Summary Basis for Regulatory Action

Date:	April 22, 2026
From:	Bo Liang, PhD, Review Committee Chair Division of Gene Therapy 1 (DGT1) Office of Gene Therapy (OGT) Office of Therapeutic Products (OTP)
BLA STN:	BLA 125874/0
Applicant:	Regeneron Pharmaceuticals, Inc.
Submission Receipt Date:	December 23, 2025
***CNPV Action Date:**	April 23, 2026
****PDUFA Goal Date:**	August 23, 2026
Proper Name:	lunsotogene parvec-cwha
Proprietary Name:	OTARMENI
Indication:	For the treatment of pediatric and adult patients with severe-to-profound and profound sensorineural hearing loss (HL; any frequency >90 dB) associated with molecularly confirmed biallelic variants in the *OTOF* gene, preserved outer hair cell function, and no prior cochlear implant in the same ear.

* CNPV = Commissioner's National Priority Voucher

** PDUFA = Prescription Drug User Fee Act

Recommended Action: The Review Committee recommends approval of this product.

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Director, Office of Clinical Evaluation/Office of Therapeutic Products

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Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
Regulatory	Helen Sansone, CBER/OTP/ORMRR Rachel Blasdell, CBER/OTP/ORMRR
CMC • CMC Product (Product Office and OCBQ/DBSQC) • CMC Device • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC) • CMC Bioinformatics (Product Office)	Bo Liang, PhD, CBER/OTP/OGT (Chair/Lead Reviewer) Mark Verdecia, PhD, CBER/OTP/OGT Meghna Thakur, PhD, CBER/OTP/OGT Bizunesh Abere, PhD, CBER/OTP/OGT Tania Rosen-Cheriyan, PhD, CBER/OTP/OGT Zachary Mandell, PhD, CBER/OTP/OGT Zhili Xu, PhD, CBER/OTP/OGT Stella Lee, PhD, CBER/OTP/OGT Lauren Kokai, PhD, CBER/OTP/OCTHT Johnny Lam, PhD, CBER/OTP/OCTHT Viviana Ramirez, CBER/OCBQ/DMPQ Carl Perez, CBER/OCBQ/DMPQ Yen Phan, CBER/OCBQ/DBSQC/LMIVTS Esmeralda Alvarado Facundo, PhD, CBER/OCBQ/DBSQC Hsiaoling Wang, PhD, CBER/OCBQ/DBSQC George Kastanis, MS, CBER/OCBQ/DBSQC Yongwook Choi, PhD, CBER/OTP/OCTHT/DCT1
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Nonclinical Pharmacology/Toxicology • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology	Kate Dabirsiaghi, VMD, CBER/OTP/OPT Lara Abramowitz, PhD, CBER/OTP/OPT
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Labeling • Promotional (OCBQ/APLB) • USPI Review	Benjamin Cyge, PhD, CBER/OCBQ/DCM/APLB Hanah Pham, CBER/OCBQ/DMPQ Afsah Amin, MD, MPH, CBER/OTP/OCE/DCEGM
Other Reviews not captured above categories, for example: • Consults (CMC Biostats) • Consult (CDRH)	Ho-Hsiang Wu, PhD, CBER/OBPV/DB/DNCE Joyce Lin, PhD, CDRH/OPEQ/OHT1 Sunny Park, PhD, CDRH/OPEQ/OHT1 Jullian Socea, PhD, CDRH/OPEQ/OHT3

• Consult (Human Factors)	Jake Lindstrom, CDRH/OPEQ/OHT3 Hanniebey D. Wiyor, PhD, FCIEHF, RAC CDRH/OPEQ/OHT3C Tania Reina, CDRH/OHT1/DHT1B/ENT

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1. Introduction

Regeneron Pharmaceuticals, Inc. submitted a Biologics License Application (BLA), STN 125874/0, for licensure of lunsotogene parvec-cwha with the proprietary name OTARMENI, under the Commissioner's National Priority Voucher (CNPV) pilot program, which provides for an expedited BLA review timeline. OTARMENI is indicated for the treatment of pediatric and adult patients with severe-to-profound and profound sensorineural hearing loss (any frequency >90 dB) associated with molecularly confirmed biallelic variants in the *OTOF* gene, preserved outer hair cell function, and no prior cochlear implant in the same ear. This document summarizes the regulatory basis for accelerated approval of OTARMENI.

OTARMENI and the Administration Kit are a cross-labeled combination product consisting of a biological product (gene therapy) and product delivery devices. OTARMENI is a dual adeno-associated virus serotype 1 (AAV1) vector-based gene therapy containing an entire coding sequence of human otoferlin (*OTOF*) gene and is delivered via intracochlear infusion at a nominal dose of 7.2×10^{12} vg in a volume of 0.24 mL per ear. It is expected to result in expression of the *OTOF* gene in inner hair cells (IHCs), which facilitates production of functional otoferlin protein and restores synaptic transmission to the auditory nerve.

The Applicant has provided substantial evidence of effectiveness to support accelerated approval of OTARMENI using average pure tone audiometry (PTA) improvement at week 24 as an intermediate clinical endpoint reasonably likely to predict clinical benefit based on a single adequate and well-controlled clinical investigation, Study DB-OTO-001, with confirmatory evidence[1]. Study DB-OTO-001 is an ongoing single-arm, open-label Phase 1/2 study assessing the safety and efficacy of OTARMENI in 24 pediatric patients with *OTOF*-associated profound hearing loss in pediatric patients with molecularly confirmed *OTOF* gene-associated profound sensorineural hearing loss with preserved outer hair cell function. In this study, all patients received OTARMENI at the dose of 7.2×10^{12} vg in a volume of 0.24 mL per ear as a single intracochlear infusion. Ears with cochlear implants were excluded from treatment. Twenty (20) patients [Intention-to-Treat (ITT) population, 10 unilateral and 10 bilateral treatment groups] received treatment in either one or both ears during a single surgical session. Of the 20 patients with available efficacy data at week 24 post-administration, 16 (80%) achieved an average PTA threshold ≤70 dB hearing level (HL), indicating improved hearing sensitivity, and 14 (70%) had auditory brainstem response (ABR) to a click stimulus of ≤90 dB normalized Hearing Level (nHL) indicating restored auditory nerve function. These results represent significant improvement from baseline (profound hearing loss, >90 dB) to conversational and loud speech level, when compared to the natural history of *OTOF*-related hearing loss, in which there is no spontaneous improvement over time in hearing without intervention.

PTA improvement at week 24 post-product administration demonstrates a short-term benefit in this chronic disease, which is considered an intermediate clinical endpoint

[1] Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence Guidance for Industry DRAFT GUIDANCE, at https://www.fda.gov/media/172166/download

(ICE) reasonably likely to predict a long-term clinical benefit of sustained hearing improvement along with speech and language development. A Postmarketing Requirement (PMR)[2], to be completed within 3-4 years post-approval, in Study DB-OTO-001 will verify this benefit over a longer follow up duration by assessing durability of hearing improvement (based on PTA assessment) along with treatment effects on clinical measures of speech development and quality of life.

Confirmatory evidence includes mechanistic evidence from nonclinical studies in the Otof-Q828X homozygous mouse demonstrating dose-dependent improvements in ABR and sustained otoferlin protein expression post-OTARMENI administration. Natural history data[3] from over 200 patients consistently demonstrate that individuals with *OTOF*-HL do not experience hearing improvement over time without intervention. These data serve as confirmatory evidence supporting the substantial evidence of effectiveness of OTARMENI for this patient population.

The safety database includes 24 patients treated in Study DB-OTO-001 who were followed over a median duration of 45.1 weeks (range 9 - 115 weeks). Ten patients received unilateral treatment, and 14 patients received bilateral treatment for a total of 38 treated ears. Treatment-emergent adverse events (TEAEs) were reported in 20 of 24 patients (83.3%), with the majority being mild (54%) or moderate (21%) in severity. The most common TEAEs included otitis media, vomiting, nausea, dizziness, procedural pain, gait disturbance, nystagmus, balance disorder, abnormal otoacoustic emissions, and wound dehiscence. These events were generally transient and resolved without sequelae.

The demonstrated benefit of OTARMENI on PTA improvement supported by improved ABR is substantial compared to the expected outcomes based on natural history data demonstrating persistent profound hearing loss with no intervention. The observed risks were mild-moderate, transient, and non-serious. Therefore, we conclude that the demonstrated benefits with OTARMENI outweigh the observed risks. The Applicant committed to conduct an observational study as a Postmarketing commitment (PMC) to assess the theoretical risk of oncogenesis associated with AAV-based gene therapy products, and long-term safety of OTARMENI. Overall, the benefit-risk assessment is favorable and supports approval.

The safety and effectiveness of OTARMENI at the tested dose is extrapolated to adult patients with *OTOF*-HL given: 1) the well-established mechanism of action of OTARMENI which targets the underlying molecular mechanism of the disease, and which is expected to have similar treatment effects across all ages; and 2) the similarities of the natural history of untreated *OTOF*-HL across all ages.

The BLA was presented to the CNPV Review Council on April 17, 2026. The council after deliberation unanimously agreed with the recommendation of the review team, to

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[2] Accelerated Approval and Considerations for Determining Whether a Confirmatory Trial is Underway Guidance for Industry DRAFT GUIDANCE; https://www.fda.gov/media/184831/download

[3] Ford CL, Riggs WJ, Quigley T, Keifer OP Jr, Whitton JP, Valayannopoulos V. The natural history, clinical outcomes, and genotype-phenotype relationship of otoferlin-related hearing loss: a systematic, quantitative literature review. Hum Genet. 2023 Oct;142(10):1429-1449. doi: 10.1007/s00439-023-02595-5. Epub 2023 Sep 7. PMID: 37679651; PMCID: PMC10511631.

grant accelerated approval for OTARMENI based on favorable benefit-risk profile. The council also concurred with the review team's recommendation for expansion of indication to include adults and the multiple CMC and clinical regulatory flexibilities that were exercised.

Regulatory Flexibility

OTOF-HL is a rare and serious genetic disease with a high unmet medical need for disease-modifying treatments that improve long-term clinical outcomes. In this therapeutic context, regulatory flexibility in the review and approval decision of OTARMENI is warranted to allow early access to this novel product. FDA exercised regulatory flexibility across review disciplines, including clinical, CMC, and device as detailed below:

1. Acceptance of a single adequate and well-controlled clinical investigation in a small number of pediatric patients (N=24) using the established natural history for comparison of treatment effects on hearing sensitivity and auditory nerve function.
2. Use of an intermediate clinical endpoint, PTA improvement over 24 weeks post-administration which is reasonably likely to predict clinical benefit on sustained improvement in hearing sensitivity, speech and quality of life in *OTOF*-HL under the accelerated approval provisions.[4] Verification of clinical benefit will be assessed as a PMR in already treated and additional patients over longer follow up.
3. Acceptance of a small safety database of 24 patients as sufficient to inform the product's safety assessment with a PMC to collect long-term safety data in an observational study[5].
4. Extrapolation of safety and effectiveness to adult patients with *OTOF*-HL based on established extrapolation principles and the scientific understanding of both the disease and the product.
5. Acceptance of relatively wide commercial lot release acceptance criteria based on data from limited number of lots that were available because of rare disease indication. The Applicant commits to re-assessing lot release acceptance criteria as a PMC. This approach aligns with FDA's January 11, 2026, announcement "Flexible Requirements for Cell and Gene Therapies to Advance Innovation."
6. Acceptance of a drug product shelf-life set based on a conservative extrapolation of limited stability data that are available, because of expedited clinical development. This approach aligns with FDA's draft guidance "Q1 Stability Testing of Drug Substances and Drug Products" dated June 2025[6].
7. Acceptance of labeling and secondary packaging validation conducted using (b) (4) vials, not the OTARMENI drug product, because the (b) (4) study can help to ensure product quality during labeling and secondary packaging.

[4] Expedited Programs for Serious Conditions — Accelerated Approval of Drugs and Biologics Guidance for Industry Draft Guidance, accessible at https://www.fda.gov/media/184120/download
[5] Long Term Follow-up After Administration of Human Gene Therapy Productshttps://www.fda.gov/media/113768/download
[6] Q1 Stability Testing of Drug Substances and Drug Products; https://www.fda.gov/media/187161/download

8. Acceptance of setting the (b) (4) acceptance limits in the drug product manufacturing process based on testing of a subset of quality attributes without potency. The Applicant commits to re-assessing the (b) (4) limits with a complete set of quality attributes, including potency, as a PMC.
9. Acceptance of the validation of (b) (4) assay for (b) (4) without assessment of robustness considering overall adequate assay performance. The Applicant commits to assessing assay robustness as a PMC.
10. Acceptance of potency assurance by measuring otoferlin (b) (4) by the product and ensuring undetectable otoferlin (b) (4) in the product. This flexibility is needed because of the difficulty in developing a bioassay that directly measures the biological activity of otoferlin.
11. Collection of additional infusion pump use and safety information in the post-market setting. This flexibility is exercised to capture the variety of commercial syringe infusion pumps.

2. Background

OTOF-associated hearing loss (*OTOF*-HL) is a genetic form of hearing loss caused by biallelic variants in the *OTOF* gene which encodes the protein otoferlin. Otoferlin mediates synaptic vesicle fusion in inner hair cells (IHCs) and synaptic transmission from inner hair cells to the auditory nerve. In *OTOF*-HL, while outer hair cells detect sound normally, defective/absent otoferlin impedes sound transmission to the auditory nerve resulting in HL of sensorineural origin.

OTOF-HL is a rare, congenital, non-progressive condition with an incidence of 50 cases per 3.6 million births (CDC, 2024) in US. Affected patients present with non-syndromic (isolated) sensorineural hearing loss, typically severe to profound (>70 dB). Delayed diagnosis and treatment can result in patients missing the critical period for speech and language development which occurs in early childhood. The diagnosis is based on genetic testing and audiometric assessments, including otoacoustic emissions (OAE) which measures outer hair cell function, pure tone audiometry (PTA) which assesses hearing sensitivity to different sound intensities, and auditory brainstem response (ABR) which assesses auditory nerve transmission.

There are no FDA-approved pharmacologic therapies for *OTOF*-HL. Traditional hearing aids are not effective for *OTOF*-HL due to the underlying auditory synapse dysfunction. Cochlear implant, a device, is the only approved therapeutic option for *OTOF*-HL as it works by bypassing the dysfunctional synapse, and directly stimulating the auditory nerve, but does not modify the underlying condition. Cochlear implant devices are approved for children as young as 9-12 months old. However, cochlear implants do not restore normal hearing but provide a different sound representation. Patients with cochlear implants often struggle with background noise, music appreciation, and sound localization. Additionally, the devices have MRI restrictions, are not waterproof, require daily power management, and are susceptible to electromagnetic interference and physical damage. Device-related limitations associated with cochlear implantation and the inability to reproduce natural hearing leave an unmet need for therapies that restore physiological auditory function.

Natural history data from over 200 patients with *OTOF*-HL consistently demonstrate that no hearing improvement occurs over time without intervention. These data serve as the comparator to the clinical study efficacy data.

PTA is the gold standard, established clinical assessment for diagnosis and characterization of hearing as it directly evaluates a patient's hearing sensitivity and characterizes the degree of hearing loss when present. As a direct measure of hearing, it is an appropriate assessment of the efficacy of OTARMENI. Given the short duration of follow up (24 weeks) after product administration in the clinical study, it is unclear whether hearing restoration at different dB sound levels continues over time and whether this clinical measure reflects long-term hearing restoration with resultant improvement in speech development and quality of life, which represent clinical benefits. As early childhood represents the optimal window for speech development, hearing improvement/ restoration in children, the population studied in the OTARMENI clinical program, are expected to result in clinical benefit. However, even if speech improvement or development are not expected with hearing restoration in adulthood, a positive effect on hearing will result in improvement in activities of daily life. Therefore, demonstration of hearing restoration at Week 24 in both children and adults with *OTOF*-HL is appropriate as an early clinical measure (intermediate clinical endpoint) that is reasonably likely to predict an effect on irreversible morbidity (profound HL with associated effects on daily life) in the long-term. As a condition of accelerated approval, the Applicant will further evaluate hearing restoration (via PTA assessment and clinical measures of speech and quality of life) in the ongoing study and in additional newly treated patients over longer follow up at 2 years (104 weeks) as a post-marketing requirement to verify and describe the clinical benefit of OTARMENI.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Pre-IND meeting	September 17, 2020
2. Rare Pediatric Disease designation granted	July 28, 2021
3. Orphan Drug designation granted	August 11, 2021
4. IND submission	September 15, 2022
5. Fast Track designation granted	August 21, 2023
6. Regenerative Medicine Advanced Therapy Designation granted	July 5, 2024
7. Pre-BLA meeting	May 5, 2025
8. CNPV Pilot Program Entry Grant Letter issued	October 29, 2025
9. BLA Rolling Submission #1 (CMC)	November 6, 2025
10. BLA Rolling Submission #2 (Clinical)	November 19, 2025
11. BLA Rolling Submission #3 (CMC)	November 25, 2025
12. BLA Rolling Submission #4 (Nonclinical)	December 11, 2025
13. BLA Rolling Submission #5 (CMC)	December 19, 2025
14. BLA Rolling Submission #6 (Clinical; Complete BLA Receipt Date)	December 23, 2025
15. BLA filed with Priority Review designation	February 21, 2026
16. CNPV BLA Action Date	April 23, 2026
17. PDUFA Goal Date	August 23, 2026

3. Chemistry, Manufacturing, and Controls (CMC)

Based on the review of the information provided in the initial submission and the subsequent amendments, the CMC review team concludes that the manufacturing and controls for OTARMENI are acceptable for commercial manufacturing under the BLA.

a. Product Quality

Manufacturing Summary
OTARMENI contains dual adeno-associated virus serotype 1 (AAV1) vectors that recombine after administration. The recombined vector genome utilizes an engineered hair cell specific promoter derived from regulatory elements of myosin 15 (*Myo15*) to drive the expression of the human *OTOF* transcript variant 5 encoding isoform e of the otoferlin protein (OTOF). The drug product contains two vector drug substances, i.e., DB-OTO-3 and DB-OTO-5, (b) (4) formulated in phosphate buffer with excipients in a 2 mL (b) (4) vial. Each vial contains an extractable volume of 0.63 mL, for single dose administration to one ear.

The two separate vectors in OTARMENI are produced in compliance with Current Good Manufacturing Practice (CGMP) requirements by transient transfection (b) (4) human embryonic kidney 293 cells (HEK 293) (b) (4) bioreactor and purified using affinity chromatography, anion exchange chromatography, and (b) (4) filtration. To manufacture the drug product, two drug substances are combined at the target concentration of 3.0×10^{13} vector genomes/mL, and filter sterilized. Drug product vials are shipped to a labeling facility to complete labeling and packaging prior to commercial distribution.

Manufacturing Control Strategy
To ensure product safety, identity, strength, purity, and potency, the CGMP manufacturing process is controlled by setting limits for (1) raw material and reagent qualification, (2) in-process monitoring and in-process control testing, (3) process validation, (4) test method validation, and (5) lot release tests. The Applicant performed innovative process characterization studies using small-scale models that determined the critical process parameters (CPPs) for process qualification and validation studies.

Process Validation
The manufacturing process was validated through production of (b) (4) successful drug substance process performance qualification (PPQ) lots and (b) (4) PPQ drug product lots at commercial scale. Process consistency will continue to be monitored and assessed post-approval through an established continued process verification (CPV) plan. Product-related and process-related impurities are controlled through in-process tests and lot release tests, with acceptable limits based on safety data from clinical lots.

Stability
(b) (4) drug product must be stored frozen at -80°C. The shelf life is (b) (4) for drug substance and 18 months for drug product. OTARMENI is light sensitive; extended exposure to light should be limited.

Comparability
All 24 patients in clinical study DB-OTO-001 received drug products manufactured with the clinical manufacturing process. The commercial manufacturing process introduces several modifications, including changes to the (b) (4) . The commercial manufacturing process was determined to produce drug product with critical quality attributes comparable to the clinical process, including statistically equivalent (b) (4) content and potency.

Manufacturing Risks, Potential Safety Concerns and Management
Key manufacturing risks are appropriately mitigated:

- Microbial/viral contamination: Controlled through (b) (4)
- Extractables and leachables: Analytical studies and toxicology risk assessment demonstrate negligible risk.
- Product defects: Controlled through 100% visual inspection and lot release testing.

CMC PMCs

Several product quality concerns were identified but could not be resolved during the BLA review cycle. To allow patient access, these issues will be resolved through PMCs outlined in Section 11.c. Briefly, the Applicant committed to further assess: (b) (4) after long term storage, the potency assurance strategy, maximum (b) (4) for drug product manufacturing and labeling operations, and lot release specifications as additional manufacturing information is obtained.

b. Testing Specifications

OTARMENI drug product commercial lot release specification is shown in Table 2.

Table 2: OTARMENI Drug Product Release Specification

Attribute Categories	Quality attributes	Methods	Acceptance Criteria
General	Appearance: Clarity	(b) (4)	(b) (4)
General	Appearance: Color		Colorless
General	Appearance: Physical Form and Condition		Essentially free from visible
General	pH		(b) (4)
General	Extractable Volume		(b) (4) 0.63 mL minimum withdrawable content
General	(b) (4)		(b) (4)

Attribute Categories	Quality attributes	Methods	Acceptance Criteria
Identity	(b) (4)		
Identity	(b) (4)		
Purity	Particulate Matter: (b) (4)	(b) (4)	
Purity	Particulate Matter: (b) (4)	(b) (4)	
Purity	(b) (4)		
Purity	(b) (4)		
Purity	Poloxamer 188	(b) (4)	0.001(b) (4) (% w/v)
Purity	(b) (4)		
Strength	Vector Genome Titer	(b) (4)	
Strength	(b) (4)		
Potency	(b) (4)		
Potency	Potency by (b) (4)		
Safety	Sterility	(b) (4)	No growth
Safety	Endotoxin	(b) (4)	

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of OTARMENI, activities performed, and inspectional histories are listed below in Table 3. One inspection (DP primary labeling and packaging facility) was conducted in support of the BLA and confirmed satisfactory facility compliance. Review of this BLA included comprehensive evaluation of recent inspection findings from all other facilities to determine suitability for the product. Based on this evaluation, facility re-inspections were waived as recent inspections demonstrated acceptable outcomes with either an NAI

classification with no Form FDA 483 issued, or VAI classification with adequate corrective actions resolving all Form FDA 483 observations.

Table 3. Manufacturing Facilities for OTARMENI

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification/ Results
(b) (4) *DS and DP manufacture, DP release testing*	(b) (4)		Waiver	CBER/DMPQ PLI (b) (4) VAI
(b) (4) *DP release testing*			Waiver	OII/DBTI Surveillance (b) (4) VAI
(b) (4) *DP release testing*			Waiver	OII/DBI Surveillance (b) (4) NAI
(b) (4) *DP release testing*			Waiver	ORA/OPQO Surveillance (b) (4) VAI
Regeneron Pharmaceuticals, Inc. (b) (4) *DP release testing*			Waiver	ORA/OPQO Surveillance (b) (4) VAI
(b) (4) *DP release testing*			Waiver	OII/DHADI Surveillance (b) (4) NAI
(b) (4) *DP release testing*			Waiver	OII/DBI Surveillance (b) (4) VAI

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification/ Results
(b) (4) *DP primary labeling and packaging*	(b) (4)		PLI	CBER/DMPQ PLI (b) (4) VAI
(b) (4) *Administration kit assembly, labeling and packaging*	(b) (4)		Waiver	OII/DMDRHI Surveillance (b) (4) NAI

Acronym key: DBI – Division of Biologics Inspectorate; DBTI – Division of Biotechnology Inspectorate; DHADI - Division of Human and Animal Drug Inspectorate; DS – drug substance; DMDRHI - Division of Medical Device and Radiological Health Inspectorate; DMPQ – Division of Manufacturing and Product Quality; DP – drug product; OII – Office of Inspections and Investigations; OPQO – Office of Pharmaceutical Quality Operations; ORA – Office of Regulatory Affairs; NAI – No Action Indicated; PLI – Pre-license Inspection; VAI – Voluntary Action Indicated.

e. Container/Closure System

The container closure system for OTARMENI DP consists of a 2-mL (b) (4) vial (b) (4) made from (b) (4), 13-mm chlorobutyl elastomeric stopper with (b) (4) and a 13-mm lacquered aluminum seal with a blue flip-top button (b) (4) (b) (4) performed the container closure integrity testing (CCIT) at the (b) (4) facility, employing the (b) (4) test method; all acceptance criteria were met.

f. Combination Product

This combination product was reviewed in consultation with CDRH. Both OHT1 and OHT3 provided 4 consultation memos including discussion of labelling strategy.

OTARMENI (biologic constituent) and the Administration Kit (device constituent) are a cross-labeled biologic-led combination product. The Administration Kit contains 510(k) cleared components and includes a 21-gauge needle (K021475), 1 mL syringe (K162081), 3 mL syringe (K182589), and Vygon Premicath® 1Fr/28G catheter (K954302/K041468). Only the syringe cap was 510(k) exempt. The Administration Kit is packaged, labeled, and shipped separately from the drug product vial due to different requirements for storage conditions and is labeled "USE ONLY WITH OTARMENI." The Administration Kit will be marketed exclusively with OTARMENI and not for use with any other therapeutic. Both packages bear National Drug Code numbers with the same labeler and product codes and include the United States Prescribing Information (USPI), which contains device-related instructions for use. Administration of OTARMENI also requires use of a commercially available syringe infusion pump provided by the treating institution. The USPI employs a general labeling approach specifying required pump performance parameters (0.9 mL/hour flow rate, capability to infuse volumes as small as

0.2 mL, compatibility with 1 mL or 3 mL syringes). This general labeling strategy was reviewed in consultation with CDRH/OHT3.

The Vygon Premicath® catheter, originally cleared for intravenous use, was bridged for intracochlear delivery through design verification testing data submitted in the BLA and reviewed in consultation with CDRH/OHT1. To assure catheter adequacy for the new intracochlear route of administration, additional testing was conducted by Regeneron to demonstrate that the catheter could safely navigate the surgical approach to the round window membrane without kinking or buckling, withstand the forces of insertion into cochlear tissue, and maintain a leak-tight seal with the syringe assembly under the pressures required for controlled infusion. The Applicant's comprehensive bridging studies included catheter (b) (4) testing through anatomical models simulating worst-case (b) (4) scenarios, (b) (4) testing to ensure the catheter would not collapse during insertion, syringe-catheter assembly (b) (4) testing at (b) (4) (b) (4) , verification of critical catheter dimensional specifications (b) (4) (b) (4) and biocompatibility testing for tissue/bone contact, all performed on (b) (4) samples after simulated shipping conditions. FDA's review confirmed that all design verification testing met predetermined acceptance criteria with zero failures across (b) (4) test samples, the clinical trial demonstrated successful drug delivery to all 24 treated patients with no catheter-related adverse events or device malfunctions, and the catheter maintained its essential performance characteristics throughout its validated (b) (4) month shelf life.

g. Environmental Assessment

The Applicant submitted an environmental assessment (EA) pursuant to 21 CFR part 25. The Agency determined that approval of OTARMENI will have no significant environmental impact.

4. Nonclinical Pharmacology/Toxicology

Nonclinical pharmacology studies were conducted in Otof-Q828X hom (homozygous) mice, a model of OTOF-related deafness that recapitulates the human phenotype with profound hearing loss and absent ABRs. OTARMENI was studied under the name of DB-OTO in nonclinical studies. Single intracochlear administration of DB-OTO at dose levels ranging from 1.6×10^{10} to 1.5×10^{11} vg/ear resulted in dose-dependent improvements in ABR thresholds. At the highest dose level, mean improvements reached 45-55 decibels (dB) in the mid-frequency range, with the majority of mice achieving thresholds within the normal range. This functional recovery in ABR correlated with otoferlin protein expression in IHCs and was sustained through the last assessment at 30 weeks, demonstrating mechanistic evidence of effect and durable therapeutic benefit.

Biodistribution studies showed local cochlear retention of DB-OTO with minimal systemic exposure in Otof-Q828X hom mice and cynomolgus monkeys. DB-OTO vector DNA was sustained in temporal bone samples through the last study endpoint at 90 days in mice and 27 weeks in monkeys, while systemic distribution was transient with rapid clearance from plasma and CSF. hOTOF mRNA expression was restricted primarily to cochlear

tissue, with minimal, transient expression in non-otic neural tissues and no detectable expression in reproductive tissues.

Single-dose toxicology studies were conducted in Otof-Q828X hom mice and cynomolgus monkeys. The intended clinical route of administration, intracochlear injection via the round window membrane, was used in adult mice and monkeys, while a posterior semicircular canal injection was used in juvenile mice. The 2-month GLP study in adult mice, and the 3-month GLP study in juvenile mice, at dose levels up to 1.3×10^{11} vg/ear showed no DB-OTO-related adverse findings, with a no observed adverse effect level (NOAEL) of 1.3×10^{11} vg/ear. The 6-month GLP study in monkeys at dose levels up to 4.4×10^{12} vg/ear demonstrated no DB-OTO-related toxicity, with a NOAEL of 4.4×10^{12} vg/ear. Based on dose scaling by concentration (vg/mL), which is appropriate for local delivery intended to replace the perilymph volume, these NOAELs provide safety margins of approximately 2.2-fold (mice) and 2.4-fold (monkeys) relative to the proposed clinical dose concentration. All observed adverse findings were attributed to the surgical procedure.

Developmental and reproductive toxicity, genotoxicity, and carcinogenicity studies were not conducted with DB-OTO. These studies were not warranted based on the intracochlear route of administration, limited systemic exposure, target patient population, and absence of safety concerns in the toxicology studies.

5. Clinical Pharmacology

The Clinical Pharmacology evaluation of OTARMENI in Study DB-OTO-001 includes the assessments of systemic distribution of vector DNA in plasma, the shedding of vector DNA in saliva, urine, and stool, and the immunogenicity of OTARMENI in serum.

Vector Distribution and Shedding

Systemic distribution of OTARMENI vector DNA in plasma and vector shedding in different matrices including saliva, urine, and stool over time in participants after unilateral (study Part A) and bilateral (study Part B) administration of OTARMENI. A qPCR assay was used for these assessments.

Samples were collected at baseline, Day 1, Weeks 2, 4, 6, 12, 24, and 36 following OTARMENI administration. Vector DNA was detected in plasma, saliva, urine, and stool samples Day 1 after treatment. Vector DNA became undetectable in plasma, saliva, and urine samples at Week 2 and in stool samples at Week 12 after treatment. Peak concentration was observed at Day 1 after OTARMENI administration and declined thereafter.

The risk for transmission from treated patients to untreated individuals is low.

Immunogenicity

Immunogenicity assessments include anti-AAV1 neutralizing antibody and anti-OTOF (protein) antibody from baseline through Week 12 post-treatment. The association between these immunogenicity profiles and clinical outcomes were also evaluated.

Primary immunogenicity assessment was based on data from 15 patients. A total of 12/15 (80%) and 1/15 (6.7%) patients had anti-AAV1 neutralizing antibodies and anti-OTOF antibody at baseline (titer <1,000), respectively. All patients developed anti-AAV1 neutralizing antibody responses through Week 12, with 10/15 (66.7%) having titer >10000, 3/15 (20.0%) having titer 1000 to 10000, and the rest having titer <1000. A total of 7/15 (46.7%) patients developed anti-OTOF antibody responses through Week 12, with 6 (40%) had titer <1000 and 1 (6.7%) had titer between 1000 and 10000.

Based on the efficacy results and immunogenicity profiles in all 15 participants, there is no observed impact of anti-AAV1 neutralizing or anti-OTOF antibody on efficacy outcomes of OTARMENI.

6. Clinical/Statistical

a. Clinical Program

The safety and effectiveness of OTARMENI was evaluated in Study DB-OTO-001, a global[7], open label, single arm, Phase 1/2 clinical study evaluating OTARMENI in 24 patients with *OTOF*-related hearing loss with a median age of 2.3 years (range 10.3 months to 16.4 years). All patients had biallelic variants in *OTOF*, profound sensorineural hearing loss (>90 dB), preserved outer hair cell function, and no prior cochlear implant in the same ear as OTARMENI administration. Out of the 24 patients, 10 received one dose of OTARMENI (unilateral administration) and 14 received two doses (one in each ear; bilateral administration). All patients received the same nominal dose of 7.2×10^{12} vg in a volume of 0.24 mL per ear administered as a single intracochlear infusion.

b. Efficacy Evaluation

The primary efficacy endpoint was the number (proportion) of patients who achieved a hearing sensitivity threshold of ≤70 dB HL assessed by average PTA at Week 24 and the key secondary efficacy endpoint was the number of patients who achieved ABR to click stimuli at ≤90 dB nHL at week 24. Additional efficacy assessments included the number (proportion) of patients who achieved the ability to hear soft conversational speech (PTA ≤45 dB HL) and those who achieved hearing thresholds in the normal range (PTA ≤25 dB HL).

Out of 24 patients, 20 patients (ITT population) had completed 24-week assessments and comprised the efficacy population and of those, 10 received unilateral and 10 received bilateral OTARMENI treatment. Results on PTA and ABR were compared to the natural history of *OTOF*-HL where no improvement is expected in either test without intervention.

- At Week 24, 16 out of 20 patients (80%; 95% CI: 56.3%, 94.3%) achieved an average PTA threshold ≤70 dB HL, enabling them to hear conversational and loud speech. Response rates were similar across patients treated unilaterally and bilaterally, with seven out of 10 (70%) of unilaterally treated patients and nine out

[7] Study DB-OTO-001 was conducted in 7 US and 4 ex-US sites.

of 10 (90%) of bilaterally treated patients achieving this threshold. Nine out of 20 patients (45%; 95% CI: 23.1%, 68.5%) achieved the ability to hear soft conversational speech (≤45 dB HL), and 3 out of 20 patients (15%; 95% CI: 3.2%, 37.9%) achieved hearing thresholds in the normal range (≤25 dB HL), demonstrating the ability to hear whispers. Additionally, 14 out of 20 patients (70%; 95% CI: 45.7%, 88.1%) demonstrated presence of ABR to a click stimulus of ≤90 dB nHL at Week 24, reflecting restoration of auditory nerve function.

- At Week 48, 12 patients were evaluated. This included nine patients who responded at Week 24 and maintained their response at Week 48.
  One additional patient who had not responded at Week 24 achieved an average PTA threshold ≤70 dB HL by Week 48, resulting in 10/12 (83%) patients achieving this threshold by Week 48. Of the 12 patients, three received bilateral treatment. All three achieved PTA primary efficacy threshold (≤70 dB HL), while two out of three had presences of ABR.

c. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) inspection assignments were issued for one foreign and two domestic clinical investigators that participated in the conduct of Protocol DB-OTO-001. The inspections did not reveal significant issues that impact the data submitted in this original BLA.

d. Pediatrics

OTARMENI has orphan drug designation for the treatment of *OTOF*-related hearing loss and is exempt from Pediatric Research Equity Act (PREA) pediatric study requirements. The single adequate and well-controlled clinical study was conducted in pediatric patients.

e. Other Special Populations

The efficacy of OTARMENI has not been studied in any other special populations.

7. Safety and Pharmacovigilance

The safety of OTARMENI was evaluated in 24 pediatric patients in the ongoing Study DB-OTO-001 with median follow-up of 45.1 weeks (range 9-115 weeks) after OTARMENI administration. There were no deaths and no study discontinuations due to adverse events. Treatment-emergent adverse events (TEAEs) were reported in 20 of 24 patients (83.3%), with the majority being mild (54.2% of patients) or moderate (20.8% of patients) in severity. TEAEs were transient and included otitis media (38%), vomiting (33%), nausea (29%), procedural pain (17%), gait disturbance (8%), abnormal otoacoustic emissions (4%), and wound dehiscence (4%). Two patients (8%) experienced unrelated severe adverse events (SAEs). One patient experienced gait disturbance on day 38 following recent varicella vaccination lasting 3 days and another patient was treated for mastoiditis in the untreated ear following cochlear implantation. Adverse events of special interest (AESI) related to vestibular system dysfunction were reported in 6 of 24 patients (25%), including dizziness (21%), nystagmus (8%), and

balance disorder (4%). All AESI were non-serious, mild or moderate in intensity, transient, and resolved without sequelae. There were no cases of malignancy in the study.

Given the limited duration of follow up in the ongoing clinical study and the potential risk of secondary malignancy based on emerging data from products utilizing other AAV serotypes, the Applicant has agreed to conduct a postmarketing observational study to assess long-term safety and the risk of secondary malignancies among OTARMENI-treated patients for at least 10 years from product administration as a PMC. There were no cases of malignancy observed in the OTARMENI clinical program. The pharmacovigilance plan includes routine pharmacovigilance (adverse event reporting and submission of periodic safety reports in accordance with 21 CFR 600.80) and enhanced pharmacovigilance (identification of potential for secondary malignancy with AAV products as an Important Potential Risk and expedited (15-day) reporting to FAERS for all events of malignancy regardless of seriousness or label status for three years post-approval, in addition to inclusion of a summary and analysis in periodic safety reports).

8. Labeling

The proposed proprietary name, OTARMENI, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on January 22, 2026, and was found acceptable. CBER communicated the acceptability of the proprietary name to the Applicant on January 30, 2026. On December 29, 2025, APLB reviewed and found Regeneron's proposed suffix, -cwha, acceptable. CBER communicated the acceptability of the suffix to the Applicant on January 30, 2026.

APLB reviewed the proposed prescribing information, and package and container labels from a promotional and comprehension perspective. APLB completed the labeling review memo on March 18, 2026.

The Office of Review Management and Regulatory Review (ORMRR) and the Office of Gene Therapy (OGT) reviewed the package and container labels on April 6, 2026. Following revisions, they determined the package and container labels meet regulatory/statutory requirements.

The Office of Clinical Evaluation (OCE) labeling review team, together with the relevant discipline review teams, reviewed and revised the proposed prescribing information to ensure that it meets regulatory/statutory requirements, is consistent with current labeling practice, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the product, and provides clear and concise information for the healthcare providers. With the agreed revisions, the prescribing information is acceptable.

Several significant changes were made to the proposed prescribing information to enhance clarity and completeness of prescribing information. The indication was revised to include adult patients and broaden the population to include severe-to-profound *OTOF* associated hearing loss. Inclusion of adults is supported by the underlying disease pathophysiology and preliminary data from adolescent patients. Extrapolation of safety

and efficacy to patients with severe-to-profound *OTOF* associated hearing loss is supported by 12 of the 20 treated patients demonstrating hearing loss at some frequencies within the 250-8000 Hz range. The Adverse Reactions Section (United States Prescribing Information (USPI), Section 6) was revised to comprehensively capture safety events occurring following OTARMENI administration. Additionally, the Clinical Studies Section (USPI, Section 14) was restructured to provide a comprehensive description of the pivotal study, population characteristics, and efficacy endpoints that served as the substantial evidence for OTARMENI's accelerated approval.

9. Advisory Committee Meeting

The submitted information, including clinical study design and trial results, did not raise unresolved scientific or regulatory questions that would benefit from advisory committee discussion. Therefore, this BLA was not referred to the Cellular, Tissue, and Gene Therapies Advisory Committee.

10. Other Relevant Regulatory Issues

N/A

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The Applicant has provided substantial evidence of effectiveness to support accelerated approval of OTARMENI for the treatment of pediatric and adult patients with severe-profound and profound sensorineural hearing loss (>90dB) with preserved outer hair cell function, molecularly confirmed biallelic variants in the *OTOF* gene, and no prior cochlear implant in the same ear as OTARMENI administration. In addition, the Applicant has provided sufficient information, in conjunction with the requirements and commitments listed below, that the manufacturing process, along with associated test methods and control measures, can yield a product with consistent quality characteristics to support accelerated approval.

b. Benefit/Risk Assessment

The submitted data provide substantial evidence of effectiveness for OTARMENI based on a clinically meaningful treatment effect on an intermediate clinical endpoint, achievement of an average PTA threshold ≤70 dB HL at 24 weeks, which is reasonably likely to predict clinical benefit on sustained hearing improvement with resultant improved speech development and quality of life in pediatric and adult patients with *OTOF*-HL. OTARMENI targets the underlying disease mechanism with expected consistent treatment effects across ages and the uniformed no spontaneous improvement in disease natural history supports extrapolation of safety and efficacy to adults with *OTOF*-HL and will be further assessed in postmarketing studies. Confirmatory evidence includes mechanistic evidence from nonclinical studies in the Otof-Q828X homozygous mouse demonstrating dose-dependent improvements in ABR and sustained otoferlin protein expression post-OTARMENI administration.

The observed risks include transient, mild-moderate, non-serious adverse events that do not outweigh these substantial clinical benefits. The limited systemic exposure following intracochlear administration and profile of observed adverse events support a favorable benefit-risk assessment for accelerated approval, with ongoing assessment during the confirmatory studies. The potential risk of tumorigenicity will be assessed in a PMC study.

Overall, *OTOF*-HL represents a serious, genetic condition causing severe to profound sensorineural hearing loss that profoundly impacts speech and language development, academic achievement, and overall quality of life. The hearing impairment demonstrates no spontaneous improvement without intervention. There is a high unmet need for disease-modifying therapies that restore physiological auditory function and improve quality of life as the only available therapeutic intervention, cochlear implantation, has several limitations and involves device implantation. The treatment effects observed in Study DB-OTO-001 on PTA and ABR are substantial considering no spontaneous hearing improvement occurs without intervention in *OTOF*-HL. The efficacy results outweigh the observed and potential risks of the product which are generally non-serious, transient, and mild to moderate in severity.

c. Recommendation for Postmarketing Activities

Accelerated approval regulations require that the Applicant conduct adequate and well-controlled trial(s) to verify and describe the clinical benefit of OTARMENI. The Applicant agreed to the following PMR:

1. Submit analyses of clinical outcomes in: 1) at least 30 lunsotogene parvec-cwha-treated pediatric patients (unilateral or bilateral treatment) enrolled in Study DB-OTO-001 with *OTOF* gene-associated sensorineural hearing loss after 104 weeks post product administration; including 2) at least 5 lunsotogene parvec-cwha newly treated patients 16 years or older, with *OTOF* associated sensorineural hearing loss (enrolled either within the same trial or in a separate trial). The analyses should evaluate at a minimum the following clinical outcomes: hearing sensitivity threshold by pure-tone audiometry (PTA), age-appropriate speech and language outcome measures, auditory brainstem response (ABR), global impression of improvement (GII) clinical scales, and quality of life (QoL) scales. These analyses should compare data from treated patients to comparable, untreated patients with the same diagnosis followed over a similar duration of follow up for purposes of verifying and describing the clinical benefit of lunsotogene parvec-cwha in pediatric and adult patients with *OTOF* gene-associated sensorineural hearing loss.

   Final Protocol Submission Date: December 30, 2026
   Study Completion Date: April 30, 2030
   Final Report Submission Date: August 30, 2030

The Applicant agreed to the following clinical PMC subject to reporting requirements under section 506B:

2. Conduct a prospective, longitudinal, observational study to characterize the long-term safety of lunsotogene parvec-cwha in a minimum of 50 patients, including patients from the ongoing Study DB-OTO-001. Propose and justify the number of adult patients to be enrolled in the study. All patients will be followed for a minimum of 10 years from product administration. The study will assess the incidence of serious adverse events including the risk of malignancy at pre-specified time intervals and assessments. In addition to annual PMC reports, interim study reports will be submitted to the BLA at 3 years and 6 years and should include, at least: cumulative counts of patients enrolled and their demographics, SAEs, deaths, all AEs, and malignancies; and for each SAE and malignancy, patient age and other demographics, descriptions of the event, time to onset after DB-OTO administration, diagnostic testing, diagnosis, treatment, and laboratory analysis (including insertional site testing).

   Final Protocol Submission Date: August 31, 2026
   Interim Study Report #1 Date: December 31, 2029
   Interim Study Report #2 Date: December 31, 2032
   Study Completion Date: December 31, 2039
   Final Report Submission Date: June 30, 2040

The Applicant agreed to the following CMC PMCs not subject to reporting requirements under section 506B:

3. Regeneron commits to assessing (b) (4) from DB-OTO Drug Product (DP), stored at ≤ -80°C for (b) (4) months, using adequately qualified assays. A final study report will be submitted in a "Postmarketing Study Commitment – DP (b) (4) Final Study Report" by December 31, 2027.

   Final Study Report Submission Date: December 31, 2027

4. Regeneron commits to assessing the robustness of the (b) (4) lot release test for the (b) (4) A final study report will be submitted as a "Postmarketing Study Commitment – (b) (4) Robustness Assessment Final Study Report" by September 30, 2026.

   Final Study Report Submission Date: September 30, 2026

5. Regeneron commits to conducting a study to re-evaluate the maximum (b) (4) for DB-OTO Drug Product (DP) and Labeled Drug Product (LDP) manufacturing processes according to the study protocol outlined in VV-IOPS-190989 V:2.0 (Evaluation of the Maximum (b) (4) (b) (4) for DB-OTO DP and LDP Manufacturing Processes). Regeneron will submit the study results as a "Postmarketing Study Commitment – (b) (4) (b) (4) Final Study Report" by November 30, 2026.

   Final Study Report Submission Date: November 30, 2026

6. Regeneron commits to implementing a drug product-specific assay control for the relative potency assay. The final study report will establish acceptance criteria for assay control as part of potency assay suitability criteria and include updated standard operating procedure (SOP) that implements the assay control along with finalized system suitability criteria.

   The study results, analysis of the data to support the assay control suitability criteria, and the updated relative potency assay SOP will be submitted as a "Postmarketing Study Commitment – Assay Control for Relative Potency Final Study Report" by May 31, 2026.

   Final Study Report Submission Date: May 31, 2026

7. Regeneron commits to reassessing the acceptance criteria for release testing of lunsotogene parvec-cwha drug substance and drug product based on manufacturing experience and revising the acceptance criteria, if appropriate. A final acceptance criteria reassessment report will be submitted as a “Postmarketing Study Commitment – Re-assessment of Lot Release Acceptance Criteria Final Study Report” after CBER lot release of (b) (4) drug product batches including PPQ lot(s) that are released for commercial distribution. If (b) (4) commercial lots have not been manufactured by December 31, 2027, Regeneron will provide an updated timeline for reassessing the lot release acceptance criteria using (b) (4) commercial lot data.

   Final Study Report Submission Date: December 31, 2027

12. Appendix I

References

1. Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence Guidance for Industry DRAFT GUIDANCE; https://www.fda.gov/media/172166/download

2. Accelerated Approval and Considerations for Determining Whether a Confirmatory Trial is Underway Guidance for Industry DRAFT GUIDANCE; https://www.fda.gov/media/184831/download

3. Ford CL, Riggs WJ, Quigley T, Keifer OP Jr, Whitton JP, Valayannopoulos V. The natural history, clinical outcomes, and genotype-phenotype relationship of otoferlin-related hearing loss: a systematic, quantitative literature review. Hum Genet. 2023 Oct;142(10):1429-1449. doi: 10.1007/s00439-023-02595-5. Epub 2023 Sep 7. PMID: 37679651; PMCID: PMC10511631.

4. Expedited Programs for Serious Conditions — Accelerated Approval of Drugs and Biologics Guidance for Industry DRAFT GUIDANCE; https://www.fda.gov/media/184120/download

5. Long Term Follow-up After Administration of Human Gene Therapy Products Guidance for Industry; https://www.fda.gov/media/113768/download

6. Q1 Stability Testing of Drug Substances and Drug Products; https://www.fda.gov/media/187161/download

7. Rare Pediatric Disease Priority Review Vouchers Guidance for Industry DRAFT GUIDANCE; https://www.fda.gov/media/90014/download

8. Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) FINAL GUIDANCE https://www.fda.gov/media/113760/download

9. Human Gene Therapy for Rare Diseases FINAL GUIDANCE https://www.fda.gov/media/113807/download

10. Rare Diseases: Natural History Studies for Drug Development DRAFT GUIDANCE https://www.fda.gov/media/122425/download

11. Rare Diseases: Considerations for the Development of Drugs and Biological Products DRAFT GUIDANCE: https://www.fda.gov/media/119757/download