Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please call 800-835-4709 or 240-402-8010, extension 1. CBER Consumer Affairs Branch or send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

# Summary Basis for Regulatory Action

| | |
|---|---|
| **Date:** | August 14, 2025 |
| **From:** | Sukyoung Sohn, PhD, Review Committee Chair<br>Division of Gene Therapy 1 (DGT1)<br>Office of Gene Therapy (OGT)<br>Office of Therapeutic Products (OTP) |
| **BLA STN:** | BLA 125832/0 |
| **Applicant:** | Precigen, Inc. |
| **Submission Receipt Date:** | December 27, 2024 |
| **PDUFA Action Due Date:** | August 27, 2025 |
| **Proper Name:** | zopapogene imadenovec-drba |
| **Proprietary Name:** | PAPZIMEOS |
| **Indication:** | Treatment of Adults with Recurrent Respiratory Papillomatosis |

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

**Acting Director, Office of Clinical Evaluation, Office of Therapeutic Products**

**Director, Office of Compliance and Biologics Quality**

| Discipline Reviews | Reviewer / Consultant - Office/Division |
|---|---|
| **Regulatory** | Helen Sansone, OTP/ORMRR |
| **CMC**<br>• CMC Product (Product Office)<br>• Facilities review (OCBQ/DMPQ)<br>• Establishment Inspection Report (OCBQ/DMPQ and Product Office)<br>• QC, Test Methods, Product Quality (OCBQ/DBSQC and Product Office) | Sukyoung Sohn, PhD, OTP/OGT/DGT1<br>Joydeep Ghosh, PhD, OTP/OGT/DGT1<br>Jianyang Wang, PhD, OTP/OGT/DGT1<br>Ou (Olivia) Ma, PhD, OCBQ/DMPQ<br>Hector Carrero, OCBQ/DMPQ<br>Alifiya Ghadiali, PhD, OCBQ/DMPQ<br>Sarah Underwood, OCBQ/DMPQ<br>Shaina Fullwood, MS, OCBQ/DMPQ<br>Jana Highsmith, OCBQ/DMPQ<br>Marie Anderson, PhD, OCBQ/DBSQC<br>Hsiaoling Wang, OCBQ/DBSQC<br>Seth Schulte, MS, OCBQ/DBSQC<br>Alicia Howard, PhD, OCBQ/DBSQC |
| **Clinical**<br>• Clinical (Product Office)<br>• Postmarketing safety Pharmacovigilance review (OBPV/DPV)<br>• BIMO | Prateek Shukla, MD, OTP/OCE/DCEGM/GMB1<br>Nhu-Hac Truong, DO, OBPV, DPV, PB3<br>Char-Dell Edwards, BS, OCBQ/DIS |
| **Statistical**<br>• Clinical data (OBPV/DB) | Yakun Wang, PhD, OBPV/DB/TEB2<br>Yuqun Abigail Luo, PhD, OBPV/DB/TEB2 |
| **Non-clinical/Pharmacology/Toxicology**<br>• Toxicology (Product Office)<br>• Developmental toxicology (Product Office)<br>• Animal pharmacology | Valerie Myers, PhD, OTP/OPT |
| **Clinical Pharmacology** | Yang Chang, PhD, PharmD, OTP/OCE/DCEGM |
| **Labeling**<br>• Promotional (OCBQ/APLB)<br>• USPI Review | Jun Lee, PhD, OCBQ/APLB<br>Afsah Amin, MD, MPH, OTP/OCE |
| **Other Reviews not captured above categories**:<br>• Consult (E&L)<br>• Consult (CMC Biostats) | Andrey Sarafanov, PhD, OTP/OPPT/DH<br>Fang Chen, PhD, OBPV/DB/DNCE |
| Advisory Committee Summary | N/A |

## Table of Contents

## 1. Introduction

Precigen, Inc. submitted a Biologics License Application (BLA), STN 125832/0, for licensure of zopapogene imadenovec-drba with the proprietary name PAPZIMEOS. PAPZIMEOS is a non-replicating adenoviral vector-based immunotherapy delivered via subcutaneous injection. PAPZIMEOS is designed to generate an immune response directed against papilloma cells, which are infected with human papillomavirus (HPV) 6 and 11, in patients with recurrent respiratory papillomatosis (RRP). The PAPZIMEOS drug substance (DS) is manufactured at the Precigen facility (Germantown, MD), and the PAPZIMEOS drug product (DP) is manufactured at the (b) (4) . PAPZIMEOS received Orphan Drug and Breakthrough Therapy designations for the treatment of RRP.

The safety and effectiveness of PAPZIMEOS were evaluated in Study PRGN-2012-201 (NCT04724980), a single-arm, open-label Phase 1/2 study in patients with RRP requiring three or more surgical procedures per year. In this study, eligible adults with a confirmed RRP diagnosis first underwent surgical debulking before receiving four subcutaneous injections of PAPZIMEOS on days 1, 15, 43, and 85. Additionally, patients underwent optional surgical debulking on day 43 and/or day 85 to maintain minimal residual disease during the treatment period.

The number of surgical interventions following treatment was compared to a patient's baseline (intra-patient baseline control) to evaluate a clinically meaningful treatment effect. The primary efficacy analysis included 35 patients who received PAPZIMEOS at the proposed commercial dose level of $5\times10^{11}$ particle units (PU) per injection. The primary endpoint, complete response (CR) rate at 12 months, defined as the percentage of subjects with no clinically indicated surgical interventions during the 12 months following treatment, was achieved in 51% of patients (18/35; 95% CI 34% to 69%). Furthermore, 15 patients maintained complete response at 2 years yielding a 24-month complete response rate of 43% (15/35; 95% CI 26% to 61%). The HPV 6/11-specific T cell response was higher in patients achieving a clinical response to treatment, suggesting a correlation between induction of HPV 6/11-specific T cells and clinical benefit consistent with the hypothesized mechanism of action for PAPZIMEOS, and providing supportive evidence of effectiveness.

Patients who received any amount of PAPZIMEOS were included in the safety analysis. The most common adverse reactions noted in adults were injection site reactions, fatigue, chills, pyrexia, oropharyngeal pain, myalgia, and nausea. All treatment-emergent adverse events (TEAEs) were Grade 2 or lower. None of the Grade 3 adverse events were considered treatment-related or treatment-emergent.

Substantial evidence of effectiveness is demonstrated in Study PRGN-2012-201, a single adequate and well-controlled trial with confirmatory evidence, demonstrating a clinically meaningful observed complete response rate at 12 months and durability of response through 2 years. The study data demonstrated a strong association with substantial effect size, clear temporal relationship with demonstrated durability, and a biologically plausible mechanism supported by immunological biomarker data (coherent with disease pathophysiology) to offset the limitations of a small single arm study. The

favorable safety profile, coupled with the observed reduction in surgical interventions for treated patients, led to the clinical team's conclusion that the benefits of PAPZIMEOS outweigh the identified risks in this patient population.

The review team recommends traditional approval for PAPZIMEOS for the treatment of adults with RRP with one Post Marketing Requirement (PMR) related to virus-detection-related safety concerns during the zopapogene imadenovec-drba DS manufacturing process, three clinical Post Marketing Commitments (PMCs) related to additional evaluation of durability of treatment effect, viral shedding and pediatric extrapolation and five CMC PMCs related to DP process validation, (b) (4) assessment in the DP, DP (b) (4), and release specifications for the DS and DP, as listed in Section 11.c of this document.

Acknowledging the rarity and serious life-threatening nature of RRP, the Agency exercised significant regulatory flexibility in the review of this BLA. The Agency incorporated patient perspectives to establish a novel endpoint which allowed a single pivotal study with change from baseline control design and small sample size to be considered as an adequate and well-controlled trial to support this BLA. This approach balanced the urgent medical need against study limitations, with substantial treatment effects justifying approval in a previously untreatable condition. Since the product received Breakthrough Therapy designation for the indication, the BLA was granted priority and rolling review.

RRP affects both adult and pediatric populations, with juvenile-onset RRP and adult-onset RRP sharing the same pathophysiology. Therefore, the Applicant has agreed to conduct additional safety and efficacy evaluation in pediatric patients with RRP in a post-approval study, even with orphan drug designation.

## 2. Background

Recurrent respiratory papillomatosis is a rare and chronic disease caused by infection with HPV type 6 or 11. Patients with RRP are thought to have dysfunctional immune responses to the HPV infections, resulting in persistence of the infection and recurrent growth of papilloma anywhere in the upper and lower respiratory tract, but most commonly, the larynx. The disease has an estimated incidence of approximately 2-4 per 100,000 in children and adults, with approximately 1000 new cases of RRP diagnosed each year in the United States.

Morbidity and mortality from RRP are primarily related to papilloma mass effect within the respiratory tract. Development and growth of papilloma can lead to changes in voice quality (dysphonia), stridor, dyspnea, and airway occlusion leading to loss of lung volume, post obstructive pneumonia or respiratory failure. Malignant conversion has been reported in 3% of patients with RRP (Schraff et al., 2004, Dedo and Yu 2001). Much of the disease burden is related to the need for repeated standard of care surgical treatment and associated morbidity.

There is currently no cure for RRP, and it is considered a chronic disease. Traditional treatment for papillomatosis is repeated endoscopic debulking with ablation or excision of papillomatous lesions. Surgical excision provides symptomatic relief, but the disease

often recurs, requiring repeated patient exposure to anesthetic and surgical risks. Adjuvant treatments, directed at limiting HPV viral replication and papilloma growth, are typically applied in concert with surgical removal of papilloma to reduce disease burden and need for further surgical intervention. However, they are used off-label and as such their efficacy is not well defined and their use is limited by their side effect profiles.

The disease burden is significant, yet the heterogeneity and rarity of RRP have made large-scale studies and the development of reliable outcome measures challenging. As natural history studies are limited, there is no single reliable outcome measure or identified biomarker of disease. Patients have previously identified any reduction in the number of surgical interventions as clinically meaningful. As such, evaluation of a complete response in patients with relatively active disease has been identified as a clinical endpoint which would provide measurable benefit for the purposes of this program.

**Table 1. Regulatory History**

| Regulatory Events / Milestones | Date |
|---|---|
| 1. IND submission | October 2, 2020 |
| 2. Orphan Drug designation granted | March 17, 2021 |
| 3. Breakthrough Therapy designation granted | June 13, 2023 |
| 4. Pre-BLA meeting | August 29, 2024 |
| 5. BLA 125832/0 submission | December 27, 2024 |
| 6. BLA filed | February 24, 2025 |
| 7. Mid-Cycle communication | May 6, 2025 |
| 8. Late-Cycle meeting | June 12, 2025 |
| 9. PMR Communication | July 16, 2025 |
| 10. PMC Communication | July 28, 2025 |
| 11. Labeling Negotiation | July 28, 2025 |
| 12. PDUFA Action Due Date | August 27, 2025 |

## 3. Chemistry Manufacturing and Controls (CMC)

The CMC review team concludes that the manufacturing and controls for PAPZIMEOS can yield drug product with consistent quality attributes. The CMC review team recommends approval. PAPZIMEOS is a non-replicating adenoviral vector-based immunotherapy delivered via subcutaneous injection. The vector is a genetically modified recombinant gorilla adenovirus GC46 with deletions in the E1 (b) (4) and an insertion of the transgene expression cassette into the E1 region. The transgene encodes a fusion antigen comprising selected regions (b) (4) from HPV 6 and HPV 11 under the control of the human cytomegalovirus (CMV) immediate early promoter and enhancer. The DP is supplied as a sterile, frozen suspension in a single-dose vial that contains $5\times10^{11}$ PU per milliliter (mL) in a final formulation buffer with 10 mM Tris base, 75 mM sodium chloride, 1 mM magnesium chloride hexahydrate, 0.0025% (w/v) polysorbate 80, and 5.5% (w/v) trehalose dihydrate. The DP is stored frozen at ≤-60°C, and each vial contains an extractable volume of 1.0 mL.

**a. Product Quality**

Manufacturing and process validation: The zopapogene imadenovec-drba DS is manufactured at the Precigen facility (Germantown, MD) using (b) (4) (b) (4) the DP undergoes aseptic filling into 2 mL vials composed of cyclic olefin polymer. The filled vials are 100% visually inspected and stored at ≤ -60°C. Each vial of DP contains an extractable volume of 1.0 mL with a labeled nominal concentration of 5 x$10^{11}$ PU/mL in 10 mM Tris base, 75 mM sodium chloride, 1 mM magnesium chloride hexahydrate, 0.0025% (w/v) polysorbate 80, and 5.5% (w/v) trehalose dihydrate.

The frozen filled vials are shipped at ≤-60°C to the labeling site, (b) (4) (b) (4) where they undergo labeling at (b) (4) Following identity testing of the labeled vial, each vial is individually packaged into a pouch made of (b) (4) . Each pouched vial is then packaged into a separate carton with each carton containing one single-dose vial. The cartons are stored at ≤-60°C at the labeling and storage sites. For distribution, the DP cartons are shipped at ≤-60°C and maintained at this temperature until the time of administration at the clinical site.

The control strategy for zopapogene imadenovec-drba manufacturing includes (1) qualification of raw materials, reagents, starting materials, and manufacturing consumables, (2) in-process monitoring and in-process control testing, (3) validation of the manufacturing process (DP process performance qualification will be completed post-approval), and (4) validated lot release tests. The manufacturer accepts raw materials based on verification of raw material specifications and routine incoming acceptance tests. Suppliers are qualified and audited according to established supplier qualification programs. Raw materials derived from animals and humans are appropriately qualified to ensure the absence of microbial or viral contamination. Additionally, the manufacturing process is controlled through testing of in-process materials, DS, and DP for microbial and viral contaminants, identity, purity, strength, and potency. The analytical methods used for lot release are appropriately validated or verified. Potency of the product is assessed using two quantitative assays and one qualitative assay: (b) (4)

The DS manufacturing process has been validated through (b) (4) consecutive successful (b) (4) process performance qualification (PPQ) runs and their subsequent (b) (4) (b) (4) PPQ runs. All DS PPQ runs met the pre-defined validation acceptance criteria (AC) and lot release AC.

To complete validation of the DP manufacturing process, concurrent release of PPQ lots is being implemented. The BLA contains the interim PPQ report including data from (b) (4) (b) (4) PPQ run, the protocol for concurrent release that includes (b) (4) additional DP PPQ runs, and additional evidence supporting control of the DP manufacturing process. Overall, the submitted information supports that the DP manufacturing process is under sufficient control for commercial distribution. The plan for concurrent release of DP PPQ lots is acceptable.

Stability: The DS is stable for up to (b) (4) when stored at the long-term storage condition of (b) (4). The DP is stable for up to 24 months when stored at the long-term storage condition of ≤-60°C. The DP must be rapidly thawed at 37°C before use and preparation for immediate administration. Once thawed, the DP in a vial and/or syringe is stable for up to 60 minutes at ambient temperature.

Comparability: The current commercial manufacturing process has been optimized from the process used for the manufacture of clinical lots. (b) (4) clinical lot was used throughout the clinical trials. The comparability between the pre-change (clinical) and post-change (commercial) lots was demonstrated by analytical studies. The current manufacturing process is deemed to produce the DP with critical quality attributes that are comparable to the clinical lot used in clinical studies.

Manufacturing risks: The risk of extractables and leachables that could originate from the product manufacturing process and the container closure system was analyzed, and the analytical studies and toxicological assessments were sufficient to mitigate this risk. The risk of product contamination with microbial and viral adventitious agents is minimized by (i) ensuring adequate control of raw materials, especially those of biological origin that are used in the (b) (4) , and product manufacturing; (ii) testing of (b) (4) for microbials and adventitious viral agents; and (iii) lot release testing of (b) (4) DP for microbials. The overall risks of AVA contamination were determined to be low. However, the validation of the adventitious viral agent (AVA) testing by (b) (4) method was found to be inadequate. The Applicant will revalidate the AVA testing by (b) (4) method as a post-marketing requirement (PMR).

PMR and PMC: In addition to the aforementioned PMR, five CMC PMCs are agreed upon by the Applicant. The first PMC is to complete the DP manufacturing process validation, including (b) (4) additional PPQ runs. The second PMC is to assess (b) (4) from the DP stored at ≤-60°C for 24 months, at the end of the shelf-life. The third PMC is to reassess the (b) (4) of the DP. The fourth and fifth PMCs are to reassess acceptance criteria (AC) for release testing of the DS and DP based on manufacturing experience and to revise the AC, as appropriate.

**b. Testing Specifications**

**Table 2. PAPZIMEOS Drug Product Release Specification**

| Quality Attribute | Parameter | Method | Acceptance Criteria |
|---|---|---|---|
| **General Test** | Appearance | Visual Inspection | Slightly Opalescent to Opalescent Colorless Liquid and Free of Visible Particulates |
| | pH | (b) (4) | |
| | Volume in Container | (b) (4) | Recoverable Volume (b) (4) 1 mL |
| | (b) (4) | | |
| **Identity** | (b) (4) | | |
| **Quantity** | (b) (4) | | |
| **Potency** | (b) (4) | | |
| | (b) (4) | | |
| | (b) (4) | | |
| | (b) (4) | | |
| **Purity/ Impurity** | Purity | (b) (4) | |
| | (b) (4) | | |
| **Safety** | Particulates | (b) (4) | |
| | Endotoxin | (b) (4) | (b) (4) |
| | Sterility | (b) (4) | No Growth |
| Abbreviations: (b) (4) | | | |

The analytical methods and their validations and/or qualifications reviewed for the PAPZIMEOS DS and DP were found to be adequate for their intended use at the time of approval. The Applicant committed to reassessing the DS and DP release AC and revising them, as appropriate, within 60 days after release of the (b) (4) commercial DS batch and the (b) (4) DP lot as PMCs.

### 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 PAPZIMEOS, the activities performed, and inspectional histories are listed in Table 3 below.

**Table 3. Manufacturing Facilities Table for PAPZIMEOS**

| Name/Address | FEI number | DUNS number | Inspection/ Waiver | Justification /Results |
|---|---|---|---|---|
| Precigen, Inc.<br>20358 Seneca Meadows Pkwy<br>Germantown, MD 20876<br><br>*DS manufacturing; DP release testing* | 3014429654 | 054652865 | Inspection | CBER/DMPQ<br>April 2025<br>NAI |
| (b) (4)<br><br>*DP manufacturing* | (b) (4) | | Inspection | CBER/DMPQ<br>(b) (4)<br>VAI |
| (b) (4)<br><br>*DP primary labeling* | (b) (4) | | Waiver* | OII<br>(b) (4)<br>NAI |
| (b) (4)<br><br>*DP release testing* | (b) (4) | | Waiver* | OII<br>(b) (4)<br>VAI |
| (b) (4) | | | Waiver* | ORA<br>(b) (4)<br>VAI |

| | | | | |
|---|---|---|---|---|
| (b) (4)<br><br>*DP release testing* | | | | |
| * Waived for this BLA.<br>Abbreviations: DMPQ - Division of Manufacturing and Product Quality; OII – Office of Inspections and Investigations; ORA – Former Office of Regulatory Affairs; NAI – No Action Indicated; VAI – Voluntary Action Indicated | | | | |

CBER Division of Manufacturing and Product Quality (DMPQ) performed a pre-license inspection (PLI) of the Precigen, Inc. facility in April 2025. No Form FDA 483 was issued, and the inspection was classified as No Action Indicated (NAI).

CBER/DMPQ performed a PLI of the (b) (4) facility in (b) (4). A Form FDA 483 was issued. All inspectional issues have been resolved, and the inspection was classified as Voluntary Action Indicated (VAI).

The Office of Inspections and Investigations (OII) performed a surveillance inspection of the (b) (4) facility in (b) (4). No Form FDA 483 was issued, and the inspection was classified as NAI.

The OII performed a surveillance inspection of the (b) (4) facility in (b) (4). A Form FDA 483 was issued. All inspectional issues have been resolved, and the inspection was classified as VAI.

The former Office of Regulatory Affairs (ORA) performed a surveillance inspection of the (b) (4). facility in (b) (4). A Form FDA 483 was issued. All inspectional issues have been resolved, and the inspection was classified as VAI.

**e. Container/Closure System**

The container closure system consists of a 2 mL (b) (4) vial manufactured by (b) (4) a 13-mm (b) (4) grey chlorobutyl rubber stopper with (b) (4) on product contact side and (b) (4) on non-product side manufactured by (b) (4), and an aluminum seal with a flip-off plastic top manufactured by (b) (4)

(b) (4) performed the container closure integrity testing, 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 Agency determined that approval of PAPZIMEOS will not result in any significant environmental impact. A Finding of No Significant Impact (FONSI) memorandum has been prepared.

## 4. Nonclinical Pharmacology/Toxicology

The nonclinical development program evaluated (b) (4) nonclinical lot of PAPZIMEOS, referred to in the nonclinical studies by the company code name, PRGN-2012. The differences made between PRGN-2012 nonclinical lot and PAPZIMEOS are scaling and the use of standardized manufacturing for PAPZIMEOS.

In vitro assessment of transduction efficiency of the gorilla adenovirus GC46 was evaluated in monocyte-derived dendritic cells (Mo-DCs) from healthy control or RRP patient peripheral blood mononuclear cells (PBMCs). The mean transduction efficiencies were above 80% in all human cell populations tested indicating consistent and effective expression of the target antigens/peptides for activation by the immune system.

Antigenicity of PRGN-2012 was evaluated in two separate co-culture studies. CD3+ T cells were isolated from healthy donors (n=3) or patients with RRP who were positive for infection with HPV 6 (n=2) or HPV 11 (n=up to 3). PBMC-derived Mo-DCs were transduced with either PRGN-2012, GC46 (b) (4) empty GC46 (GC46.empty), (b) (4) The T cells from healthy donors and patients with RRP co-cultured with multiple rounds of PRGN-2012-transduced Mo-DCs expanded to a greater extent and produced higher levels of interferon-gamma (IFN-ɣ), granzyme-B, and granulocyte-macrophage colony-stimulating factor (GM-CSF) at all timepoints assessed compared to controls. In addition, the transduction of Mo-DCs with PRGN-2012 increased total cytokine production by both CD8+ and CD4+ T cells isolated from RRP patients compared to the healthy control donor indicating a recall response.

Immunogenicity from ex vivo isolated T cells was evaluated on Day 14 from mice (b) (4) immunized subcutaneously with PRGN-2012 or empty vector on Days 0 and 7. Isolated T cells from both groups (b) (4) IFN-ɣ levels were subsequently assessed. Mice immunized with PRGN-2012 demonstrated a marked, HPV antigen-specific IFN-ɣ response compared to mice immunized with empty vector alone. In a second study of healthy wildtype animals (C57BL/6 mice), T cells were isolated on Day 14 and 21 from mice immunized subcutaneously with either PRGN-2012, GC46.empty vector, or FFB on Day 0. Responsiveness of ex vivo isolated T cells and APCs from immunized mice was assessed by direct stimulation with OP from both HPV 6 E6 and HPV 11 E6 on Day 14 or antigenic E6/E7 peptides on Day 21. Compared to controls, the HPV-specific peptides activated increased IFN-ɣ frequencies from PRGN-2012 immunized animals from both the Days 14 and 21 harvest and also induced production of the chemokines RANTES and (b) (4) from Day 21 assessments.

Local tolerance and systemic toxicity were assessed as part of the repeat dose toxicity study of PRGN-2012 in wild type (WT) C57BL/6 mice. PRGN-2012 or GC46.empty vector was administered once weekly for three weeks at $1\times10^{10}$ VP/administration. Local tolerance (i.e., injection site reactions) was assessed by examination of the injection sites at 3±1 and 24±4 hours after each administration. There were no local tolerance or systemic toxicity findings reported for the duration of the study.

A bioinformatics screen for potential endogenous antigen immunogenicity was performed in silico using (b) (4) to assess for homology of the PRGN-2012 antigen amino acid sequence against (b) (4) proteins. The only protein sequences with alignment to the PRGN-2012 fusion antigen were proteins expressed by HPV, indicating a low potential for off-target human endogenous protein immunogenicity.

Repeat administration of a dose level approximately 5-fold higher than the intended clinical dose of $5\times10^{11}$ PU of PRGN-2012, once weekly on Days 0, 7, and 14 was well tolerated in WT C57BL/6 mice with no safety findings reported at termination after 21 Days.

No biodistribution (BD), genotoxicity, carcinogenicity, reproductive and developmental toxicity, juvenile, nor dedicated local tolerance studies of PRGN-2012 were conducted. These studies are not warranted based on the product characteristics and nonclinical safety profile of PRGN-2012.

## 5. Clinical Pharmacology

The clinical pharmacology evaluation of PAPZIMEOS is based on a Phase 1/2, ongoing, single-arm, non-randomized, open-label study (Study PRGN-2012-201).

Biodistribution and Vector Shedding

No biodistribution and vector shedding studies have been conducted with PAPZIMEOS. The potential risk of viral shedding following PAPZIMEOS administration is considered very low due to the replication-defective nature of the vector and the subcutaneous route of administration. Based on the product-specific shedding profile, favorable safety data with no serious safety signals, rare disease indication with significant unmet medical need, and Priority Review designation, FDA has determined that vector shedding evaluation can be conducted post-marketing for PAPZIMEOS. The Applicant has agreed to conduct viral shedding studies following administration of PAPZIMEOS in adult patients with RRP in a future study under a post-marketing commitment.

Pharmacodynamics

The pharmacodynamic effect of PAPZIMEOS was evaluated in Study PRGN-2012-201. In 30 patients evaluated at 6-weeks post treatment, clinical responders demonstrated significantly higher induction of HPV 6- and HPV 11-specific T cell responses compared to non-responders, with mean fold-change from baseline of 164.9 versus 5.1, respectively ($p<0.018$). This difference persisted at 12 weeks post-treatment, with mean fold-change of 61.5 in responders versus 11.5 in non-responders. These pharmacodynamic results provide mechanistic supportive evidence for the efficacy of PAPZIMEOS treatment.

## 6. Clinical/Statistical

### a. Clinical Program

Primary evidence of effectiveness for PAPZIMEOS comes from Study PRGN-2012-201, a prospective, open-label, single-arm, Phase 1/2 study evaluating PAPZIMEOS in patients with RRP, conducted under IND 26884. The study enrolled adults who had

histological and clinically diagnosed RRP and required 3 or more debulking procedures to remove laryngotracheal papilloma in the 12 months prior to treatment with PAPZIMEOS. Prior to initiation of treatment with PAPZIMEOS (i.e., Day 1), patients underwent a standard-of-care surgical debulking procedure to remove laryngotracheal papilloma. Physicians also had the option to remove any visible papilloma during the treatment interval at Days 43 and/or 85. The planned duration of follow-up for patients enrolled in the study was 36 months.

The primary efficacy endpoint was complete response, defined as having no requirement for surgical intervention in the 12 months following treatment. Additional efficacy outcome measures taken into consideration include complete response at 24 months and T-cell response.

Efficacy

In Study PRGN-2012-201, 38 patients received any amount of PAPZIMEOS. The median age was 50 years (range 20 to 88 years) and 60% were male. The demographic characteristics were as follows: 33 patients (87%) were White, 1 patient (3%) was Asian, 1 patient (3%) was African American, 1 patient (3%) was of “other” race, 2 patients (5%) were unknown. Generalizability could not be determined based on limitations of sample size and disease rarity. The median number of baseline surgical procedures performed in the 12 months prior to treatment was 4 (range 3 to 10). Patients were evenly distributed across body mass index (BMI) weight categories: 12 healthy weight (31.6%), 13 overweight (34.2%), and 13 obese (34.2%). All patients completed the full treatment course of four subcutaneous injections of PAPZIMEOS on Day 1, and at weeks 2, 6 and 12.

Of the 38 patients enrolled in PRGN-2012-201, 3 patients were treated with PAPZIMEOS at a dose of $1\times10^{11}$ PU per injection. The 35 patients who received PAPZIMEOS at the commercial dose level of $5\times10^{11}$ PU per injection were included in the primary efficacy analysis population. Of the 35 patients treated, 34 were evaluable for the primary analysis at 12-months and additional analysis at 24-months and 12 completed the ongoing three-year study. There was one death 10 months after treatment which was not considered treatment-related and was counted as treatment failure in the efficacy analyses.

The primary efficacy endpoint of complete response at 12 months was achieved in 51% of patients (18/35; 95% CI 34% to 69%). Furthermore, 15 patients maintained complete response at 2 years yielding a 24-month complete response rate of 43% (15/35; 95% CI 26% to 61%). HPV 6/11-specific T cell response was higher in patients achieving a clinical response to treatment, suggesting a correlation between induction of HPV 6/11 T cells and clinical benefit consistent with the hypothesized mechanism of action for PAPZIMEOS and providing supportive evidence of effectiveness.

Variables affecting statistical analysis, including tabulation of baseline surgical interventions, minimal residual disease status, potential regression to the mean, design changes to the ongoing study, missing data, and concomitant medications were taken into consideration when reviewing efficacy of PAPZIMEOS. In view of the available data and multiple analyses, the clinical and statistical reviewers determined that the treatment effect size, especially on the 24-month complete response rate, is large and

demonstrates continued benefit sufficient to outweigh the biases and additional uncertainties considered.

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

Bioresearch Monitoring (BIMO) inspection assignments were issued for the Applicant, and one domestic clinical investigator site that participated in the conduct of study protocol PRGN-2012-201: A Phase 1/2 Study of Adjuvant PRGN-2012 in Adult Participants with Recurrent Respiratory Papillomatosis. The inspections did not reveal substantiative issues that impact the data submitted in this original BLA.

### c. Pediatrics

PAPZIMEOS has orphan drug designation for the treatment of RRP and is exempt from Pediatric Research Equity Act (PREA) pediatric study requirements. As RRP affects both adult and pediatric populations, the Applicant has agreed to conduct additional evaluation of pediatric patients with RRP in a future study under a post-marketing commitment with expected final study report by December 31, 2028.

### d. Other Special Populations

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

## 7. Safety and Pharmacovigilance

Safety
Safety of PAPZIMEOS was evaluated in all 38 patients who received any amount of PAPZIMEOS in the prospective Study PRGN-2012-201. This included the 35 patients evaluated for efficacy who received PAPZIMEOS at the commercial dose of $5\times10^{11}$ PU per injection and 3 patients who received PAPZIMEOS at the initial tested dose of $1\times10^{11}$ PU per injection. The most frequently occurring adverse reactions reported following injection with PAPZIMEOS were injection site reactions, fatigue, chills, pyrexia, oropharyngeal pain, myalgia, and nausea.

Given the small study population for this rare disease, the clinical team concluded that the potential risk of thrombotic events associated with adenoviral vector therapies could not be excluded even though this was not observed in the clinical study of PAPZIMEOS. Therefore, additional precautions were included in PAPZIMEOS prescribing information.

Pharmacovigilance Plan
The Applicant submitted a pharmacovigilance plan for PAPZIMEOS. No important identified risks have been observed for inclusion. The important potential risk associated with PAPZIMEOS include a risk of thrombosis in adeno-viral based products. Postmarketing safety monitoring will include:

- Routine pharmacovigilance: Adverse event reporting and submission of periodic safety reports in accordance with 21 CFR 600.80
- Enhanced pharmacovigilance: Identification of potential thrombotic events as an Important Potential Risk and expedited (15-day) reporting to FAERS for all events

of thrombosis regardless of seriousness or label status for three years post-approval, in addition to inclusion of a summary and analysis in periodic safety reports.

Data available at this time do not suggest any safety signals that warrant a Risk Evaluation and Mitigation Strategy. Completion of the ongoing clinical Study PRGN-2012-201 and evaluation of viral vector shedding in patients who have received PAPZIMEOS for the approved indication will further characterize the safety of PAPZIMEOS in the indicated population.

## 8. Labeling

The proposed proprietary name, PAPZIMEOS, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on March 20, 2025, and was found acceptable. CBER communicated the acceptability of the proprietary name to the Applicant on April 1, 2025. On May 28, 2025, APLB reviewed and found the Precigen's fourth proposed suffix, -drba, acceptable. CBER communicated the acceptability of the suffix to the Applicant on July 14, 2025.

APLB reviewed the proposed prescribing information and package and container labels on June 30, 2025, and found them acceptable from a comprehension, readability, and promotional perspective.

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.

## 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

The review of this BLA for PAPZIMEOS demonstrates significant regulatory flexibility tailored to the unique challenges of rare disease drug development. Most notably, FDA accepted a single-arm, open-label Phase 1/2 study as a single adequate and well controlled study with confirmatory evidence for licensure due to RRP's rarity and the impracticality of placebo-controlled designs given the current surgical standard of care. The Agency incorporated patient perspectives from listening sessions that emphasized any reduction in surgical interventions would be meaningful, leading to acceptance of a novel complete response endpoint defined as absence of surgical interventions for 12 months. Additional flexibility included accepting uncertainty related to retreatment,

converting the application from accelerated to traditional approval based on durability data, allowing final process validation report as post-marketing commitment and concurrent release of PPQ lots, permitting vector shedding studies to be conducted post-marketing rather than pre-approval, and accepting pediatric studies as post-marketing commitments rather than pre-approval requirements. This comprehensive approach balanced the urgent unmet medical need for this life-threatening rare condition against study limitations, ultimately determining that the substantial treatment effect (51% complete response at 12 months, 43% at 24 months) in a previously untreatable condition justified approval with appropriate post-marketing oversight while maintaining scientific rigor.

## 11. Recommendations and Benefit/Risk Assessment

### a. Recommended Regulatory Action

The Applicant has provided substantial evidence of effectiveness from an adequate and well controlled study based on complete response at 12 months following treatment and sustained treatment effect through 24 months. The review team recommends traditional approval for PAPZIMEOS.

### b. Benefit/Risk Assessment

The benefit of PAPZIMEOS was demonstrated in Study PRGN-2012-201. The study demonstrated a 12-month complete response rate of 51% and a 24-month complete response rate of 43% which is considered a clinically meaningful benefit in the indicated population. PAPZIMEOS' effects on induction of HPV 6/11-specific T cells in patients achieving a clinical response to treatment provides supportive evidence of benefit. PAPZIMEOS is indicated for use in adults with RRP.

The observed safety risks of injection site reactions, fatigue, chills, pyrexia, oropharyngeal pain, myalgia, and nausea were common adverse reactions identified during this study and consistent with the risks seen with existing immunotherapy options. These risks can be adequately mitigated through product labeling and therefore, routine pharmacovigilance is warranted at this time. Based on the totality of presented data and the unmet need for patients with the rare disease, recurrent respiratory papillomatosis, the benefit outweighs the risks for this product.

### c. Recommendation for Postmarketing Activities

The Applicant agreed to the following PMRs and PMCs:

Post Marketing Requirements (PMR)

1. Precigen, Inc. will conduct an (b) (4) laboratory safety study to address the virus-detection-related safety concerns for the analytical method used to detect adventitious viral contamination in the (b) (4) during the zopapogene imadenovec-drba drug substance manufacturing process. This study will include: (1) validation of assay specificity and detection limits for control viruses by (b) (4); and (2)

verification of method suitability by (b) (4)

Final Validation Protocol Submission Date for FDA's Review: September 30, 2025
Study Completion Date: January 31, 2026
Final Report Submission Date: February 28, 2026

Post Marketing Commitments (PMC)

Clinical PMC item subject to reporting requirements under section 506B:

2. Precigen, Inc. commits to complete and submit the study report and dataset for Study PRGN-2012-201, a single-arm, open-label Phase 1/2 study conducted in adult patients requiring 3 or more surgical interventions for management of RRP in the 12 months prior to treatment.

   Final study report submission: December 31, 2026

3. Precigen, Inc. commits to conduct viral shedding studies following administration of zopapogene imadenovec-drba in adult patients with recurrent respiratory papillomatosis.

   Final study report submission: December 31, 2026

4. Precigen, Inc. commits to conduct a prospective, single arm, open label study of the safety and efficacy of zopapogene imadenovec-drba in pediatric patients with recurrent respiratory papillomatosis.

   Final study report submission: December 31, 2028

CMC PMC items not subject to reporting requirements under section 506B:

5. Precigen, Inc. commits to completing the manufacturing process validation for the zopapogene imadenovec-drba drug product, including (b) (4) additional process performance qualification runs. A final study report for the drug product manufacturing process validation will be submitted as a "Post-marketing Study Commitment – Final Study Report".

   Final study report submission: December 31, 2025

6. Precigen, Inc. commits to assessing (b) (4) from the zopapogene imadenovec-drba drug product stored at ≤ -60°C for 24 months, at the end of the proposed shelf-life. A final (b) (4) assessment report will be submitted as a "Post-marketing Study Commitment – Final Study Report".

   Final study report submission: June 30, 2026

7. Precigen, Inc. commits to reassessing the (b) (4) of the zopapogene imadenovec-drba drug product. A final study report will be submitted as a "Postmarketing Study Commitment – Final Study Report".

   Final study report submission: December 31, 2025

8. Precigen, Inc. commits to reassessing the acceptance criteria for release testing of the zopapogene imadenovec-drba drug substance based on manufacturing experience and revising the acceptance criteria, as appropriate. A final acceptance criteria reassessment report will be submitted as a "Postmarketing Study Commitment – Final Study Report" within 60 days after release of the (b) (4) commercial drug substance batch.

   Final study report submission: December 31, 2027

9. Precigen, Inc. commits to reassessing the acceptance criteria for release testing of the zopapogene imadenovec-drba drug product based on manufacturing experience and revising the acceptance criteria, as appropriate. A final acceptance criteria reassessment report will be submitted as a "Postmarketing Study Commitment – Final Study Report" within 60 days after release of the (b) (4) commercial drug product lot.

   Final study report submission: December 31, 2031

## 12. References


a. Benedict, P. A., Ruiz, R., Yoo, M., Verma, A., Ahmed, O. H., Wang, B., Dion, G. R., Voigt, A., Merati, A., Rosen, C. A., Amin, M. R., & Branski, R. C. (2018). Laryngeal distribution of recurrent respiratory papillomatosis in a previously untreated cohort. Laryngoscope, 128(1), 138-143. doi.org/10.1002/lary.26742
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. Dedo, H. H., & Yu, K. C. (2001). CO(2) laser treatment in 244 patients with respiratory papillomas. Laryngoscope, 111(9), 1639-1644. doi.org/10.1097/00005537-200109000-00028
d. 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