# ENT
# 耳科 Seminar

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ORIGINAL ARTICLE

# DB-OTO Gene Therapy for Inherited Deafness

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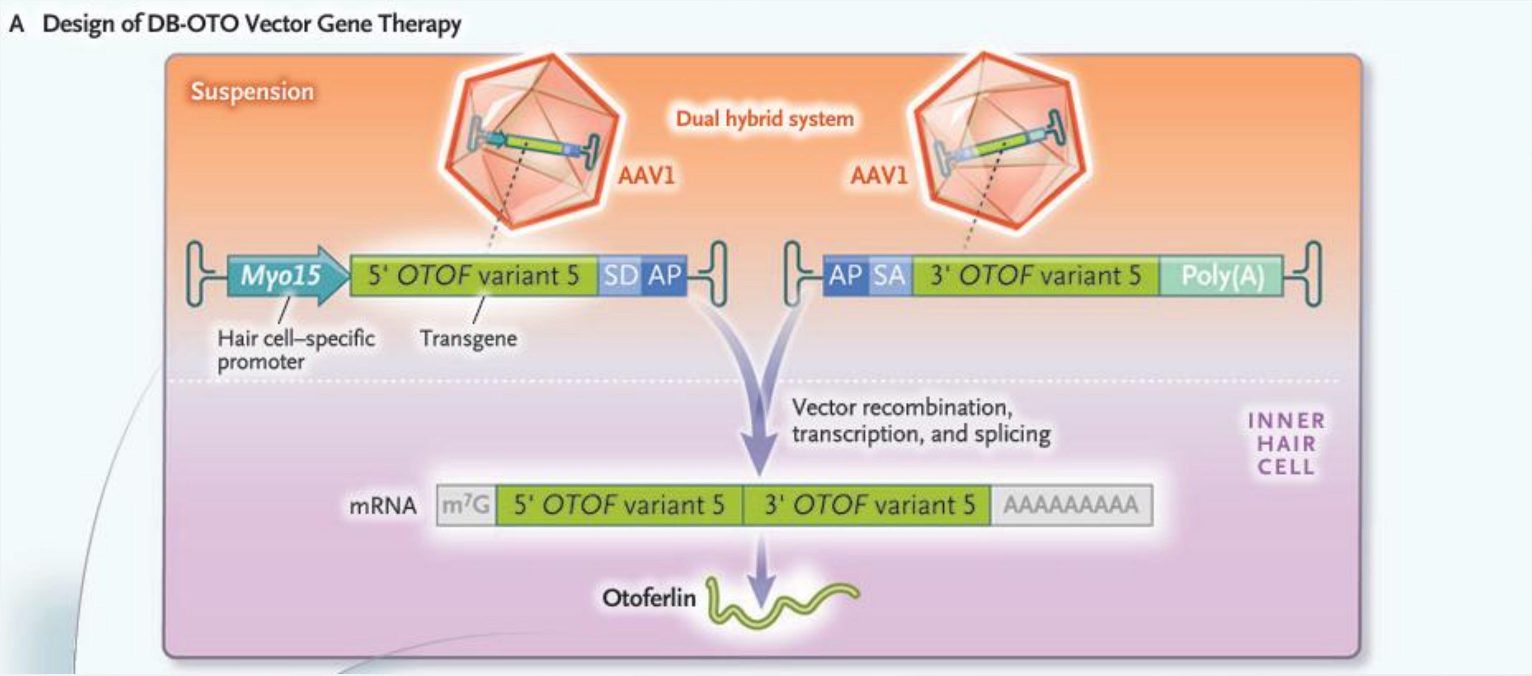
# Introduction

## OTOF Gene Defects

- OTOF gene→ otoferlin protein→ regulates synaptic transmission between sensory inner hair cells and the cochlear nerve.
- Biallelic pathogenic variants in OTOF account for 1 to 3% of cases of congenital genetic deafness.
- Children with pathogenic variants in OTOF are born with profound deafness, and their hearing does not spontaneously improve
- Management: lifelong use of cochlear implants.




A dual adeno-associated virus 1 (AAV1) vector carrying the human OTOF transgene was developed that contains a Myo15 promoter to drive the specific expression of otoferlin in the sensory inner hair cells of the cochlea.

# CHORD Trial

## Study Overview

- Open-label, single-arm Phase 1-2 clinical trial

## Study Design & Methods

**Part A: Single Ear Treatment**
→ **One ear:** DB-OTO
→ Contralateral ear: cochlear implant or no treatment

**Part B: Bilateral Treatment**
→ **Both ears:** DB-OTO

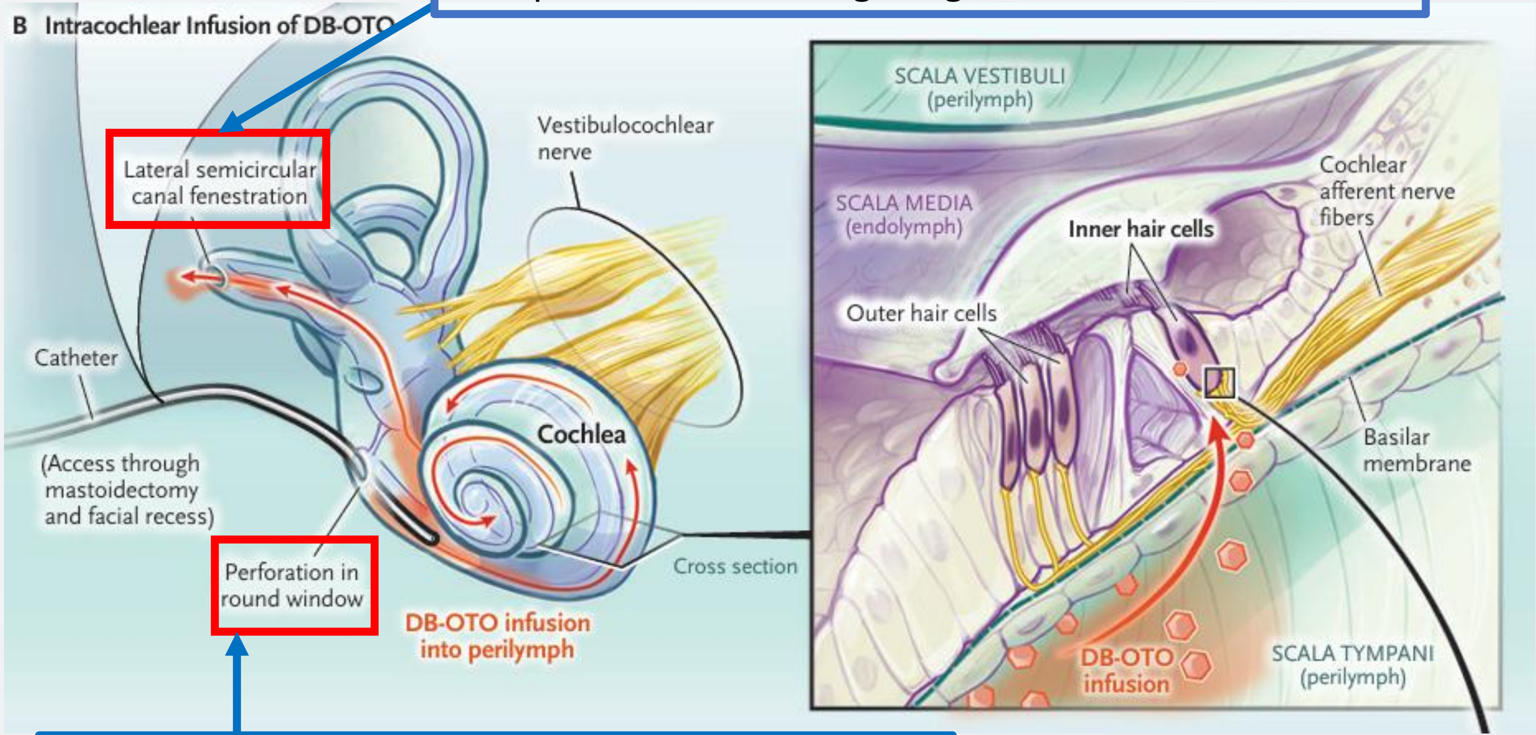
## Dosing Regimen

| 7.2×10^12 | 240 μL |
| --- | --- |
| Vector genomes per ear | Administration volume |

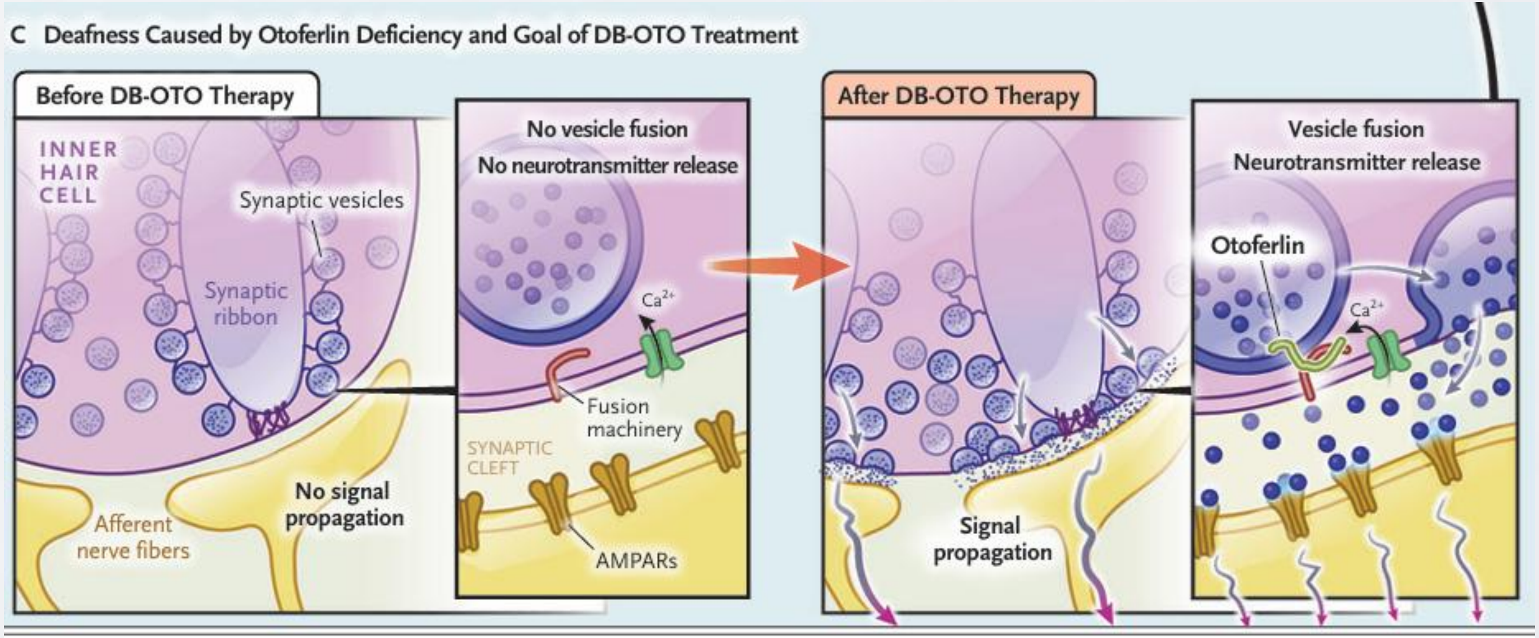
## Surgical Delivery Method

- **Single Intracochlear Infusion**
- **Round Window Membrane Delivery**
  Using mastoidectomy and facial recess approach
- **Pressure Management**
  Lateral semicircular canal windowing to prevent excessive pressure

- egress perilymph and lower the pressure
- repaired with autologous grafts




- Infused at a fixed rate with a syringe pump
- repaired with muscle or fascia




- α-amino-3-hydroxy-5-methyl-4 isoxazolepropionic acid receptor
- AP alkaline phosphatase recombinogenic region
- mRNA messenger RNA
- SA splice acceptor site
- SD splice donor site

# Methods

## Participant Selection

- One participant was excluded because of an inability to complete behavioral testing .
- Twelve participants between 10 months and 16 years of age who had OTOF variants and profound deafness

### Inclusion Criteria

- Age < 18 years, Biallelic OTOF variants
- Severe deafness (HT >90 dB HL)
- Treatment ear with intact outer hair cell function

### Exclusion Criteria

- Previous gene therapy
- Cochlear implant in treatment ear

## End Points

- Primary efficacy endpoint
  - ➢ Week 24: Behavioral pure-tone audiometry (PTA) ≤ 70 dB HL
  - ➢ Lower thresholds→ better hearing
    higher thresholds→ inability to detect loud sounds.
- Key secondary end point
  - ➢ Week 24: Auditory brain stem response ≤ 90 dB normalized hearing level (nHL)

# Method

## End Points

- Other key secondary endpoints measured
  - Week 24: average PTA ≤45 dB
  - Week 24: average PTA ≤25 dB
- Additional secondary endpoints: Speech perception
  - Early Speech Perception test
  - Global Impression Scales

- Exploratory endpoints (Week 48)
  - Auditory
  - Language assessments
    Example: Auditory Skills Checklist

## Detection – the ability to determine the presence or absence of sound

***Does your child…***

**1.** wear the amplification device during his/her waking hours?

**2.** use body language to indicate when something is heard *(ex. turns head, and/or eye widening, quiets, stops action, changes facial expressions*)?

**3.** show awareness (*alerts or quiets in response to loud sound, turns to the sound source*) of loud environmental sounds (ex. *dog barking*)?

**4.** show awareness (*quiets to the sound and/or turns to the sound source*) of soft environmental sounds (*ex. microwave bell, clock ticking etc.*)?

**5.** show awareness of voices (*quiets to the sound and/or turns to the sound source*), spoken at typical loudness levels (*in a regular voice*)? (*ex. gets excited when they hear their mother's voice, child playing on the floor with toy cars looks up when people are talking in the room)?*

**6.** detect the Ling Six Sounds (M,AH,OO,E,SH,S)?

S= the child detects **all** of the Ling Six Sounds
E= the child detects **at least one** of the six sounds (circle what sounds the child hears)
D= the child **does not detect any** of the six sounds

**7.** detect the speaker's voice when background noise (softer than the speaker's voice) is present?

**8.** search to find out where a sound is coming from?

**9.** localize to the correct sound source (*to the direction the sound is coming from*)?
S= the child localizes the correct sound source most of the time
E= the child searches to find out where a sound is coming from and/or localizes the correct sound source some of the time
D= the child does not search or localize the sound source

## Discrimination – the ability to distinguish or notice the difference between sounds and/or words

***Does your child…***

**10.** notice a difference or respond differently between someone talking vs. a common environmental sound (*difference between mom talking and someone clapping their hands*)?
Qualitative information can be gained by then asking: "how do you know?"

**11.** notice a difference or respond differently between different environmental sounds (*ex. dog barking versus a telephone ringing*)?

**12.** notice a difference or respond differently between a speaker using a soft voice (*a whisp*er) and a speaker using a loud voice (above conversational range)?

**13.** notice the difference (discriminate) between a person singing (*ex. "Happy Birthday"*) from a person having a conversation?

**14.** notice the difference between family members voices (*ex. Dad's voice vs. Mom's voice vs. a sibling's voice*)?

**15.** notice the difference between minimal pair words (*similar sounding words such as pat, bat, mat*)?

**16.** notice the difference between similar sounding phrases and sentences (*How old are you? vs. How are you?*)?

## Identification – the ability to listen to a word or phrase and point to the object or picture requested.

***Does your child…***

**17.** identify if the speaker is happy, angry, or surprised by the change in vocal tones?

**18.** respond to his or her name when called?

**19.** identify an object or item with an associated sound (*a train goes “choo choo”, a dog goes “woof woof”, a cat goes “meow”*)?

**20.** identify one syllable words versus two syllable words versus three syllable words (*ball vs. hotdog vs. computer*)?

**21.** identify or recognize words used in the child’s natural environment (these words may vary with age and exposure)?

**22.** identify the Ling Six Sounds (M, AH, OO, E, SH, S)?

S= the child identifies **all** of the Ling Six Sounds
E= the child can identify **at least one** of the six sounds (circle what sounds the child identified)
D= the child is **not able to identify any** of the six sounds

**23.** identify familiar songs ( *“Happy Birthday”, “Itsy Bitsy Spider”, “Old McDonald”*)?

S= the child can identify $\geq$ **4** familiar songs
E= the child can identify **1** familiar song

## Comprehension – the ability to understand what is being said.

***Does your child…***

**24.** understand frequently heard phrases/sentences (*ex. "It's time for bed." and "Brush your teeth and get ready for bed."*)?

**25.** follow one step directions (*Get your shoes.*)?

S= the child can follow ≥ **10** one step directions
E= the child can follow ≥ **3** one step directions
D= the child is **not able to** complete this task

**26.** follow two step directions (*Get your shoes and open the door.*)?
S= the child can follow ≥ **10** two step directions
E= the child can follow ≥ **3** two step directions
D= the child is **not able to** complete this task

**27.** follow three step directions (*Get your shoes, open the door, and walk outside.*)?
S= the child can follow ≥ **7** three step directions
E= the child can follow **> 2** three step directions
D= the child is **not able to** complete this task

**28.** have an auditory memory for phrases/sentences (*ex. "I see the dog." or "The girl jumped over the fence to get the ball."*)? *Also asked "Can your child repeat the phrase 'The girl jumped over the fence to get the ball'?".*
S= the child is able to remember ≥ **7** sentences
E= the child is able to remember ≥ **3** sentences
D= the child is **not able to** complete this task

**29.** have an auditory memory for items__2 __3 __4 __5 __6 __7 __8 __9 or more (*ex. being able to remember the following objects: apple, boat, cup, and shoe would be 4 items*)?

S= the child is able to remember **≥ 7** items
E= the child is able to remember **≥ 3** items
D= the child is **not able to** complete this task

**30.** auditorily sequence __3 events __4 events __4+ events of a story (*ex. 1st event – "Steve went to the store.", 2nd event – "He bought dog bones.", 3rd event – "Steve took the bones home to the dog."*)?

S= the child is able to sequence **≥ 4** events of a story
E= the child is able to sequence **3** events of a story
D= the child is **not able to** complete this task

**31.** understand the question forms __what __where __who __why __ when (*ex. "What is that?" "Where is the dog?" "Who broke the cup?"*) in phrases and sentences?

S= the child understands **5** "WH" questions
E= the child understands **> 2** "WH" questions
D= the child is **not able to** complete this task

**32.** understand concepts in phrases and sentences (ex. in, under, between, in front, beside, above, below)?

S= the child understands **≥ 7** concepts
E= the child understands **≥ 2** concepts
D= the child is **not able to** complete this task

**33.** understand the use of negatives in phrases and sentences (*ex. no, not, no more, "We're not going to Grandma's house today"*)?

**34.** obtain information incidentally through audition/hearing alone?

**35.** through audition/hearing alone, understand most of what is said?

https://successforkidswithhearingloss.com/wp-content/uploads/2011/12/Auditory-Skills-Checklist-Cincinatti-Childrens-Hosp.pdf

# Method

## Tests for Speech Perception

Early Speech Perception (ESP)

- For children ≥2 years
- Child listens to standardized speech stimuli and selects the corresponding toy or image from a standardized closed set
- mono-, di-, and tri-syllabic words
- Higher score indicating better pattern or word recognition

Global Impression Scales

- Reported by clinicians and parents or caregivers
- Single-item questionnaires used to evaluate the severity of and changes in specific skill domains
- severity of speech perception ability:
  "none", "mild, moderate", "severe", and "very severe"
- change in speech perception ability: "very much worse" to "very much improved"

**Table 1. Characteristics of the Participants at Baseline.***

| Participant No. | Sex | Age in Years at Infusion | *OTOF* Genotype† | Treatment | | Anti-AAV1 Neutralizing Antibody Titer |
|---|---|---|---|---|---|---|
| | | | | Right Ear | Left Ear | |
| 1 | F | 0.9 | c.2676+1G→T/c.2887C→T (p.Arg963*) | DB-OTO | CI (concomitant) | 1:5 |
| 2 | M | 4.0 | c.4819C→T (p.Arg1607Trp) homozygous | DB-OTO | CI (concomitant) | 1:5 |
| 3 | F | 1.3 | c.2485C→T (p.Gln829*) homozygous | DB-OTO | No treatment | 1:10 |
| 4 | F | 2.3 | c.2485C→T (p.Gln829*) homozygous | No treatment | DB-OTO | 1:5 |
| 5 | M | 4.1 | c.762C→G (p.Tyr254)/c.1469C→G (p.Pro490Arg) | CI (previous) | DB-OTO | 1:5 |
| 6 | F | 16.3 | c.2485C→T (p.Gln829*) homozygous | CI (previous) | DB-OTO | 1:5 |
| 7 | F | 16.4 | c.5714G→A (p.Gly1905Asp) homozygous | CI (previous) | DB-OTO | Negative |
| 8 | F | 1.9 | c.2485C→T (p.Gln829*)/c.5566C→T (p.Arg1856Trp) | DB-OTO | No treatment | Negative |
| 9 | F | 1.0 | c.2239G→T (p.Glu747*) homozygous | DB-OTO | DB-OTO | 1:5 |
| 10 | F | 2.8 | c.1621G→A (p.Gly541Ser)/c.1961_1964dup (p.Arg656Alafs*8) | CI (previous) | DB-OTO | 1:320 |
| 11 | M | 1.3 | c.2485C→T (p.Gln829*) homozygous | DB-OTO | DB-OTO | 1:5 |
| 12 | F | 1.2 | c.2485C→T (p.Gln829*)/c.5103+2T→A | DB-OTO | DB-OTO | 1:10 |

* AAV1 denotes adeno-associated virus 1, and CI cochlear implant.
† Genotypes are based on the *OTOF* complementary DNA reference sequence NM_001287489.1.

| Category | Details |
| --- | --- |
| Disease, problem, or condition under investigation | *OTOF*-related deafness, an ultra-rare disease |
| Special considerations related to | |
| Sex and gender | Based on published articles after 2000 that report *OTOF*-related deafness by sex in the US and European countries (N=98),[9–15] it appears to affect more male patients (56.1%) than female patients (43.9%). |
| Age | There are no publications reporting the distribution of sex among patients with *OTOF*-related deafness. Since *OTOF*-related deafness is a congenital condition that is not expected to affect life expectancy, we assume that the age distribution of prevalent cases would reflect that of general US population. |
| Race or ethnic group | There are no publications reporting the distribution of race or ethnicity among patients with *OTOF*-related deafness. We assume that the racial and ethnic distributions of patients with *OTOF*-related deafness reflect those of US births from 2020 to 2022.[16] *OTOF*-related deafness are estimated to dominantly affect White patients (68.3%), followed by Black (19.1%) and Asian patients (8.0%). |
| Geography | *OTOF*-related deafness has been reported in the US and many countries in Europe, including Spain, France, Italy, Germany, and Belgium.[9–15] |
| Other considerations | As *OTOF*-related deafness is an ultra-rare disease, finding clinical trial candidates is a challenge. |
| Overall representativeness of this trial | In this trial, population-specific enrollment strategies were incorporated as dictated by science. As biallelic *OTOF* mutations are extremely rare, recruitment was driven by any eligible candidate that has the genotype, and testing was extended to centers that serve underrepresented populations. Although the current participants (N=12) in this ongoing pediatric trial did not reflect the expected ratio of sex, additional patients are being enrolled. Demographic information was obtained from parents/caregivers of participants. Data included biologic sex (male, female), ethnicity (Hispanic or Latino, Not |

| Participant no. | Treatment | Biallelic *OTOF* mutation zygosity | Visit | Anti-AAV1 neutralizing antibody titer |
|---|---|---|---|---|
| 1 | Unilateral DB-OTO | Heterozygous | Baseline | 1:5 |
| | | | Week 2 | 1:2560 |
| | | | Week 12 | 1:2560 |
| 2 | Unilateral DB-OTO | Homozygous | Baseline | 1:5 |
| | | | Week 2 | 1:5120 |
| | | | Week 12 | 1:5120 |
| 3 | Unilateral DB-OTO | Homozygous | Baseline | 1:10 |
| | | | Week 2 | 1:640 |
| | | | Week 12 | 1:320 |
| 4 | Unilateral DB-OTO | Homozygous | Baseline | 1:5 |
| | | | Week 2 | 1:5120 |
| | | | Week 12 | 1:10240 |
| 5 | Unilateral DB-OTO | Heterozygous | Baseline | 1:5 |
| | | | Week 2 | 1:10240 |
| | | | Week 12 | 1:20480 |
| 6 | Unilateral DB-OTO | Homozygous | Baseline | 1:5 |
| | | | Week 2 | 1:1280 |
| | | | Week 12 | 1:20480 |
| 7 | Unilateral DB-OTO | Homozygous | Baseline | Negative |
| | | | Week 2 | 1:1280 |
| | | | Week 12 | 1:10240 |
| 8 | Unilateral DB-OTO | Heterozygous | Baseline | Negative |
| | | | Week 2 | 1:2560 |
| | | | Week 12 | 1:2560 |

| | | | | |
|---|---|---|---|---|
| 9 | Bilateral DB-OTO | Homozygous | Baseline | 1:5 |
| | | | Week 2 | 1:10240 |
| | | | Week 12 | 1:2560 |
| 10 | Unilateral DB-OTO | Heterozygous | Baseline | 1:320 |
| | | | Week 2 | 1:10240 |
| | | | Week 12 | 1:40960 |
| 11 | Bilateral DB-OTO | Homozygous | Baseline | 1:5 |
| | | | Week 2 | 1:10240 |
| | | | Week 12 | 1:5120 |
| 12 | Bilateral DB-OTO | Heterozygous | Baseline | 1:10 |
| | | | Week 2 | 1:20480 |
| | | | Week 12 | 1:10240 |

AAV denotes adeno-associated virus.

# Primary Endpoint Results

## Definition

Primary endpoint: Achieving a PTA average threshold ≤70 dB HL

## Main Results

- **9 of 12 participants (75%)** met the primary endpoint at week 24.

## Breakdown by Ear Treated

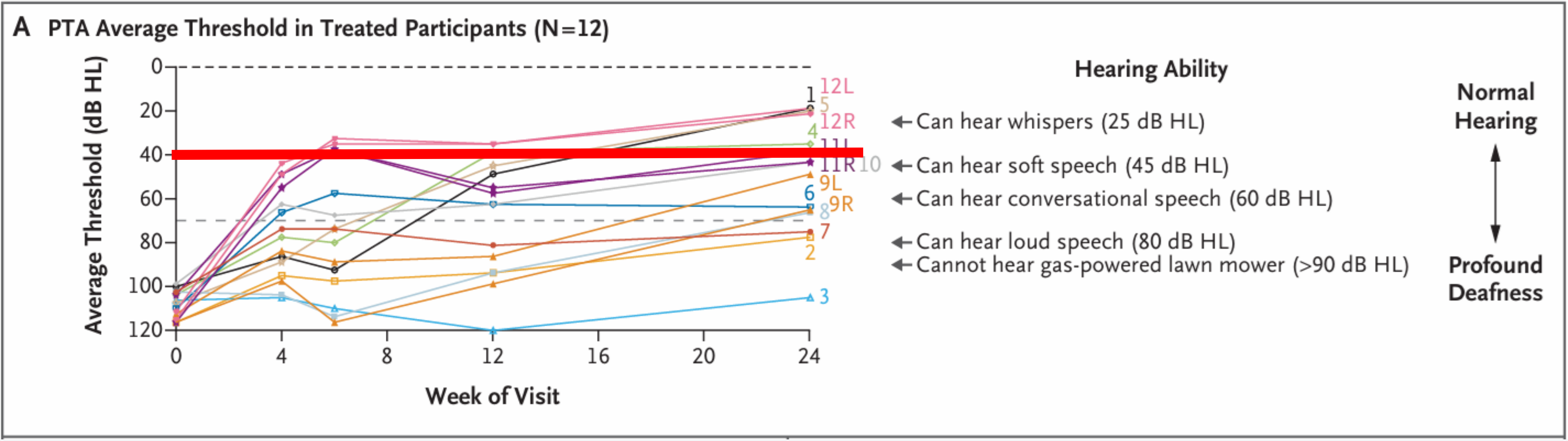
- Participants treated in one ear:
  - 6/9 treated ears met the primary endpoint.
  - 0/9 untreated ears met the endpoint.
- Participants treated in both ears:
  - All 3 participants met the primary endpoint.

## Additional Hearing Improvement Milestones

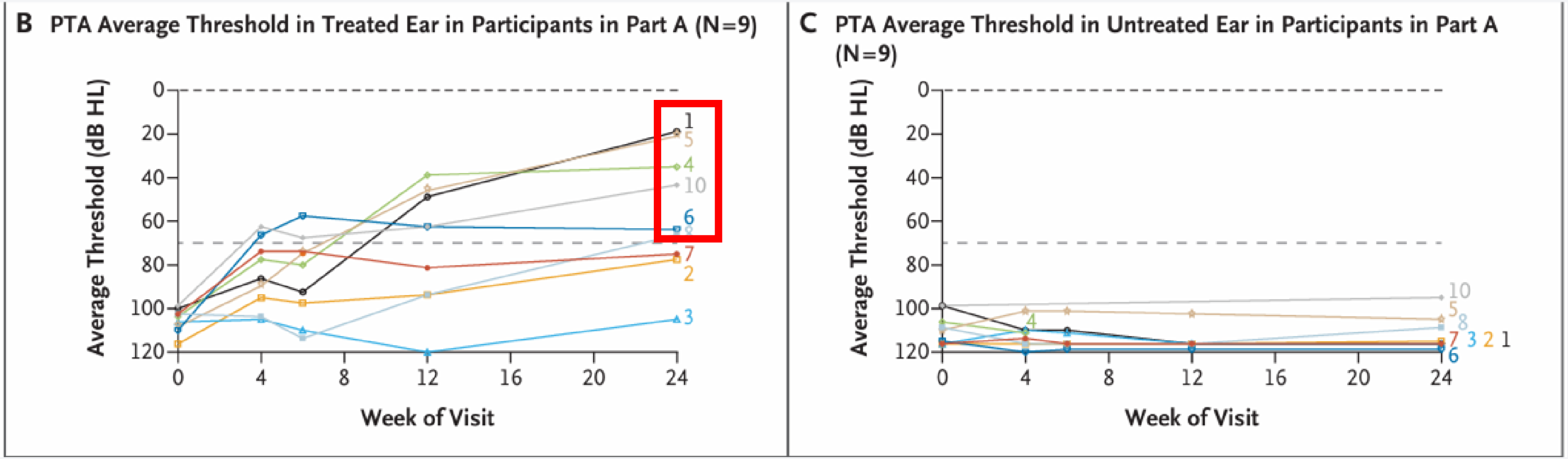
- 6 participants achieved soft-speech sensitivity (≤45 dB HL).
- 3 participants achieved normal hearing (≤25 dB HL) by week 24.

## Participants Not Meeting the Primary Endpoint

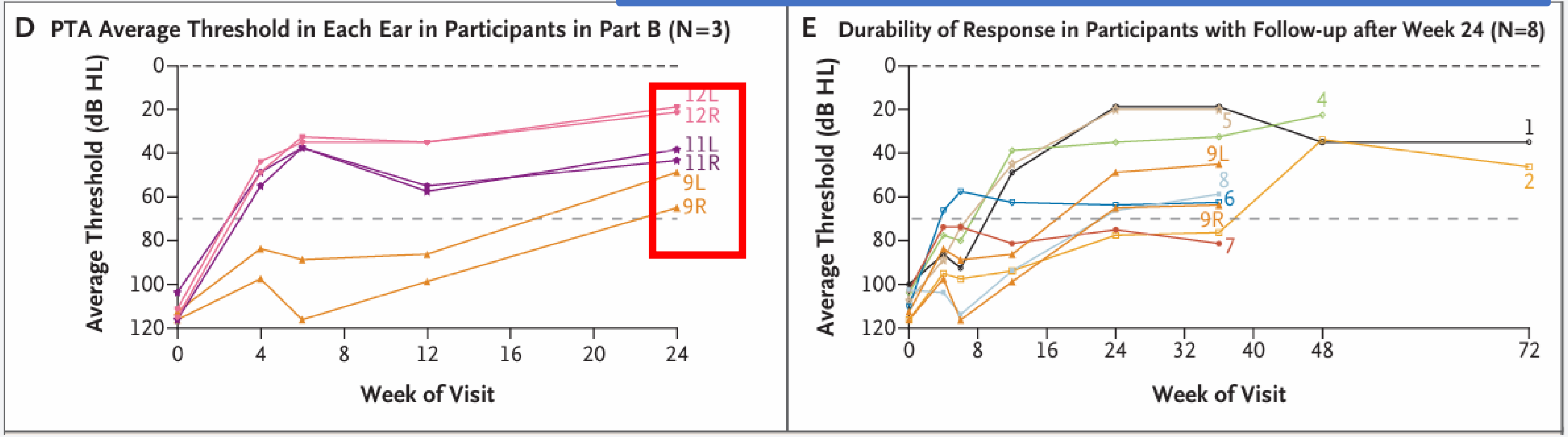
- Participant 3: No improvement.
- Participants 2 and 7: Did not meet the threshold but still showed improvement from baseline.


A PTA Average Threshold in Treated Participants (N=12)
Average Threshold (dB HL)
0
20
40
60
80
100
120
0
4
8
12
16
20
24
Week of Visit
1
12L
5
12R
4
11L
11R
10
9L
6
9R
8
7
2
3
Hearing Ability
Can hear whispers (25 dB HL)
Can hear soft speech (45 dB HL)
Can hear conversational speech (60 dB HL)
Can hear loud speech (80 dB HL)
Cannot hear gas-powered lawn mower (>90 dB HL)
Normal Hearing
Profound Deafness

- Two participants were 16 years old at the time of treatment, both had improvements in hearing in the DB-OTO–treated ear

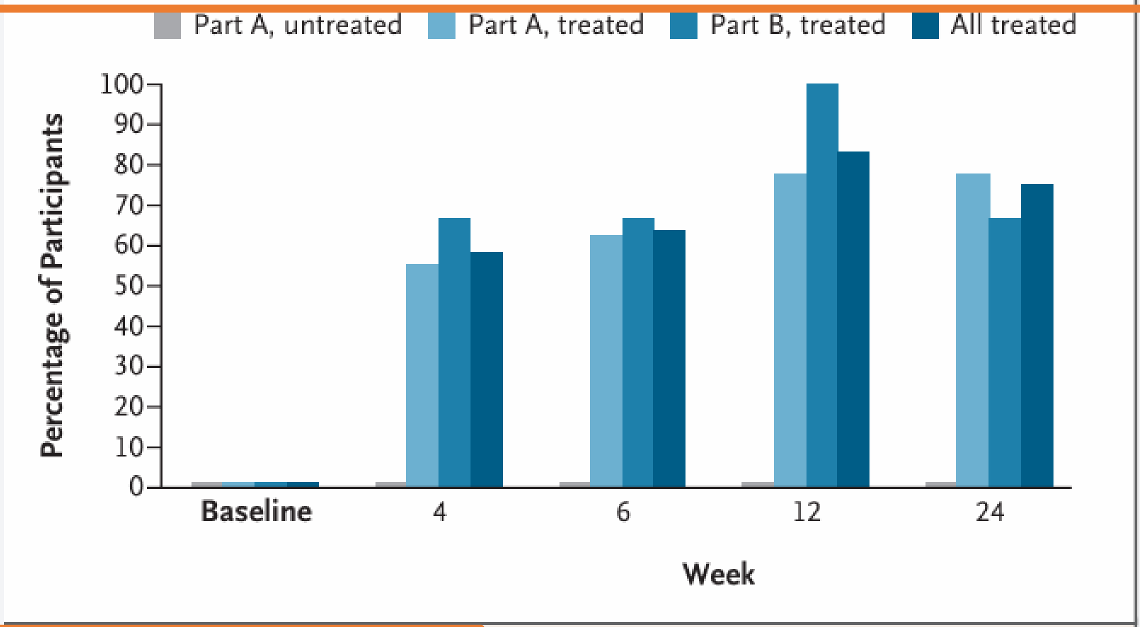


- Eight participants were followed up for more than 24 weeks (up to 72 weeks)
- The hearing in all 8 remained stable or continued to improve during this interval



Week 24

- Auditory brain-stem response at or below 90 dB nHL was found in 9 of the 12 participants (75%)
- Participants who received treatment in one ear: 7/9
- Untreated ears: 0/9.
- Treatment in both ears : 2/3




At baseline, neural responses at a threshold above 90 dB nHL were absent in all participants

# Speech Perception

## Speech Perception Improvements

### General Findings

- Speech development assessed through parental/clinician reports and formal tests when appropriate.
- **Four participants** reached ≥48 weeks of follow-up.
  - **Participant 3:** No response; received cochlear implant at 36 weeks → excluded from further speech assessment.

## Participant with Gene Therapy Only (No Contralateral Implant)

### Participant 4

- Received DB-OTO in one ear at **28 months old**.
- **Week 48:**
  - Parents: “Very much improvement”
  - Clinicians: “Much improvement”
- Behavioral testing not completed; however:
  - **Auditory Skills Checklist:**
    - Baseline: **8%**
    - Week 48: **60%**

# Secondary Outcomes and Speech Perception

## Participants with Gene Therapy + Contralateral Cochlear Implant

**Participant 1**

- Treated at **10 months old** with DB-OTO; cochlear implant in the other ear.
- **Week 24:** Normal hearing (18.75 dB HL)
- **Week 72:**
  - "Much improvement" on Global Impression Scale
  - Early Speech Perception test (CI off):
    - **100%** accuracy: two-syllable words
    - **50%** accuracy: single-syllable words
- **Week 96:**
  - **100%** accuracy: two-syllable words
  - **70%** accuracy: single-syllable words

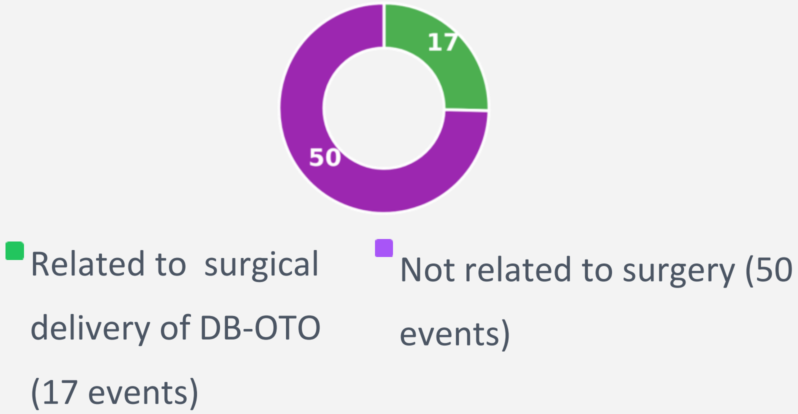
**Participant 2**

- Treated at **4 years old**; DB-OTO in one ear and cochlear implant in the other.
- Baseline: **No spoken or sign language**
- **Week 48:** "Minimal improvement"
- **Week 72 (CI off):**
  - **100%** accuracy: syllable-pattern discrimination
  - **50%** accuracy: two-syllable words (no visual cues)

# Safety Profile and Adverse Events

## Adverse effect

- 67 adverse events recorded
- Adverse Events Distribution




## Adverse Events Details

- Many of the adverse events were related to the surgical approach
- All remaining adverse events during or after treatment were transient.

## Serious Adverse Events

- **Mastoiditis:** Grade 3, related to untreated contralateral ear
- **Walking Instability:** Grade 3, after varicella vaccination

Resolved without sequelae

**Table S4 Summary of adverse events**

| Event | Part A (Treatment in One Ear) (N=9) | Part B (Treatment in Both Ears) (N=3) | Overall (N=12) |
|---|---|---|---|
| | | *No. of patients* | |
| Adverse event | 57 | 10 | 67 |
| Treatment-related adverse events | 13 | 4 | 17 |
| Related to study drug | 0 | 0 | 0 |
| Related to study procedures | 13 | 4 | 17 |
| Adverse event leading to study discontinuation | 0 | 0 | 0 |
| Adverse event leading to dose interruption | 0 | 0 | 0 |

# Discussion

## Results

- By 24 weeks, several participants improved from **not hearing a lawn mower** to **detecting whispers**.
- Indicates intact cochlear structures suitable for gene therapy.
- Benefits observed in participants up to **16 years old**, not only young children.
- Hearing improvement occurred across all clinically assessed frequencies (0.125–8 kHz).
- DB-OTO supported speech and language development:
  - Of 4 children followed ≥48 weeks, 3 showed progress in speech perception and language acquisition.
  - One participant gained **distant sound detection**, which is difficult for cochlear implant users.

# Discussion

## Long-term Follow-up Study

- In 8 participants followed >24 weeks, improvements persisted.
- Two participants showed mild decline in high-frequency hearing, without affecting speech perception.

## Non-Responder Case (Participant 3)

- One participant showed no response; cause remains unclear.
- Surgery was uncomplicated; however, this participant had a low immune response to AAV1, suggesting insufficient vector delivery.
- Later received a cochlear implant with improvement → DB-OTO does not interfere with future implantation.

# Discussion

## Limitation

- Small size and its limited duration
- Limited follow-up duration.
- Study converted mid-course to a registrational trial → some endpoints were not prespecified.

## Broad Treatment Potential

- DB-OTO gene therapy shows promise for treating other forms of congenital deafness caused by mutations in genes expressed in inner ear hair cells.

## Conclusion & Future Development

- Results support continued development of DB-OTO for congenital deafness due to OTOF variants.
- Ongoing study will assess outcomes for 5 years after treatment.
- Whether similar gene-addition strategies can treat other forms of deafness remains unknown.