

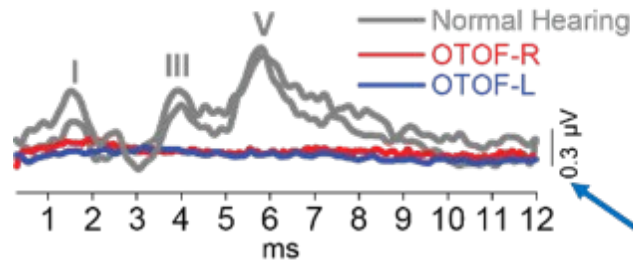
Intracochlear Administration of DB-OT0

September 2025

REGENERON[®]

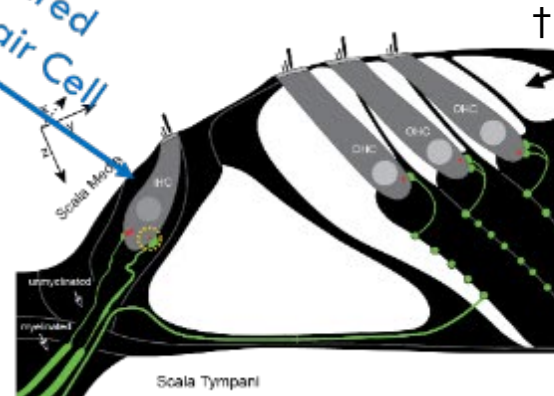
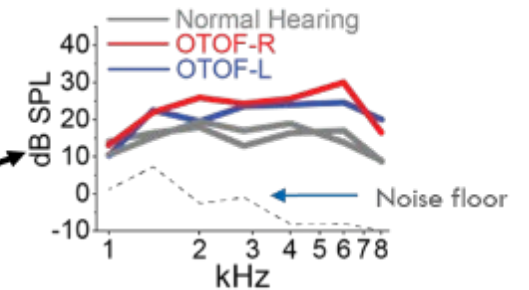
Biallelic *OTOF* variants result in auditory neuropathy

ABR¹



Peastock/Shutterstock.com

Distortion product otoacoustic emissions¹



Normal
Outer Hair Cell

Impaired
Inner Hair Cell

Baby image from Peastock/Shutterstock.com

†Scala tympan diagram: Courtesy of EPL Charles Lieberman.

ABR, auditory brainstem response; OTOF, otoferlin gene; OTOF-L, otoferlin left ear; OTOF-R, otoferlin right ear; SPL, sound pressure level.

1. Vogl C et.al. EMBO J. 2016;35:2536–2552.

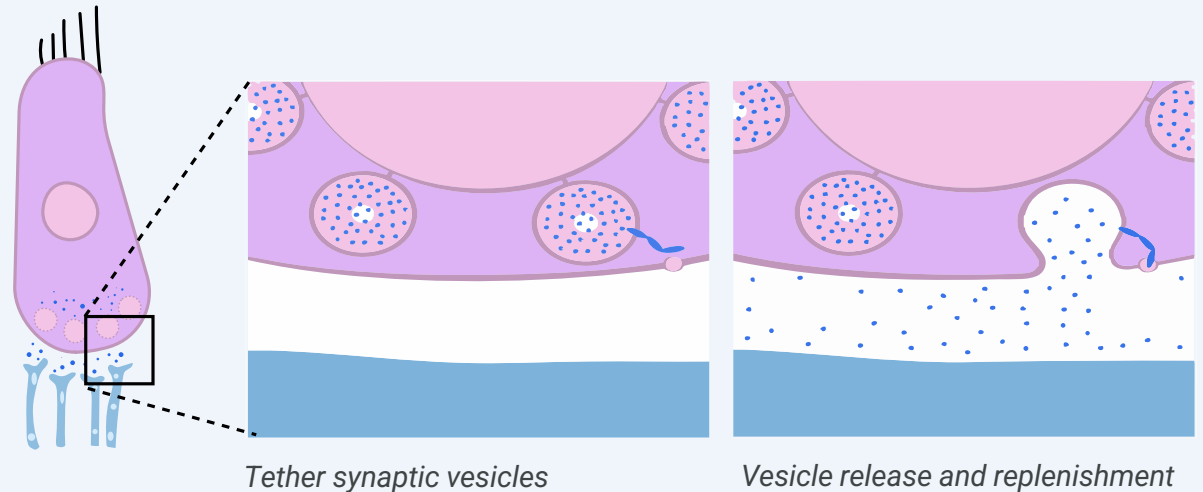
DB-OTO: A locally delivered AAV gene therapy for congenital deafness due to *OTOF* pathogenic variants

Local, controlled delivery of *OTOF* with DB-OTO

- Ultra-rare cause of deafness (~20-50 new patients/year in the US)
- Well-established audiometric natural history
- Currently in phase 1/2 clinical trial (CHORD; DB-OTO-001; NCT05788536) with sites open in the US, the UK, and Spain¹

OTOF is critical for synaptic transmission in the ear

The *OTOF* protein is critical for neurotransmission between the inner ear hair cell synapses and the auditory nerve



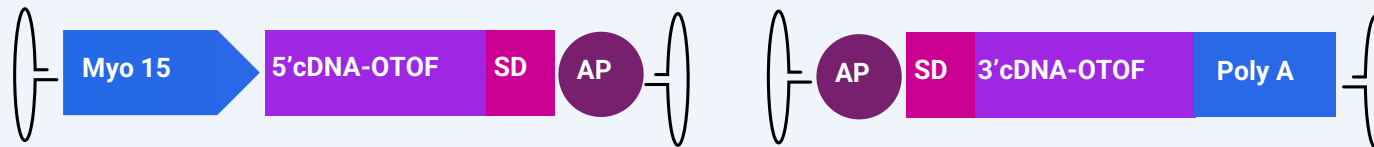
DB-OTO: A locally delivered AAV gene therapy for congenital deafness due to *OTOF* pathogenic variants (continued)

Local, controlled delivery of *OTOF* with DB-OTO

Ultra rare DB-OTO is a dual AAV vector (AAV1) that is designed to specifically express *OTOF* cDNA in the inner hair cells of the ear via a hair cell-specific promoter (Myo15)

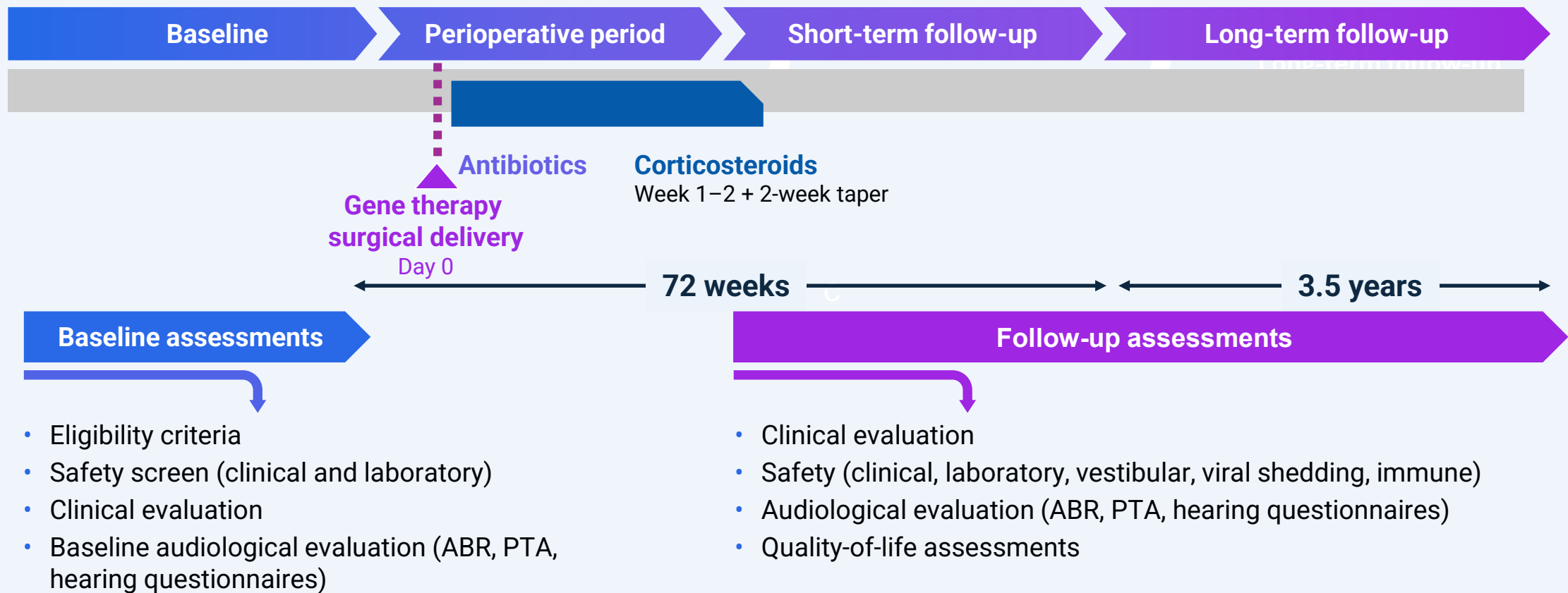
Engineered for cell-specific expression

Local intracochlear delivery utilizes the same clinically established surgical approach as cochlear implantation



CHORD: DB-OTO-001 trial design

The CHORD study (NCT05788536) was conducted to assess the effect of DB-OTO, a dual AAV1 gene therapy, in children and infants with biallelic *OTOF* variants



DB-OTO demonstrates the potential to provide hearing to deaf children (from infancy to adolescence)

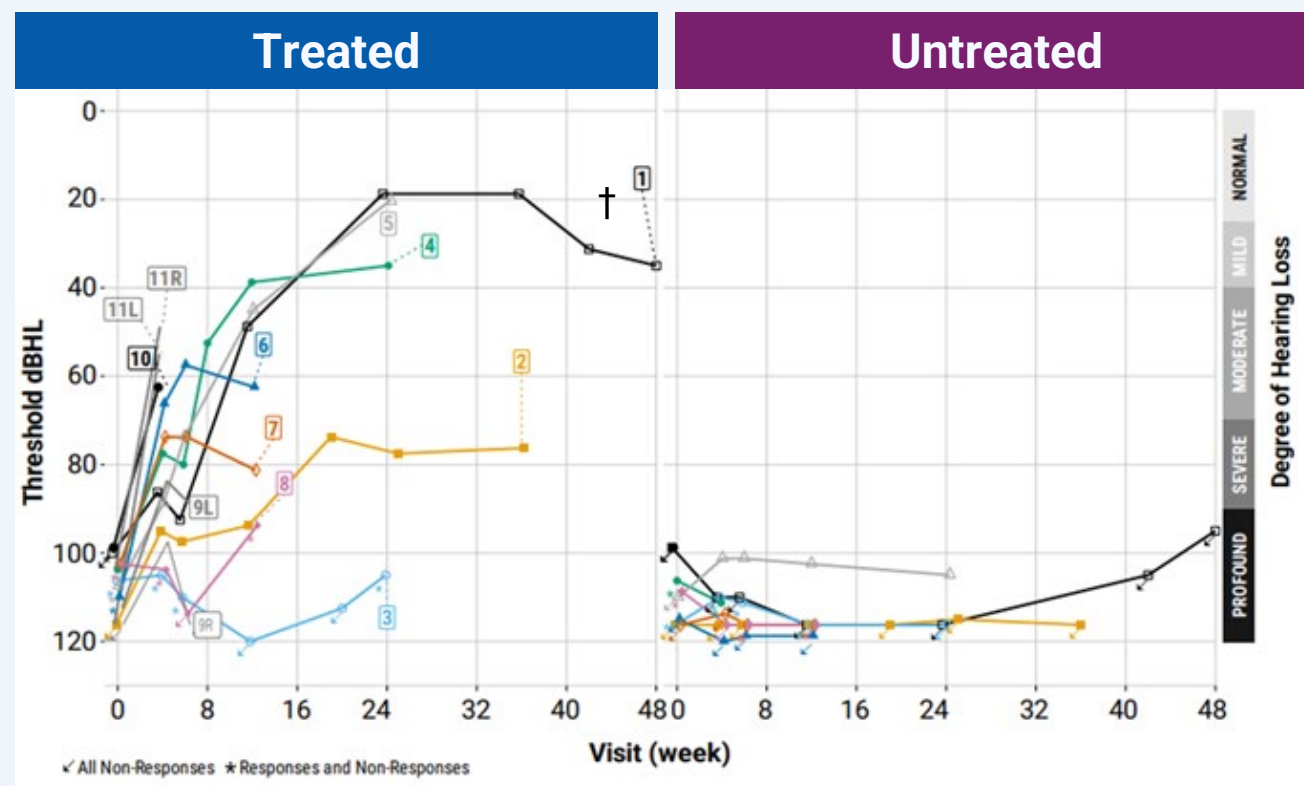
12 participants between the ages of 10 months and 16 years have been dosed with DB-OTO

Pure tone audiometry (PTA)

- 10 of 11 participants with ≥ 1 post-treatment assessment showed a notable response, with improved hearing at various dBHLs
- 3 of 5 participants with Week 24 assessments showed improvement in hearing thresholds to ≤ 40 dBHL, and 2 of 5 participants showed improvement in hearing thresholds to ≤ 25 dBHL

Auditory brainstem response (ABR)

- ABR corroborated behavioral PTA findings
- Measurement of far-field physiologic responses sometimes lag behavioral responses
- 8 of 11 participants had measurable responses at early timepoints



Behavioral PTA – threshold average of key speech frequencies (0.5, 1, 2, and 4 kHz)

[†]Observed high frequency threshold elevation (4–8 kHz), stable since Week 43, following bilateral chronic otitis media.
dB, decibel; dBHL, decibel hearing level

Congenital Hearing Loss | Diagnosis Codes

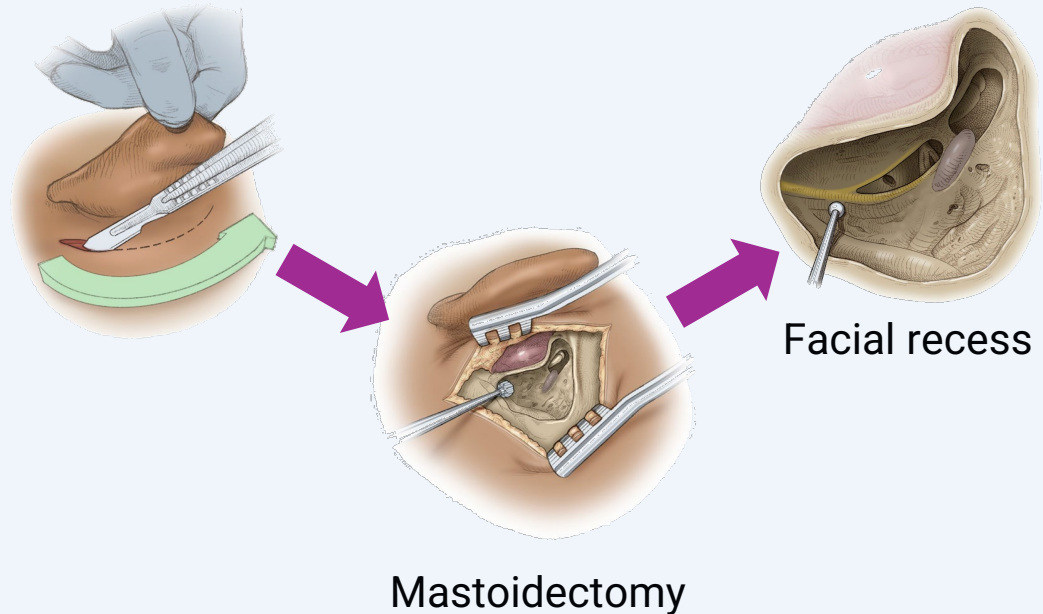
ICD-10-CM codes that describe patients with profound genetic deafness due to variants of the otoferlin gene

ICD-10 Code	Code Description
H90.3	Sensorineural hearing loss, bilateral
H90.5	Unspecified sensorineural hearing loss
H91.3	Deaf nonspeaking, not elsewhere classified
H93.8	Other specified disorders of ear, bilateral
H93.3X1	Disorders of right acoustic nerve
H93.3X2	Disorders of left acoustic nerve
H93.3X3	Disorders of bilateral acoustic nerves
H93.3X9	Disorders of unspecified acoustic nerve

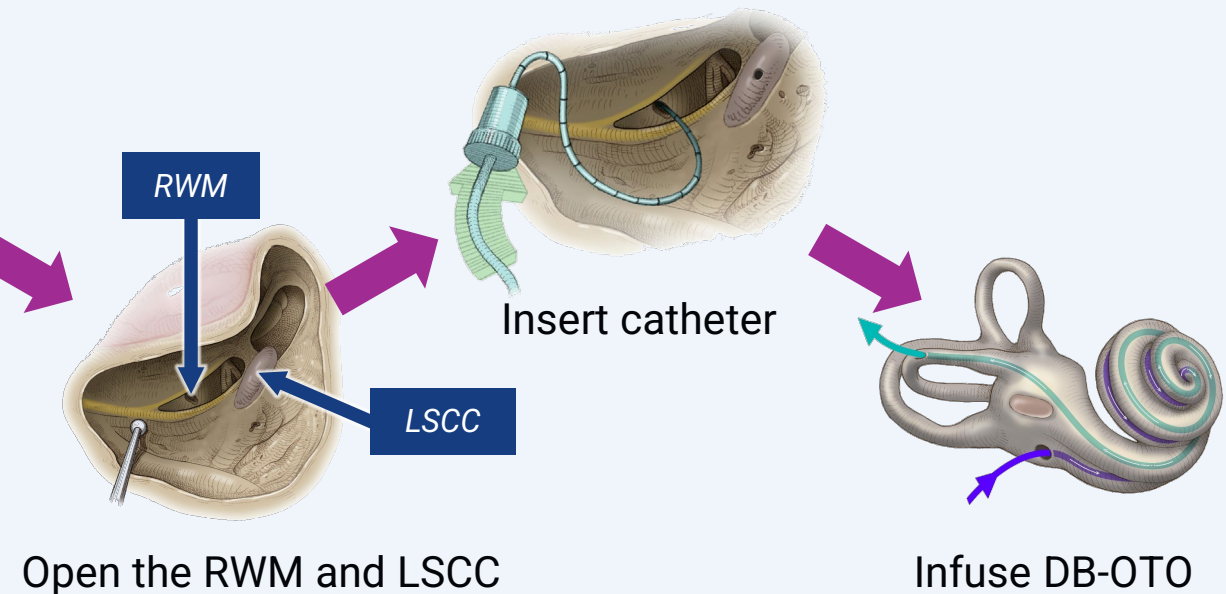
DB-OTO leverages a novel route of administration: direct infusion of gene therapy product into inner ear perilymph

The surgical approach accesses the middle ear, then the inner ear at two points (the RWM and the LSCC), allowing insertion of a catheter through the round window into the perilymph for DB-OTO infusion

Surgical approach (standard)



Route of administration (novel)



Initial safety outcomes: No DB-OTO–related adverse events have been noted so far

- 53 TEAEs reported in 10 of 12 participants to date
- No AEs considered related to DB-OTO
- 5 of 12 participants experienced transient post-surgical vestibular AEs (e.g., nystagmus, nausea, dizziness, and vomiting), which resolved within 6 days of dosing
- 2 serious TEAEs were reported, neither of which were considered related to DB-OTO
 - Participant 1 had an SAE of mastoiditis (Grade 3) in the contralateral ear (cochlear implant ear), which was considered unrelated to DB-OTO and resolved after a course of antibiotics; this participant also had AEs of recurrent upper respiratory tract infection and chronic otitis media in both ears
 - Participant 11 had an SAE of walking instability (Grade 3), which was considered unrelated to DB-OTO and resolved within 3 days; this was attributed to a reaction to varicella vaccine
- The majority of AEs were commonly occurring medical conditions in a young pediatric population (e.g., upper respiratory tract infections, rash)



Setting of Care, Documentation and Terminology

Inpatient Administration:

- DB-OTO may be administered in the inpatient setting; additional settings of care are to be determined

Medical Record Documentation:

- Information regarding DB-OTO and its associated administration procedure will be documented in the medical record and identifiable from multiple perspectives (e.g., Medication Administration Record [MAR], Electronic Health Record [EHR], physician orders, pharmacy notes, treatment summary, progress notes, procedure notes, etc.)

Terms or Naming Conventions:

- No brand or generic name has been finalized for DB-OTO and no other terms are currently used to describe this novel product



Summary

- DB-OTO is an investigational cell-selective, dual adeno-associated virus (AAV) vector gene therapy designed to provide durable, physiological hearing to individuals with profound, congenital hearing loss caused by variants of the *OTOF* gene
- There are no approved medications for the treatment of deafness due to biallelic pathogenic variants of the *OTOF* gene. Some patients are managed with surgically placed cochlear implants, providing limited hearing performance when compared to natural hearing
- DB-OTO requires a novel surgical approach to administer the gene therapy as an infusion into the cochlea