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Priority Review	Priority (CNPV)
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Review Completion Date / Stamped Date	April 6, 2026
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Applicant	Regeneron Pharmaceuticals, Inc.
Established Name	Lunsotogene Parvec-cwaha (DB-OTO)
(Proposed) Trade Name	OTARMENI
Pharmacologic Class	adeno-associated virus (AAV) vector-based gene therapy

Formulation(s), including Adjuvants, etc	Suspension
Dosage Form(s) and Route(s) of Administration	Vial for a single intracochlear infusion
Dosing Regimen	3.0E13 vector genomes (vg)/mL/ear
Indication(s) and Intended Population(s)	Treatment of pediatric and adult patients with severe-to-profound and profound sensorineural hearing loss (any frequency >90 dB HL) associated with molecularly confirmed biallelic variants in the <i>OTOF</i> gene, preserved outer hair cell function, and no prior cochlear implant in the same ear.

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## GLOSSARY

AAV: adeno-associated virus  
ABR: auditory brainstem response  
AE: adverse event  
AESI: adverse event of special interest  
CI: confidence interval  
CMC: chemistry, manufacturing, and control  
CTCAE: Common Terminology Criteria for Adverse Events  
DPOAE: distortion product otoacoustic emissions  
FDA: Food and Drug Administration  
IDMC: independent data monitoring committee  
MedDRA: Medical Dictionary for Regulatory Activities  
OTOF: otoferlin gene  
PT: preferred term  
PTA: pure tone audiometry  
RMAT: regenerative medicine advanced therapy  
SAE: serious adverse event  
SAP: statistical analysis plan  
SOC: system organ class  
TEAE: treatment emergent adverse event  
UK: United Kingdom  
US: United States

## 1. EXECUTIVE SUMMARY

Biallelic pathogenic variants of the otoferlin gene (OTOF) cause congenital severe-to-profound deafness. Congenital deafness resulting from biallelic OTOF variants impairs language development, cognitive development, music appreciation, academic achievement, and reading skills. Severe-to-profound deafness is diagnosed using pure tone audiometry (PTA), and auditory brainstem response (ABR) testing almost universally reveals complete absence of neural responsiveness to sound.

Currently, there are no approved pharmacological or biological therapies that address the underlying genetic cause of OTOF-related deafness. The standard of care for patients with severe-to-profound deafness due to biallelic OTOF variants is surgical cochlear implantation within the first two years of life and lifelong use of the device.

DB-OTO is a dual adeno-associated virus serotype 1 (AAV1) vector-based gene therapy. Intracochlear infusion of DB-OTO is intended to result in expression of otoferlin protein in inner hair cells, where it facilitates synaptic transmission to the auditory nerve, potentially enabling uninterrupted natural hearing function.

The clinical development program for DB-OTO consists of a single ongoing clinical study, DB-OTO-001 (CHORD). Study DB-OTO-001 was initially designed as a first-in-human, multicenter, phase 1/2, single-arm trial. Based on preliminary efficacy data from the study, the applicant revised the statistical analysis plan (SAP) to introduce hypothesis

testing for the primary and key secondary endpoints specified at that time. The protocol and SAP were subsequently amended to include the current plan for hypothesis testing.

The primary database agreed upon prior to this BLA is based on data from the first 12 treated participants. Out of 12 participants, 9 (75%) achieved the primary efficacy endpoint (PTA  $\leq 70$  dB HL) at Week 24, described as representing a hearing level that typically avoids the need for cochlear implantation and enables natural hearing. Additionally, 9 of 12 participants (75%) met the key secondary efficacy endpoint (ABR to click at  $\leq 90$  dB nHL). Six (6) participants achieved average PTA threshold  $\leq 45$  dB HL (ability to hear soft conversational speech level) and 3 participants experienced complete hearing normalization (PTA  $\leq 25$  dB HL, whisper-level hearing).

During the BLA review, the review team decided to use the primary database based on available data from the first 20 treated participants, who had reached Week 24 prior to this BLA. Out of 20 participants, 16 (80%) had observed average PTA  $\leq 70$  dB HL at Week 24. In addition, 14 of 20 participants (70%) had ABR to click at  $\leq 90$  dB nHL. Nine (9) and 3 participants achieved average PTA thresholds  $\leq 45$  dB HL and  $\leq 25$  dB HL, respectively, at Week 24.

Due to the lack of pre-specification and Type I error control, there is no basis for statistical inference based on the results within this application. However, compared to the applicant-conducted natural history study and data from the untreated ear of unilaterally-treated participants, the efficacy results are remarkable, as no spontaneous hearing improvement has been observed without treatment. This statistical review will focus on descriptive analyses and will not include a recommendation regarding approval.

## 2. CLINICAL AND REGULATORY BACKGROUND

### 2.1 Disease or Health-Related Condition(s) Studied

The prevalence of congenital, permanent deafness globally is roughly 1 to 2 per 1,000 children regardless of region. In the United States (US), the prevalence of congenital deafness of any severity is reported in 1.7 per 1,000 births through Early Hearing Detection and Intervention programs. In Europe, the prevalence is reported as 1.1 (95% confidence interval [CI] 0.9, 1.3) per 1,000 children. In China, South Korea, and Japan, the reported prevalence ranges between 1 and 2 infants per 1,000 births.

It is estimated that, worldwide, over half of all congenital deafness cases are caused by single gene pathogenic variants. OTOF is the gene coding for the otoferlin protein which is expressed in inner hair cells and involved in the transduction of sound. OTOF-mediated deafness is an ultra-rare form of genetic deafness. Of the estimated 6,100 new cases of congenital deafness in the US each year, approximately 50 cases are due to biallelic OTOF pathogenic variants. Of the 3,240 new cases of bilateral congenital deafness each year in Europe, approximately 46 cases are due to biallelic OTOF pathogenic variants. In Japan, of the estimated 1,100 new cases of congenital deafness, there are approximately 7 new cases of congenital deafness due to biallelic OTOF pathogenic variants each year.

Patients with OTOF-related deafness are typically born unable to hear even very loud sounds (e.g., gas-powered lawnmower), and they are diagnosed with severe-to-profound deafness that is permanent. For these patients, deafness is caused by dysfunction of the synapse involving sensory inner hair cells and the vestibulocochlear nerve due to the critical role of the otoferlin protein in synaptic transmission. Otoferlin is a calcium sensor that is predominantly expressed in sensory inner hair cells and functions in presynaptic vesicle exocytosis and endocytosis. Thus, establishing expression of functional otoferlin in inner hair cells was hypothesized to enable hearing by restoring a functional synapse with vesicle docking and neurotransmitter release.

## **2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)**

Currently, there are no approved pharmacological or biological therapies that address the underlying genetic cause of OTOF-related deafness. The standard of care for patients with severe-to-profound deafness due to biallelic OTOF variants is surgical cochlear implantation within the first two years of life and lifelong use of the device. While providing benefit, cochlear implants are limited by the diminished resolution of electrical hearing, impaired speech understanding in noisy environments (e.g., only understand 20% of words in classroom noise), impaired music appreciation, and an inability to use the implant in certain settings (e.g., at night when removed for sleeping or in the water). Limited speech perception also leads to impaired cognitive development and delayed academic achievement. In addition, cochlear implant may result in cochlear tissue damage, potentially precluding patients from future therapeutic approaches that target the intact cochlear structure, like gene therapy. Current interventions provide imperfect and, in many cases, inadequate hearing because they do not address the underlying genetic defect, leaving patients with lifelong impairments despite intervention.

## **2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission**

### Pre-submission (IND 28864)

- September 17, 2020: Type B pre-IND (PS005838) meeting for chemistry, manufacturing, and control (CMC), pharmacology/toxicology and clinical aspects of the program.  
During the meeting, it was agreed that the sponsor should discuss with the Food and Drug Administration (FDA) about proceeding to Part B (bilateral dosing) of the DB-OTO-001 (CHORD) study after completing and analyzing data from Part A (unilateral dosing).
- September 15, 2022: Original IND submission by the original sponsor, Decibel Therapeutics, Inc.  
The submission included version 2 (dated September 1, 2022) of the protocol for study CHORD. The primary objective was to evaluate the safety and tolerability of DB-OTO in young children and infants diagnosed with biallelic OTOF mutations. Sample size was planned to be at least 12 and up to 18, with at least 6 participants in each part. Descriptive statistics were to be presented. No formal statistical testing was planned. There were two planned interim analyses, the first after Part A was

complete (last patient, including any additional patients enrolled beyond the original 6 who completed the 12-week assessments), and the second after the last patient from Part B completed the 24-week assessment.

- November 14, 2022 (amendment 3): Protocol amendment version 2/US-1 (dated November 10, 2022).

Sample size was increased to at least 16 and up to 22 in this protocol amendment, where at least 10 Part A participants and at least 6 Part B participants were specified. The first interim analysis was moved to after the first 7 participants in Part A completed the 12-week assessments. It was noted that this first interim analysis result would be shared with the relevant health authorities.

- February 29, 2024 (amendment 18): Protocol amendment version 2/US-4 (dated February 28, 2024).

The sponsorship had been transferred to Regeneron Pharmaceuticals, Inc. Sample size was revised to at least 14 and up to 22 in this protocol amendment, where at least 8 Part A participants and at least 6 Part B participants were specified. The specific number of Part A participants for the first interim analysis was removed. Thus, it stated that the first interim was to be conducted after Part A was complete.

- July 25, 2024 (amendment 23): Protocol amendment version 2/US-5 (dated July 23, 2024).

Sample size was revised to at least 12 and up to 22 in this protocol amendment. Part A was to enroll 6 to 16 participants and Part B 6 participants.

- August 13, 2024 (amendment 24): Statistical analysis plan (SAP) version 2 (dated August 12, 2024).

The sponsor noted the conversion of CHORD study into a registrational study in this submission. The proposal included the primary efficacy endpoint of pure tone audiometry (PTA) and several key secondary endpoints, including PTA response defined by different cutoffs and auditory brainstem response (ABR) response, to be evaluated at Week 48. The sponsor stated that no patients had completed week 48 assessments, and one patient had completed their Week 24 assessments at the time of this SAP finalization. SAP version 1 and track change document of SAP version 2 were not provided to the FDA, so it was unknown what had been revised at that time. However, based on the accompanying documents, it was clear that formal statistical hypothesis testing was added in this version of SAP. The thresholds for PTA response and ABR response hypothesis testing were specified as 2% and 4%, respectively. The SAP did not mention interim analysis or any precise number of participants for the analyses. The sample size section specified a total of 19 participants. The protocol was not amended at that time.

- September 17, 2024 (amendment 31): Type B Regenerative Medicine Advanced Therapy (RMAT) Initial Comprehensive Multidisciplinary meeting request.

- October 25, 2024 (amendment 35): Clinical amendment.

This submission was to support the transition to Part B. It included data from Part A that were reviewed by Independent Data Monitoring Committee (IDMC) on October 9, 2024. The sponsor requested response from the FDA by November 1, 2024, prior to discussion at the then scheduled Type B RMAT meeting, stating in the submission that since the IDMC had recommended proceeding to Part B with the dose in Part A and patients suitable for bilateral dosing were identified, the sponsor was eager to



initiate Part B. The Part A results provided in this submission were based on data cutoff on September 12, 2024. Eight (8) participants were treated with data from the first 7 participants provided. Out of 7 participants, the sponsor identified 6 PTA responders and 5 ABR responders any time during the study with only 2 having reached 24-week follow-up.

- November 15, 2024 (amendment 36): Type B RMAT meeting package.  
The same IDMC data were provided with the proposal for an accelerated approval submission based on 6-month (24-week) data, with the 48-week data specified in SAP version 2 to support full approval.
- December 6, 2024: Type B RMAT Multidisciplinary meeting.  
During this meeting, the FDA agreed with the sponsor's proposal to streamline the ongoing CHORD study into a single, pivotal study to support a registrational package. Specifically, the FDA agreed to a BLA submission for accelerated approval with data package of 12 participants with a minimum of 24 weeks of follow-up data, 9 from Part A and 3 from Part B. The primary efficacy endpoint was agreed to be achievement of a PTA threshold of 70 dB or less. At the same meeting, the FDA agreed with submitting a BLA for traditional approval with the same 12 participants but with a minimum of 48 weeks of follow-up data on the same primary endpoint. The FDA also agreed that natural history data derived from a retrospective chart review conducted at Ramon y Cajal Hospital combined with a systematic literature review, part of which has been published, could potentially serve to infer the null rate hypothesis for the analysis planned for the registrational study primary and key secondary endpoints and to support a BLA submission. The thresholds proposed for the hypothesis testing, however, had been specified in SAP version 2 nearly four months prior to this meeting discussion. With 12 participants, 2 responders are needed to claim statistical significance with threshold 2% and 3 needed with 4%.
- March 6, 2025 (amendment 47): Protocol amendment version 3 (dated February 18, 2025) and SAP version 3 (February 28, 2025).  
Sample size was revised to at least 12 and up to 30. Minimum sample size was specified as 6 for each part with no upper limit. The sample size section was revised to specify 12 participants in total for both documents. The Week 24 primary endpoints hypothesis testing was added for Region A, which includes US. The Week 48 endpoints hypothesis testing was relabeled as the second-step analysis for Region A and the only analysis for Region B. The set of primary and key secondary endpoints to be formally tested had also been revised in this version of SAP. The threshold for both PTA and ABR response testing was specified as 2%. The protocol amendment added formal statistical testing for the first time and removed interim analysis. At that time, 7 participants had 24-week follow-up.

Summary of main changes during the study:

- *Introduction and subsequent change of primary efficacy endpoint of PTA and key secondary efficacy endpoint of ABR*
- *Addition of hypothesis testing for PTA and ABR*
- *Shortening of primary timepoint of efficacy endpoint after addition of hypothesis testing*
- *Reduction of the threshold for ABR hypothesis testing from 4% to 2%*

- *Multiple changes in sample size, both minimum and maximum, for each part of the study*
- *Reduction of number of interim analyses from two to one and change of interim analysis timing*

#### Post-submission

During the rolling review submission, the applicant and the FDA agreed that the traditional approval BLA would be based on the same first 12 participants but with a minimum of 24 months (2 years) of follow-up data. The primary endpoint remained the same, but a key secondary endpoint of speech perception scores was added to assess hearing sensitivity. This discussion does not affect this review.

During the labeling review, the FDA has decided to use the primary database based on available Week 24 data from the first 20 treated participants for this application. The applicant accepted the FDA's recommendation. Thus, the additional analyses section (Section 6.1.11.5) of this review will discuss results from this database.

### **2.6 Other Relevant Background Information**

The applicant conducted a natural history analysis of OTOF-related deafness through a comprehensive literature review (DB-100-100), which included studies published up to 2024. This review encompassed a meta-analysis and a retrospective chart review of patients with biallelic OTOF variants at Ramón y Cajal University Hospital in Madrid, Spain (total N=322). The dataset provided contains limited information given the nature of the retrospective chart review and there is no effort to remove potential duplicate data from multiple studies. The applicant stated that the findings indicated that patients with OTOF-related deafness do not experience spontaneous recovery of their hearing, as assessed by behavioral audiometry (PTA) and electrophysiological studies (ABR).

No patients in the natural history study demonstrated meaningful improvement in hearing. Based on this analysis of over 200 patients with no observed spontaneous hearing improvement (0%, Clopper-Pearson 95% CI, 0%, 1.8%), a 2% null response rate was proposed by the applicant as an upper limit benchmark for hypothesis testing.

Based on the natural history review, there is no evidence of the ABR spontaneously becoming measurable in patients with biallelic OTOF pathogenic variants during the natural course of the disease. The maximum sound level that is generated by clinical equipment to measure tone-evoked ABR is ~100 dB nHL. At this maximal sound presentation level, neural responses to sound are not able to be measured in patients with biallelic OTOF pathogenic variants.

## **3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES**

### **3.1 Submission Quality and Completeness**

This BLA was submitted through rolling review process. The study documents (i.e., protocol, SAP, and clinical study report) and primary datasets were submitted on

November 19, 2025. Although all screened and treated participants' baseline data were submitted (such as ADSL), only efficacy data from the first 12 treated participants were provided in that submission. Data errors were reported by the applicant in the submission but not addressed in the datasets submitted. The FDA also informed the applicant of several minor dataset structure issues shortly after that submission and requested data from all treated participants.

The final module of this BLA was submitted on December 23, 2025. It contains data from all study participants and a brief, abbreviated report of updated efficacy and safety analyses. At that data cutoff, 20 participants had at least 24-week follow-up data. The applicant noted additional data errors with this database while the previous data errors had been fixed. Upon the FDA's inquiry, the applicant claimed that these errors had been fixed in its database which would be reflected in future dataset submissions.

Upon the FDA inquiry, the applicant responded on January 15, 2026 (STN 31) that

As this is an ongoing study with a live database, additional data changes from the sites or any data discrepancies noted based on ongoing data reviews (that may need updates/corrections), can occur based on continuation of study conduct activities and communication with clinical sites. *The Sponsor confirms all data submitted to the agency has been 100% cleaned, including source-data verification.* (emphasis added)

However, FDA site inspection conducted spot check of efficacy data and discovered two subjects' baseline PTA entries did not match the source data. The site staff indicated that these data entries in the electronic data capture (EDC) would be corrected. Please consult BIMO review for more details.

### **3.2 Compliance With Good Clinical Practices And Data Integrity**

Study DB-OTO-001 (CHORD) was designed as a phase 1/2 exploratory study and is an ongoing single-arm trial. Although prior agreement had been reached with the FDA regarding converting this study into a registrational study and defining the data package for the initial BLA submission supporting accelerated approval, the duration of this conversion process was merely eight months after the applicant made the decision by amending the SAP. In contrast, the amendment of the SAP occurred approximately one year after study initiation. Notably, the applicant submitted an amended SAP more than a month prior to submitting the meeting request for discussion with the FDA. The protocol at that time did not contain any language regarding formal statistical testing. More than a month before the meeting, the applicant informed the FDA that the study would proceed to Part B despite previous agreement to wait until after an opportunity to discuss with the FDA. The actual proposal presented at the meeting differed from the proposal in the SAP amendment, which led to another amendment in both the protocol and the SAP three months after the agreement was reached. There was very little time for the FDA to adequately review this proposal and the subsequent revisions, and details regarding the hypothesis threshold and the natural history data from which this threshold was derived were not thoroughly evaluated.

The sponsor's decision on conversion was based on preliminary CHORD study data from the first 7 treated participants. At the time of the analysis, 6 of 7 participants had met the PTA response threshold during the study. One (1) of the 2 participants who had reached 24-week follow-up (the first participant) had met the PTA response threshold. With 12 participants, only 2 responders are needed to claim statistical significance with a threshold of 2% for PTA response primary hypothesis testing. Statistical significance in the primary endpoint comparison was nearly certain given the data available at that time. When protocol and SAP version 3 were finalized, the applicant possessed at least 24-week data from 7 participants and was aware that more than 2 PTA responders and ABR responders were in the database. Thus, statistical significance in both endpoints according to the sponsor's revised SAP was guaranteed by that time.

Reviewer's Comment:

*The applicant claims that the hypothesis testing for the primary and key secondary endpoints was prespecified "ahead of any participants reaching the initially proposed 48-week primary analysis timepoint." Since CHORD is a single-arm study, it must be assumed that the applicant has full access to the study data and that data are continuously monitored. The applicant has not provided any evidence to the contrary. The assertion that the formal statistical hypothesis was "pre-specified" because the decision was made prior to a set date (such as any participant reaching 48-week) is an unsupported conclusion because pre-specification is a fundamental statistical principle for robust statistical inference. Furthermore, although final agreement on the general regulatory pathway was reached, many decisions were made by the applicant without prior discussion with the FDA. Given the totality of these circumstances, there was no Type I error control. Hence, I do not agree with the applicant's aforementioned claim. All results within this application should therefore be considered descriptive.*

## 5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

### 5.1 Review Strategy

As agreed prior to the BLA submission, 24-week data from the first 12 participants will be treated as the primary database. Thus, this review will focus on the first datasets submission on November 19, 2025 with data cutoff date of June 11, 2025. However, due to the data issues, updated data from the second datasets submission on December 23, 2025, with data cutoff date of November 18, 2025, will be used for the analysis of the primary datasets and for supportive analyses. The second datasets submission addressed the data issues in the first data submission but presented new data issues, which do not affect the primary efficacy evaluation in this review. Therefore, these data issues in the second datasets submission will not be addressed in this review and the datasets will be analyzed as submitted.

The additional analyses section (Section 6.1.11.5) of this review will discuss results from the second dataset submission, which was decided to be the primary database for this application during this BLA review. Relevant data issues will be discussed.

## 5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

Clinical study report, all versions of the CHORD study protocol, SAP versions 3, study datasets (SDTM and ADaM) for the primary database (12 participants 24-week follow-up) based on data cutoff date June 11, 2025, and the natural history dataset are located at: (b) (4) (STN 4).

Clinical study report addendum and study datasets (SDTM and ADaM) for all available data based on data cutoff date November 18, 2025, are located at: (b) (4) (STN 21).

In addition to the Module 5 contents mentioned above, this review is also based on Module 1 in both STN 4 and STN 21 and Module 2 in STN 21. There is no integrated summary of efficacy or safety as only one study in this clinical program. Therefore, Modules 2.7.3 and 2.7.4 are condensed to Module 2.5 in STN 21.

## 5.3 Table of Studies/Clinical Trials

This clinical program contains one study DB-OTO-001 (CHORD).

## 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

### 6.1 Study DB-OTO-001 (CHORD)

Study DB-OTO-001 (CHORD) is an ongoing first-in-human clinical trial for DB-OTO. The trial is designed to assess the safety and efficacy of DB-OTO in pediatric patients with profound hearing loss secondary to pathogenic OTOF pathogenic variants. The study description in this section is based on the most recent protocol (version 4), which contains one minor change from protocol version 3 regarding study drug storage temperature, and the most recent SAP (version 3). The data results in this section, except for additional analyses, are based on STN4 datasets with data errors corrected using updated data from STN21. Additional analyses are based on STN21 datasets as submitted, with data errors uncorrected.

#### 6.1.1 Objectives (Primary, Secondary, etc)

The primary objective of study DB-OTO-001 is to evaluate the safety and efficacy of DB-OTO in pediatric participants diagnosed with biallelic OTOF pathogenic variants. The secondary objective is to evaluate efficacy of DB-OTO in pediatric participants diagnosed with biallelic OTOF pathogenic variants in domains of hearing and age-appropriate speech perception.

#### 6.1.2 Design Overview

The DB-OTO-001 study is a first-in-human, multicenter, single-arm, two-part trial with a unilateral, dose escalation cohort (Part A) and a bilateral expansion cohort (Part B) to evaluate the safety, tolerability, and efficacy of DB-OTO in participants with profound deafness due to biallelic OTOF pathogenic variants. The study was originally designed as an open-label phase 1/2 trial primarily to evaluate the safety of DB-OTO and to

determine the optimal biological dose of DB-OTO. However, based on the preliminary efficacy data, especially the remarkable 48-week efficacy data from the first participant, the applicant revised the SAP to add hypothesis testing for the added primary and key secondary efficacy endpoints. Following consultation with health authorities, the protocol was also revised to become registrational.

The study design underwent several modifications during the study. In the original global protocol, in Part A, two dose cohorts (lower and higher doses) were planned, with staggered dosing (initially with a six-week stagger, which was then reduced to two weeks) to allow review of safety and efficacy data by the IDMC. At the time the protocol was amended to convert the study into a registrational study, all age cohorts in Part A had been enrolled and all planned IDMC meetings had occurred with no safety concerns raised. The IDMC therefore allowed continued unilateral dosing and recommended opening Part B with the first (lower) dose tested in Part A based on review of the safety and efficacy data.

#### 6.1.3 Population

This study enrolled infants ( $\leq 24$  months of age), children ( $> 24$  months to  $< 12$  years of age), and adolescents ( $\geq 12$  to  $< 18$  years of age) with biallelic, likely pathogenic or pathogenic OTOF variants and profound deafness ( $\geq 90$  dB HL) based on behavioral (PTA) and physiologic (ABR) measurements of inner ear function. In infants, outer hair cell presence was confirmed via presence of otoacoustic emissions ( $\geq 6$  dBSNR) at  $\geq 3$  frequencies from 1 to 8 kHz in the ear(s) to be treated with DB-OTO. For children and adolescents  $> 24$  months to  $< 18$  years of age, outer hair cell presence could be confirmed via presence of otoacoustic emission or the cochlear microphonic in the ear(s) to be treated with DB-OTO. Participants could not have a cochlear implant or history of having had an implant in the ear(s) to be infused with DB-OTO.

#### 6.1.4 Study Treatments or Agents Mandated by the Protocol

The frozen vial of DB-OTO was thawed for approximately 30 minutes at room temperature, then gently inverted-reverted five times and inspected to ensure there was no cloudiness, particulates, or color. If a dilution was required, a diluent vial was removed from  $4^{\circ}\text{C}$  storage and allowed to come to room temperature and then gently inverted-reverted five times. The investigational product was then withdrawn into the provided syringe and kept at room temperature. It had to be used within four hours of thawing. In the case of bilateral dosing, the investigational product was prepared at staggered intervals to ensure it was used within four hours of preparation.

DB-OTO was infused into the cochlea using a delivery system composed of a catheter, syringe, and syringe pump. The device used for the infusion was a repurposed catheter used for intravenous parenteral nutrition in premature infants.

DB-OTO was administered under general anesthesia as a single intracochlear infusion into the perilymph through the round window membrane, using standard cochlear implantation surgical approaches. The procedure involved creating a fenestration in the lateral semicircular canal to provide an exit path for displaced perilymph, followed by

careful insertion of a Vygon® catheter approximately 4 mm through a small opening in the round window membrane. Special care was taken to avoid suction near sensitive structures to prevent inner ear damage. The DB-OTO vector suspension was infused over 16 minutes at a fixed rate using a syringe pump, after which the catheter was slowly removed, and both the round window membrane and lateral semicircular canal fenestration were repaired with autologous grafts such as fascia, muscle, or bone pate. For bilateral treatments, the same procedure was repeated on the contralateral side.

#### 6.1.6 Sites and Centers

A total of 22 participants were enrolled at the first datasets submission with data cutoff date June 11, 2025. Ten of the participants were enrolled in the US at seven sites; eight in Spain at two sites; two in the United Kingdom (UK) at one site; and two in Germany at one site.

A total of 24 participants were enrolled at the second datasets submission with data cutoff date November 18, 2025. One additional participant was each enrolled in US and Germany.

#### 6.1.7 Surveillance/Monitoring

The trial has been monitored by an IDMC. Based on a review of the data, the IDMC can recommend early termination of the trial. If the trial is paused, the IDMC will review and make a recommendation to terminate or continue the trial.

If Regeneron (applicant) senior management determines that the stopping criterion has not been met, the applicant will continue the study and notify health authorities in the regions where the study is being conducted. If the applicant determines that the stopping criteria have been met, enrollment in the study will be stopped and the applicant will inform the regulatory/ethics committees in accordance with local regulatory requirements. If after stopping enrollment in the study, the applicant later determines it is appropriate to restart enrollment in the study, dosing of study drug will be resumed only after agreement with the investigator(s) and completion of regulatory procedures.

Dosing in the trial will be paused upon the occurrence of a clinical or laboratory adverse event (AE) or serious adverse event (SAE) that is Grade 3 or higher (as defined in the Common Terminology Criteria for Adverse Events [CTCAE] version 5.0 or more recent) that is considered related to study drug.

In case of an emerging AE or pattern of AEs related to DB-OTO, the IDMC may recommend a reduction in dose, halt the study, or make other changes in the study conduct. This will prompt a review by the applicant who will decide to implement, modify, or reject the recommendation. Applicable regulatory procedures will be adhered to as required by local laws in relation to any decisions related to a change in study conduct, temporary halt, study termination, or study restart.

#### 6.1.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint and several secondary efficacy endpoints are based on behavioral PTA, evaluating and determining hearing sensitivity including type of deafness (i.e., sensorineural versus conductive), category of hearing ability and deafness (normal, mild, moderate, severe, profound), and course of treatment (e.g., hearing aid, cochlear implant). The PTA endpoint evaluates the average of hearing sensitivity thresholds (measured in decibels) at the key speech frequencies (0.5, 1.0, 2.0, and 4.0 kHz). Different standardized procedures (visual reinforcement audiometry, conditioned play audiometry, and standard audiometry) were used to obtain reliable behavioral audiometry results based on the participant's developmental age.

Pure tone audiometry (PTA) is designed for measuring hearing sensitivity and assesses detection thresholds across sound frequencies. Lower thresholds indicate better hearing sensitivity (25 dB HL represents whisper detection), while higher thresholds indicate inability to detect even loud sounds (>90 dB HL represents the noise level of a gas-powered lawn mower).

A change from profound deafness (baseline in all participants) to behavioral PTA average of  $\leq 70$  dB HL represents a clinically meaningful change in hearing that typically obviates the need for cochlear implantation and enables natural hearing. Week 24 was selected for the primary efficacy endpoint in the first-step analysis for Region A, which includes US.

The key secondary endpoint is ABR to click (a brief broadband sound that activates a wide range of frequencies in the cochlea) at  $\leq 90$  dB nHL at week 24. ABR is an objective electrophysiological assessment that complements and supports the benefit seen with PTA. ABR evaluates the neural response to sound conveyed to the auditory nerve, brainstem, and midbrain using surface electrodes placed on the scalp.

ABR is used clinically to assess the integrity of the auditory pathway function, detect the potential site-of-lesion, and estimate hearing sensitivity in newborns/infants who cannot yet complete behavioral testing. Its complete absence is a hallmark finding in patients with profound deafness due to OTOF pathogenic variants.

As a key secondary endpoint, the ABR to click at  $\leq 90$  dB nHL was evaluated through the presence/restoration of wave V, a marker of auditory evoked neural function of the brainstem, that is absent in patients with OTOF deficiency. ABR equipment was claimed to be standardized across all participating sites, and all ABR results underwent quality control checks.

#### 6.1.9 Statistical Considerations & Statistical Analysis Plan

##### Analysis of Primary Efficacy Endpoints

Percentage of participants who achieved a hearing sensitivity threshold of  $\leq 70$  dB at Week 24 is proposed to be tested against the null response rate of 2% using a binomial exact test, based on participants who have completed Week 24 assessments (or discontinued prior to Week 24) at time of the first-step analysis for Region A, which includes US.



Percentage of participants who achieved a hearing sensitivity threshold of  $\leq 70$  dB at Week 48 is proposed to be tested against the null response rate of 2% using a binomial exact test, based on participants who have completed Week 48 assessments (or discontinued prior to Week 48) at time of the second-step (single-step for Region B) analysis for Region A.

Average PTA is computed as the average of available thresholds at the speech frequencies of 0.5, 1.0, 2.0, and 4.0 kHz at each visit. In cases where a threshold was not obtained (i.e., the participant did not reliably respond to sound at any level), the maximum stimulation level tested was used to calculate the average instead. Rate of average PTA threshold of  $\leq 70$  dB and corresponding exact 95% two-sided CI will be calculated by the Clopper-Pearson method.

#### Analysis of Key Secondary Efficacy Endpoints

Similar to the primary efficacy endpoint, the percentage of participants who achieved various hearing sensitivity thresholds ( $\leq 70$  dB,  $\leq 45$  dB, or  $\leq 25$  dB) at given timepoint by PTA and ABR to click will be summarized and is proposed to be tested against the null response rate of 2% for PTA and ABR using a binomial exact test. The point estimate and corresponding exact 95% two-sided CI will be calculated by the Clopper-Pearson method.

#### Multiplicity Adjustment

Hierarchical testing strategy is proposed to control the family-wise type I error rate of one-sided 0.025 for the primary and key secondary endpoints for Regulatory Region A and Regulatory Region B separately. The testing sequence is proposed as from the first-step analysis with Week 24 assessment for Region A to the second-step analysis with Week 48 assessment. Within each step, the testing sequence is proposed as from the primary endpoint of PTA to key secondary endpoint(s), ABR for the first-step analysis and ABR, PTA  $\leq 45$  dB, and PTA  $\leq 25$  dB for the second-step analysis.

#### Reviewer's Comment:

*There are multiple significant modifications of the study protocol and SAP during the study as detailed in Section 2.5 of this review. Per discussion in Section 3.2 of this review, type I error rate is not properly controlled despite the applicant's proposal, and thus only descriptive analysis results are discussed in this review.*

#### Analysis Populations

The Screened Analysis Set is comprised of all participants who were screened for eligibility in this study. It will be used for participation disposition analysis.

The Enrolled Analysis Set includes all participants who signed informed consent, met all inclusion and no exclusion eligibility criteria, and were considered eligible to receive DB-OTO. It will be used for demographic and baseline characteristics analysis.

The Safety Analysis Set is comprised of all participants who received DB-OTO regardless of age. It will be used for safety analysis.

Efficacy Evaluable Analysis Set is comprised of all participants, regardless of age, treated with DB-OTO and have at least one post baseline efficacy assessment, for the efficacy assessment of interest. This analysis set will be used for descriptive analyses of efficacy endpoints.

Reviewer's Comment:

*As discussed above, data from the first 12 participants and 20 participants constitute the primary databases for this review although more participants were enrolled and treated at the time of each data cutoff date, June 11 and November 18, 2025.*

Missing Data Handling

Participants treated bilaterally will use the better ear regarding hearing sensitivity by PTA and ABR response to click to determine the response status at a given timepoint. For analyses of responder endpoints, DB-OTO treated ears that later receive a cochlear implant before the analysis time (Week 24 for first-step analysis, and Week 48 for second-step analysis) will be considered non-responders. If participants withdraw from the study prior to Week 24/48 due to an AE or due to lack of efficacy, these participants will be considered as non-responders at Week 24/48, respectively.

For Week 24 or Week 48 PTA (or ABR) assessment, if participants miss the Week 24 or Week 48 PTA (or ABR) assessment but have a later PTA (or ABR) assessment, the participants' later PTA (or ABR) assessment will be used as the Week 24 or Week 48 PTA (or ABR) assessment.

Reviewer's Comment:

*In the applicant's analysis submitted, the only participant received a cochlear implant in DB-OTO treated ear had the assessments with the implant activated per protocol instruction and the average PTA was not produced. Furthermore, target date for each visit was specified in the SAP and the following instruction from SAP Section 11 Data Conventions is implemented:*

*If more than one assessment (scheduled or unscheduled) occurs within a single visit window, then the assessment closest to the target day will be used for analysis. If the 2 assessments are equidistant from the target day, then the assessment with the later date will be used for analysis.*

#### 6.1.10 Study Population and Disposition

##### 6.1.10.1 Populations Enrolled/Analyzed

A total of 25 participants were screened up to the time of the data cutoff for the first-step analysis on June 11, 2025; 3 (12%) failed screening. Of the 22 participants who were enrolled in the study, 20 received DB-OTO at the time of the first-step analysis: 10 participants were treated in one ear (unilaterally-dosed cohort, Part A) and 10 were

treated in both ears (bilaterally-dosed cohort, Part B). Two (2) participants were enrolled but not yet treated with DB-OTO at the time of the data cutoff on June 11, 2025.

In detail, of the 20 treated participants, 8 were excluded from the efficacy evaluable analysis set at Week 24 because they had not reached Week 24 at the time of this data cutoff. The remaining 12 participants (9 treated unilaterally and 3 treated bilaterally) were included in the Week 24 efficacy assessments. Four (4) participants from the unilateral cohort had completed Week 48 assessments at the time of the data cutoff on June 11, 2025.

#### 6.1.10.1.1 Demographics

Overall, the median age of the 20 participants was 2.2 years at the time of consent, with a range of 8 months to 16.3 years. At the time of dosing, the median age was 2.4 years, with a range of 10.3 months to 16.4 years. Nearly half of the participants were  $\leq 2$  years of age while 40.0% were between the ages of 2 and 7 years. Overall, most participants were female (65.0%) and White (70.0%), and 50.0% were Hispanic or Latino (i.e., originating from a Spanish-speaking country or culture, including people of Latin American descent, regardless of nationality). Participants who were treated unilaterally (Part A) were on average older (including three 16-year-olds), and predominantly female compared with participants treated bilaterally (Part B). Table 1 presents baseline demographics of the 20 treated participants in database with data cutoff date June 11, 2025.

**Table 1. Demographics – All Treated Participants**

	<b>Part A (Unilateral) N = 10</b>	<b>Part B (Bilateral) N = 10</b>	<b>Overall N = 20</b>
<b>Age at Treatment (years)</b>			
Median	3.4	1.5	2.3
Min: Max	0.9: 16.4	1.0: 4.6	0.9: 16.4
<b>Age at Treatment (months)</b>			
Median	40.9	17.8	27.4
Min: Max	10.3: 197.4	11.7: 55.6	10.3: 197.4
<b>Age Group (years), n (%)</b>			
$\leq 2$	3 (30.0%)	6 (60.0%)	9 (45.0%)
$>2$ to $<7$	4 (40.0%)	4 (40.0%)	8 (40.0%)
$\geq 7$ to $<12$	0	0	0
$\geq 12$	3 (30.0%)	0	3 (15.0%)
<b>Sex, n (%)</b>			
Male	2 (20.0%)	5 (50.0%)	7 (35.0%)
Female	8 (80.0%)	5 (50.0%)	13 (65.0%)
<b>Ethnicity, n (%)</b>			
Hispanic or Latino	7 (70.0%)	3 (30.0%)	10 (50.0%)
Not Hispanic or Latino	3 (30.0%)	7 (70.0%)	10 (50.0%)
<b>Race, n (%)</b>			
Asian	1 (10.0%)	2 (20.0%)	3 (15.0%)

	<b>Part A (Unilateral)</b> <b>N = 10</b>	<b>Part B (Bilateral)</b> <b>N = 10</b>	<b>Overall</b> <b>N = 20</b>
White	7 (70.0%)	7 (70.0%)	14 (70.0%)
Not Reported	2 (20.0%)	1 (10.0%)	3 (15.0%)

Source: Reviewer's Table

As presented in Table 2, the primary database of 12 participants presents similar demographics as those of the 20 treated participants. Ages at the time of dosing are presented, which are about 0 - 2.3 months later than age at consent and does not affect any participant's age group.

**Table 2. Demographics**

	<b>Part A (Unilateral)</b> <b>N = 9</b>	<b>Part B (Bilateral)</b> <b>N = 3</b>	<b>Overall</b> <b>N = 12</b>
<b>Age at Treatment (years)</b>			
Median	2.8	1.2	2.1
Min: Max	0.9: 16.4	1.0: 1.3	0.9: 16.4
<b>Age at Treatment (months)</b>			
Median	33.5	14.8	25.3
Min: Max	10.3: 197.4	11.7: 15.8	10.3: 197.4
<b>Age Group (years), n (%)</b>			
≤2	3 (33.3%)	3 (100.0%)	6 (50.0%)
>2 to <7	4 (44.4%)	0	4 (33.3%)
≥7 to <12	0	0	0
≥12	2 (22.2%)	0	2 (16.7%)
<b>Sex, n (%)</b>			
Male	2 (22.2%)	1 (33.3%)	3 (25.0%)
Female	7 (77.8%)	2 (66.7%)	9 (75.0%)
<b>Ethnicity, n (%)</b>			
Hispanic or Latino	6 (66.7%)	2 (66.7%)	8 (66.7%)
Not Hispanic or Latino	3 (33.3%)	1 (33.3%)	4 (33.3%)
<b>Race, n (%)</b>			
Asian	1 (11.1%)	1 (33.3%)	2 (16.7%)
White	6 (66.7%)	2 (66.7%)	8 (66.7%)
Not Reported	2 (22.2%)	0	2 (16.7%)

Source: Reviewer's Table

#### 6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Overall, the median age at which hearing loss was diagnosed was 5.5 months, with a range of 0 to 24 months. All participants had deafness in both ears as measured with PTA and ABR and had intact outer hair cell function in the treated ear as measured by distortion product otoacoustic emissions (DPOAE). No participant had tinnitus, temporal bone abnormalities, or vestibular manifestations.

As per the inclusion criteria, all participants had biallelic OTOF likely pathogenic or pathogenic variants of which 50% were compound heterozygous and 50% homozygous. Overall, all participants had variants that were interpreted as pathogenic or likely pathogenic in baseline genetic testing.

5 of 10 (50%) unilaterally-treated participants (Part A) had a cochlear implant at baseline, with the opposite ears being treated on study. In the bilaterally-treated group (Part B), 2 of 10 (20%) participants had hearing aids at baseline, but were taken off for the on-study assessments. The duration of use of assistive devices ranged from 72 days to almost 15 years. Overall, 7 (35%) participants had at least 1 medical history finding. Medical history was generally similar between the unilateral and bilateral treatment cohorts (Parts A and B, respectively).

Overall, 9 out of 20 (45%) participants had used at least one prior medication, i.e., medications that were used and stopped prior to dosing with DB-OTO. Four (20%) participants had used analgesics (paracetamol, fentanyl), and 3 (15%) participants had used at least 1 of the following: anesthetics (propofol), anti-inflammatory products (e.g., ibuprofen), psycholeptics (e.g., chloral hydrate), or antibacterials. All other types of prior medications had been used by no more than 2 (10%) participants. Table 3 presents baseline disease characteristics of the 20 treated participants in database with data cutoff date June 11, 2025.

**Table 3. Baseline Disease Characteristics – All Treated Participants**

	<b>Part A (Unilateral) N = 10</b>	<b>Part B (Bilateral) N = 10</b>	<b>Overall N = 20</b>
<b>Age at Diagnosis of Hearing Loss (months)</b>			
Median	11.5	1.0	5.5
Min: Max	0.0: 24.0	0.2: 24.0	0.0: 24.0
<b>Baseline Genetic Testing Zygosity, n (%)</b>			
Homozygous	6 (60.0%)	4 (40.0%)	10 (50.0%)
Heterozygous	4 (40.0%)	6 (60.0%)	10 (50.0%)
<b>Prior Assistive Device, n (%)</b>			
Yes	5 (50.0%)	2 (20.0%)	7 (35.0%)
No	5 (50.0%)	8 (80.0%)	13 (65.0%)

Source: Reviewer's Table

Selected baseline disease characteristics are presented below in Table 4 for the primary database of 12 participants. The characteristics are consistent with those of the 20 treated participants.

**Table 4. Baseline Disease Characteristics**

	<b>Part A (Unilateral) N = 9</b>	<b>Part B (Bilateral) N = 3</b>	<b>Overall N = 12</b>
<b>Age at Diagnosis of Hearing</b>			

	Part A (Unilateral) N = 9	Part B (Bilateral) N = 3	Overall N = 12
<b>Loss (months)</b>			
Median	12.0	2.0	9.5
Min: Max	0.0: 24:0	0.2: 5.0	0.0: 24.0
<b>Baseline Genetic Testing</b>			
<b>Zygosity, n (%)</b>			
Homozygous	5 (55.6%)	2 (66.7%)	7 (58.3%)
Heterozygous	4 (44.4%)	1 (33.3%)	5 (41.7%)
<b>Prior Assistive Device, n (%)</b>			
Yes	4 (44.4%)	1 (33.3%)	5 (41.7%)
No	5 (55.6%)	2 (66.7%)	7 (58.3%)

Source: Reviewer's Table

#### 6.1.10.1.3 Subject Disposition

All 20 treated participants are ongoing in the study: 12 (9 treated unilaterally and 3 treated bilaterally) have completed the Week 24 visit, and 4 (treated unilaterally) have completed the Week 48 visit. The median duration of follow-up (i.e., time from dosing with DB-OTO) for all participants is 28.8 weeks (ranging from 2 to 92 weeks). At the time of the data cutoff on June 11, 2025, the median duration of follow-up was longer for participants treated unilaterally (45.6 weeks overall, ranging from 19 to 92 weeks) than for participants treated bilaterally (14.5 weeks overall, ranging from 2 to 31 weeks).

Overall, a total of 13 important protocol deviations were documented for 10 (50%) participants. The most common types of important protocol deviations were deviations related to trial procedures (e.g., laboratory sample not taken or audiology assessment not done at a visit) or informed consent. The deviations related to re-consenting were due to site oversight that occurred once for each participant involved and were addressed at a subsequent visit. There were no protocol deviations related to handling of the investigational product.

#### 6.1.11 Efficacy Analyses

##### 6.1.11.1 Analyses of Primary Endpoint(s)

Table 3 presents the results on PTA response rates at Week 24. Out of 12 participants, 9 (75.0%; 95% CI: 42.8%, 94.5%) achieved the primary efficacy endpoint (PTA  $\leq$  70 dB HL) at Week 24.

**Table 5. Pure Tone Audiometry (PTA) Response Rates at Week 24**

	Part A (Unilateral) N = 9	Part B (Bilateral) N = 3	Overall N = 12
<b>PTA <math>\leq</math> 70 dB HL</b>			
n (%)	6 (66.7%)	3 (100.0%)	9 (75.0%)
95% CI	(29.9%, 92.5%)	(29.2%, 100.0%)	(42.8%, 94.5%)

Source: Reviewer's Table

There were 4 participants in Part A who received concomitant cochlear implant. One (1) out of 4 was in the same ear treated with DB-OTO due to lack of treatment effect. The other 3 received DB-OTO in the right ear and cochlear implant in the left ear; 2 of these were on the same day.

#### 6.1.11.2 Analyses of Secondary Endpoints

The key secondary endpoint, corresponding to the objective enablement of the neural pathway to sound (presence of ABR to a click stimulus [broadband sound] at  $\leq 90$  dB nHL at Week 24), was achieved by 9 of 12 participants (75%; 95% exact CI: 0.43, 0.95).

In addition to the primary efficacy endpoint, several secondary endpoints were based on behavioral PTA measurements at Week 24. Of note, 6 of 12 (50.0%) participants were able to hear sounds at the level of soft speech without an assistive device (average PTA of  $\leq 45$  dB HL) and 3 of 12 (25.0%) achieved normal hearing sensitivity (average PTA of  $\leq 25$  dB HL) and were able to hear sounds at the level of whispers after DB-OTO dosing.

**Table 6. Secondary Endpoints Response Rates at Week 24**

	<b>Part A (Unilateral) N = 9</b>	<b>Part B (Bilateral) N = 3</b>	<b>Overall N = 12</b>
<b>ABR <math>\leq 90</math> dB nHL</b>			
n (%)	7 (77.8%)	2 (66.7%)	9 (75.0%)
95% CI	(40.0%, 97.2%)	(9.4%, 99.2%)	(42.8%, 94.5%)
<b>PTA <math>\leq 45</math> dB HL</b>			
n (%)	4 (44.4%)	2 (66.7%)	6 (50.0%)
95% CI	(13.7%, 78.8%)	(9.4%, 99.2%)	(21.1%, 78.9%)
<b>PTA <math>\leq 25</math> dB HL</b>			
n (%)	2 (22.2%)	1 (33.3%)	3 (25.0%)
95% CI	(2.8%, 60.0%)	(0.8%, 90.6%)	(5.5%, 57.2%)

Source: Reviewer's Table

It should be noted that based on the data from 10 unilaterally-treated Part A participants, the opposite ear from that treated with DB-OTO showed no spontaneous hearing improvement in terms of PTA or ABR throughout the study. It corroborates the conclusion from the applicant's natural history study findings.

#### 6.1.11.3 Subpopulation Analyses

The applicant performed subgroup analyses on the primary endpoint to summarize treatment effect across the subgroups of age ( $\leq 2$ ,  $> 2$  to  $< 7$ , and  $\geq 12$  years old [there were no participants in the  $\geq 7$  to  $< 12$  subgroup]), use of cochlear implants in one ear prior to study (Yes/No), sex (male or female), ethnicity (Hispanic or non-Hispanic), race (Asian, White, and Not reported), and comorbidities (autism spectrum disorder, ear tube insertion, and myringotomy). There was no indication of an altered treatment effect in any of the subgroup categories summarized, however the numbers of participants per subgroup category were low. Selected subpopulation analyses are presented below.

**Table 7. Efficacy Endpoints Response Rates at Week 24 – Subpopulation**

	<b>N</b>	<b>n (%)</b>	<b>95% CI</b>
<b>Age Group (years), n (%)</b>			
≤2	6	5 (83.3%)	(35.9%, 99.6%)
>2 to <7	4	3 (75.0%)	(19.4%, 99.4%)
≥12	2	1 (50.0%)	(1.3%, 98.7%)
<b>Sex, n (%)</b>			
Male	3	2 (66.7%)	(9.4%, 99.2%)
Female	9	7 (77.8%)	(40.0%, 97.2%)
<b>Ethnicity, n (%)</b>			
Hispanic or Latino	8	7 (87.5%)	(47.3%, 99.7%)
Not Hispanic or Latino	4	2 (50.0%)	(6.8%, 93.2%)
<b>Race, n (%)</b>			
Asian	2	1 (50.0%)	(1.3%, 98.7%)
White	8	7 (87.5%)	(47.3%, 99.7%)
Not Reported	2	1 (50.0%)	(1.3%, 98.7%)

Source: Reviewer's Table

#### 6.1.11.4 Dropouts and/or Discontinuations

All participants remain on study. No participant permanently discontinued the study.

#### 6.1.11.5 Additional Analyses

The datasets submitted in STN 21 contain 24-week data from 20 participants with data cutoff date November 18, 2025. The baseline characteristics and efficacy results of these participants were presented in Tables 1 and 2, and were described above, as they coincide with the treated participants for the primary database with data cutoff date June 11, 2025.

The results on PTA and ABR response rates at Week 24 and Week 48 are presented in Tables 8 and 9, respectively. The results are consistent with the results from the primary database of 12 participants. Furthermore, the treatment effect appears to sustain through 48 weeks of follow-up.

**Table 8. Efficacy Endpoints Response Rates at Week 24 – Additional Analysis**

	<b>Part A (Unilateral) N = 10</b>	<b>Part B (Bilateral) N = 10</b>	<b>Overall N = 20</b>
<b>PTA ≤70 dB HL</b>			
n (%)	7 (70.0%)	9 (90.0%)	16 (80.0%)
95% CI	(34.8%, 93.3%)	(55.5%, 99.7%)	(56.3%, 94.3%)
<b>ABR ≤90 dB nHL</b>			
n (%)	7 (70.0%)	7 (70.0%)	14 (70.0%)
95% CI	(34.8%, 93.3%)	(34.8%, 93.3%)	(45.7%, 88.1%)
<b>PTA ≤45 dB HL</b>			
n (%)	4 (40.0%)	5 (50.0%)	9 (45.0%)
95% CI	(12.2%, 73.8%)	(18.7%, 81.3%)	(23.1%, 68.5%)
<b>PTA ≤25 dB HL</b>			
n (%)	2 (20.0%)	1 (10.0%)	3 (15.0%)



	<b>Part A (Unilateral)</b> <b>N = 10</b>	<b>Part B (Bilateral)</b> <b>N = 10</b>	<b>Overall</b> <b>N = 20</b>
95% CI	(2.5%, 55.6%)	(0.3%, 44.5%)	(3.2%, 37.9%)

Source: Reviewer's Table

Note: One participant did not have PTA assessment at Week 24 and was counted as non-responder

**Table 9. Efficacy Endpoints Response Rates at Week 48 – Additional Analysis**

	<b>Part A (Unilateral)</b> <b>N = 9</b>	<b>Part B (Bilateral)</b> <b>N = 3</b>	<b>Overall</b> <b>N = 12</b>
<b>PTA <math>\leq</math>70 dB HL</b>			
n (%)	7 (77.8%)	2 (66.7%)	9 (75.0%)
95% CI	(40.0%, 97.2%)	(9.4%, 99.2%)	(42.8%, 94.5%)
<b>ABR <math>\leq</math>90 dB nHL</b>			
n (%)	7 (77.8%)	2 (66.7%)	9 (75.0%)
95% CI	(40.0%, 97.2%)	(9.4%, 99.2%)	(42.8%, 94.5%)
<b>PTA <math>\leq</math>45 dB HL</b>			
n (%)	5 (55.6%)	2 (66.7%)	7 (58.3%)
95% CI	(21.2%, 86.3%)	(9.4%, 99.2%)	(27.7%, 84.8%)
<b>PTA <math>\leq</math>25 dB HL</b>			
n (%)	3 (33.3%)	2 (66.7%)	5 (41.7%)
95% CI	(7.5%, 70.1%)	(9.4%, 99.2%)	(15.2%, 72.3%)

Source: Reviewer's Table

Note: Per applicant's data errata, one bilaterally-treated participant's left ear PTA was assessed at Week 48 but not entered into the database prior to submission (STN 21). Based on applicant's report, this participant reached average PTA threshold 38.75 dB HL. Hence, one additional responder for PTA  $\leq$ 70 dB HL and  $\leq$ 45 dB HL in Part B.

#### 6.1.12 Safety Analyses

The safety database consists of two datasets from the DB-OTO-001 study: the first-step analysis dataset with data cutoff date June 11, 2025 and the contemporaneous larger second dataset with data cutoff date November 18, 2025. The first-step analysis dataset consists of 20 treated participants (30 treated ears) with a median duration of follow-up of 28.8 week (ranging 2 to 92 weeks). The second contemporaneous larger dataset included 4 additional treated participants (bringing it to a total of 24 treated participants and 38 treated ears), almost doubled the median follow-up duration (to 45.1 weeks ranging from 9 to 115 weeks) and the number of participants completing week 24 assessments (from 12 to 20 participants), and tripled the number of participants who completed week 48 assessments (from 4 to 12 participants). The safety profile based on this expanded dataset is consistent with that of the first-step analysis with no new safety signals.

The safety profile of DB-OTO in this first-in-human registrational study was favorable, with no treatment-related treatment emergent adverse events (TEAEs) identified. The majority of TEAEs were mild or moderate in intensity, transient, and consistent with events expected from the surgical procedure, general anesthesia, or common pediatric conditions. The safety profile in bilaterally-treated participants was generally similar to

that observed in unilaterally-treated participants. The two SAEs reported were considered unrelated to DB-OTO.

Vestibular system dysfunction events, identified as adverse events of special interest (AESIs), occurred in 25% (6/24) of participants but were mild or moderate, transient, and resolved without sequelae. No hypersensitivity or immune responses were observed, and there were no clinically meaningful changes in laboratory values, vital signs, or other safety assessments. There were no AESIs of potential perilymph leak from the round window opening and lateral canal fenestration.

#### 6.1.12.1 Methods

The safety analysis plan for DB-OTO included comprehensive evaluation of all safety parameters. All TEAEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC), preferred term (PT), severity, and relationship to treatment. Specific analyses included:

- AESIs of:
  - Vestibular system dysfunction following surgical delivery of DB-OTO
  - Suspected perilymph leak from the round window opening and lateral canal fenestration following surgical delivery of DB-OTO
- Laboratory parameter shifts from baseline to post-treatment time points
- Immunogenicity parameters and impact on safety outcomes

Descriptive statistical methods were used for safety analyses. The safety database will be continuously updated with emerging data from the ongoing DB-OTO-001 study, with periodic safety reports submitted to regulatory authorities.

#### 6.1.12.3 Deaths

There were no deaths in the study.

#### 6.1.12.4 Nonfatal Serious Adverse Events

Two participants (10%) experienced treatment-emergent SAEs that were considered unrelated to DB-OTO or to the surgical procedure:

- In a unilaterally-treated participant: Mastoiditis in the contralateral ear with a cochlear implant that was inserted during the same surgical procedure (onset on day 77, resolved in 17 days with antibiotic)
- In a bilaterally-treated participant: Gait disturbance (onset on day 38, related to a recent varicella vaccination, resolved in 3 days)

#### 6.1.12.5 Adverse Events of Special Interest (AESI)

Six participants (30%) experienced TEAEs classified as AESIs of vestibular system dysfunction following the surgical delivery of DB-OTO: Dizziness (3 participants, 15%), Nystagmus (2 participants, 10%), Balance disorder (1 participant, 5%), Dizziness postural (1 participant, 5%), and Procedural dizziness (1 participant, 5%). All vestibular dysfunction events were non-serious, mild, or moderate in intensity, and transient, resolving without sequelae. All but one event (Dizziness postural) were assessed as related to the study procedure.

There were no AESIs of potential perilymph leak from the round window opening and lateral canal fenestration.

## 10. CONCLUSIONS

### 10.1 Statistical Issues and Collective Evidence

This BLA is supported by 24-week data from 12 participants in an ongoing single-arm study DB-OTO-001 (CHORD), which was originally designed as an exploratory phase 1/2 study. Out of 12 participants, 9 (75%) achieved the primary efficacy endpoint (PTA  $\leq 70$  dB HL) at Week 24, reported to represent a hearing level that typically avoids the need for cochlear implantation and enables natural hearing. Additionally, 9 of 12 participants (75%) met the key secondary efficacy endpoint (ABR to click at  $\leq 90$  dB nHL). Six (6) participants achieved average PTA threshold  $\leq 45$  dB HL (ability to hear soft conversational speech level) and 3 participants experienced complete hearing normalization (PTA  $\leq 25$  dB HL, whisper-level hearing).

Additionally, database based on available data from the first 20 treated participants, who had reached Week 24 have been reviewed. Out of 20 participants, 16 (80%) had observed average PTA  $\leq 70$  dB HL at Week 24. In addition, 14 of 20 participants (70%) had ABR to click at  $\leq 90$  dB nHL. Nine (9) and 3 participants achieved average PTA thresholds  $\leq 45$  dB HL and  $\leq 25$  dB HL, respectively, at Week 24.

Based on preliminary efficacy data from the study, the applicant revised the SAP to introduce hypothesis testing for the primary and key secondary endpoints specified at that time. The protocol and SAP were subsequently amended to include the current plan for hypothesis testing. The timing of the analysis appears to have been selected arbitrarily based on convenience rather than pre-specified criteria. Although the subsequently imposed hypothesis testing appears reasonable on the surface, examination of the study conduct timeline and document amendments reveals that statistical significance was nearly guaranteed at the time of imposition. Consequently, valid inferential statistical conclusions cannot be drawn from this unplanned, post-hoc hypothesis testing framework.

### 10.2 Conclusions and Recommendations

The PTA and ABR efficacy endpoint results lack statistical robustness given that the applicant presumably continuously monitored this single-arm study and introduced hypothesis testing nearly a year after study initiation. In conclusion, the results presented in this BLA should be considered descriptive only and cannot be used to statistically infer efficacy of the investigational product DB-OTO. Therefore, this review does not include a recommendation regarding approval.