



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)
Division of Pharmacovigilance (DPV)**

PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM

From:	Deborah Thompson, MD, MSPH Medical Officer, Pharmacovigilance Branch 3 (PB3), DPV, OBPV, CBER, FDA
To:	Bo Liang, PhD Chair of the Review Committee Office of Therapeutic Products (OTP)
Through:	Jaspal Ahluwalia, MD, MPH Acting Division Director, DPV
Subject:	Review of Pharmacovigilance Plan
Sponsor:	Regeneron Pharmaceuticals, Inc.
Product:	DB-OTO (lunsotogene parvec)
Application Type / Number	BLA 125874/0
Proposed Indication	Treatment of patients with biallelic <i>OTOF</i> variant-associated hearing loss
Submission Date:	December 23, 2025
Action Due Date:	April 22, 2026

1 OBJECTIVE

The purpose of this review is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) submitted under original BLA 125874/0 based on the safety profile of DB-OTO (lunsotogene parvec). Our review will determine whether any safety-related studies such as Postmarketing Requirements (PMRs) are warranted, or if there will be any safety-related agreed upon studies as Postmarketing Commitments (PMCs), or if Risk Evaluation and Mitigation Strategies (REMS) are required for DB-OTO, should the indication for this product be approved. Please refer to the Appendix for the complete list of materials reviewed for this memorandum.

2 BACKGROUND

Congenital hearing loss affects one in 500 newborns with sequence variations in the *OTOF* gene causing 1-8% of congenital, non-syndromic hearing loss. (Ford, 2023) The *OTOF* gene encodes the protein otoferlin, which is a transmembrane protein involved in glutamate neurotransmitter release at inner hair cell ribbon synapses. (Santarelli, 2021) Lack of functional otoferlin results in an auditory synaptopathy due to defective synaptic transmission from normally functioning cochlear inner hair cells to the auditory nerve. (Azaiez, 2025) *OTOF*-related hearing loss has an autosomal recessive inheritance. (Azaiez, 2025)

Most patients with otoferlin-related hearing loss have severe to profound hearing loss with prelingual onset, although 10-15% may have atypical phenotypes including mild to moderate, progressive, and temperature-sensitive hearing loss. (Ford, 2023) There is no cure for *OTOF*-related hearing loss and early intervention is critical for speech and language development. (Azaiez, 2025) Hearing aids are typically not beneficial due to the underlying issue of auditory synaptopathy although cochlear implants may be beneficial since they bypass the dysfunctional synapse and directly stimulate the auditory nerve (Azaiez, 2025). Hearing loss in children can lead to worse outcomes in speech, language, education, social functioning, cognitive abilities, and quality of life. (Lieu, 2020)

3 PRODUCT INFORMATION

3.1 Product Description

Per the sponsor's draft U.S. package insert (USPI) Section 11, DB-OTO is a "dual adeno-associated virus serotype 1 (AAV1) gene therapy vector". The vector "utilizes an engineered hair cell-specific promoter derived from regulatory elements of myosin 15 (*Myo15*) to drive complementary DNA (*cDNA*) expression of human *OTOF* transcript variant 5 encoding isoform e of the otoferlin protein (*OTOF*). Lunsotogene parvec-xxxx is produced in human embryonic kidney cells by recombinant DNA technology."

The product is a sterile, aqueous suspension administered as a single dose (7.2×10^{12} vector genomes) by intracochlear infusion using the provided administration kit. Product excipients include sodium phosphate, sodium chloride, sucrose, and poloxamer 188.

3.2 Proposed Indication

The sponsor's proposed indication statement as submitted to the original BLA 125874/0 is "treatment of patients with biallelic *OTOF* variant-associated hearing loss." Proposed limitations of use include that "the safety and effectiveness of TRADENAME have not been evaluated in ears that have received cochlear implants since cochlear implants impact the structure of the inner ear."

OBPV defers to the product office on the final language for the indication statement. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon indication after FDA review.

4 PERTINENT REGULATORY HISTORY

This is an original BLA submission, and no patients have been treated with DB-OTO in the postmarket/commercial setting.

5 DESCRIPTION OF DB-OTO CLINICAL TRIAL SAFETY DATABASE

5.1 Clinical Study DB-OTO-001 (CHORD)

The clinical study safety data reviewed are from the Clinical Overview and Pharmacovigilance Plan submitted to STN 125874/0. OBPV defers to the product office on final review of the clinical database, including safety and efficacy outcomes, which will inform the final language in the USPI. Below is our *focused* review of the sponsor data initially submitted to the BLA, to inform decisions pertaining to pharmacovigilance planning, should this BLA 125874/0 be approved. Please refer to the package insert for the final clinical safety data.

The sponsor submitted data from the ongoing Phase 1/2 clinical study DB-OTO-001 (CHORD), which is first-in-human, multicenter, global, open-label, 2-part registrational trial with a unilateral, dose escalation cohort (Part A) and a bilateral expansion cohort (Part B). There is no control group (natural history benchmark). The study evaluated the safety, tolerability, and efficacy of DB-OTO administered by intracochlear infusion to participants aged <18 years of age with profound deafness due to biallelic *OTOF* pathogenic variants. The study was originally designed as a Phase 1/2 clinical trial, and the statistical analysis plan (SAP) was revised with pre-specified hypothesis testing for primary and key secondary endpoints based on preliminary efficacy data from the first participant.

The study plans to enroll 30 participants and follow them for 5-years post-infusion of DB-OTO. As of the first-step analysis (cut-off date of June 11, 2025), 20 participants had been dosed (10 who were unilaterally-treated and 10 who were bilaterally-treated), including twelve participants who completed the week 24 visit and four who completed the 48-week visit. The median duration of follow-up was 28.8 weeks. The first 20 participants had a median age of 2.4 years (range 10.3 months to 16.4 years) at dosing. A follow-up analysis was conducted when the first 12 participants completed 48-weeks of follow-up (data cut-off November 18, 2025). As of the follow-up analysis, a total of 24

participants had been dosed with DB-OTO (total of 10 unilaterally-treated and 14 bilaterally-treated participants); 20 participants had completed the week 24 visit and 12 completed the 48-week visit. The median duration of follow-up was 45.1 weeks.

5.2 Adverse events: Clinical Study DB-OTO-001 (CHORD)

First Data Analysis (data cut-off June 11, 2025):

- i) Most common AEs: Among the 20 participants who received a dose of DB-OTO, 18 (90%) experienced a treatment-emergent adverse event (TEAE). The most common MedDRA Preferred Terms (PTs) were Upper respiratory tract infection, vomiting, otitis media (6 each), nausea (5), dizziness (3), gait disturbance, hand-foot-and-mouth disease, nasopharyngitis, nystagmus, and rhinitis (2 each). Most TEAEs were mild or moderate in severity. No TEAEs were life-threatening or fatal, and none led to study discontinuation.
- ii) Serious AEs (SAEs): Two SAEs were reported, and both were considered by investigators as unrelated to DB-OTO or the surgical procedure: 1) mastoiditis (in contralateral ear that received cochlear implant; resolved after antibiotic treatment) and 2) gait disturbance (assessed in study as related to recent varicella vaccination; symptoms resolved within 3 days).
- iii) Deaths: None
- iv) Adverse events of special interest (AESIs): AESIs included vestibular system dysfunction and potential perilymph leak from the round window opening and lateral canal fenestration following surgical delivery of DB-OTO. Events related to vestibular dysfunction occurred in 6 participants, including dizziness (3), nystagmus (2), balance disorder, dizziness postural, and procedural dizziness (1 each). Vestibular events were nonserious, mild, or moderate in severity, transient, and resolved without sequelae. No cases of perilymph leak were reported as of the data cut-off.

Follow-up Data Analysis (data cut-off November 18, 2025):

The sponsor reported that the follow-up data analysis was consistent with the first data analysis with a cumulative TEAE incidence of 83.3% (20/24 participants). There were no life-threatening or fatal events reported. No TEAEs led to dose interruption or study discontinuation. No new AESIs or SAEs were identified in the follow-up analysis. No TEAEs of hypersensitivity or immune reactions were identified.

The sponsor concluded that no adverse reactions to DB-OTO were identified, and that DB-OTO is generally well-tolerated with an acceptable emerging safety profile.

Reviewer comment: Findings from clinical study DB-OTO-001 showed that most participants experienced TEAEs, which were mild to moderate in severity. Two SAEs were reported; one event of mastoiditis occurred in the contralateral ear that received a

cochlear implant and one event of gait disturbance was attributed by study investigators to a recent vaccination. Vestibular system dysfunction occurred in 25% (6/24) of participants; events were mild or moderate, transient, and resolved without sequelae. No TEAEs were life-threatening or fatal, and none led to study discontinuation. Please see the final USPI submitted by the sponsor for the final agreed upon language and safety data after FDA review.

6 SPONSOR'S PHARMACOVIGILANCE PLAN

The sponsor submitted a PVP (version 1, dated December 4, 2025) and revised PVP (version 3, dated February 20, 2026) proposing routine pharmacovigilance (PV) and a postmarketing, prospective, observational long-term follow-up (LTFU) study (Table 1). In addition, there is the ongoing clinical study DB-OTO-001 which is following clinical trial participants for 5-years post-DB-OTO infusion to assess long-term safety, efficacy, and durability. The sponsor did not propose enhanced pharmacovigilance activities or a REMS for DB-OTO.

Table 1. Summary of Sponsor's Pharmacovigilance Plan*

Type of Concern	Safety Concern	Proposed Action
Important identified risk	None	None
Important potential risk	Risks from the non-standard aspects of the surgical delivery Immunogenicity (Including cellular and humoral immunogenicity) Risk of germline transmission	<ul style="list-style-type: none"> • Routine pharmacovigilance activities • Postmarketing, prospective, non-interventional, observational study to characterize the long-term effectiveness and safety of patients of any age who receive at least one dose of DB-OTO will be conducted
Important potential risk	Risk of malignancy in relation to vector integration in the DNA of body cells	<ul style="list-style-type: none"> • Routine pharmacovigilance activities • Postmarketing, prospective, non-interventional, observational study to characterize the long-term effectiveness and safety of patients of any age who receive at

		least one dose of DB-OTO will be conducted <ul style="list-style-type: none"> • Comprehensive testing and analysis of tumor and surrounding tissue samples for reported malignancies, when possible
Missing information	Long-term effect Use in pregnancy and lactation	<ul style="list-style-type: none"> • Routine pharmacovigilance activities • Postmarketing, prospective, non-interventional, observational study to characterize the long-term effectiveness and safety of patients of any age who receive at least one dose of DB-OTO will be conducted

*Adapted from Table 2, Pharmacovigilance Plan (version 3), STN 125874/0.67, Module 1.16.

Reviewer comment:

OBPV defers to OTP for review of the ongoing study DB-OTO-001 for clinical trial participants.

The following IRs were sent regarding the sponsor's PVP:

DPV IR #1

We are reviewing your pharmacovigilance plan (PVP) submitted for DB-OTO BLA 125874/0 and have the following questions and comments:

- 1.) Important potential risk: Risk of malignancy in relation to vector integration in the DNA of body cells.

We note your PVP includes routine pharmacovigilance, which will be complemented with continued safety data collected in ongoing study DB-OTO-001 where all participants will be followed for a total of 5-years after administration of DB-OTO to assess long-term safety, efficacy, and durability. Considering the novel route of administration and potential risk of secondary malignancy for AAV-based therapies, please consider strengthening your proposed activities to monitor for the occurrence of malignancies, which could have a long latency.

- a.) Please propose a plan to assess the long-term risk of AAV associated malignancy in patients enrolled in DB-OTO-001. Long term follow up may be limited to annual focused assessment for potential treatment related events.
- b.) Please propose a step-wise approach including parameters to enhance the monitoring plan in the LTFU protocol and PVP to address a detected safety signal.
- c.) In case a patient develops a malignancy in the postmarket setting, please describe your plans for collection and testing of clinical specimens (e.g., tissue biopsy of tumor and non-tumor) for vector copy number, presence of transgene, and integration site analysis (ISA) to assess for possible insertional oncogenesis and to evaluate the potential causal role of DB-OTO.

2.) Important potential risk: Risks from the non-standard aspects of the surgical delivery

The PVP (p. 10) indicates that the surgical procedure will be performed in authorized treatment centers and that a commercial training plan will be implemented that is identical to the clinical training plan.

Please provide details regarding how treatment centers will be authorized, what criteria will be required for authorization, and how the commercial training plan will be implemented.

3.) Missing Information: There are no nonclinical or clinical data available to characterize the safety of DB-OTO in pregnant or lactating individuals. Please revise the PVP to include “use in pregnancy and lactation” as missing information or provide rationale for why use in pregnancy and lactation is not considered missing information.

Reviewer comment: The sponsor’s IR response (STN 125874/0.67, sequence 0068) acknowledged the Agency’s concerns regarding the potential risk of malignancy associated with AAV-based therapies and highlighted the following: 1) DB-OTO is administered at a relatively low dose compared to systemic gene therapies, 2) systemic distribution outside the ear is limited, and 3) DB-OTO uses a cell-selective promoter, myo15, that is only expressed in inner hair cells and would remain inactive in cells where the myo15 promoter is not expressed (i.e., cells other than inner hair cells). Furthermore, inner hair cells are not proliferating cells which lowers the risk of oncogenesis.

The sponsor proposes to extend monitoring for delayed onset of AAV-related AEs and will conduct a postmarketing, prospective, non-interventional, observational study to characterize the long-term effectiveness and safety of patients who receive DB-OTO. The study plans to enroll 50 patients globally who were treated in real-world clinical practice or who have completed the 5-year DB-OTO-001 study (target enrollment of

n=30 from study DB-OTO-001). The study will ask for patients to receive annual follow-up for up to a total of 10-years post-DB-OTO infusion. The LTFU plan includes detailed physical exams at each visit with annual assessments for malignancy; additional assessments will be required in the interventional study and requested in the observational study if any “abnormalities” are identified.

In the event a malignancy occurs following treatment with DB-OTO in the postmarket setting, the sponsor will attempt to obtain and analyze all relevant follow-up information including relevant family history, patient-specific or environmental risk factors, method of diagnosis, and interventions provided. Also, the sponsor will conduct comprehensive testing and analysis of tumor and tumor-adjacent tissues including vector copy number, integration site analyses, and whole genome sequencing (for assessment of other possible cancer driver mutations or structural variants), when feasible, to understand potential underlying mechanisms. Healthcare professionals who report a malignancy will be given instructions by the sponsor on obtaining informed consent and handling patient samples.

The sponsor’s IR response also outlined plans for how treatment centers will be authorized and activated to administer DB-OTO which includes the following requirements: 1) site capabilities verification (i.e., infrastructure and supplies to store, prepare, and administer product), 2) implementation of the commercial surgical training plan, 3) training on AE reporting, and 4) education on prescribing information and product handling. There will be a closed distribution system and only activated treatment centers will be allowed to order and administer DB-OTO. The sponsor anticipates activating fewer than 20 treatment centers across the U.S. in the first year.

The commercial surgical training plan will include in-person cadaveric model training, a walk-through demonstration for the multidisciplinary team and clinical pharmacy team members, a DB-OTO surgical training video, a DB-OTO surgical training slide deck, and the DB-OTO USPI (also see additional details below in Section 7.2.1 Risks from the non-standard aspects of the surgical delivery). The sponsor indicates the training plan also has criteria for re-training of surgeons based on time elapsed since the date of the most recent training and/or DB-OTO administration.

As requested, the sponsor submitted a revised PVP (version 3) with the IR response that includes the missing information category of “Use in pregnancy and lactation” and provides updates regarding the planned postmarketing observational LTFU study, plans to assess the risk of malignancy, and details regarding the commercial training program and treatment center authorization.

DPV IR #2

We are reviewing your revised Pharmacovigilance Plan and IR response submitted for DB-OTO (STN 125874/0.67) and have the following questions/comments:

- 1) We acknowledge your plans to conduct a postmarketing, prospective, non-interventional, observational study to characterize the long-term effectiveness and safety of patients who receive DB-OTO. Your proposed study will have a target enrollment of 50 patients globally, including an estimated 30 patients from clinical study DB-OTO-001 and the remaining patients will be those treated in real-world clinical practice. Patients will be followed annually for up to a total of 10-years post-DB-OTO infusion.

Please submit a draft or concept study protocol for your proposed postmarketing long-term follow-up study.

- 2) Should DB-OTO be approved, you will be required to perform enhanced pharmacovigilance for 3-years post-approval as follows:

Malignancies:

(i) Submit expedited (15-day) reports to FAERS for events of malignancy, regardless of seriousness or labeled status.

(ii) In your periodic safety reports, provide aggregate safety assessments (based on interval and cumulative postmarketing safety data) for the risk of malignancies. In your assessments, specify the data sources for reports of malignancy, i.e., clinical trial data, or data from postmarketing safety study(ies), or data from postmarketing spontaneous reports.

***Reviewer Comment:** The sponsor's IR response (STN 125874/0.83) committed to the requested enhanced pharmacovigilance. The sponsor also submitted an expanded synopsis for the proposed postmarketing LTFU study (see Section 6.1 below).*

6.1 Postmarketing Safety Study (DB-OTO-NSHL-2610)

The sponsor proposes to conduct a postmarketing study entitled "A post-authorization, prospective, non-interventional study on the long-term safety and effectiveness of DB-OTO." The primary objective is to characterize the long-term safety of DB-OTO in patients who receive at least one dose of DB-OTO. The primary study endpoints include the type and frequency of AEs, including procedure-related AEs, SAEs, other local AEs, unexpected auditory or vestibular AEs, malignancy, all-cause mortality, and pregnancy and lactation.

The secondary study objectives are to: 1) describe the effectiveness of DB-OTO in patients who receive at least one dose of DB-OTO in the post-marketing setting, 2) describe the durability of effect of DB-OTO in patients who receive at least one dose of DB-OTO, and 3) describe speech perception and production in patients who receive at least one dose of DB-OTO. An exploratory objective will assess educational outcomes of school-aged patients who receive at least one dose of DB-OTO.

The study plans to enroll a total of 50 patients over a 3-year period, including an estimated 30 patients from clinical study DB-OTO-001 and the remaining patients will be those treated in real-world clinical practice in accordance with country-specific prescribing information. Patients will be followed for up to a total 10-years post-DB-OTO treatment (10 years for patients receiving commercial DB-OTO and an additional 5 years for patients who complete the 5-year study DB-OTO-001).

The study is non-interventional and will not impose a treatment protocol, diagnostic/therapeutic procedures, or visit schedule. Data will be collected from electronic health records, medical notes, and hospital discharge files, including data from visits with otolaryngologists, primary care physicians, local/primary audiologists, and speech-language pathologists. Annual questionnaires will collect additional data from patients, parents/caregivers, treating physicians, and/or teachers. For malignancy, a detailed physical exam will be performed at each annual visit and may include medical history review, ear canal and middle ear status checks, hearing examination to detect hearing changes associated with potential intracochlear tumors or tumors in the ascending auditory system, neurological function, lymph node examination, and hepatosplenomegaly screening. If abnormalities are detected, then secondary assessments will be performed (or requested), including focused neurological examinations and laboratory tests, if performed as part of routine clinical care. Further assessments, such as imaging or diagnostic testing, will be based on clinical judgement due to the young age of patients. If a malignancy develops in the postmarket setting, the sponsor will aim to obtain and analyze all relevant follow-up information to conduct a thorough assessment, including comprehensive testing and analysis of tumor and surrounding tissue samples to understand potential underlying mechanisms.

The sponsor plans to implement an annual data analysis schedule with formal descriptive interim analyses once a predefined minimum sample size (e.g., $n \geq 10$) is reached. Each annual report will include descriptive summaries of baseline patient characteristics and key outcome measures. All descriptive analyses will be pre-specified in a statistical analysis plan.

The sponsor proposed the following study milestones:

Final protocol submission: August 31, 2026

Study completion date: December 31, 2039

Final study report submission: June 30, 2040

Reviewer comment: Please see Reviewer Comments in Section 6 of this memo (Sponsor's Pharmacovigilance Plan) for further details in the sponsor's IR response regarding investigation plans if a patient develops a malignancy in the postmarket setting. In addition, the sponsor commented that the LTFU postmarketing study sample size is based on disease incidence and anticipated postmarketing uptake of DB-OTO.

After discussion with the clinical team, it was determined that the sponsor's proposed postmarketing LTFU study would be recommended as a PMC study due to the novelty of the product with a dual AAV1 vector, novel intracochlear route of administration, small sample size and limited duration of follow-up in the clinical study, and emerging data from other AAV products regarding the potential risk of malignancies with AAV therapies. The postmarketing LTFU study was presented to the CBER Safety Working Group (SWG) on March 12, 2026, and SWG concurred with plans for a PMC. The sponsor was notified on March 20, 2026 and provided their agreement on March 31, 2026 (STN 125874, sequence 0098).

7 ANALYSIS OF SPONSOR'S PHARMACOVIGILANCE PLAN

7.1 Important Identified Risks

The sponsor's proposed PVP does not list any important identified risks.

Reviewer comment: Based on the safety data reviewed from study DB-OTO-001, it is acceptable for the PVP to not have important identified risks.

7.2 Important Potential Risks

7.2.1 Risks from the non-standard aspects of the surgical delivery

DB-OTO is administered via "intracochlear injection into the perilymph of each inner ear through the round window membrane using a surgical approach that is generally analogous to the well-established cochlear implant procedure." The PVP indicates that the "theoretical risk profile is expected to be broadly similar, including vertigo, dizziness, imbalance, tinnitus, cerebrospinal fluid leak, ipsilateral facial paresis, ipsilateral change in taste, meningitis, wound infection, mastoiditis, otitis media, numbness around ear, blood and fluid collection at surgical site, and labyrinthitis, as well as systemic events related to anesthesia, and sedation." In addition, potential risks from the surgical approach for DB-OTO include vestibular signs or symptoms or damage to the inner ear anatomy that could cause challenges and/or reduced therapeutic benefit if a cochlear implant is needed in the future. Safety data from clinical study DB-OTO-001 showed that 11 (55%) of 20 participants experienced procedure-related events which were non-serious, grade 1 or 2 in severity, had short latency, and resolved.

Specific differences in the surgical approach for DB-OTO as compared to cochlear implant surgery include that the catheter for DB-OTO is inserted 3-4 mm past the round window membrane rather than the 20-30 mm cochlear electrode implant lengths. The PVP indicates that while the shallower catheter placement might be less traumatic to cochlear structures, it's possible that trauma to cochlear structures could occur beyond the catheter length due to pressure from fluid as DB-OTO flows from the catheter through the cochlea. The sponsor indicates the risk of increased pressure is mitigated during the surgical procedure by the creation of a fenestration in the lateral semi-circular canal which provides a site of effusion for the perilymph and DB-OTO. While the fenestration could result in acute or chronic vestibular effects, the PVP states this risk is

“mitigated by the use of standard surgical repair techniques for canal dehiscence to close the fenestration and reduce the potential for third window abnormalities.”

In addition, the PVP indicates that if a cochlear implant is needed in the future, insertion of the electrode array might be more challenging and potential impacts on spiral ganglion neurons could theoretically affect the maximum potential benefit of a cochlear implant. The PVP states “these potential risks can be mitigated through proper surgical technique, surgical repair, and intraoperative monitoring, adjunct therapies and/or applicable rehabilitation.”

The important potential risks from non-standard aspects of the surgical delivery will be monitored through routine pharmacovigilance activities and a postmarketing, prospective, non-interventional, observational 10-year LTFU study. In addition, there will be a commercial training plan identical to the clinical training plan and the procedure will be performed in authorized treatment centers by physicians with formal education and clinical experience. Review of the sponsor’s “Use-Related Risk Analysis and Human Factors Justification” and sponsor’s IR response (STN 125874/0.67) revealed that training of clinicians will include the following:

- In-person cadaveric model training: Demonstration of the surgery using a cadaveric model in the context of a practical lab for one or more surgeons at each treatment center by a surgeon with prior experience in administering DB-OTO
- Walk-through demonstration for the multidisciplinary team (i.e., surgical team and others involved in dose prep) including use of the pump, catheter, and positioning of equipment during the surgical procedure
- DB-OTO surgical training video and transcript describing the surgical delivery of DB-OTO on a cadaveric model, including background of the anatomy, basics of the surgical approach, positioning of equipment in the operating room, the entire surgical procedure performed on a cadaveric model, and preparation of the syringe pump
- DB-OTO surgical training slide deck, including DB-OTO mechanism of action, storage and handling, syringe preparation, pump operation, equipment positioning in the operating room, illustrated steps of the surgical procedure, and key best practices
- Regeneron-led surgical training opportunities at regular, planned intervals for surgeons at treatment centers
- USPI and additional training resources that will include information from the clinical study surgery and pharmacy manuals
- Surgeons will be deemed “experienced” if they have performed at least one dosing and are able to train their peers with support from Regeneron, if needed

The sponsor also proposes routine risk communication via the USPI:

- Section 1, Indications and Usage, including limitations of use
- Section 2, Dosage and Administration
- Section 5, Warnings and Precautions for Procedure-Related Risks
- Section 6, Adverse Reactions

- Section 13.2, Animal Toxicology and/or Pharmacology
- Section 16, How Supplied/Storage and Handling

Reviewer comment: The sponsor's proposed PVP is appropriate to monitor the potential risks from the non-standard aspects of the surgical delivery.

7.2.2 Immunogenicity (including cellular and humoral immunogenicity)

The PVP indicates that the theoretical risk of immunogenicity for DB-OTO is considered “very low” since DB-OTO will be locally administered in the inner ear with limited systemic exposure and the cochlea is relatively immune privileged. The sponsor reports that DB-OTO was designed under the regulation of a hair cell-specific promoter which presents a lower risk of off-target expression and immune reactions compared to systemically administered gene therapies and those with “ubiquitous promoters.” In addition, prophylactic corticosteroids are administered on the day of infusion and for 2-weeks post-infusion with a 2-week steroid taper. In study DB-OTO-001, pre-screening for anti-AAV antibodies was not necessary for eligibility, and the sponsor did not identify any effects of immunogenicity on safety or efficacy. There were no clinically detectable allergic reactions or other immune-mediated AEs reported.

The important potential risk of immunogenicity will be monitored through routine pharmacovigilance activities and a postmarketing, prospective, non-interventional, observational 10-year LTFU study.

In addition, risk mitigation will include communication via the USPI:

- Section 2 Dosage and Administration (prophylaxis against inflammatory and immunological responses by administration of prophylactic corticosteroids)
- Section 12.6 Immunogenicity

Reviewer comment: OBPV defers to OTP for review of immunogenicity data submitted by the sponsor for study DB-OTO-001. The sponsor's proposed PVP is appropriate to monitor the potential risk of immunogenicity.

7.2.3 Risk of malignancy in relation to vector integration in the DNA of body cells

Vector-based gene therapies have the theoretical risk of vector integration leading to malignancy. However, AAV vectors are generally thought to not have a propensity to modify the genome or integrate/modify the genome at very low frequencies. The recommended duration for LTFU is up to five years for AAV vectors (FDA Guidance for Industry, Long Term Follow-Up After Administration of Human Gene Therapy Products, January 2020). The PVP indicates that while there is limited clinical evidence of low-frequency, random integration of AAV into the human genome following systemically administered gene therapies, no causal relationships have been identified for tumorigenicity.

DB-OTO is locally administered via the cochlea with low systemic exposure and specifically targets inner hair cells which have lower mitotic potential than target cells for other gene therapies. The PVP indicates the theoretical risk of tumorigenesis is considered “very low.” Study DB-OTO-001 did not report any AEs for neoplasms,

benign, malignant, or unspecified. In addition, the sponsor reports that non-clinical biodistribution and toxicology studies in mice and cynomolgus monkeys using equivalent or higher total doses of DB-OTO relative to body weight did not detect macro- or microscopic pathological findings in any tissues nor signs of abnormal cellular growth or tissue hyperplasia.

The important potential risk of malignancy in relation to vector integration in the DNA of body cells will be monitored through routine pharmacovigilance activities and a postmarketing, prospective, non-interventional, observational 10-year LTFU study which will be an agreed upon PMC study. In addition, the sponsor has committed to enhanced pharmacovigilance with expedited reporting to FAERS for any cases of malignancy and aggregate safety assessments for the risk of malignancy in periodic safety reports. If a malignancy develops in the postmarket setting, the sponsor will aim to obtain and analyze all relevant follow-up information to conduct a thorough assessment, including comprehensive testing and analysis of tumor and surrounding tissue samples to understand potential underlying mechanisms.

In addition, the sponsor proposes routine risk communication via the USPI:

- Section 13.1, Carcinogenesis, Mutagenesis, and Impairment of Fertility (no animal studies have been performed to evaluate carcinogenicity or mutagenesis)

Reviewer comment: Please see Section 6 of this memo for the sponsor's IR response regarding the important potential risk of malignancy in relation to vector integration in the DNA of body cells and plans for follow-up if a malignancy develops in the postmarket setting following treatment with DB-OTO. The sponsor's proposed PVP is appropriate to monitor the potential risk of malignancy in relation to vector integration in the DNA of body cells.

7.2.4 Risk of germline transmission

The PVP reported that non-clinical data in mice and non-human primates at dose concentrations 2-fold higher than the clinical dose showed limited evidence for vector distribution to the gonads, and there was no detectable hOTOF mRNA nor DB-OTO-related gross or microscopic findings in male or female gonads. The sponsor concluded that "vector distribution to gonads is highly unlikely in the clinical setting."

Study DB-OTO-001 excluded females of childbearing potential if they were pregnant, breastfeeding, or planning to become pregnant at any time during the short-term (48-week) study period. Study participants also agreed to use a highly effective contraception method and females agreed not to become pregnant during the 48-week short-term follow-up period and males agreed to not father a child or donate sperm for the 48-week short-term follow-up period (or for at least 12-months in case of early study withdrawal). Pregnancy testing was routinely conducted at standardized intervals during the study; no pregnancies were reported during study DB-OTO-001. The draft USPI indicates there are no clinical data in pregnant women, and that animal reproductive and developmental toxicity studies have not been conducted and recommends that negative pregnancy status should be verified before administration of DB-OTO.

The important potential risk of germline transmission will be monitored through routine pharmacovigilance and a postmarketing, prospective, non-interventional, observational 10-year LTFU study.

In addition, the sponsor proposes routine risk communication via the USPI:

- Section 8, Use in Specific Populations
- Section 12.3, Pharmacokinetics

Reviewer comment: The sponsor's proposed PVP is appropriate to monitor the potential risk of germline transmission.

7.3 Important Missing Information

7.3.1 Long-term effect

The long-term safety and efficacy of DB-OTO is not known, and the median duration of follow-up for clinical trial participants in study DB-OTO-001 is 28.8 weeks. Study DB-OTO-001 is ongoing and will follow participants for 5-years to assess long-term safety, efficacy, and durability of treatment with DB-OTO. In addition, missing information on the long-term safety of DB-OTO will be monitored through routine pharmacovigilance activities and a postmarketing, prospective, non-interventional, observational 10-year LTFU study.

In addition, the sponsor proposes routine risk communication via the USPI:

- Section 6, Adverse Reactions
- Section 14, Clinical Studies

Reviewer comment: The sponsor's proposed PVP is appropriate to monitor for missing information on the long-term safety of DB-OTO.

7.3.2 Use in Pregnancy and Lactation

There are no non-clinical or clinical data on the use of DB-OTO in pregnant or lactating individuals. Please see Section 7.2.4 for Risk of germline transmission regarding exclusion criteria in study DB-OTO-001 for pregnant or breastfeeding females.

Missing information on use of DB-OTO in pregnancy and lactation will be monitored through routine pharmacovigilance activities and a postmarketing, prospective, non-interventional, observational LTFU study. In addition, this missing information is labeled in Section 8, Use in Specific Populations, including Section 8.1 Pregnancy, Section 8.2 Lactation, and Section 8.3 Females and Males of Reproductive Potential.

Reviewer comment: The sponsor's proposed PVP is appropriate to address missing information on the use of DB-OTO during pregnancy and lactation.

8 DPV ASSESSMENT

Based on review of available data, the safety concerns from the ongoing Phase 1/2 clinical study DB-OTO-001 can be monitored through routine pharmacovigilance, enhanced pharmacovigilance, and a postmarketing, prospective, non-interventional,

observational 10-year LTFU study (DB-OTO-NSHL-2610) which will be an agreed upon PMC. If a malignancy develops in the postmarket setting, the sponsor aims to obtain and analyze all relevant follow-up information to conduct a thorough assessment, including comprehensive testing and analysis of tumor and surrounding tissue samples (i.e., vector copy number, integration site analyses, and whole genome sequencing) to understand potential underlying mechanisms. In addition, study DB-OTO-001 will continue to follow participants for 5-years to assess long-term safety, efficacy, and durability of treatment with DB-OTO. Furthermore, the risks of treatment with DB-OTO will be mitigated through risk communication and risk minimization measures as recommended in the USPI.

The review team has determined that no FDAAA Title IX safety PMR studies are warranted based on the available safety data. Furthermore, the sponsor does not propose a REMS due to the absence of a specific safety concern and considering the expected benefit to patients with very limited treatment options for a serious condition, the small size of the patient population expected to be treated, and the anticipated small number of highly specialized treatment centers that will administer the product. The review team agrees that a REMS is not necessary to ensure the benefits of the product outweigh the risks.

9 DPV RECOMMENDATIONS

Should the product be approved for the treatment of patients with biallelic *OTOF* variant-associated hearing loss, the sponsor's proposed PVP (version 3, dated February 20, 2026) is adequate to monitor the postmarketing safety for DB-OTO which will include:

1. Routine PV, which includes AE reporting in accordance with 21 CFR 600.80.
2. Enhanced PV for 3-years post-approval to require expedited (15-day) reporting of malignancies (regardless of seriousness or label status) following licensure. The sponsor will also provide aggregate safety assessments of the risk of malignancies in periodic safety reports, including specifying the data sources for any reports of malignancies (i.e., clinical trial data, data from postmarketing safety studies, or data from postmarketing spontaneous reports).
3. Agreed upon postmarketing PMC study: Postmarketing, prospective, non-interventional, observational 10-year LTFU study (DB-OTO-NSHL-2610) to assess the long-term safety of DB-OTO. The study plans to enroll 50 patients of any age with hearing loss who receive at least one dose of DB-OTO, including patients from the DB-OTO-001 clinical study and patients from the real-world setting.

In addition, clinical study DB-OTO-001 is ongoing and will follow participants for 5-years to assess long-term safety, efficacy, and durability of treatment with DB-OTO. OBPV defers to OTP for review of clinical study DB-OTO-001.

At this time, there are no postmarketing safety-related PMR studies. The review team determined that a REMS is not necessary for DB-OTO. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon content and language.

REFERENCES

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APPENDIX

Materials Reviewed

Table A1: Materials reviewed in support of this assessment

Date	Source	Document Type	Document(s) Reviewed
December 11, 2025	Sponsor	STN 125874/0.14	Module 1.16.1, Pharmacovigilance Plan (version 1)
November 6, 2025	Sponsor	STN 125874/0.0	Module 1.14, Draft Labeling Text
December 23, 2025	Sponsor	STN 125874/0.21	Module 2.5, Clinical Overview
December 11, 2025	Sponsor	STN 125874/0.13	Module 5.3.5.4 Use-Related Risk Analysis and Human Factors Justification
February 20, 2026	Sponsor	STN 125874/0.67	Module 1.11.3, IR Response to DPV IR #1
February 20, 2026	Sponsor	STN 125874/0.67	Module 1.16.1 Pharmacovigilance Plan (version 3)
March 11, 2026	Sponsor	STN 125874/0.83	Module 1.11.3, IR Response to DPV IR #2 and Module 5.3.6 Expanded synopsis for DB-OTO-NSHL-2610