing the brain to process sound.

Why The OTOF Gene?

- **The Function**: The OTOF gene produces **otoferlin**, a protein that allows the ear's hair cells to communicate with the auditory nerve.
- **The Fix**: The therapy delivers a functional version of the OTOF gene directly into the inner ear, allowing the body to produce the missing protein and restore natural hearing.
  While other genes like **GJB2** (Connexin 26) are the subject of intense research and clinical trials, they have not yet received official FDA approval for general use.

To receive **Otarmeni** (the OTOF gene therapy), patients must meet several specific clinical and genetic requirements. Here are the primary eligibility criteria as of the 2026 FDA approval:

1. **Genetic Confirmation**

- **Biallelic OTOF Mutations**: Patients must have a laboratory-confirmed diagnosis of hearing loss caused by mutations in **both** copies of the OTOF gene.
- The hearing loss must be primarily attributed to this genetic mutation rather than environmental factors (like infection) or other genetic syndromes.

2. **Clinical Hearing Status**

- **Severity**: The therapy is indicated for patients with **severe-to-profound** bilateral (both ears) sensorineural hearing loss.
- **Auditory Nerve Integrity**: The auditory nerve must be intact and functional, as the therapy relies on the nerve's ability to carry signals from the ear to the brain once protein production is restored.

3. **Age and Health**

- **Age Range**: While originally tested in children, the FDA approval covers **pediatric and adult patients**. However, centers often prioritize younger children (infants and toddlers) because early intervention is critical for speech and language development.

- **Surgical Fitness**: Patients must be healthy enough to undergo a surgical procedure under general anesthesia.

4. **Previous Treatments**

- **Cochlear Implants**: Eligibility for patients who already have a cochlear implant in one or both ears is determined on a case-by-case basis. The therapy is prioritized for the "non-implanted" ear or for patients who have not yet received an implant.

5. **Commitment to Follow-up**

- **Post-Op Monitoring**: Families must be able to commit to long-term follow-up appointments, which include regular hearing tests (audiograms) and speech perception evaluations to track the therapy's effectiveness.

- Several leading medical institutions in the United States and abroad are currently authorized to administer the **OTOF gene therapy** (**Otarmeni**) following its FDA approval on April 23, 2026. These centers typically have specialized departments in pediatric otolaryngology and gene therapy.

Peri-Operative Pathway

The process for the recently approved therapy, **Otarmeni**, typically follows these steps:

1. **Surgical Delivery**: Surgeons perform a one-time, minimally invasive procedure under general anesthesia. Using an endoscope or a fine catheter, they inject the therapy through the **round window membrane**, a tiny opening that leads directly into the fluid-filled **cochlea** of the inner ear.

2. **Viral Transport**: Because the OTOF gene is too large for a single carrier, the therapy uses **dual viral vectors** (modified, harmless adeno-associated viruses). These vectors act as "delivery trucks" to carry halves of the healthy gene into the target sensory cells.

3. **Gene Reassembly**: Once inside the inner ear's hair cells, the cellular machinery automatically joins the two gene halves together to form a complete, functional OTOF gene.

4. **Protein Production**: The newly delivered gene provides instructions for the cells to start producing **otoferlin**, a protein essential for hearing that was previously missing or defective.

5. **Signal Transmission**: With otoferlin present, the hair cells can finally release neurotransmitters to the auditory nerve. This allows sound vibrations to be converted into electrical signals that the brain can "hear".

Key Benefits Over Traditional Methods

Cochlear implants which bypass damaged parts of the ear to stimulate the nerve electronically, gene therapy aims to restore **natural acoustic hearing**. This can lead to better sound quality, improved speech perception, and the ability to appreciate music more clearly.

The approved treatment, **Otarmeni** (generic name: lunsotogene parvec-cwha), was authorized on April 23, 2026, to treat hearing loss caused by mutations in this specific gene.

Comparison to Cochlear Implants

It is been the standard for decades, they do not address the root genetic cause and require external hardware and batteries. Gene therapy aims to restore **natural acoustic hearing** by repairing the biological mechanism within the ear itself.

Current Limitations and Next Steps

- **Specific Scope**: Current approval is limited to OTOF-related deafness, which accounts for about 1% to 8% of congenital hearing loss cases.
- **Future Research**: Scientists are now exploring similar approaches for other common genetic causes, such as the GJB2 (Connexin 26) gene , using tools like CRISPR/Cas9 for gene editing.
- **Cost and Access**: While many gene therapies are priced in the millions, manufacturer Regeneron has indicated that Otarmeni will initially be available at **no cost** to eligible patients in the United States through a priority voucher program

Gene therapy for deafness works by repairing the biological mechanism of hearing at the molecular level, specifically by replacing a non-functional gene with a healthy one to restore protein production.

How to Access Treatment

If a person has been diagnosed with **biallelic OTOF mutations**, you can typically begin the process by:

1. **Genetic Confirmation**: Undergoing molecular testing to confirm the specific OTOF mutation.
2. **Specialist Referral**: Contacting a designated **Center of Excellence** (like those listed above) for an initial evaluation.

3. **Financial Support**: In the U.S., Regeneron is currently providing the therapy for **free** through a national priority voucher program to eligible patients
   The FDA-approved gene therapy for deafness, **Otarmeni** (lunsotogene parvec-cwha), specifically targets the **OTOF** gene.

   As of April 2026, clinical data from the pivotal CHORD trial demonstrates a high success rate in restoring hearing for patients with severe-to-profound hearing loss caused by OTOF mutations:

Leading Authorized Medical Centers (U.S.)

- **Boston Children's Hospital**
  Children's hospital, Boston, MA, United States
  A primary site for the pivotal clinical trials (CHORD trial) and a leader in providing coordinated care for children receiving this therapy.

- **Columbia University Irving Medical Center**
  Medical Center, New York, NY, United States
  Home to key specialists like Dr. Lawrence Lustig who have been instrumental in the therapy's development.
- **University of California San Francisco Parnassus Campus**
  University, OpenSan Francisco, CA, United States
  A major West Coast hub for pediatric otolaryngology and early-access gene therapy programs.

- **Mass General Brigham / Mass Eye and Ear (Boston, MA)**
  Co-led international studies on OTOF restoration and serves as a major treatment and research site.

International Clinical Trial & Treatment Sites

While the therapy is currently FDA-approved in the U.S., Regeneron's multicenter trials also involve sites in the following countries, which may serve as future regional treatment hubs:

- **United Kingdom**
- **Spain**
- **Germany** (e.g., University Medical Center Göttingen)
- **Japan**
- **China** (e.g., Eye & ENT Hospital of Fudan University)

Success Rates & Clinical Outcomes

- **Overall Improvement**: **80% of participants** (16 out of 20) achieved the primary goal of hearing sounds at or below **70 decibels** within 24 weeks. This level typically allows for natural hearing and conversation without the need for a cochlear implant.

- **Normal Hearing Restoration**: In longer-term follow-up (48 weeks), **42% of participants** reached hearing levels categorized as **normal** (≤25 decibels), which includes the ability to hear soft whispers.

- **Objective Confirmation**: **70% of participants** showed a confirmed auditory brainstem response (ABR), which is an objective measurement of electrical signals reaching the brain in response to sound.

- **Durability**: Results have shown to be stable, with 100% of initial responders maintaining their hearing gains through at least **48 weeks** of follow-up.

Key Clinical Results

- **Successful Restoration**: In trials, approximately **80% to 90%** of participants experienced significant hearing improvement.
- **Normal Hearing**: Some children reached "normal" hearing thresholds, allowing them to hear soft speech and appreciate music—milestones often difficult to achieve with traditional cochlear implants.
- **Longevity**: Early evidence suggests the hearing restoration is stable for at least **2.5 years** post-treatment.

Important Considerations

Accelerated Approval: The FDA granted accelerated approval U.S. Food and Drug Administration (.gov) based on these strong interim results. Continued approval may depend on further data showing long-term benefits in speech and quality of life.

Age Factors: While both children and adults are eligible, the strongest gains in hearing and speech recognition were observed in patients **18 years old and younger**.

- **Genetic Specificity**: This success rate applies only to deafness caused by the OTOF gene; it does not currently treat hearing loss from other genetic causes like GJB2 or environmental factors.

Conclusion:

The FDA's approval of Otarmeni, the first gene therapy for genetic deafness, marks a significant advancement in treating severe-to-profound hearing loss caused by OTOF gene mutations. This innovative therapy utilizes a one-time injection of a viral vector to deliver a functional copy of the OTOF gene directly into the cochlea, ultimately restoring the production of otoferlin and enabling natural sound transmission to the auditory nerve. With a high success rate shown in clinical trials, including significant improvements in hearing for a majority of participants, Otarmeni offers a promising alternative to traditional cochlear implants. While currently limited to OTOF-related deafness,

ongoing research may pave the way for similar treatments targeting other genetic causes of hearing loss, heralding a new era in audiology and patient care.

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