Summary Basis for Regulatory Action

Date:	October 30, 2026
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BLA STN:	125825/0
Applicant:	Inovio Pharmaceuticals, Inc.
Submission Receipt Date:	October 30, 2025
PDUFA Action Due Date:	October 30, 2026
Proper Name:	doruxapapogene ralaplasmid and lalikinogene sifuplasmid-gxfd
Proprietary Name:	VOCERYQ
Indication:	To reduce the frequency of surgical papilloma excisions in adults with recurrent respiratory papillomatosis.

***** PDUFA=Prescription Drug User Fee Act

Recommended Action: The Review Committee recommends approval of doruxapapogene ralaplasmid and lalikinogene sifuplasmid-gxfd via accelerated approval pathway.

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Acting Director, Product Office

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Acting Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC	
• CMC Product (Product Office)	Maitreyi Chattopadhyay, PhD Zhong Zhao, MD, PhD
• Facilities review (OCBQ/DMPQ)	Zainab Mansaray-Storms, PhD
• Establishment Inspection Report (OCBQ/DMPQ and Product Office)	Maureen DeMar
• QC, Test Methods, Product Quality (OCBQ/DBSQC)	Marie Anderson, MS, PhD CAPT Simleen Kaur, MSc Laura Kesner, PhD Jing Lin, PhD
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• Postmarketing safety, Pharmacovigilance review (OBPV/DPV)	Stephanie Ajuzie, MD, MPH
• BIMO	Haecin Chun, MS
Statistical	
• Clinical data (OBPV/DB)	Jingyi Zhai, PhD Yuqun Abigail Luo, PhD
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• Promotional (OCBQ/APLB)	CDR Jun Lee, PharmD, PhD (Labeling) CDR Hanah Pham, PharmD, MS (PNR, Suffixes)
• Regulatory Review	Crystal Daniel, MT, BSN, RN Jessica Lee, MD, PhD
Other Reviews	
• CDRH Consultant	Shruti Mistry Sarah Hanif Kyran Gibson
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1. Introduction

Inovio Pharmaceuticals, Inc. submitted a Biologics License Application (BLA), STN 125825/0 on October 30, 2025, for licensure of doruxapapogene ralaplasmid and lalikinogene sifuplasmid-gxfd, with the proprietary name of VOCERYQ, administered using the CELLECTRA 5PSP electroporation device. VOCERYQ is a DNA plasmid-based immunotherapy comprised of two active plasmid (b) (4) doruxapapogene ralaplasmid (pGX3024) and lalikinogene sifuplasmid (pGX6010). Plasmid pGX3024 expresses 4 distinct human papillomavirus (HPV) antigen peptides (HPV-11 E6, HPV-11 E7, HPV-6 E6, and HPV-6 E7) and plasmid pGX6010 expresses human IL-12 (b) (4) which functions to stimulate immune responses to the HPV peptides. VOCERYQ is delivered via intramuscular injection with electroporation (EP) and is intended to generate an immune response directed against papilloma cells infected with HPV type 6 and/or 11 in adult patients with recurrent respiratory papillomatosis (RRP). The VOCERYQ drug product (DP) is supplied as sterile, preservative-free, clear to slightly opalescent, colorless solution in saline-sodium citrate (SSC) buffer in a 1.5 mL clear glass cartridge containing 1 mL of the DP at a concentration of 6.25 mg/mL.

VOCERYQ received Breakthrough Therapy and Orphan Drug designations for the treatment of RRP.

Conclusions on Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness based on a single, adequate and well-controlled trial, Study RRP-001 (NCT04398433), with confirmatory evidence based on measurable antigen-specific cellular immune responses to support accelerated approval of VOCERYQ. Study RRP-001 was a single-arm, open-label, Phase 1/2 study in adult patients with RRP requiring two or more surgical procedures per year. In this study, eligible adult patients with confirmed diagnosis of RRP underwent surgical debulking of airway papilloma prior to receiving four intramuscular injections of VOCERYQ (with EP using the CELLECTRA 5PSP device) on Day 0, and at Weeks 3, 6, and 9 (total 4 doses). Of the 32 patients enrolled, 26 patients comprise the primary efficacy analysis population based on baseline surgical requirements of 3 or more surgical interventions (mean 4.6 surgical interventions in the year prior to treatment) for papilloma excision in the 12 months prior to treatment with the product, a subpopulation enriched with patients with high-burden, high-recurrence disease at baseline.

Efficacy was assessed using an intra-patient baseline control design, comparing the number of surgical interventions in the 12 months following treatment to each patient's pre-treatment baseline in the 12 months prior to treatment. Of the 26 patients in the primary efficacy population, a complete response (CR; complete elimination/absence of clinically indicated surgical papilloma excisions) at 12 months after treatment was observed in 27% of patients (7/26; 95% CI 12% to 48%). In this refractory, high-recurrence population, complete elimination of surgical interventions is not expected without intervention, and it is used as an intermediate clinical endpoint that is reasonably likely to predict clinical benefit (durable elimination of surgical papilloma excisions, symptomatic improvement). In addition, there was a mean reduction of 1.4 surgical interventions per year (median reduction 1.6; 95% CI: −2.2, −0.7) following treatment with VOCERYQ. These findings are further supported by a sustained reduction in

modified Derkay RRP Staging Assessment scores (which evaluates disease severity based on a combined scoring of tumor size and clinical symptomatology) through month 12, compared to the average scores of the three years prior to treatment (mean change in total clinical score: −11.0; 95% CI: −16.7, −5.3), which provides additional supportive evidence that the observed reduction in surgical interventions reflects genuine disease improvement.

Confirmatory evidence includes mechanistic data from clinical immunogenicity assessments in patients treated in Study RRP-001, demonstrating measurable antigen-specific cellular immune responses through Week 52 following treatment with VOCERYQ (with electroporation).

In the 32 adults with RRP enrolled in Study RRP-001, the most commonly reported adverse reactions included injection site reactions, headache, fatigue, hypertension, nausea and dizziness; the majority having mild-moderate severity and resolving without sequelae. No serious or severe adverse reactions were reported.

The favorable safety profile, coupled with the observed treatment effect on the number of surgical papilloma excisions over 12 months support a favorable benefit-risk evaluation of VOCERYQ and supports approval.

Basis for Accelerated Approval

The review team recommends the accelerated approval of VOCERYQ based on short-term (12 months) demonstration of reduction/elimination of surgical papilloma excisions over a follow up period of 12 months post-treatment in adults with RRP. The Applicant is required to conduct a post-approval, adequate and well-controlled clinical study as a Post Marketing Requirement (PMR) study to verify and describe the clinical benefit of VOCERYQ with respect to evaluating durable elimination of surgical papilloma excisions and symptomatic improvement in adult and pediatric patients with RRP.

The clinical management of RRP involves repeated surgical excisions of papillomas to minimize and improve clinical symptoms caused by papilloma regrowth. At a patient-listening session in 2022, FDA heard from patients with RRP that any reduction in the need for surgical papilloma excision is clinically meaningful to them and, as such, we consider the reduction of surgical interventions as a clinical outcome that is used as an intermediate clinical endpoint reasonably likely to predict clinical benefit (durable elimination of surgical papilloma excisions, symptomatic improvement). Recently, Papzimeos (zopapogene imadenovec-drba), an adenovirus-based immunotherapy administered via four subcutaneous injections over 12 weeks, was approved for the treatment of adults with RRP based on demonstration of durable elimination of surgical papilloma excisions over at least two years. Treatment with Papzimeos requires simultaneous surgical excision of visible papillomas at the time of the administration of the third and fourth doses of the product, to maintain minimal residual disease. VOCERYQ is granted accelerated approval on the basis of the following:

1. Substantial evidence of effectiveness is established based on an intermediate clinical endpoint (reduction/elimination of surgical papilloma excisions over 12 months of follow up duration) that is reasonably likely to predict clinical benefit (durable reduction/elimination of surgical papilloma excisions, symptomatic

improvement) in patients with RRP with confirmatory evidence of generation of targeted cellular immune responses against the injected antigens; and

2. The treatment regimen of VOCERYQ provides a meaningful therapeutic benefit over the available therapy, Papzimeos, given that treatment with VOCERYQ does not require additional surgical papilloma excisions to maintain minimal residual disease (as is the case for treatment with Papzimeos). Papzimeos requires surgical excision of visible papilloma at the time of the 1st, 3rd and 4th dose (Day 0, 43, and 85) to maintain minimal residual disease. VOCERYQ requires excision of visible papilloma at the time of the 1st dose only (Day 0). Although there is no data available directly comparing the rates of absence of surgical procedures for papilloma excision following VOCERYQ and Papzimeos product administration, this difference in the treatment regimen (reducing the number of surgical excisions required) provides therapeutic and public health benefits. Specifically, avoiding additional surgical excisions in patients with RRP helps preserve healthy laryngeal and airway tissue, reducing the risk of scarring, stenosis, and long-term functional complications, as well as reducing the general risks associated with surgery. Thus, VOCERYQ treatment regimen avoids risks that occur with the available therapy. In addition, it is expected that the treatment regimen of VOCERYQ provides a meaningful therapeutic benefit over Papzimeos in patients with RRP who do not have a clinical response or are intolerant of Papzimeos.

3. The Applicant is required to conduct a post-approval, adequate and well-controlled clinical study as a PMR under 21 CFR 601 subpart E to verify and describe the clinical benefit (i.e., durable reduction/elimination of surgical papilloma excisions, clinical symptom improvement) of VOCERYQ in adult and pediatric patients with RRP over at least 3 years of follow up post-product administration.

In addition to the clinical PMR, six CMC and two device Post Marketing Commitments (PMCs) are issued as a condition of approval. The CMC PMCs include additional linearity and robustness assessment of two cell-based potency assays, bridging of the clinical lots with the commercial reference standard, re-evaluation of content and potency acceptance criteria and performing a container closure integrity (CCIT) study using a positive control with an established sensitivity that correlates to risk and detection of microbial ingress. The device PMCs include a statistical reliability validation of the Array's sharps safety feature and a complete data re-evaluation of the human factor validation study. The PMCs are listed in Section 11.c of this document.

2. Background

Recurrent Respiratory Papillomatosis (RRP) is a rare, serious, chronic condition driven by persistent infection caused by human papillomavirus subtypes 6 and 11 (HPV-6, HPV-11). The disease primarily affects the larynx and upper respiratory tract and leads to recurrent growth of benign lesions of the respiratory tract. RRP is the most common benign tumor of the laryngeal epithelium and is well-established in its HPV etiology. The incidence rate is estimated at 1.8 per 100,000 adults in the United States. Age of diagnosis ranges from young children (juvenile-onset RRP defined as age at first diagnosis <12 years) to older adults (adult-onset RRP defined as age at first diagnosis ≥12 years). RRP is a chronically recurring condition; however, the clinical course of RRP

is variable with growth of papilloma waxing and waning over several years. RRP poses a significant disease burden due to its recurrent nature, which necessitates frequent and repeated surgical interventions. The disease profoundly impacts voice quality, respiratory function, and quality of life, which represent meaningful impairments in daily functioning in addition to the clinical risks from repeated surgical procedures and anesthesia exposure. While most lesions are benign, malignant conversions have been reported in 3% of patients with RRP (Schraff et al., 2004, Dedo and Yu 2001).

Management of RRP centers on clearing airway obstruction, preserving voice quality, and reducing the recurrence frequency of papillomas through repeated surgical removal of papillomas. Repeated surgical papilloma excisions create substantial morbidity from cumulative procedures, anesthetic exposure, secondary sequelae (scarring) and psychosocial burden. Adjuvant therapies have historically been used off-label in moderate-to-severe cases, most notably intralesional or systemic bevacizumab and intralesional cidofovir, though inconsistent efficacy and safety concerns have limited their widespread adoption. Prophylactic HPV vaccination is broadly recommended and is associated with reduced surgical frequency. In 2025, zopapogene imadenovec-drba (Papzimeos) became the first FDA-approved treatment for adult RRP, targeting the underlying HPV infection directly and is now recommended as first-line medical therapy for adults seeking to reduce surgical burden by the RRP foundation. Treatment with Papzimeos consists of four subcutaneous administrations over 12 weeks alongside maintenance of residual disease by surgical excision of visible lesions prior to the first, third and fourth administrations.

Table 1. Regulatory History

Regulatory Events/Milestones	Date
Pre-IND meeting	October 29, 2018
IND submission	January 10, 2020
Orphan Drug designation granted	July 28, 2020
Breakthrough Therapy designation granted	August 31, 2023
Pre-BLA meeting (IND 19508/38)	August 1, 2024
Rolling Review (IND 19508/46)	August 27, 2025
BLA 125825/0 (final module submission)	October 30, 2025
BLA filed	December 23, 2025
Mid-Cycle communication	April 30, 2026
Late-Cycle meeting	July 15, 2026
PDUFA Action Due Date	October 30, 2026

3. Chemistry, Manufacturing, and Controls (CMC) Evaluation

VOCERYQ and CELLECTRA® 5PSP are a cross-labeled combination product. VOCERYQ is administered only with CELLECTRA® 5S5P and by a healthcare provider trained in its use. VOCERYQ will be administered intramuscularly with electroporation via CELLECTRA® 5PSP every three weeks for a total of four doses.

Based on the review of the information provided in the initial BLA submission and the subsequent amendments, the CMC review team concludes that the manufacturing and controls for VOCERYQ and CELLECTRA® 5PSP are acceptable for commercial manufacturing.

a. Product Quality

Manufacturing Summary

The plasmids pGX3024 and pGX6010 are manufactured (b) (4) manufacturing processes. The manufacturing process begins with (b) (4) (b) (4) The DP (b) (4) filled into the final container closure containing 6 mg pGX3024 and 0.25 mg pGX6010 in 1 mL. The finished DP vials are stored at 2°C to 8°C and are shipped to a labeling and secondary packaging facility to complete the DP labeling.

Manufacturing Control Strategy

To ensure product safety, identity, strength, purity, and potency, the CGMP manufacturing process is controlled by (1) using (b) (4) raw materials, reagents, and product-contact consumables, (2) in-process monitoring and in-process control testing, (3) validation of the manufacturing process, and (4) validated release testing. The manufacturer accepts raw materials based on incoming acceptance tests and verification of raw material specifications. Suppliers are qualified and audited according to established supplier qualification programs. There are no materials of human or animal origin used in DS or DP manufacturing.

The manufacturing process control strategy includes setting acceptable limits for process parameters and testing the in-process materials, (b) (4) DP for microbial contaminants, identity, purity, strength, and potency. The (b) (4) DP are controlled by lot release tests including quantitative assays that measure DP concentration, quality in terms of (b) (4) plasmid, process and product related impurities and product potency. Two biologically relevant potency assays assess expression of peptide antigens and IL-12 from transfected cells. Lot release test methods are suitably validated or verified, except for the two potency lot release assays that need additional validation studies, which will be addressed through PMCs. VOCERYQ specifications are adequate to ensure product quality and consistency. However, due to the small number of VOCERYQ lots produced to date, reevaluation of some lot release acceptance criteria is being requested through PMCs.

The risks associated with process- and product-related impurities were minimized through a well-designed control strategy. For product-related impurities, (b) (4) (b) (4) are tested as part of in-process, release, and stability testing for (b) (4) and (b) (4) with all results meeting the predefined acceptance criteria, confirming that the control strategy for product-related impurities is acceptable. For process-related impurities, the (b) (4) specification includes proposed tests for (b) (4) (b) (4) with quantitative acceptance criteria. The risk of residual

kanamycin (b) (4) was minimized by demonstrating robust removal across commercial manufacturing batches, with levels consistently falling below the limit of detection. The risk of extractables and leachables that could originate from the product manufacturing process, and the container closure system were analyzed. As no leachables were detected above the analytical evaluation threshold in the final DP, a toxicological assessment was not warranted, and the analytical studies were sufficient to mitigate this risk.

Process Validation

The manufacturing process was validated through production of (b) (4) process performance qualification (PPQ) batches each for (b) (4) and (b) (4) DP PPQ lots at commercial scale. All (b) (4) DP PPQ batches met all pre-defined PPQ acceptance criteria. Additional validation studies were also performed, including shipping validation, and a cumulative of extractables and leachables assessment.

Stability

The plasmids are stable for (b) (4) when stored at (b) (4) The (b) (4) shelf life is (b) (4) months when stored at (b) (4) The DP shelf life is set at 36 months when stored at 5°C ± 3°C based on real-time stability data from commercial lots and supportive data from (b) (4) . The DP in the original carton can be stored at the room temperature for up to 24 hours prior to administration.

Comparability

Patients in the clinical studies used to support licensure of VOCERYQ received DP manufactured at the clinical manufacturing facility. For commercialization, the manufacturing processes were moved to commercial manufacturing sites, though the manufacturing processes themselves remained mostly unchanged with no major process modifications. Additionally, some analytical method changes were implemented. A thorough comparability study was conducted and the clinical and commercial manufacturing processes were found to produce products with comparable critical quality attributes, including content, (b) (4) and potency.

Manufacturing Risks

The risk of product contamination with microbial and viral adventitious agents is minimized by ensuring adequate control of raw materials and the manufacturing process, which includes not using any human- or animal-derived components in production and implementing adequate controls throughout the manufacturing process and in (b) (4) DP release testing. Therefore, the risks from bacterial, fungal, mycoplasma, and TSE-causing agents are considered negligible.

Device Description

The CELLECTRA™ 5PSP electroporation device is the device constituent of this combination product designed to deliver the biologic constituent, VOCERYQ (doruxapapogene ralaplasmid and lalikinogene sifuplasmid-gxfd), via intramuscular injection, followed by electroporation to enhance cellular uptake of the DNA plasmids. The system is intended for use by qualified and trained healthcare professionals.

The device system is comprised of three main components and two accessories:

1. 5PSP Base Station which serves as a charging dock for the handset and can accept limited data inputs and store records.
2. 5PSP Handset is a reusable, battery-powered component that delivers the electroporation pulse pattern. The handset accepts the array component.
3. The sterile, single-use disposable array consists of five (5) needle-electrodes molded into a plastic housing that also accepts the (shipped separately) drug cartridge.
4. Two accessories support operation (power supply) and data transfer (flash drive).

The single-use sterile Array is packaged in a thermoform tray with a (b) (4) lid which serves as the primary packaging and sterile barrier system. This packaging configuration is terminally sterilized using (b) (4) and has been validated to maintain sterile barrier integrity through shipping, handling, and storage.

The treatment process involves the handset delivering the drug from the cartridge into the muscle tissue, followed by a programmed sequence of electrical pulses (electroporation) to increase cell membrane permeability, thereby enhancing the uptake of the DNA-based drug.

CMC and Device PMCs

Six CMC PMCs are agreed upon by the Applicant. The first and second PMCs are to complete the linearity and robustness assessment of the potency assay that assesses expression of peptide antigens and IL-12 from the transfected cells. The third PMC is to complete the bridging study between the clinical lots and the current reference standard with additional clinical lots, which was initially conducted with only (b) (4) clinical lots. The fourth and fifth PMCs are to reevaluate and revise, as appropriate, the acceptance criteria for quantity and potency based on more manufacturing experience, given the limited number of VOCERYQ lots produced to date. The sixth PMC is to conduct a CCIT study for the DP 1.5 mL glass cartridges using a positive control with an established sensitivity, in accordance with (b) (4) (b) (4) and that correlates to the risk and detection of microbial ingress.

In addition, two device PMCs are agreed upon by the Applicant. The first PMC is to complete a comprehensive data re-evaluation of the human factor validation study using task rating categories that separate close calls from use difficulties and provide a consolidated root-cause risk analysis. The second PMC is to complete the comprehensive verification and simulated clinical-use validation of the single-use Array's passive sharps safety feature to demonstrate (b) (4) (b) (4)

b. Drug Product Specification

The final lot release specifications for the VOCERYQ DP are shown in Table 2. The analytical methods and their validations and/or qualifications reviewed for the VOCERYQ (b) (4) DP were found to be adequate for their intended use.

Table 2. VOCERYQ Drug Product Lot Release Specification

Test	Method	Acceptance Criteria
Container Content	(b) (4)	1.0 (b) (4) mL/cartridge
Quantity- Content	(b) (4)	(b) (4)
Bioassay	IL-12 (b) (4) HPV11 (b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)		(b) (4)
Sterility	(b) (4)	No Growth
Endotoxin	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Particulates	(b) (4)	(b) (4)
Identity	(b) (4)	(b) (4)
Appearance	(b) (4)	Clear to slightly opalescent (b) (4) (b) (4) colorless solution essentially free of visible particles
Container Closure Integrity Test (CCIT)	(b) (4)	(b) (4)
Identity of finished DP (Labeled)	(b) (4)	Conforms (b) (4) (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 doruxapapogene ralaplasmid and lalikinogene sifuplasmid (VOCERYQ) and the CELLECTRA® 5PSP electroporation device are listed in Table 3. The activities performed and inspectional histories are noted in Table 3.

Table 3. Manufacturing Facilities for VOCERYQ and CELLECTRA® 5PSP Electroporation Device

Name/Address	FEI Number	DUNS Number	Inspection/ Waiver	Justification/ Results
(b) (4) *Manufacture of* (b) (4) (b) (4)*, release testing of DP*	(b) (4)	(b) (4)	PLI	CBER/DMPQ (b) (4) NAI
Inovio Pharmaceuticals, Inc. 11055 Flintkote Avenue, Suite A San Diego, CA 92121 *Release testing of DP*	3030656025	079131268	PLI	CBER/DMPQ August 2026 VAI
Inovio Pharmaceuticals, Inc. 6769 Mesa Ridge Road San Diego, CA 92121 *Manufacture, assembly, labeling, packaging, and release testing of CELLECTRA 5PSP device*	3013931315	111745425	PLI	OII/DBI3 June 2026 NAI
Alliance Medical Products, Inc. 9342 and 9292 Jeronimo Road Irvine, CA 92618-1903 *Manufacture of DP, release testing of DP*	2027189	102688657	Waiver	OII/DHADI6 October 2025 VAI
(b) (4) *Release testing of DP*	(b) (4)	(b) (4)	Waiver	(b) (4) Assessed by ORA: VAI
(b) (4) *Release testing of DP*	(b) (4)	(b) (4)	Waiver	(b) (4) Assessed by ORA: VAI
(b) (4) *Release testing of DP*	(b) (4)	(b) (4)	Waiver	OII/DHADI4 (b) (4) VAI
(b) (4) *Primary labeling of DP*	(b) (4)	(b) (4)	Waiver	ORA/PHRM2 (b) (4) NAI

Acronym key: CBER: Center for Biologics Evaluation and Research; DBI3: Division of Biotechnology Inspectorate 3; DHADI4: Division of Human and Animal Drug Inspectorate 4; DHADI6: Division of Human and Animal Drug Inspectorate 6; DMPQ: Division of Manufacturing Product Quality; DP: Drug product; DS: Drug substance; (b) (4) (b) (4) FEI: FDA establishment identifier; (b) (4) NAI: No Action Indicated; OII: Office of Inspections and Investigations; ORA: Office of Regulatory Affairs; PLI: Pre-license inspection; PHRM2: Pharmaceutical Division; VAI: Voluntary Action Indicated

CBER/DMPQ led a PLI of (b) (4) in (b) (4) No Form FDA 483 was issued, and the inspection was classified as NAI.

CBER/DMPQ led a PLI of Inovio Pharmaceuticals, Inc. in August 2026, and a Form FDA 483 Inspectional Observations was issued at the end of the inspection. The firm responded to the observations, and the corrective actions were reviewed and found to be adequate. All inspectional issues were resolved, and the inspection was classified as VAI.

OII/DBI3 conducted a PLI for CBER at Inovio Pharmaceuticals, Inc. in June 2026. No Form FDA 483 was issued, and the inspection was classified as NAI.

OII/DHADI6 performed a surveillance inspection of Alliance Medical Products, Inc. in October 2025. A Form FDA 483 Inspectional Observations was issued at the end of the inspection. The firm responded to the observations, and the corrective actions were reviewed and found to be adequate. All inspectional issues were resolved, and the inspection was classified as VAI.

(b) (4) performed a GMP inspection of (b) (4) (b) (4) in (b) (4) In accordance with the (b) (4) and (b) (4) ORA assessed the inspection report and determined the inspection was classified as VAI.

(b) (4) performed a GMP inspection of (b) (4) in (b) (4) In accordance with the (b) (4) and (b) (4) ORA assessed the inspection report and determined the inspection was classified as VAI.

OII/DHADI6 performed a combined pre-approval and surveillance inspection of (b) (4) (b) (4) in (b) (4) A Form FDA 483 Inspectional Observations was issued at the conclusion of the inspection. The firm responded to the observations, and the corrective actions were reviewed and found to be adequate. All inspectional issues were resolved, and the inspection was classified as VAI.

ORA/PHRM2 conducted a surveillance inspection of (b) (4) in (b) (4) No Form FDA 483 was issued, and the inspection was classified as NAI.

e. Container/Closure System

The DP container closure system is a 1.5 mL (b) (4) borosilicate Type (b) (4) glass cartridge manufactured by (b) (4) siliconized bromobutyl plunger manufactured by (b) (4) (b) (4) and an (b) (4) rubber-aluminum combination seal manufactured by (b) (4) performed the container closure integrity testing at the (b) (4) employing a (b) (4) test method; all acceptance criteria were met.

f. Environmental Assessment

The applicant submitted an environmental assessment (EA) pursuant to 21 CFR part 25. The EA provided an assessment of VOCERYQ environmental exposure based on

known biology of the DNA plasmids, genetic modifications made to the plasmids, biodistribution data, waste disposal procedures, lot release testing, and a worst-case assumption in each case. The Agency determined that approval of VOCERYQ will not result in any significant environmental impact. A Finding of No Significant Impact memorandum has been prepared.

4. Nonclinical Pharmacology/Toxicology Evaluation

The nonclinical program for VOCERYQ® demonstrated: (1) induced cellular and humoral immune responses in vivo in two species; (2) limited biodistribution (BD) of the plasmid construct to intended target tissues; and (3) an acceptable safety profile following administration of an analogous product at dose levels comparable to or exceeding the intended clinical dose via the clinical ROA and dosing regimen.

In vitro studies confirmed expression of HPV-6 and HPV-11 E6 and E7 antigens from (b) (4) in human cells. In vivo pharmacology was evaluated using analogous INO-3107 (b) (4) in (b) (4) and (b) (4) mice, and INO-3107 (b) (4) in New Zealand White (NZW) rabbits, all administered via IM injection and EP with the CELLECTRA® 2000. Dose-dependent cellular and humoral immune responses against HPV-6 and HPV-11 E6 and E7 antigens were demonstrated in both mouse strains. Co-administration of the IL-12 plasmid enhanced humoral responses. In NZW rabbits administered INO-3107 at the clinical dosing regimen (Weeks 0, 3, 6, and 9), T-cell and humoral responses against HPV-6 and HPV-11 E6 antigens were demonstrated, with more limited E7 responses observed.

The safety and biodistribution (BD) of INO-3107 are supported by comprehensive nonclinical Good Laboratory Practice (GLP) studies conducted with analogous DNA-based plasmids sharing the (b) (4) (b) (4) administered via (b) (4) IM injection (note that the clinical protocol calls for repeat administration with four total doses) and EP with the CELLECTRA® 2000 device. Plasmid DNA was localized primarily to the injection site and surrounding tissue with no evidence of systemic BD or genomic integration. EP increased plasmid persistence at the injection site relative to IM injection (b) (4). In repeat-dose toxicology studies, primary findings included localized injection site reactions and transient clinical pathology changes (elevated creatine kinase [CK], neutrophilia, elevated C-reactive protein [CRP]) attributed to the EP procedure and immune response. No significant systemic toxicity was identified.

A GLP fertility and postnatal developmental toxicity study was conducted in NZW rabbits administered 4–5 doses of 6.23 mg INO-3107 via IM injection and EP with the intended clinical device. Transient, non-adverse reductions in body weight (BW) and food consumption were observed in treated males and females during the premating phase. No effects on mating performance, fertility, fetal development, or litter parameters were observed. A transient reduction in kit BW at Day 4 postpartum resolved by later timepoints. No INO-3107-related malformations or developmental variations were identified.

No carcinogenicity studies were performed. These studies are not warranted based on the administration regimen, product characteristics, and safety profile.

5. Clinical Pharmacology Evaluation

VOCERYQ is a synthetic DNA plasmid product administered via intramuscular (IM) injection followed by electroporation (EP). VOCERYQ is designed to generate an immune response directed against HPV-6 and 11 proteins in patients with recurrent respiratory papillomatosis.

Traditional clinical pharmacology assessments such as pharmacokinetic (PK) studies are not applicable to VOCERYQ due to the molecular characteristics of the product. The VOCERYQ biodistribution assessment was based on non-clinical study results.

The clinical pharmacology assessments of VOCERYQ include the induced immunogenicity (immunological responses) to VOCERYQ.

Immune Responses

Immune responses induced by VOCERYQ were characterized through profiling peripheral T-cells for antigen-specific production of interferon gamma (IFN-γ) measured by enzyme-linked immunosorbent spot (ELISpot), antigen-specific dynamic regulation of activation markers measured by multiparametric flow cytometry, emergent T-cell clonal populations measured by T-cell receptor-β (TCR-β sequencing), and transcriptional Profile of Airway/Papilloma Tissue Immune Infiltration assessed by RNA sequencing.

These immunogenicity assessments in Study RRP-001 demonstrated that VOCERYQ followed by EP induced measurable antigen-specific cellular immune responses through Week 52. The observations that complete responders had more robust immune responses (particularly CD8+/CD38+/perforin+/PD-1+ T cells) compared to incomplete responders and nonresponders provide biological plausibility for the mechanism of action.

Dose Justification

The selected dose of VOCERYQ is 6.25 mg (6 mg pGX3024 + 0.25 mg pGX6010) administered as a 1 mL IM injection followed immediately by EP with the CELLECTRA™ 5PSP device. The dosing schedule consists of four doses administered at Day 0, Week 3, Week 6, and Week 9.

In Study RRP-001, the dose was not escalated and all subjects received the same dose level of the product. Given the acceptable efficacy and safety profiles, the selected dose appears reasonable.

Overall, the clinical pharmacology information supports the approval of VOCERYQ for the proposed indication.

6. Clinical/Statistical Evaluation

a. Efficacy Assessment

Primary evidence of effectiveness for VOCERYQ comes from Study RRP-001, an open-label, single-arm, Phase 1/2, 12-month study evaluating VOCERYQ in adult patients with RRP, conducted under IND 19508. The study enrolled adults with confirmed diagnosis of RRP who had required 2 or more debulking procedures to remove laryngotracheal papilloma in the 12 months prior to treatment with

VOCERYQ. All treated patients underwent a standard of care surgical debulking procedure to remove laryngotracheal papillomas on Day 0 prior to initiation of treatment with VOCERYQ. All enrolled patients were treated with four doses of 6.25 mg per injection of VOCERYQ delivered intramuscularly with electroporation, which was administered on Day 0, Weeks 3, 6, and 9. No additional protocol-mandated surgeries were required during the product dosing window.

Efficacy

There is limited published, prospective natural history data for RRP to formally benchmark treatment outcomes in the absence of a concurrent-controlled trial. The pre-treatment surgical frequency for individual patients enrolled in Study RRP-001 serves as the intra-subject historical control for this clinical study. While some patients may experience spontaneous fluctuation in disease activity which contributes to the variable natural history of RRP, the study's requirement for multiple surgical interventions in the year prior to enrollment establishes that each enrolled patient had a minimum confirmed burden of disease at baseline. The efficacy analysis relied on a subpopulation with high threshold of 3 or more surgical interventions in the 12 months prior to treatment, defining a severely affected, refractory, and high-recurrence population to increase confidence in the efficacy endpoint of a complete response, defined as having no requirement for surgical intervention in the 12 months following treatment. Additional efficacy outcome measures taken into consideration include a reduction in the annualized rate of surgical interventions compared to a 3-year baseline for each patient and improvement in the Derkay clinical scoring.

In Study RRP-001, 26 patients with clinically and histologically diagnosed RRP and a history of 3 or more surgeries to remove laryngotracheal papillomas in the 12 months preceding study enrollment constitute the primary efficacy population and have the following demographic characteristics: mean age 49.6 years (range 25 to 82 years), 19 patients (73.0%) were male, 23 patients (88%) were White, 2 patients (8%) were African American, 1 patient (4%) was Asian, and 24 patients (92%) were non-Hispanic or Latino. The median number of surgical interventions for papilloma excision in the year prior to treatment was 4.5.

The primary efficacy endpoint was the percentage of patients requiring 3 or more surgeries in the 12 months prior to treatment who had a complete response to VOCERYQ, defined as absence of RRP surgical interventions in the 12 months after treatment. This included the clinically indicated papilloma debulking procedure prior to initiation of treatment.

The primary efficacy endpoint of complete response at 12 months was achieved in seven out of 26 patients who required three or more surgical interventions in the 12 months prior to treatment including surgery on Day 0, resulting in a complete response rate of 27% [95% confidence interval 12 to 48%], which is not expected as part of the natural history of the disease when untreated.

Additionally, there was a sustained reduction in modified Derkay RRP Staging Assessment scores through month 12 (mean change in total clinical score: −12.1; 95% CI: −19.0, −5.2), which standardize papillomatous growth by combining an anatomical score (the extent of tumor growth) and a clinical score (the patient's

symptoms). Clinical findings were supported by immunogenicity assessments showing a sustained measurable antigen-specific cellular immune response through week 52.

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

Two Bioresearch Monitoring (BIMO) inspection assignments were issued for two clinical investigators that participated in the conduct of Study RRP-001. The inspection did not reveal significant issues impacting the data submitted in this original BLA.

c. Pediatrics

VOCERYQ has orphan drug designation for the treatment of recurrent respiratory papillomatosis and is therefore exempt from Pediatric Research Equity Act (PREA) requirements. As RRP affects both pediatric and adult patients, the Applicant has agreed to conduct additional evaluation of pediatric patients with RRP in their confirmatory study under an accelerated approval post-marketing requirement study with expected final study report by August 31, 2031.

d. Other Special Populations

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

7. Safety Evaluation and Pharmacovigilance

Safety

Safety of VOCERYQ was evaluated in all 32 patients who received VOCERYQ in the prospective Study RRP-001, including one patient who failed to receive electroporation with dose 4. This included the 26 patients evaluated for efficacy who required three or more surgical interventions in the 12 months prior to treatment with VOCERYQ and 6 patients who required two surgical interventions in the 12 months prior to treatment. The demographic characteristics of this entire study population (i.e., safety dataset) were as follows: the median age was 46.5 years (range 25 to 82 years), 24 patients (75.0%) were male, 26 patients (81%) were white, 4 patients (13%) were African American, 1 patient (3%) was Asian, 1 (3%) was of “other” race, and 29 patients (91%) were non-Hispanic or Latino. The median BMI was 26.2 kg/m2 (range: 18 to 46 kg/m^2). The median number of surgeries in the 12 months prior to the first dose was 4.0 (range: 3 to 8).

The most frequently occurring adverse reactions reported following treatment with VOCERYQ were injection site reactions, headache, fatigue, hypertension, nausea and dizziness.

Given the small study population, the clinical team concluded that potential risks associated with electroporation could not be excluded even though this was not observed in the clinical study of VOCERYQ. Therefore, general procedure-related adverse events associated with electroporation, available from the literature, were included in the VOCERYQ prescribing information and include brief muscle contractions or tetany, temporary bleeding at the administration site, anxiety, vasovagal reactions including lightheadedness and dizziness, and transient changes in creatine phosphokinase.

Pharmacovigilance

The Applicant's pharmacovigilance plan (PVP) does not identify any important identified or potential risks. Areas of missing information include use during pregnancy, use during lactation, and use in children. The proposed PVP is adequate.

The Applicant will conduct routine pharmacovigilance with adverse event reporting in accordance with 21 CFR 600.80.

The available safety data does not substantiate a need for a safety-related postmarketing commitment (PMC) or requirement (PMR) or Risk Evaluation and Mitigation Strategy (REMS).

8. Labeling

The Office of Review Management and Regulatory Review (ORMRR) and the Office of Gene Therapy (OGT) reviewed the package and container labels on October 27, 2026. Following revisions, they determined the package and container labels meet regulatory/statutory requirements.

Advertising and Promotional Labeling Branch (APLB)

The proposed proprietary name, VOCERYQ, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on January 12, 2026, and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on January 29, 2026. On September 21, 2026, APLB reviewed and found Inovio's proposed suffix, -gxfd, acceptable. CBER communicated the acceptability of the suffix to the Applicant on September 25, 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 September 29, 2026.

OTP Associate Director for Labeling (ADL) Team

The Office of Therapeutic Products (OTP) 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.

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 and evidence of safety to support accelerated approval of VOCERYQ to reduce the frequency of surgical papilloma excisions required to manage clinical symptoms in adults with recurrent respiratory papillomatosis (RRP). 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

RRP is a rare, serious condition causing recurrent airway papillomas due to chronic HPV 6 and/or 11 infection which can profoundly impact voice quality, respiratory function, and quality of life leading to meaningful impairments in daily functioning. There is an unmet need for additional therapeutic options in patients who have recurrent, refractory papilloma growth needing multiple surgical excisions (which lead to secondary procedural complications) and in those who do not have a clinical response or are intolerant of the currently available therapy, Papzimeos. The available therapy, another immunotherapeutic biological agent, Papzimeos, requires maintenance of minimal residual disease through additional surgical papilloma excisions during the treatment period. Of note, the therapeutic regimen of VOCERYQ does not require additional surgical papilloma excisions during the dosing window and, thus, can provide a meaningful benefit over the available therapy for accelerated approval.

The submitted data provides substantial evidence of effectiveness of VOCERYQ based on a treatment effect on an intermediate clinical endpoint, complete response rate at 12 months (reduction/elimination of surgical papilloma excisions) in patients with active, refractory RRP (defined as requiring 3 or more surgical papilloma excisions in the 12 months prior to treatment with VOCERYQ). Confirmatory evidence includes mechanistic evidence from clinical immunogenicity assessments showing sustained and measurable antigen-specific cellular immune responses through month12 post-treatment.

The observed risks include transient, mild-moderate, non-serious adverse events that are manageable and can be appropriately mitigated through product labeling and routine post-marketing pharmacovigilance. The evidence supports a favorable benefit-risk assessment for accelerated approval, with further verification of the clinical benefit in a post-approval, adequate and well-controlled clinical study in adult and pediatric patients with RRP assessing durable reduction/elimination of surgical papilloma excisions and symptomatic improvements in a PMR.

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 VOCERYQ. The Applicant agreed to the following postmarketing requirement (PMR):

1. Inovio commits to conduct an adequate and well-controlled clinical study to verify and describe the clinical benefit of doruxapapogene ralaplasmid and lalikinogene sifuplasmid-gxfd (VOCERYQ) in patients with recurrent respiratory papillomatosis (RRP). The study should enroll at least 50 adult and pediatric patients with RRP requiring 3 or more surgical interventions for papilloma management in the 12 months prior to treatment with the product. The study should evaluate the number of surgical interventions needed for papilloma management over at least 3 years following completion of treatment with the product and compare this to an appropriate external control group or scientifically justified threshold. Product redosing may be explored in patients without sustained “complete response” (no surgical interventions over the assessment period) to doruxapapogene ralaplasmid and lalikinogene sifuplasmid-gxfd beyond 36 months.

   Draft Protocol Submission: December 30, 2026
   Final Protocol Submission: June 30, 2027
   Study completion: December 30, 2031
   Final Study Report Submission: August 30, 2032

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

2. Inovio commits to conducting additional linearity studies using a minimum of (b) (4) concentrations for the IL-12 bioassay and HPV11 (b) (4) assay in accordance with ICH Q2(R1), Section 2. The results of these studies will be submitted as a Postmarketing Commitment - Final Study Report on or before June 30, 2027.

   Final Study Report submission: June 30, 2027

3. Inovio commits to conducting an additional robustness assessment of the HPV11 (b) (4) assay by varying some of the detection components, e.g., different lots of primary and secondary antibodies and different (b) (4) The results of these assessments will be submitted as a Postmarketing Commitment - Final Study Report on or before June 30, 2027.Final Study Report submission: June 30, 2027.

   Final Study Report submission: June 30, 2027

4. Inovio commits to conducting a total of (b) (4) assay runs for the HPV11 (b) (4) (b) (4) and the IL-12 Bioactivity assays to bridge clinical lots with the current reference standard. The results of these assessments will be submitted as a Postmarketing Commitment - Final Study Report on or before January 31, 2027.

Final Study Report submission: January 31, 2027

5. Inovio commits to reevaluating the acceptance criterion for quantity of plasmid of (b) (4) of the target dose (b) (4) using data from a minimum of (b) (4) additional manufactured lots (b) (4) lots total). The results of the reevaluation will be submitted as a Postmarketing Commitment - Final Study Report on or before October 31, 2031.

   Final Study Report submission: October 31, 2031

6. Inovio commits to reevaluating the acceptance criterion for potency of (b) (4) using data from a minimum of (b) (4) additional manufactured lots ((b) (4) lots total). The results of the reevaluation will be submitted as a Postmarketing Commitment.

   Final Study Report on or before October 31, 2031
   Final Study Report submission: October 31, 2031

7. Inovio commits to conducting a comprehensive re-evaluation of the human factors (HF) validation study for the CELLECTRA™ 5PSP device. This re-evaluation will consist of a complete data reanalysis using (b) (4) categories aligned with FDA's human factors guidance (separating close calls from difficulties) and a consolidated root cause and clinical risk analysis for all observed use errors, difficulties, and close calls. Based on this re-evaluation, Inovio will determine if risk-mitigation modifications (design, labeling, or training) are necessary.

   a. If no device modifications are warranted based on the re-evaluation, Inovio will submit the final report containing the reanalysis and risk evaluation as a Postmarketing Commitment - Final Study Report before June 30, 2027.

      If device modification is not required:
      Final Study Report Submission: June 30, 2027

   b. If device modifications are necessary, Inovio will submit the proposed device modifications and supplemental validation testing protocol on or before June 30, 2027, as product correspondence for FDA review. Inovio will then conduct supplemental human factors validation testing on the modified interface to demonstrate that the changes effectively mitigate risks without introducing new hazards. The final report containing the reanalysis, risk evaluation, proposed revision of the device, and any subsequent validation testing results of the revised device will be submitted as a Prior Approval Supplement to the BLA on or before December 30, 2027.

      If device modification is required:
      Product correspondence submission: June 30, 2027
      Prior Approval Supplement: December 30, 2027

8. Inovio Pharmaceuticals Inc. commits to perform and provide results of a container closure integrity testing (CCIT) study for the VOCERYQ drug product 1.5mL glass cartridges using a positive control with an established sensitivity [i.e., minimum

critical leak defect (size) that can be reliably detected] in accordance with (b) (4) (b) (4) and that correlates to risk and detection of microbial ingress. The final study report will be submitted as a Postmarketing Commitment - Final Study Report submission: April 30, 2027.

Final Study Report Submission: April 30, 2027

9. Inovio commits to conducting comprehensive verification and validation testing of the sharps injury prevention feature for the CELLECTRA™ 5PSP device in accordance with (b) (4) and FDA guidance "Medical Devices with Sharps Injury Prevention Features - Guidance for Industry and FDA Staff". This testing will consist of (b) (4)

   Based on this testing, Inovio will determine if risk-mitigation modifications (design, labeling, or training) to the sharps injury prevention feature are necessary.

   a. If no device modifications are warranted based on the testing (i.e., all acceptance criteria are met), Inovio will submit the final report containing the verification and validation testing results as a Final Study Report before June 30, 2027.

      If device modification is not required:
      Final Study Report Submission: June 30, 2027

   b. If device modifications are necessary, Inovio will submit the proposed device modifications and supplemental validation testing protocol on or before June 30, 2027, as product correspondence for FDA review. Inovio will then conduct supplemental testing on the modified device to demonstrate that the changes effectively mitigate risks without introducing new hazards. The final report containing the proposed revision of the device and any subsequent validation testing results of the revised device will be submitted as a Prior Approval Supplement to the BLA on or before December 30, 2027.

      If device modification is required:
      Product correspondence submission: June 30, 2027
      Prior Approval Supplement: December 30, 2027

12. References

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b. Carifi, M., Napolitano, D., Morandi, M., & Dall'Olio, D. (2015). Recurrent respiratory papillomatosis: current and future perspectives. Ther Clin Risk Manag, 11, 731-738. doi.org/10.2147/TCRM.S81825
c. Schraff, S., Derkay, C. S., Burke, B., & Lawson, L. (2004). American Society of Pediatric Otolaryngology members' experience with recurrent respiratory papillomatosis and the use of adjuvant therapy. Arch Otolaryngol Head Neck Surg, 130(9), 1039-1042. Doi.org/10.1001/archotol.130.9.1039
d. Recurrent respiratory papillomatosis patient-led FDA listening session. Recurrent Respiratory Papillomatosis Foundation. Published October 27, 2022. Accessed April 23, 2025. https://www.rrpf.org/s/RRPF-FDA-Listening-Session-Summary_FINAL_12423.pdf