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BLA Clinical and Clinical Pharmacology Review Memorandum

Application Type	BLA, Original Application
STN	125832/0
CBER Received Date	December 27, 2024
PDUFA Goal Date	August 27, 2025
Division / Office	DCEGM/OCE/OTP
Priority Review (Yes/No)	Yes
Clinical Reviewer	Prateek Shukla, MD
Clinical Pharmacology Reviewer	Yang Chang, PhD, PharmD
Review Completion Date / Stamped Date	August 11, 2025
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Team Leader (Acting) Clinical Pharmacology	Xiaofei Wang, PhD
Division Director (Acting), DCEGM Office Director (Acting), OCE	Asha Das, MD
Applicant	Precigen, Inc.
Established Name	zopapogene imadenovec-drba (PRGN-2012)
(Proposed) Trade Name	PAPZIMEOS
Pharmacologic Class	Non-replicating adenoviral vector-based immunotherapy
Formulation(s), including Adjuvants, etc.	Formulated in 10 mM Tris, 75 mM NaCl, 1 mM MgCl ₂ •6H ₂ O, 5.5% trehalose dihydrate, 0.0025% polysorbate 80, pH ^{(b) (4)} , and stored frozen at ≤ -60°C.
Dosage Form(s) and Route(s) of Administration	Suspension for subcutaneous injection, supplied in a single-dose vial formulated to contain a recoverable dose of 5.0×10 ¹¹ adenoviral vector particles in a 1.0 mL suspension
Dosing Regimen	5×10 ¹¹ particle units per subcutaneous injection administered four times over a 12-week interval
Indication(s) and Intended Population(s)	For the treatment of adults with recurrent respiratory papillomatosis
Orphan Designated (Yes/No)	Yes

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GLOSSARY

AE	adverse event
APC	antigen-presenting cell
AVA	adventitious viral agent
BLA	Biologics License Application
BMI	body mass index
CBER	Center for Biologics Evaluation and Research
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CR	complete response
DL	dose level
ELISpot	enzyme-linked immunospot
HPV	human papillomavirus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	investigational new drug
IR	information request
LTFU	long-term follow-up
MAX	maximum
MIN	minimum
MRD	minimal residual disease
NAb	neutralizing antibody
NIH	National Institutes of Health
ORR	objective response rate
PIL	papilloma-infiltrating lymphocyte
PMC	postmarketing commitment
PR	partial response
PU	particle units
RRP	recurrent respiratory papillomatosis
SAE	serious adverse event
SD	standard deviation
STFU	short-term follow-up
TEAE	treatment-emergent adverse event
USPI	United States Prescribing Information
VHI-10	Voice Handicap Index-10

1. EXECUTIVE SUMMARY

On December 27, 2024, Precigen, Inc. (the Applicant) submitted an original BLA 125832 for licensure of zopapogene imadenovec-drba (PRGN-2012) with the proposed indication, “for treatment of adults with recurrent respiratory papillomatosis.”

PRGN-2012 is a non-replication competent gorilla adenovirus-based immunotherapy delivered via subcutaneous injection which is designed to generate an immune response directed against papilloma cells, which have been infected with human papillomavirus (HPV) 6 and 11, in patients with recurrent respiratory papillomatosis (RRP).

RRP is a rare and chronic disease caused by persistent HPV 6 and/or HPV 11 resulting in recurrent growth of papilloma anywhere in the upper and lower respiratory tract. Juvenile disease often presents before 5 years of age and is usually acquired through vertical transmission from mother to child during birth, while adult onset often presents between 20 and 40 years of age and is thought to be acquired through sexual contact. The underlying pathophysiology of juvenile and adult onset does not differ. Morbidity and mortality from RRP are primarily related to papilloma mass effect within the respiratory tract, which contribute to clinical symptoms of dysphonia, stridor, dyspnea, and airway occlusion. Recurrent airway lesions lead to loss of lung volume, post-obstructive pneumonia, or respiratory failure and in rare instances may lead to malignant transformation. Rarity of disease combined with variable expression and disease course lead to a lack of understanding of the natural history of the disorder and makes large-scale studies impractical. Because of these issues, there has been no single reliable outcome measure or identified biomarker of disease that can be used to track treatment outcomes.

There is no curative option for RRP. Standard of care treatment for RRP is repeated endoscopic debulking with ablation or excision of papillomatous lesions. Repeated procedures often lead to structural airway complications contributing to significant disease morbidity. In addition to surgical removal of papilloma, adjuvant therapy is available to patients requiring more than three surgical procedures annually, rapid recurrence of papilloma with airway compromise, and distal multisite spread of the disease through off license use of existing therapies aimed at immunomodulation (e.g., imiquimod), disruption of HPV replication (e.g., cidofovir), control of inflammation (e.g., celecoxib), or prevention of angiogenesis (e.g., bevacizumab). However, use of these therapies is limited by inconsistent effectiveness, recurrence of disease after treatment cessation and the potential for severe side effects.

Evidence to support safety and efficacy of PRGN-2012 comes from an ongoing single-arm, open-label, baseline-controlled Phase 1/2 study (PRGN-2012-201). In this study, eligible adults with a confirmed RRP diagnosis first underwent surgical debulking before receiving four subcutaneous injections of PRGN-2012 on Days 1, 15, 43, and 85. Additionally, patients underwent surgical debulking on Days 43 and/or 85, if needed, to maintain minimal residual disease (MRD) during the treatment period. The Phase 1 portion was a dose-escalation and expansion study evaluating two dose levels: 1×10^{11} and 5×10^{11} particle units (PU) per injection. Phase 2 further evaluated safety and efficacy through dose expansion of the 5×10^{11} PU dose level in patients with RRP requiring 3 or more surgical procedures per year. Patients who received any amount of PRGN-2012 in Phases 1 or 2 were included in the safety analysis. The efficacy analysis

assessed response only in patients who received PRGN-2012 at the proposed commercial dose level of 5×10^{11} PU per injection.

In the original submission, the Applicant provided 12-month data for 38 patients treated with any amount of PRGN-2012 in either the Phase 1 or Phase 2 study. Due to the ongoing nature of the study, initial conclusions regarding durability of treatment effect beyond 12 months were limited and a confirmatory study evaluating patients over a longer period was considered. In the 120-day safety update, the Applicant also provided additional clinical efficacy data allowing for evaluation of 38 patients through 2 years and 15 patients through end of study at 3 years.

Efficacy

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 PRGN-2012 at the proposed commercial dose level of 5×10^{11} 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). Fifteen patients maintained complete response at 2 years yielding a 24-month complete response rate of 43% (15/35; 95% CI 26% to 61%). Six of these patients were evaluated through the end of the study, at 3 years, and had continued complete response further supporting durability of treatment effect.

Supportive efficacy data from the study includes evaluation of patients who achieved a > 50% reduction in the number of surgical interventions during the 12 months following treatment. Further analysis of this group found induction of HPV 6/11-specific T cells was higher in patients achieving a clinical response to treatment as compared to patients who did not reach an objective clinical response (mean best overall fold change from baseline 164.9 versus 5.1, respectively; $p < 0.018$). Overall, these data suggest a correlation between induction of HPV 6/11 T cell response and clinical benefit. This would be consistent with the hypothesized mechanism of action for PRGN-2012.

Subgroup analyses of response rates conducted by HPV type (i.e., HPV type 6 or HPV type 11), number of surgeries prior to treatment, and age at disease onset (juvenile or adult onset) were generally consistent with the results of the overall population.

Safety

The safety analysis included 38 patients who received any amount of PRGN-2012 in Phase 1 or 2. The most common adverse reactions were injection site reactions (97.4%), fatigue (73.7%), chills (65.8%), pyrexia (63.2%), oropharyngeal pain (55.3%), myalgia (28.9%), and nausea (26.3%). No dose-limiting toxicities were observed, and all treatment-emergent adverse events (TEAEs) were Grade 2 or lower. Four treatment-unrelated Grade 3 adverse events were reported in one patient each (i.e., four patients, 10.5%), and included upper gastrointestinal hemorrhage, bacterial laryngitis, syncope, and hypertension. One death due to cardiac arrest occurred on Day ^{(b) (6)} in a patient treated at dose level 2, but this event was not considered treatment-related or treatment-emergent.

Recommendation

Study PRGN-2012-201 serves as a single adequate and well-controlled trial with confirmatory evidence as the basis of approval for PRGN-2012. The complete response rate at 12 months and durability of response up to 3 years observed with PRGN-2012 in patients with RRP represent a clinically meaningful treatment effect and provide substantial evidence of effectiveness in the context of a serious rare disease with very limited treatment options. The favorable safety profile, coupled with the observed reduction in surgical interventions for treated patients at 12 and 24 months, suggests that the benefits of PRGN-2012 outweigh the identified risks in this patient population. Despite limitations of a small single arm study, the clinical data demonstrates a strong association with substantial effect size, clear temporal relationship with demonstrated durability, and a biologically plausible mechanism supported by immunological biomarker data which is coherent with disease pathophysiology. Therefore, the Clinical and Clinical Pharmacology reviewers recommend traditional approval for PRGN-2012 for the treatment of adults with RRP.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Demographic information for the 38 patients who received PRGN-2012 in study PRGN-2012-201 are shown in [Table 1](#). Efficacy analyses were performed on 35 patients who received PRGN-2012 at dose level 2 while safety analyses were performed on 38 total patients receiving any amount of PRGN-2012 in either Phase 1 or Phase 2.

Table 1. Key Demographic Characteristics, PRGN-2012-201

Characteristic	Phase 1 Dose Level 1 1×10 ¹¹ n=3	Phase 1 Dose Level 2 5×10 ¹¹ n=12	Phase 2 Dose Level 2 5×10 ¹¹ n=23	Phase 1/2 Total N=38
Sex, n (%)	--	--	--	--
Male	3 (100%)	7 (58.3%)	13 (56.5%)	23 (60.5%)
Female	0 (0%)	5 (41.7%)	10 (43.5%)	15 (39.5%)
Age, years	--	--	--	--
Mean (SD)	56.3 (15.1)	49.7 (12.8)	49.2 (17.3)	49.9 (15.6)
Median (min, max)	63.0 (39, 67)	49.5 (30, 73)	49.0 (20, 88)	49.5 (20, 88)
Race, n (%)	--	--	--	--
Asian	1 (33.3%)	0	0	1 (2.6%)
Black or African American	0	1 (8.3%)	0	1 (2.6%)
White	1 (33.3%)	11 (91.7%)	21 (91.3%)	33 (86.8%)
Other	0	0	1 (4.3%)	1 (2.6%)
Unknown or not reported	1 (33.3%)	0	1 (4.3%)	2 (5.3%)
Ethnicity, n (%)	--	--	--	--
Hispanic or Latino	0 (0%)	0	4 (17.4%)	4 (10.5%)
Not Hispanic or Latino	3 (100%)	11 (91.7%)	18 (78.3%)	32 (84.2%)
Unknown or not reported	0 (0%)	1 (8.3%)	1 (4.3%)	2 (5.3%)
BMI at baseline (kg/m ²)	--	--	--	--
Mean (SD)	25.6 (5.6)	27.3 (5.0)	28.0 (6.6)	27.6 (6.0)
Median (min, max)	23.4 (21.4, 32.0)	26.2 (20.8, 36.7)	26.4 (19.3, 50.2)	25.9 (19.3, 50.2)

Characteristic	Phase 1 Dose Level 1 1×10 ¹¹ n=3	Phase 1 Dose Level 2 5×10 ¹¹ n=12	Phase 2 Dose Level 2 5×10 ¹¹ n=23	Phase 1/2 Total N=38
Weight category based on BMI	--	--	--	--
Healthy weight (18.5 to 24.9 kg/m ²)	2 (66.7%)	4 (33.3%)	6 (26.1%)	12 (31.6%)
Overweight (25 to 29.9 kg/m ²)	0	4 (33.3%)	9 (39.1%)	13 (34.2%)
Obese (≥30 kg/m ²)	1 (33.3%)	4 (33.3%)	8 (34.8%)	13 (34.2%)
Primary disease site	--	--	--	--
Larynx	2 (66.7)	8 (66.7)	19 (82.6)	29 (76.3)
Other	1 (33.3)	4 (33.3)	4 (17.4)	9 (23.7)
Number of years from diagnosis	--	--	--	--
Mean (SD)	18.7 (20.6)	13.8 (14.1)	23.9 (20.5)	20.3 (18.8)
Median (min, max)	11.0 (3, 42)	6.0 (1, 35)	22.0 (1, 65)	15.5 (1, 65)
Age at disease onset, n (%)	--	--	--	--
Juvenile onset (<18 years)	0	2 (16.7)	10 (43.5)	12 (31.6)
Adult onset (≥18 years)	3 (100)	10 (83.3)	13 (56.5)	26 (68.4)
HPV viral type	--	--	--	--
6	2 (66.7)	9 (75.0)	15 (65.2)	26 (68.4)
11	1 (33.3)	3 (25.0)	8 (34.8)	12 (31.6)

Source: Applicant dataset (PRGN-2012-201), CSR Table 14.1.3.2, 14.1.4.1

Abbreviations: BMI = body mass index; HPV = human papillomavirus; max = maximum; min = minimum; SD = standard deviation

1.2 Patient Experience Data

On October 27, 2022, the Recurrent Respiratory Papillomatosis Foundation held a Patient-Led Listening Session with the FDA. The objective of the session was to provide FDA staff with the patient and caregiver perspectives on living with RRP. Key points provided by patients during this listening session include the following:

- RRP exacts a heavy social, mental, and emotional toll on patients and their families. Patients' inability to use their speaking voice and constant interruptions to daily life caused by repeated surgical interventions contributes to this toll.
- Patients and families are desperate for non-surgical treatments for RRP, indicating that an end to surgery would mean "everything." As a result, patients with RRP and their caregivers have a significant risk tolerance for new therapies. Many have indicated that any decrease in the number of surgeries would be worth the possible risk of side effects.
- Given that RRP is a rare disease with a heterogeneous presentation, and the current standard of care is surgery leading to an accumulation of scarring and damage to the anatomy, randomized placebo-controlled trial design(s) are not ideal and therefore should be carefully considered.
- Any reduction in the number of surgeries is a meaningful outcome for patients and caregivers.

The Applicant did not submit these data in their application; however, these data, which comprised patient and caregiver perspectives, were considered in review of this BLA.

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
<input type="checkbox"/>	Patient-reported outcome	
<input type="checkbox"/>	Observer-reported outcome	
<input checked="" type="checkbox"/>	Clinician-reported outcome	Section 6.1.11
<input type="checkbox"/>	Performance outcome	
<input type="checkbox"/>	Patient-focused drug development meeting summary	
<input type="checkbox"/>	FDA Patient Listening Session	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies	
<input type="checkbox"/>	Other: (please specify)	
<input checked="" type="checkbox"/>	If no patient experience data were submitted by Applicant, indicate here.	
Check if Considered	Type of Data	Section Where Discussed, if Applicable
<input type="checkbox"/>	Perspectives shared at patient stakeholder meeting	
<input type="checkbox"/>	Patient-focused drug development meeting	
<input checked="" type="checkbox"/>	FDA Patient Listening Session	Section 1.2
<input type="checkbox"/>	Other stakeholder meeting summary report	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Other: (please specify)	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition Studied

Recurrent respiratory papillomatosis is a rare and chronic disease caused by infection with HPV 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 neoplastic growth of exophytic papilloma anywhere in the upper and lower respiratory tract, but most commonly the larynx (Benedict et al., 2018; Carifi et al., 2015). The disease has an estimated incidence of approximately 2-4 per 100,000 in children and adults (Gerein et al., 2005; Lindeberg & Elbrond, 1990; Reeves et al., 2003; Wiatrak, 2003) with approximately 1,000 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 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 & Yu, 2001).

The disease burden is significant, yet the variable expression and rarity of RRP have made large-scale studies and the development of reliable outcome measures challenging. One of the main difficulties in studying RRP is the lack of understanding of the natural history of the disorder. The disease is variable in expression between individuals and, even within individuals, the course can wax and wane (Fortes et al., 2017). In addition, because of the rarity of the disease and different ways that it is managed across the world, conducting large-scale studies can be challenging. Because of these issues, there has been no single reliable outcome measure or identified biomarker of disease that can be used to track treatment outcomes. Additionally, there are no guidelines or best practices because there is poor evidence upon which to base the current therapies.

The burden of disease is tremendous, both for patients and their caregivers. Patients often undergo dozens of surgical debulking procedures over their lifetime, with considerable associated economic and emotional burden (Loizou et al., 2014; Montano-Velazquez et al., 2017; San Giorgi et al., 2017). For patients with RRP, there is a significant loss of quality of life and increased depression scores (Loizou et al., 2014; Montano-Velazquez et al., 2017; San Giorgi et al., 2017). Much of the disease burden is related to the need for repeated surgical treatment which is standard of care.

2.2 Currently Available, Pharmacologically Unrelated Treatments/Intervention for the Proposed Indication

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. In particular, patients with RRP are at increased risk of iatrogenic laryngeal injury due to repeated surgeries. Surgical debulking of the exophytic portion of the papilloma is performed to address the symptoms of RRP but does not address the causative HPV infection and thus cannot prevent papilloma recurrences. Off-label use of adjuvant therapies is typically applied in concert with surgical removal of papilloma to reduce disease burden and need for further surgical intervention. However, indications and efficacy for adjuvant therapies have yet to be defined. Current adjuvant therapy options are directed at limiting HPV viral replication and papilloma growth and include cidofovir, bevacizumab, and two related supplements—indole-3 carbinol and diindolylmethane. All are used relatively commonly, but most physicians reserve them for patients requiring more than three to four operations per year or patients with distant pulmonary spread (Derkay, 1995). Data to support efficacy of adjuvant therapies have been limited by the rarity of this disease and lack of appropriately powered studies. Furthermore, toxicities related to adjuvant therapies have limited widespread use.

Reviewer Comment:

RRP is a rare disease. The clinical manifestation of RRP in patients is heterogenous, which makes it difficult to understand the natural history, predict recurrence, and effectively manage the disease. Progression of clinical symptoms is primarily due to surgical management, which is the current standard of care for RRP. Repeated surgical

intervention contributes to distal spread of the disease and causes trauma to the larynx, which leads to much of the morbidity associated with the disease. Due to the variability of disease, it is difficult to identify an appropriate clinically meaningful endpoint. In the clinical setting, both patients and providers have identified a reduction of as few as one surgical intervention per year as being meaningful from a patient perspective.

2.3 Safety and Efficacy of Pharmacologically Related Products

There are no pharmacologically related products currently available.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

PRGN-2012 has not been approved in any country. Experience with PRGN-2012 comes from the clinical study included in this submission.

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

The clinical development of PRGN-2012 was originally submitted under IND 26884 on October 13, 2020. Under this IND, a Phase 1 study was initiated by the National Institutes of Health (NIH) and subsequently expanded to a Phase 1/2 study in adult patients with RRP (PRGN-2012-201; NCT04724980). Following Breakthrough Therapy Designation and in accordance with the FDA/CBER Appeal Granted letter (August 18, 2023), the ongoing PRGN-2012-201 study is considered the pivotal study supporting this request for licensure.

In the original submission, the Applicant requested accelerated approval based on preliminary efficacy at 12 months for patients treated with PRGN-2012 in the Phase 1/2 study. In support of an accelerated approval request, the Applicant also initiated a confirmatory study (PRGN-2012-301) designed as a single-arm study to confirm efficacy in patients who require ≥ 3 surgeries to treat their disease in the year prior to treatment. During the BLA review, the Applicant submitted additional follow up data in the 120-day safety submission. Following review of updated datasets with additional longitudinal data, the review team recommend traditional approval, and a confirmatory study is no longer required.

Table 2. Key Applicant Regulatory Interactions

Date	Interaction
October 13, 2020	Original IND submission (IND 26884 permitted to proceed Nov. 10, 2020)
March 17, 2021	Orphan Drug Designation granted (DRU-2020-8055)
April 11, 2022	IND 26884 transferred from NIH to Precigen, Inc.
June 07, 2022	(b) (4)
July 7, 2022	Type B, end-of-phase 1 meeting <ul style="list-style-type: none"> - FDA does not consider this open-label, single-arm trial as an adequate and well-controlled study to provide evidence of effectiveness.
December 20, 2022	Type C meeting <ul style="list-style-type: none"> - FDA does not agree that the ongoing single-arm study in adult patients with RRP as currently designed meets the criteria for an adequate and well-controlled study as defined in 21 CFR 314.126 to provide substantial evidence of effectiveness to support approval for PRGN-2012 for treatment of patients with RRP with severe, aggressive disease.
June 13, 2023	Breakthrough Therapy Designation granted (b) (4)
August 18, 2023	Informal dispute appeal granted <ul style="list-style-type: none"> - FDA will consider Precigen's Phase 1/2 clinical study data as pivotal for the purposes of filing an accelerated approval request for licensure of PRGN-2012. - Additional RCT not required to support submission of accelerated approval BLA. - Confirmatory study will be initiated prior to BLA submission and will utilize either: <ul style="list-style-type: none"> • a) Single-arm study to confirm efficacy in patients who require ≥3 surgeries at baseline using the same study design as the Phase 1 and 2 trials, and prospective Derkey scoring to determine the requirement for surgery in the year prior to/after treatment. Encourage a redosing option for partial responders. • b) Randomized, placebo-controlled cross-over study in RRP patients stratified for the number of surgeries in the year prior to enrollment to address efficacy (as few as one surgery)
August 29, 2024	Pre-BLA meeting

Source: Reviewer Table

Abbreviations: CFR = Code of Federal Regulations; FDA = Food and Drug Administration;
IND = investigational new drug; NIH = National Institutes of Health; RCT= randomized controlled trial;
RMAT = regenerative medicine advanced therapy; RRP = recurrent respiratory papillomatosis

2.6 Other Relevant Background Information

Not Applicable

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was sufficiently organized and integrated to accommodate the conduct of a complete clinical review. It was submitted electronically and formatted as an electronic Common Technical Document according to the FDA Guidance for Electronic Submissions. The submission contained the five modules in the common technical document structure.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The prospective study, PRGN-2012-201, was performed in accordance with Good Clinical Practice, according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines including the archival of essential documents. This report was prepared according to the ICH E3 clinical study report guidelines.

A summary of the Bioresearch Monitoring inspections conducted at the NIH study site that participated in support of the clinical review of the BLA is included in [Table 3](#). No violations of the Food, Drug, and Cosmetic Act and other Acts or regulations were identified.

Table 3. Summary of Bioresearch Monitoring Inspections

Clinical Study Site for Inspection	Form 483 Issued	Final Inspection Classification
CI: Scott M. Norberg, DO Genitourinary Malignancies Branch National Cancer Institute Building 10, Rm 3-3132 9000 Rockville Pike Bethesda, MD 20892	No	NAI
Sponsor: Precigen, Inc. 20358 Seneca Meadows Parkway Germantown, MD 20876	No	NAI

Source: Reviewer table

Abbreviations: CI = clinical investigator; NAI = no action indicated

3.3 Financial Disclosures

Covered clinical study (name and/or number): PRGN-2012-201
Was a list of clinical investigators provided? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (Request list from applicant)
Total number of investigators identified: <u>22</u>
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Not Applicable

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____

Significant payments of other sorts: _____

Proprietary interest in the product tested held by investigator: _____

Significant equity interest held by investigator in sponsor of covered study: _____

Is an attachment provided with details of the disclosable financial interests/arrangements? ☐ Yes ☐ No (Request details from applicant)

Is a description of the steps taken to minimize potential bias provided? ☐ Yes ☐ No (Request information from applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0

Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant)

Reviewer Comment:

No significant issues with financial disclosures were identified that could suggest undue bias in the data submitted in support of this BLA.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

PRGN-2012 is a non-replicating gorilla adenoviral vector-based immunotherapy delivered via subcutaneous injection. The vector is genetically engineered adenovirus with deletions in the E1 (b) (4) and an insertion of the transgene expression cassette encoding a fusion antigen composed of selected regions (b) (4) from HPV 6 and 11 under the control of cytomegalovirus immediate early promoter and enhancer. PRGN-2012 is designed to generate an immune response directed against papilloma cells infected with HPV 6 or 11.

(b) (4)

The drug product is supplied as a sterile, frozen suspension containing 5×10^{11} PU per milliliter of PRGN-2012 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 drug product is stored frozen at $\leq -60^\circ\text{C}$, and each vial contains an extractable volume of 1.0 mL.

Please refer to the Chemistry, Manufacturing and Controls review memo for further details.

Reviewer Comment:

The validation of the adventitious viral agent 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). In addition, five Chemistry, Manufacturing and Controls post marketing commitments (PMC) 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 $\leq -60^\circ\text{C}$ 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.

4.2 Assay Validation

Not Applicable

4.3 Nonclinical Pharmacology/Toxicology

The nonclinical development program evaluated (b) (4) nonclinical lot of PRGN-2012. The Applicant conducted in vitro assessment of transduction efficiency and antigenicity in addition to immunogenicity and toxicity studies in a murine model. No nonclinical pharmacology/toxicology review issues were identified and there are no outstanding requests for additional nonclinical testing. Please refer to the Pharmacology/Toxicology review memo for further details.

4.4 Clinical Pharmacology

Formal clinical pharmacokinetics studies were not performed, with clinical pharmacology assessment focusing on evaluation of HPV 6/11-specific T cell responses in peripheral blood.

4.4.1 Mechanism of Action

PRGN-2012 is a non-replication competent gorilla adenoviral vector-based immunotherapy designed to express a fusion antigen comprising selected regions of HPV 6/11 proteins. PRGN-2012 is engineered to elicit T cell-mediated immune responses directed against papilloma cells infected with HPV 6 or HPV 11 to reduce or eliminate the need for surgery. Administration of PRGN-2012 via subcutaneous injection is thought to result in the transduction of antigen-presenting cells (APCs). In turn, the APCs present small peptide segments of the protein/antigen bound to major histocompatibility complex Class I located on the cell surface of APCs. The presentation

of these small peptide segments by APCs is expected to lead to induction of de novo T cell responses that are directed against papilloma cells that have been infected with HPV 6 or 11.

4.4.2 Human Pharmacodynamics

HPV 6/11-Specific T Cell Response in Peripheral Blood

The induction of HPV 6/11-specific T cell responses was evaluated as an exploratory correlate of PRGN-2012's mechanism of action using enzyme-linked immunospot (ELISpot) assay to detect IFN- γ secretion in peripheral blood mononuclear cells in response to HPV 6/11-specific peptide pools. Analysis focused on responses at end of treatment (Day 85) and 12 weeks following completion of treatment, with samples available for at least one timepoint in 30 subjects. Specific T cell response was compared between patients who demonstrated an objective response, defined as patients who achieved a >50% reduction in the number of surgical interventions during the 12 months following treatment, and those who did not.

Treatment with PRGN-2012-induced HPV 6/11-specific T cell responses to one or more peptide pools in 86% of patients with objective responses (18/21) compared to 67% of patients without objective responses (6/9). The induction of HPV 6/11-specific T cells was higher in patients achieving an objective response compared to non-responders, with mean best overall 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-changes of 61.5 in responders versus 11.5 in non-responders. The correlation between T cell response and clinical response had the highest significance level ($p = 0.0802$) among evaluated factors in logistic regression analysis, though it did not reach statistical significance due to limited patient numbers.

HPV 6/11-Specific T Cell Response in Papilloma Tissue

Evaluation of papilloma-infiltrating lymphocytes (PIL) was conducted to assess T cell-mediated clearance of HPV-infected papilloma cells. Due to the high number of complete responders precluding robust analysis (i.e., no post-treatment papilloma available for biopsy), evaluation was limited to Phase 1 patients with available pre- and post-treatment papilloma biopsies ($n = 9$). In all responders with paired baseline and post-treatment samples, increased HPV-specific T cell responses were detected in post-treatment PIL compared to pre-treatment PIL. A greater magnitude of HPV-specific responses was observed in PIL from responders compared to non-responders ($p = 0.01$, Mann-Whitney two-tailed test), consistent with PRGN-2012's proposed mechanism of action.

Intrinsic Factors Analysis

The Applicant's analysis of intrinsic factors including age, sex, and HPV subtype (HPV 6 or HPV 11) showed no significant impact on induction of T cell response or clinical outcomes. In logistic regression modeling, no significant associations were found for age, sex, or HPV type with clinical response. Summary statistics of T cell responses by sex and HPV type showed no meaningful differences between male and female patients

or between HPV 6 and HPV 11 subtypes. However, these data should be considered informational and inconclusive due to the limited subject numbers distributed across each category, which precluded robust statistical analysis of potential intrinsic factor effects.

Neutralizing Anti-PRGN-2012 Antibodies

PRGN-2012 exhibited low antigenic potential based on neutralizing antibody (NAb) assessment using a qualified (b) (4) -based method. Prior to treatment, no seropositivity was observed in the majority of patients (18/35) treated with 5×10^{11} PU per injection, with only low-level seropositivity observed in remaining patients. Post-treatment, low levels of NAb titers were detected in the majority of patients, with peak titers observed by 12 weeks post-treatment followed by decline in all patients. There was no correlation between NAb incidence or titer and clinical response. Linear regression analysis of clinical response versus NAb titer showed a generally horizontal trendline with poor fit ($R^2 \leq 0.05$), indicating lack of correlation between NAb development and clinical benefit.

4.4.3 Human Pharmacokinetics

No biodistribution studies have been conducted with PRGN-2012.

Reviewer Comment (Clinical Pharmacology):

Induction of HPV 6/11-specific T cells is being evaluated as an exploratory correlate of the mechanism of action of PRGN-2012 in patients with RRP.

The pharmacodynamic results support the primary efficacy endpoints of PRGN-2012 treatment. The correlation between HPV 6/11 specific T cell responses in peripheral blood and clinical outcomes ($p < 0.018$) provides evidence for the proposed mechanism of action. The 32-fold higher mean T cell response in patients achieving objective responses compared to non-responders (164.9- versus 5.1-fold change) demonstrates a pharmacodynamic-efficacy relationship. The sustained T cell responses observed at 12 weeks post-treatment and the lack of impact from NABs on clinical benefit indicate durability of the immune response.

Overall, these data demonstrate that the clinical benefit with PRGN-2012 correlates with the mechanism of action of PRGN-2012; i.e., induction of HPV 6/11-specific T cell responses.

4.5 Statistical

The Statistics review team has evaluated the impact of various sources of potential biases associated with this single-arm trial, and corresponding correction/mitigation strategies. Variables affecting statistical analysis, including tabulation of baseline surgical interventions, minimal residual disease status, regression to the mean phenomenon, design changes to the ongoing study, missing data, and concomitant medications were taken into consideration when reviewing efficacy of PRGN-2012. 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 sufficient to outweigh the biases and additional uncertainties considered.

Please see Statistics review memo for further details.

4.6 Pharmacovigilance

Routine pharmacovigilance will be done following approval and will include trend analysis to identify unexpected increases in adverse events and their potential relationship to patient subgroups, concomitant medications, or other risk factors. The important potential identified risks associated with PRGN-2012 include a risk of thrombosis in adeno-viral based products. Postmarketing safety monitoring will include enhanced pharmacovigilance for 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.

Additional Chemistry, Manufacturing, and Controls PMCs were recommended for drug product process performance qualification validation, (b) (4) assessment, and reassessment of the acceptance criteria for commercial drug product release after manufacturing additional lots.

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

5.1 Review Strategy

This review memo contains the combined review of the Clinical and Clinical Pharmacology reviewers. In this original BLA submission, the Clinical reviewer evaluated the clinical study report and accompanying datasets for Study PRGN-2012-201 in addition to the individual patient narratives of each subject enrolled in the study. Key outcome measures reviewed included surgical interventions performed before and after treatment, imaging to support Derkey anatomic scoring of papilloma, and HPV-specific T cell responses in peripheral blood and papilloma. Specific T cell responses were also evaluated by the Clinical Pharmacology reviewer.

For evaluation of safety, the Clinical reviewer evaluated data from all patients receiving any amount of the investigational product in study PRGN-2012-201, inclusive of patients in both 1×10^{11} PU and 5×10^{11} PU per injection dosing cohorts. Evaluation of efficacy was based on the subset of patients who received PRGN-2012 at a dose level of 5×10^{11} PU per injection consistent with the proposed dosing for licensure.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical and Clinical Pharmacology Reviews

The sources for this review are the data submitted in the licensing application, which includes data from study PRGN-2012-201 and the relevant modules in the BLA submission:

- The administrative and prescribing information in module 1.
- Summary clinical information in modules 2.5 and 2.7.
- Clinical study reports in module 5 including the narrative clinical study reports, appendices, tabulation and analysis datasets, case report forms, and literature references submitted by the Applicant.
- 120-day safety update submitted under BLA 125832/27.
- Clinical information request responses received under the following amendments:
 - BLA 125832/0.18
 - BLA 125832/0.31
 - BLA 125832/0.36
 - BLA 125832/0.43
 - BLA 125832/0.46
 - BLA 125832/0.49
 - BLA 125832/0.51
 - BLA 125832/0.65

In addition, the Clinical reviewer considered perspectives of patients provided during the RRP Foundation Patient-Led Listening Session and used publicly available resources including UpToDate and PubMed to understand the impact of disease and indication for treatment.

5.3 Table of Studies/Clinical Trials

The BLA includes the single study PRGN-2012. PRGN-2012-201 is a Phase 1/2 single- arm, non-randomized, open-label trial to support safety and efficacy of PRGN-2012.

Table 4. Clinical Studies Submitted in the Biological License Application

Trial Identifier	Trial Design	Study Population, n	Study Objective
PRGN-2012-201 NCT#04724980	Phase 1/2 single-arm, non-randomized, open-label	<p><i>Phase 1</i> Adult patients with RRP requiring $\geq 2^a$ surgeries in 12 months prior, with or without pulmonary involvement Dose escalation (3+3) Dose Level 1 (1×10^{11} PU), n=3 Dose Level 2 (5×10^{11} PU; RP2D), n=12.</p> <p><i>Phase 2</i> Adult patients with RRP requiring ≥ 3 surgeries in 12 months prior, with or without pulmonary involvement Dose expansion at RP2D (5×10^{11} PU), n=23</p>	<p><i>Phase 1</i> Safety: Determine safety, tolerability, and RP2D of PRGN-2012. Efficacy: Evaluate percentage of patients with no clinically indicated surgical interventions during the follow-up period^b</p> <p><i>Phase 2</i> Demonstrate efficacy by evaluating the CR rate, defined as percentage of patients with no clinically indicated surgical interventions during the 12 months following treatment with PRGN-2012 at the RP2D in a larger cohort.</p>

Source: Applicant Clinical Overview (PRGN-2012-201, Table 2)

a. The inclusion criteria for Phase 1 patients specified ≥ 2 surgical interventions for the treatment of RRP in the 12 months prior to treatment; in fact, all Phase 1 patients experienced ≥ 3 surgeries in the 12 months prior to treatment

b. As of Protocol Version 4.0 the Phase 1 Short Term Follow-up was amended from 24 weeks to 12 months

Abbreviations: CR = complete response; n = sample size; NCT = National Clinical Trial Identifier; PU = particle units; RP2D = recommended phase 2 dose; RRP = recurrent respiratory papillomatosis

5.4 Consultations

5.4.1 Advisory Committee Meeting

An advisory committee was not held for this application because the information submitted, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefitted from an advisory committee discussion.

5.4.2 External Consults/Collaborations

No external consults were obtained.

5.5 Literature Reviewed

During review of the BLA, this reviewer consulted FDA regulatory guidance documents, as well as academic literature, for background and context regarding the targeted disease and the mechanism of action of the product. The literature consulted follows below.

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 - PRGN-2012-201

Study Title: A Phase 1/2 Study of Adjuvant PRGN-2012 in Adult Participants with Recurrent Respiratory Papillomatosis.

Clinical Trial Registry Identifiers: NCT 04724980

Enrollment has completed (first patient enrolled: March 16, 2021; last patient 12-month visit: June 5, 2024). Long-term follow-up (LTFU) evaluation is ongoing.

6.1.1 Objectives (Primary, Secondary, etc.)

Primary Efficacy Objective

- Demonstrate the efficacy of PRGN-2012 by evaluating the complete response rate, defined as percentage of subjects with no clinically indicated surgical interventions during the 12 months following treatment with PRGN-2012.

Secondary Efficacy Objectives

- Determine the objective response rate (ORR), defined as percentage of subjects with a complete response or partial response (PR). Partial response is defined as at least a 50% decrease in the number of surgeries during the 12-month period following completion of PRGN-2012 treatment as compared to the number of surgeries during the 12 months prior to PRGN-2012 treatment initiation
- Determine the duration of response, defined as the interval to the first surgical debulking from the completion of PRGN-2012 treatment
- Compare the number of surgeries during the 12-month post-treatment interval following completion of PRGN-2012 treatment to the number of surgeries during the 12 months prior to PRGN-2012 treatment initiation
- Evaluate the rate of complete response to PRGN-2012 across cohorts of patients based on number of surgeries required during the 12 months prior to the initial treatment with PRGN-2012
- Determine changes in Voice Handicap Index-10 (VHI-10) scores over time following PRGN-2012 treatment initiation
- Determine changes in Derkay anatomic scores over time following PRGN-2012 treatment initiation

Safety Objective

- Determine the safety and tolerability of PRGN-2012 in adult patients with RRP
- Determine the potential for shedding of the PRGN-2012 adenoviral vector following subcutaneous administration by evaluation of PRGN-2012 in specific tissues at timepoints up to 6 weeks following the last administration of PRGN-2012

Exploratory Objective

- Evaluate induction of HPV-specific T cell responses in peripheral blood and papilloma
- Development of NABs to PRGN-2012

Reviewer Comment:

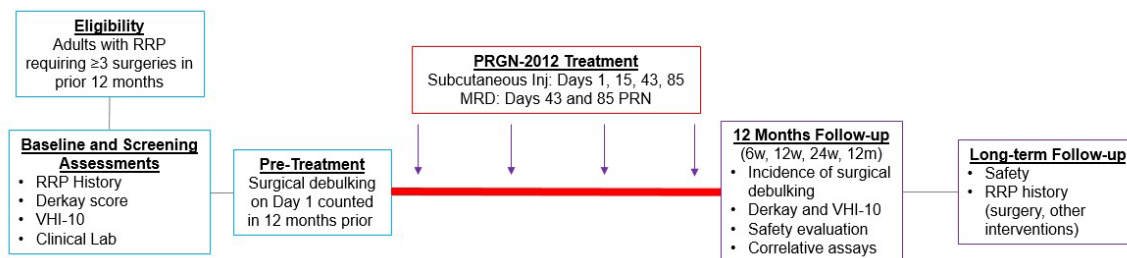
In the original version of the clinical protocol, assessment of the potential for shedding of the PRGN-2012 adenoviral vector following subcutaneous administration was included as a safety objective. Due to the replication-defective nature of the gorilla adenovirus vector and subcutaneous route of administration, the risk of viral shedding was deemed low and the protocol was revised in version 4.0 to include evaluation of viral shedding at a later stage. See [Section 9.2](#) for further details related to viral shedding.

6.1.2 Design Overview

The study is a prospective, single-center, open-label, 3+3 dose-escalation Phase 1 study followed by dose expansion at the recommended Phase 2 dose.

- The Phase 1 portion was a dose-escalation and expansion study utilizing a standard 3+3 dose-escalation design to evaluate PRGN-2012 at two dose levels: 1×10^{11} PU and 5×10^{11} PU.
- The Phase 2 portion was designed as a dose expansion study where patients were treated at a dose of 5×10^{11} PU.

Figure 2. Protocol Schema, PRGN-2012-201



Source: Adapted from BLA 125832/0.1, Protocol PRGN-2012-201

a. As of Protocol Version 4.0, the minimum number of surgeries (≥ 3 in the prior 12 months) required for Phase 2 was revised. MRD procedures occurred in Phase 1 and Phase 2; however, the criteria for maintenance of MRD via surgical debulking was added; and the Phase 1 Short Term Follow-up was amended from 24 weeks to 12 months.

Abbreviations: d = day; MRD = minimal residual disease; PRN = as needed; PU = particle units; RP2D = recommended Phase 2 dose; RRP = recurrent respiratory papillomatosis; SCI = subcutaneous injection; VHI-10 = Voice Handicap Index-10

After the last treatment with PRGN-2012, there was a 12-month short-term follow-up (STFU) period with visits at 6, 12, 24, and 52 weeks, after which eligible patients entered the 2-year LTFU period and are contacted by telephone every 3 months. This LTFU portion of the study is ongoing.

This study evaluates the safety and efficacy of PRGN-2012 in adult patients with RRP. The protocol was revised while the study was ongoing with the following major amendments:

- Original Version (July 2020) – Protocol revised during enrollment to clarify criteria for removal from protocol therapy, which indicate that washout period of intralesional bevacizumab is not required, and that remove HPV vaccination from Prohibited Medications.
- Version 2.0 (December 2021) – Protocol amended to expand the study to include a Phase 2 portion, including changes to: primary objective, treatment assignment, study design, number of patients, and dose of drug. Statistical Considerations were also updated.
- Version 3.0 (April 2022) – Transfer of Sponsorship to PGEN Therapeutics with subsequent change to protocol including changes to: statement of compliance, recruitment strategies, cost and compensation, data-sharing plans, NIH reporting requirements/data and safety monitoring plan, collaborative agreements, consent process, and documentation.

- Version 4.0 (Mar 2023) – update to the patient eligibility, image acquisition and analysis, and statistical analysis. The primary objective and subsequent analyses were revised to assess complete response rate as defined by percent of patients with no surgical interventions during the 12 months following treatment. Secondary objectives were updated to allow evaluation of patients with any decrease or >50% decrease in the number of surgeries. Evaluation of NAb to PRGN-2012 was added to exploratory objectives. Disease criteria for eligibility were updated to reflect an RRP population with severe disease. Included language to the study design to include Derkey scoring of all endoscopic imaging assessments performed from 12 months prior to treatment and through 12 months following treatment by a central blinded imaging review for a quantitative, objective assessment of requirement for surgical intervention. Criteria for removal of visible papilloma to maintain MRD during treatment interval was added.
- Version 5.0 (Feb 2024) – Provided additional details pertaining to the exploratory endpoints of induction of HPV-specific T cell responses. Language was added to further describe the enzyme-linked immunosorbent assay, ELISpot, or comparable analyses to evaluate the induction of HPV-specific T cells. Added clarifications to the ORR definition to be calculated at 12 months.

A total of 38 adult patients (>18 years) were enrolled and received PRGN-2012. All 15 patients enrolled in the Phase 1 part of study PRGN-2012-201 were enrolled under Protocol Version 1. Two patients from Phase 2 were enrolled under Protocol Version 2.0 with the remaining patients enrolled under Version 4.0.

Reviewer Comment:

Twelve-month primary endpoint evaluation was conducted via telephone for 16 of the 38 patients enrolled in this study under prior versions of the protocol. All subsequent patients were evaluated in person at 12 months following implementation of Protocol Version 4.0 on March 30, 2023. The telephone contact included a medical and medication history and a review of adverse events, RRP treatments, and intervention. Information pertaining to incidence of RRP interventions was confirmed in medical records. As the study was conducted in a single clinical site, evaluation of patients by their respective home institutions contributes to the generalizability of study results and mitigates concerns regarding bias in surgical interventions post treatment to some extent.

6.1.3 Population

Adult patients were considered for enrollment if they had a histological diagnosis of papilloma with presence of laryngotracheal papilloma and required three or more surgical interventions in the 12 months prior to treatment on Day 1. The Phase 1 protocol initially included patients with two or more surgical interventions in the 12 months prior to treatment; however, all patients enrolled under this version of the protocol had three or more surgical interventions within the pre-treatment time period.

Key Inclusion Criteria

- Men and women aged 18 years and older,
- Clinical diagnosis of RRP based on histological diagnosis and presence of laryngotracheal papilloma,

- A history of ≥ 2 surgical interventions in the last 12 months (Phase 1) or ≥ 3 surgical interventions in the last 12 months (Phase 2) for control of RRP,
- Clinical performance status of Eastern Cooperative Oncology Group of 0-1 ([APPENDIX 1](#)),
- No systemic therapy for RRP for at least 3 half-lives of the prior drugs,
- Adequate organ and marrow function

Key Exclusion Criteria

- History of surgical papilloma debridement, which would make it unlikely to be able to safely have a 6-week interval between clinically indicated interventions,
- Patients with a condition that required systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration,
- Pregnant women because PRGN-2012 is an agent with unknown potential for teratogenic or abortifacient effects.

6.1.4 Study Treatments or Agents Mandated by the Protocol

All patients received PRGN-2012 manufactured at the Precigen facility in Germantown, Maryland.

Maintenance of Minimal Residual Disease

Endoscopic surgical debulking of papilloma, either by ablation or excision, was performed on all subjects on Day 1 of this protocol prior to the first injection of PRGN-2012. MRD was maintained for the duration of the 12-week PRGN-2012 treatment interval. Patients underwent flexible nasopharyngolaryngoscopy and/or tracheoscopy in the clinic on treatment Days 43 ($\pm 2d$) and 85 ($\pm 7d$). Visible papilloma identified during endoscopic evaluation were removed unless removal of the papilloma was not in the best interest of the subject, per investigator's discretion.

6.1.5 Directions for Use

PRGN-2012 is a suspension for subcutaneous injection, supplied in a single-dose vial. The recommended dose of PRGN-2012 is 5×10^{11} PU per injection administered by subcutaneous injection four times over a 12-week interval, on Days 1, 15, 43, and 85. The minimum required time between administrations of PRGN-2012 for an individual patient was 11 days. A window of ± 7 days for a scheduled treatment was allowed in the event of scheduling issues (i.e., holidays, bad weather, or other scheduling issues). To maintain minimal residual disease during treatment with PRGN-2012, remove visible papilloma, if present, prior to the third and fourth administration of PRGN-2012.

Subsequent administrations of PRGN-2012 were withheld for Grade 2 adverse reactions (ARs) that were clinically significant and possibly related to PRGN-2012 until resolution to Grade ≤ 1 . A delay of up to 2 months for scheduled assessments and dosing was allowed in the event of non-medical logistical reasons and unrelated acute illness. In the Phase 1 portion of the study, a dose of 1×10^{11} (dose level 1) or 5×10^{11} PU per injection (dose level 2) was administered. In the Phase 2 portion, the recommended Phase 2 dose identified in Phase 1 (5×10^{11} PU per injection) was administered to patients.

MRD was to be maintained for the duration of the PRGN-2012 treatment interval. Patients underwent final baseline surgical debulking on Day 1 prior to first administration of PRGN-2012. On treatment Days 43 (± 2 days) and 85 (± 7 days), patients underwent a flexible nasopharyngolaryngoscopy and/or tracheoscopy in the clinic and a Derkay score was determined. If a patient had a Derkay score ≥ 1 , indicating visible papilloma, then the papilloma was removed.

Vital signs were measured within 30 minutes before and 30 minutes following administration of PRGN-2012. Patients were observed for 2 hours after the first administration of PRGN-2012. If no adverse reactions were observed, the patient was monitored for only 30 minutes after subsequent doses.

No dose modifications were allowed in this study.

6.1.6 Sites and Centers

PRGN-2012-201 was conducted at a single center in the United States at the NIH (Bethesda, Maryland).

6.1.7 Surveillance/Monitoring

After the last treatment with PRGN-2012, patients entered a 12-month STFU period with visits at 6, 12, 24, and 52 weeks with assessments as noted in [Table 5](#) below. Patients then entered the 2-year LTFU period, in which patients are contacted by telephone every 3 months to determine incidence of surgical debulking procedures, Derkay score, and/or imaging evaluations.

Table 5. Schedule of Events, Study PRGN-2012-201

Event	Screening -14 days	D1 Pre-Tx ^a	D1 Post-Tx ^b	D15 ±2d	D43 ±2d	D85 ±7d	STFU ^c 6w ±1w	STFU 12w ±1w	STFU 24w ±1w	STFU 52w ±2w	LTFU q3m×2y ±14d
Informed consent	X										
Demographics	X										
Medical history ^d / Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test ^e	X										
Focused physical exam	X	X	X	X	X	X	X	X	X	X	
Complete physical exam, ECOG	X										
Vital signs	X	X	X	X	X	X	X	X	X	X	
Adverse events ^f			X	X	X	X	X	X	X	X	X
Infectious disease panel ^g	X										
Hematology and chemistry	X	X	X	X	X	X	X	X	X	X	
Coagulation	X	X	X	X	X	X	X	X	X	X	
VHI-10	X	X	X	X	X	X	X	X	X	X	
Derkey staging ^h	X	X	X	X	X	X	X	X	X	X	
CT neck/chest ⁱ	X						X				
Evaluation of airways ^j	X	X		X	X	X	X	X	X	X	
PRGN-2012 SQ injection		X		X	X	X					
Surgical intervention		X ^k									
Blood sample for correlative ^l		X	X	X	X	X	X	X	X	X	
Tissue sample (papilloma) ^m		X			X	X					

Source: Protocol PRGN-2012-201

a. Prior to initial administration of PRGN-2012, subjects will have a clinic visit and surgical debulking procedure. This can be done the same day as the Day 1 treatment or can occur the day prior.

b. Assessments do not need to be repeated if performed within 3 days prior.

c. Short-term follow-up visits to occur at 6, 12, 24, 52 weeks following completion of PRGN-2012 treatments.

d. Medical history to include dates of all interventions (surgical and non-surgical treatment) for RRP from the 12 months prior to initiation of PRGN-2012 through completion of the 52-week follow-up. Medical history also includes collection of endoscopic images performed at outside sites during the same range.

e. Women of childbearing potential must have a negative serum or urine pregnancy test ≤7 days prior to treatment initiation.

f. Beyond 42 days after the last administration of the study therapy, only adverse events that are serious and related to the study treatment shall be captured.

g. HIV and hepatitis testing to be done within 90 days of initial treatment.

h. All subjects will have flexible nasopharyngolaryngoscopy and/or tracheoscopy to stage disease using the Derkey system.

i. Disease response will be evaluated by RECIST criteria only in subjects with concurrent pulmonary RRP.

j. Clinic-based flexible nasopharyngolaryngoscopy and/or tracheoscopy.

k. All subjects will undergo surgical removal of papilloma prior to first injection of PRGN-2012.

l. Blood samples were evaluated for induction of HPV 6/11-specific T cells, neutralizing antibodies, and for biomarkers of safety, efficacy, and immune profile pre- and post-treatment with PRGN-2012.

m. Papilloma tissue was evaluated for induction of HPV 6/11-specific T cells, neutralizing antibodies, and for biomarkers of safety, efficacy, and immune profile pre- and (if available) post-treatment with PRGN-2012.

Abbreviations: CT = computed tomography; d = day; ECOG = Eastern Cooperative Oncology Group Performance Status; HPV 6/11 = human papillomavirus type 6 or type 11; LTFU = long-term follow-up; RECIST = Response Evaluation Criteria in Solid Tumors; RRP = recurrent respiratory papillomatosis; q3m = every 3 months; STFU = short-term follow-up; SQ = subcutaneous; Tx = treatment; VHI-10 = voice handicap index score; w = week

A Data Monitoring Committee was implemented to review safety on an ongoing basis and provide recommendations about stopping, continuing, or modifying the study.

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint

- The complete response rate, defined as percentage of patients with no clinically indicated surgical interventions during the 12 months following treatment with PRGN-2012.

Secondary Efficacy Endpoint

- The ORR, defined as percentage of patients with a complete response or partial response, defined as at least a 50% decrease in the number of surgeries during the 12-month period following completion of PRGN-2012 treatment as compared to the number of surgeries during the 12 months prior to PRGN-2012 treatment initiation.
- The percentage of patients with any decrease in the number of surgeries during the 12-month period following completion of PRGN-2012 treatment as compared to the number of surgeries during the 12 months prior to PRGN-2012 treatment initiation.
- The absolute and percent change in the number of surgeries during the 12-month period following completion of PRGN-2012 treatment as compared to the number of surgeries during the 12 months prior to PRGN-2012 treatment initiation.
- The absolute and percent change in the number of surgeries during the 6 months following completion of PRGN-2012 treatment compared to the number of surgeries during the 6 months prior to PRGN-2012 treatment initiation.
- Duration in time to first surgical debulking from the completion of PRGN-2012 treatment.
- Rate of pulmonary RRP responses (complete response and partial response) in patients with pulmonary disease.
- Changes in Derkey and VHI-10 scores over time following PRGN-2012 treatment initiation.

Reviewer Comment:

There are no established grading systems for severity or treatment response in RRP. In listening sessions, patients advised that a reduction in as little as one surgical intervention per year would be clinically meaningful. Due to uncertainty related to the natural history of the disease, the primary endpoint evaluating a complete response for individuals with a history of 3 or more surgical interventions in the 12 months prior to treatment was selected to better identify a treatment effect in a patient population with active disease. The assessment of treatment over a 12-month period allows for an intrasubject comparator in disease burden, which accounts for the heterogeneity in disease among different patients.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Study Hypothesis

This was a nonrandomized, single-arm, open-label study. Efficacy endpoints were summarized descriptively.

Sample Size

Fleming's two-stage design was utilized in this study. The null hypothesis that the true complete response rate is 10% was tested against a one-sided alternative that the true complete response rate is 30% or higher. In Phase 1, 15 patients were enrolled. If there were 2 or fewer responses in these 15 patients, the study was to be stopped for futility. If there were 5 or more responses in 15 patients, the study could be stopped, and the null hypothesis rejected. Otherwise, 20 additional patients were to be enrolled for a total of 35 patients. The null hypothesis would be rejected if 8 or more responses were observed in 35 patients. This design yielded a one-sided type I error rate of 0.025 and power of 80% when the true response rate is 30% or higher.

Analysis Population

The analysis population is defined as adult patients with RRP who require 3 or more surgical interventions to manage papillomatous disease in the 12 months prior to treatment. A total of 38 patients receiving any amount of PRGN-2012 were included in the safety analysis population. Thirty-five patients receiving PRGN-2012 at the proposed commercial dose were included in the efficacy analysis to evaluate the complete response rate and allow the conclusion on efficacy of PRGN-2012 in this population.

Handling of Intercurrent Events

The Applicant utilized a composite strategy, where data were collected continuously and used for analysis regardless of the occurrence of the discontinuation. Any patients without complete assessment for the 12-month follow-up or discontinuing treatment prior to administration of all four doses of PRGN-2012 were counted as non-responders. One patient death prior to month 12 was counted as a non-response.

Handling of Missing Data

No missing data handling strategies were provided.

Reviewer Comment:

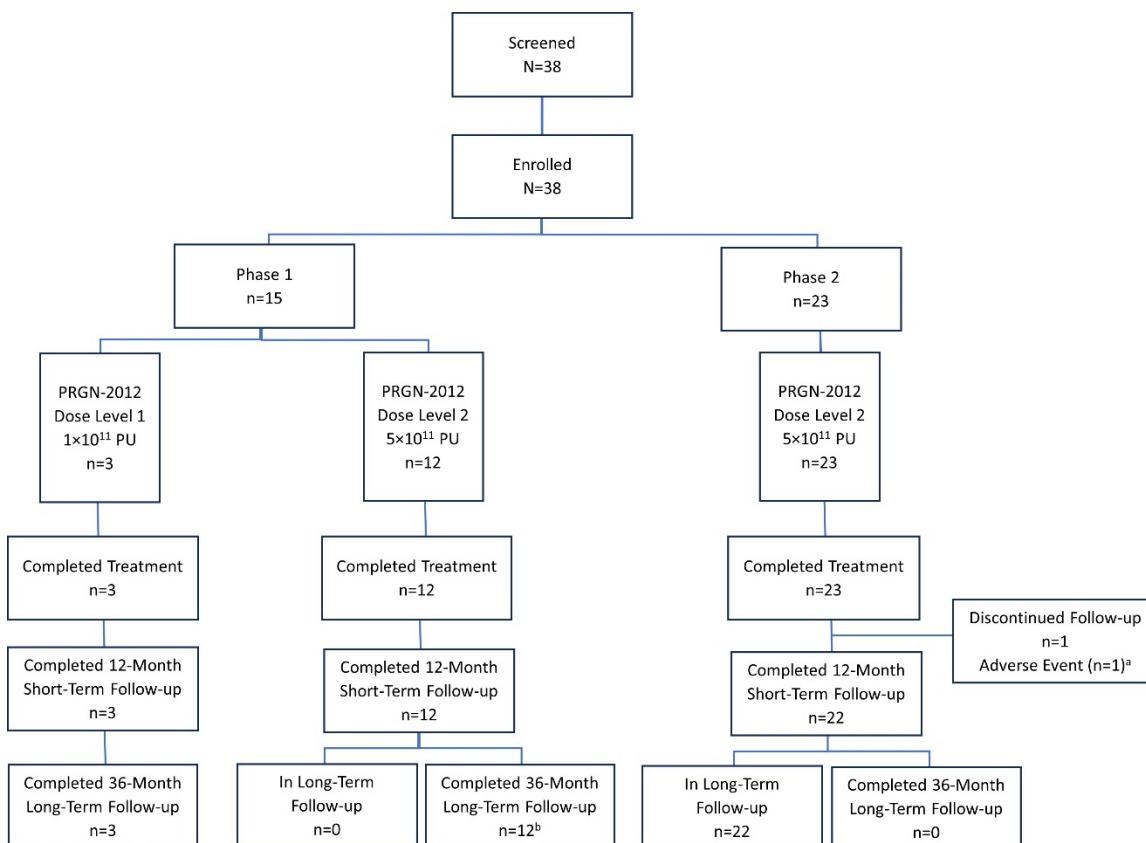
The Statistics team raised concerns related to surgical interventions counted prior to treatment and during the treatment period. The inclusion of surgical interventions performed as standard of care on Day 1, prior to treatment administration, has the potential to introduce bias by inflating the number of pre-treatment interventions. Additionally, the maintenance of MRD through surgical excision of papilloma identified during the treatment period at Days 43 and 85 establishes a baseline "clear out" prior to assessment during the 12-month follow-up period. This is in contrast to the historical comparator data, which did not include such establishment of minimal disease state. During pre-BLA discussions, Precigen clarified that maintenance of MRD during the treatment period was considered part of the treatment protocol.

6.1.10 Study Population and Disposition

All patients who signed the informed consent form met the eligibility criteria for inclusion in the study, and no patient failed screening. A total of 38 patients were enrolled and completed treatment with four doses of PRGN-2012: 15 in the Phase 1 portion (three at dose level 1 [1×10^{11} PU per injection] and 12 at dose level 2 [5×10^{11} PU per injection]), and 23 in the Phase 2 portion (5×10^{11} PU per injection). Across Phase 1 and Phase 2,

35 patients were enrolled and treated at a dose level of 5×10^{11} PU per injection. Of the 38 patients treated, 37 completed the 12-month STFU visit. One patient, who died of cardiac arrest that was not related to treatment, had a last follow-up visit at 5 months and was counted as treatment failure. As of the original data cutoff date of August 28, 2024, five (13.2%) patients had completed the 36-month follow-up and 32 (84.2%) were in the LTFU period, with a median (minimum, maximum) duration of follow-up after treatment of 24 (12, 33) months. During the review process, the Applicant provided updated safety and efficacy data for enrolled patients. As of the secondary data cutoff date of March 21, 2025, 15 (39%) patients had completed the 36-month follow-up and 22 (58%) were in the LTFU period, with a median (minimum, maximum) duration of follow-up after treatment of 30 (21, 36) months. There were no screen failures and no patients discontinued treatment.

Figure 3. Patient Disposition, Full Analysis Population, PRGN-2012-201



Source: Derived from BLA 125832/0; Module 5.3.5.2, Clinical Study Report and amendment 125832/27

a. Patient (b) (6) died of cardiac arrest that was not related to treatment and had a last follow-up visit at 5 months after treatment

b. During the review process, 10 additional patients treated at the commercial dose of 5×10^{11} PU per injection completed the 36-Month study.

Abbreviations: n= sample size; N = total number of patients; PU = particle units

6.1.10.1 Populations Enrolled/Analyzed

The safety population consisted of all 38 study patients who received any amount of PRGN-2012, regardless of follow-up status.

The primary efficacy population included 35 patients who received PRGN-2012 at the recommended dose of 5×10^{11} PU per injection.

6.1.10.1.1 Demographics

Subject demographics are presented in [Table 1](#). The population included 38 patients who received PRGN-2012 to treat RRP. This includes three patients (b) (6) who were evaluated at dose level 1 (1×10^{11} PU per injection). The age of subjects ranged from 20 to 88 years with a median of 49.5 years and a mean of 49.9 years.

All 38 patients screened for enrollment in study PRGN-2012-201 were enrolled in the study and completed treatment with four doses of PRGN-2012. Of the 38 patients in study PRGN-2012-201 who received any amount of PRGN-2012, three patients had completed the study with 36 months of follow-up and 34 patients were ongoing at the time of initial review. There was one patient not evaluable at Month 12 due to death. Further details about patient disposition are provided in section [6.1.10.1.3 Subject Disposition](#).

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

In the study population, the majority of patients had disease arising from the larynx (n=29 [76.3%]), caused by HPV 6 (n=26 [68.4%]), which initially presented in adulthood (n=26 [68.4%]). [Table 6](#) demonstrates disease characteristics within the study population.

Table 6. Medical Classification for Patients, PRGN-2012-201

Characteristic	Phase 1 Dose Level 1 1×10^{11} n=3	Phase 1 Dose Level 2 5×10^{11} n=12	Phase 2 Dose Level 2 5×10^{11} n=23	Phase 1/2 Total N=38
Primary disease site	--	--	--	--
Larynx	2 (66.7)	8 (66.7)	19 (82.6)	29 (76.3)
Other	1 (33.3)	4 (33.3)	4 (17.4)	9 (23.7)
Number of years from diagnosis	--	--	--	--
Mean (SD)	18.7 (20.6)	13.8 (14.1)	23.9 (20.5)	20.3 (18.8)
Median (min, max)	11.0 (3, 42)	6.0 (1, 35)	22.0 (1, 65)	15.5 (1, 65)
Number of surgical interventions in 12 months prior to treatment	--	--	--	--
Mean (SD)	6.3 (2.1)	5.8 (2.8)	3.7 (0.8)	4.6 (2.1)
Median (min, max)	7 (4, 8)	5 (3, 10)	4 (3, 5)	4 (3, 10)
Disease onset	--	--	--	--
Juvenile onset	0	2 (16.7)	10 (43.5)	12 (31.6)
Adult onset	3 (100)	10 (83.3)	13 (56.5)	26 (68.4)
HPV viral type	--	--	--	--
6	2 (66.7)	9 (75.0)	15 (65.2)	26 (68.4)
11	1 (33.3)	3 (25.0)	8 (34.8)	12 (31.6)

Source: Derived from BLA 125832/0; Module 5.3.5.2, Clinical Study Report

Abbreviations: HPV = human papilloma virus; max = maximum; min = minimum; n = sample size; N = number of patients; SD = standard deviation

The most common prior medical conditions, other than RRP, by Preferred Term occurring in $\geq 15\%$ of patients were dysphonia (n=34 [89.5%] patients), hypertension (14 [36.8%] patients), gastroesophageal reflux disease (13 [34.4%] patients), hyperlipidemia

(12 [31.6%] patients), drug hypersensitivity (11 [28.9%] patients), asthma (10 [26.3%] patients), and appendectomy and seasonal allergy (6 [15.8%] patients).

Concomitant Therapies and Procedures

The most common prior therapies ($\geq 20\%$ of patients) included bevacizumab (28 patients [73.7%]), cidofovir (20 [52.6%]), HPV vaccine VLP R11 4v (16 [42.1%]), HPV vaccine (12 [31.6%]), and indole-3-carbinol (10 [26.3%]). Prior to the initial administration of PRGN-2012, a washout period of 30 days or ≥ 3 half-lives was required. During the study, some patients received bevacizumab after failing to meet the primary endpoint.

With the exception of MRD procedures, no patient required surgical intervention for RRP during the treatment period. Most patients (32 [84.2%]) had at least 1 MRD procedure during the treatment period as described in [Table 7](#) below. The MRD procedure was completed to remove papilloma if a patient had a Derkey score ≥ 1 , indicating visible papilloma. The mean (SD) Derkey scores at Days 43 and 85 were 2.9 (2.6) and 3.9 (3.8), respectively.

Table 7. Incidence of MRD Procedures During Treatment, PRGN-2012-201

Characteristic	Phase 1 Dose Level 1 1×10^{11} n=3	Phase 1 Dose Level 2 5×10^{11} n=12	Phase 2 Dose Level 2 5×10^{11} n=23	Phase 1/2 Total N=38
Required MRD at Day 43 only	0	2 (16.7)	0	2 (5.3)
Required MRD at Day 85 only	0	4 (33.3)	9 (39.1)	13 (34.2)
Required MRD at both Days 43 and 85	3 (100)	4 (33.3)	10 (43.5)	17 (44.7)
Did not require MRD at Days 43 or 85	0	2 (16.7)	4 (17.4)	6 (15.8)

Source: Derived from BLA 125832/0; Module 5.3.5.2, Clinical Study Report

Abbreviations: MRD = minimal residual disease; n = sample size; N = number of patients

6.1.10.1.3 Subject Disposition

A total of 38 patients were enrolled and completed treatment with PRGN-2012; 37 patients completed 12-month follow-up for the primary endpoint. In 16 of these patients, the evaluation was conducted via a telephone contact as the 52 weeks clinic visit was not implemented until Protocol Version 4.0 (March 30, 2023). At the time of BLA submission, five patients had completed three-year follow-up. ([Table 8](#)).

Table 8. Patients Evaluable at Different Timepoints, PRGN-2012-201

Patient Disposition	Original Submission Patients, n (%)	120-day Update Patients, n (%)
Total number of patients	38 (100%)	38 (100%)
Patients evaluated at Month 12	37 (97%)	37 (97%)
Patients evaluable at 2 years	21 (55%)	34 (89%)
Patients evaluable 3 years/end of study	5 (13%)	15 (39%)

Source: Derived from Applicant clinical dataset

Abbreviations: n = sample size

In the 120-day safety update, the Applicant provided additional follow-up data for patients from the ongoing study. Of the 23 patients who had not completed the end-of-

study visit, one patient is excluded due to death and 22 patients have at least 21 months of follow-up data.

Reviewer Comment:

In the initial submission, the Applicant provided complete data through 12 months for assessment of the primary endpoint. Evaluation of treatment effect beyond this timepoint was limited due to the ongoing nature of the study. In the 120-day update, the Applicant provided additional follow-up data for patients enrolled in this study to support efficacy. Three patients who had not completed 24-month evaluation were identified as treatment failure at 12-months and therefore were included in 24-month efficacy evaluation.

6.1.11 Efficacy Analyses

Efficacy analyses were conducted in the cohort of 35 patients who received 5×10^{11} PU per injection of PRGN-2012 as treatment for RRP. At dose level 1 (1×10^{11} PU per injection) in the Phase 1 portion of the study no patient achieved a complete response.

6.1.11.1 Analyses of Primary Endpoint

The primary efficacy endpoint was the rate of complete response as defined by the requirement for no surgical interventions in the 12 months after completion of study treatment. Thirty-four of the 35 patients who received PRGN-2012 at the dose of 5×10^{11} were evaluated at 12 months. One patient, who died of cardiac arrest that was not related to treatment, did not complete the 12 months study visit and was counted as treatment failure.

The complete response rate at 12 months was 51% (95% CI 34% to 69%).

Table 9. Patient Response to Treatment at 12 Months, PRGN-2012-201

Parameter	Phase 1 Dose Level 2 5×10^{11} n=12	Phase 2 Dose Level 2 5×10^{11} n=23	Phase 1/2 Dose Level 2 ^a Total N=35
Number of complete responses ^b	6	12	18
Complete response rate (95% CI)	50 (21,79)	52 (31,73)	51 (34,69)
Number of partial responses ^c	2	4	6
Partial response rate (95% CI)	17 (0.2,39)	17 (5,9)	17 (5,30)
Number of objective responses ^d	8	16	24
Objective response rate (95% CI)	67 (28,85)	70 (47,87)	69 (48,81)

Source: Derived from BLA 125832/0; Module 5.3.5.2, Clinical Study Report and Applicant clinical dataset

a. Patients treated at dose level 2 represent the efficacy evaluation population

b. Complete response was defined as no requirement for surgical intervention in the 12 months after treatment

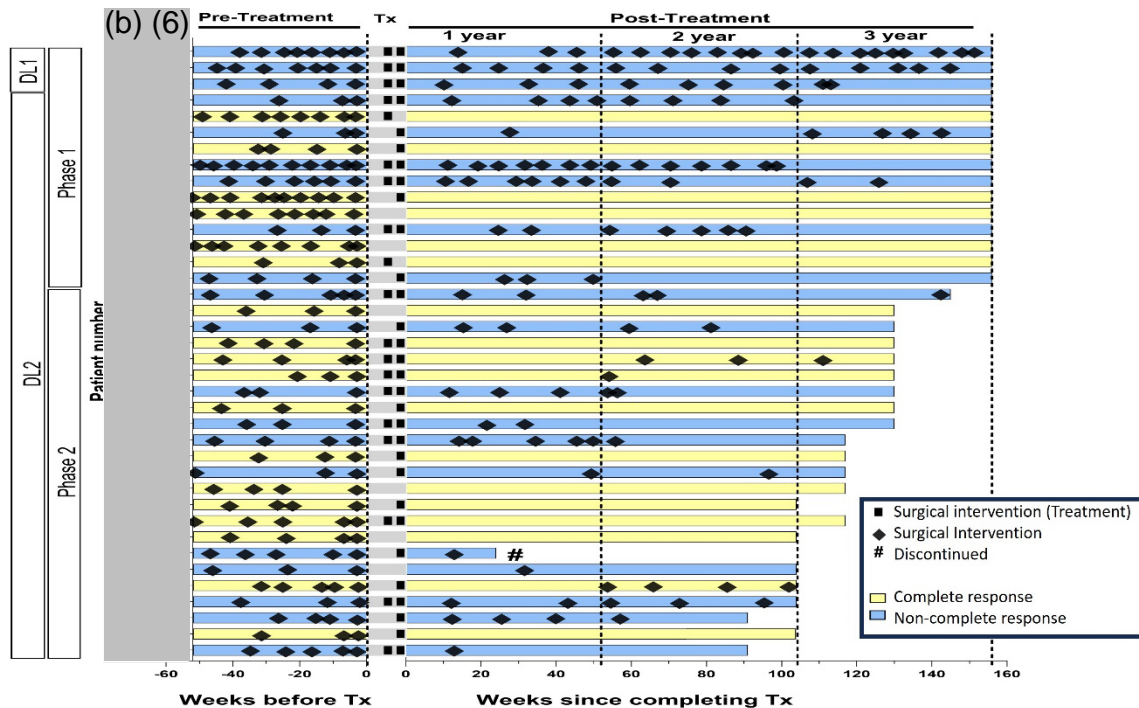
c. Partial response was defined as at least a 50% reduction (excluding complete responders) in the number of surgeries in the 12 months following completion of treatment with PRGN-2012 as compared to the 12 months prior to start of treatment with PRGN-2012

d. Objective response rate was defined as percentage of patients with a complete response or partial response

Abbreviations: CI = confidence interval; n = sample size; N = number of patients

Figure 4 shows individual level surgeries during baseline, treatment and post-treatment periods. Additional follow up data submitted during the review cycle demonstrates durability of treatment effect in patients beyond 12 months. PRGN-2012 was not efficacious at the lower tested dose level. When evaluating the three patients treated at dose level 1 (1×10^{11} PU per injection) there is a generally stable trend in surgery frequency across baseline and post-treatment follow up periods .

Figure 4. Number of RRP Surgical Interventions 12 Months Prior to and After PRGN-2012 Treatment, PRGN-2012-201



Source: Derived from Applicant dataset, Listing 16.2.4.4.2 and updated following secondary data cutoff of March 21, 2025. Abbreviations: DL1 = dose level 1; DL2 = dose level 2

Durability of treatment effect

The Applicant submitted additional efficacy data in amendments 27 and 31, which provided further follow-up for patients enrolled in this ongoing study. Of the 18 patients who demonstrated a complete response at 12 months, 15 patients maintained a complete response at 2 years for a 24-month complete response rate of 43% (95% CI 26% to 61%). Six patients from the complete response cohort completed study at 3 years and remained surgery free. ([Table 10](#)).

Table 10. Patient Response to Treatment through 24 Months, PRGN-2012-201

Parameter	Phase 1 Dose Level 2 5×10 ¹¹ n=12	Phase 2 Dose Level 2 5×10 ¹¹ n=23	Phase 1/2 Dose Level 2 ^a Total N=35
Number of complete responses at 12 months	6	12	18
Complete response rate at 12 months (95% CI)	50 (21,79)	52 (31,73)	51 (34,69)
Number of complete responses at 24 months ^b	6	9	15
Complete response rate at 24 months (95% CI)	50 (21,79)	39 (20,62)	43 (26,61)

Source: Derived from BLA 125832/0; Module 5.3.5.2, Clinical Study Report and Applicant clinical dataset provided in amendments 27 and 31

a. Patients treated at dose level 2 represent the efficacy evaluation population

b. Inclusive of data for all patients treated at Dose Level 2 as provided in amendment 31

Abbreviations: CI = confidence interval; n = sample size; N = number of patients

Reviewer Comment:

Patients and caregivers have previously identified a reduction of a single surgical intervention as a meaningful endpoint. However, for this heterogeneous disease, the number of required surgical interventions can fluctuate from year to year for any given patient. In establishing the primary endpoint of complete response at 12 months, the study relied on both input from patient listening sessions and limited published literature to support the rationale that a patient with active disease, defined as requiring three or more surgical interventions in any given 12-month period, are unlikely to demonstrate complete response/absence of symptoms warranting surgical intervention in the subsequent 12-month period. In evaluating the results of this study, the likelihood of 51% of patients achieving a complete response after a period of active disease, as defined in the protocol, goes against current beliefs related to the natural history of the disease. This finding is strengthened by the observation in this ongoing study that 43% of patients who were evaluated through 24 months remained surgery free. The additional data support durability of treatment effect, which was a primary concern for this reviewer in initial review of this submission.

6.1.11.2 Analyses of Secondary Endpoints

Key Secondary Endpoints

- ORR during 12-month after completion of PRGN-2012
- Time to first surgical debulking from the completion of PRGN-2012 treatment.
- Rate of pulmonary RRP responses in patients with pulmonary disease.

Objective Response Rate

Six patients (14%; 95% CI 5 to 30) achieved a partial response as defined by the requirement for ≥50% to <100% surgical interventions in the 12 months after completion of study treatment when compared to the 12 months prior to treatment. When combined with the complete response rate, 24 out of 35 patients contributed to an ORR of 69% (95% CI 48 to 81).

Time to First Surgical Debulking

Following treatment at the 5×10¹¹ PU per injection dose level, 20 (57%) out of 35 patients had disease recurrence requiring surgical intervention. This includes four patients who did not require surgical intervention in the 12 months following treatment

and were counted as a complete response under the primary endpoint. The mean time to recurrence for the 20 patients with disease recurrence treated at dose level 2 was 267 days (Range= 162-537 days). Sub-analysis between Phase 1 and Phase 2 did not demonstrate any significant difference. RRP recurrence-free probability at dose level 2 was 43% (95% CI 26 to 58). As this study is still ongoing, the assessment of time to recurrence and RRP recurrence-free probability at all timepoints is not complete.

Table 11. Time to Recurrence of Disease, Efficacy Analysis Population, PRGN-2012-201

Parameter	Phase 1 Dose Level 2 5x10 ¹¹ n=12	Phase 2 Dose Level 2 5x10 ¹¹ n=23	Phase 1/2 Dose Level 2 ^a Total N=35
Number of patients with observed disease recurrence (%)	6 (50)	14 (61)	20 (57)
Number of censored observations ^b	6 (50)	9 (39)	15 (40)
Time to recurrence (days)	223	286	267
Median (range)	209 (162-537)	218 (162-294)	215 (170-537)

Source: Derived from BLA 125832/0; Module 5.3.5.2, Clinical Study Report and Applicant clinical dataset

a. Patients treated at dose level 2 represent the Efficacy Evaluation Population

b. Observations censored if patient did not have recurrence at any point until data cutoff or end of study, or if patient did not have recurrence prior to death before end of study

Abbreviations: n = sample size; N = number of patients; NE = not evaluable

6.1.11.3 Subpopulation Analyses

Age at Disease Onset

In a sub-analysis evaluating response by age of disease onset 12 (32%) patients had juvenile onset and 26 (68%) patients had adult onset. Within the efficacy cohort, most patients treated at dose level 2 had adult onset RRP (n = 23) compared to the number of patients who had juvenile onset RRP (n = 12). The complete response rate between the two groups was similar, with 50% (95% CI 21 to 78) for juvenile onset and 52% (95% CI 30 to 73) for adult onset. The ORRs were also similar between patients who had juvenile onset RRP (67% [95% CI 35 to 90]) and adult onset RRP (65% [95% CI 43 to 84]). The trends observed in the overall population for Derkey scores, and VHI-10 scores were generally consistent with those seen in patients with juvenile onset RRP and adult onset RRP.

Table 12. Sub Analysis by Age of Onset, Efficacy Analysis Population, PRGN-2012-201

Parameter	Juvenile Onset n=12	Adult Onset n=23	Total N=35
Number of complete responses	6	12	18
Complete response rate (95% CI)	50 (21-79)	52 (31-73)	51 (34-69)
Number of partial responses	2	3	6
Partial response rate (95% CI)	17 (0.2-39)	13 (3-34)	17 (5-30)
Number of objective responses	8	15	24
Objective response rate (95% CI)	67 (28-85)	65 (43-84)	69 (48-81)

Source: Derived from BLA 125832/0; Module 5.3.5.2, Clinical Study Report and Applicant clinical dataset

Abbreviations: CI = confidence interval; n = sample size; N = number of patients

Rate of Pulmonary RRP Responses

Four (patients (b) (6)) of the 35 patients treated at dose level 2 had pulmonary RRP involvement based on computed tomography of the neck/chest performed at baseline and at the 6-week follow-up following completion of treatment. Two of the four patients developed RRP symptoms in childhood. One of the patients achieved a complete response.

Reviewer comment:

Subgroup analyses of response rates (complete response and objective response rate) conducted by HPV type (HPV type 11 or HPV type 6), number of surgeries prior to treatment category (low, medium, or high), and age of onset (juvenile or adult onset) were generally consistent with the results of the overall population.

Due to the small number of patients with pulmonary RRP evaluated in this study, it is challenging to make any conclusions related to the treatment effect of PRGN-2012 in patients with pulmonary involvement.

6.1.11.4 Dropouts and/or Discontinuations

All patients who signed the informed consent form met the eligibility criteria for inclusion in the study, and no patient failed screening. One patient who died of cardiac arrest prior to the 12-month visit was counted as treatment failure.

6.1.11.5 Exploratory and Post Hoc Analyses

The potential associations between HPV type (6/11) and clinical response were examined in exploratory analyses. Subgroup analyses of response rates (complete response and objective response rate) conducted by HPV type (HPV 6 or HPV 11) were generally consistent with the results of the overall population. These findings are also consistent with the mechanism of action of PRGN-2012; the product is designed to generate T cell-mediated immune responses directed against cells expressing HPV 6/11-associated proteins.

HPV 6/11-Specific T Cell Response in Peripheral Blood

Induction of HPV 6/11-specific T cells was evaluated as an exploratory endpoint as PRGN-2012 is designed to generate an immune response targeted at the papilloma cells infected with HPV 6 and 11. Whole blood was analyzed to quantify induction of HPV-specific T cells following treatment with PRGN-2012 and for detection of NAb to PRGN-2012 in serum.

Induction of HPV specific T cell responses was measured at the end of treatment and 12 weeks following completion of treatment using ELISpot assay to detect cytokine secretion in peripheral blood (IFN- γ) in response to HPV 6 and 11-specific peptide pools. A sample was available for at least one timepoint for 30 subjects. HPV 6/11-specific T cell responses were compared in patients achieving an objective response to PRGN-2012 (objective responses = complete response or partial response) to patients who did not achieve an objective clinical response (defined as less than a 50% reduction from baseline in the number of RRP surgical interventions in the 12 months following completion of treatment). Treatment with PRGN-2012 induced an HPV 6/11-specific T

cell response to one or more peptide pools in 86% of patients with objective responses and 67% of patients without objective responses ([Table 13](#)).

Table 13. Summary of Fold Change From Baseline in HPV 6/11-Specific T cell Response at Dose Level 5×10^{11} PU per injection, PRGN-2012-201^a

Statistic	Clinical Response (CR or PR)	No Clinical Response (NR)
Day 85	--	--
N	19	9
Mean (SD)	164.9 (336.5)	5.1 (4.4)
Median (25 th , 75 th percentile)	15 (3.0, 130.0)	5 (1.0, 8.6)
Min, max	1, 1173	0.5, 12.5
Week 12	--	--
N	17	7
Mean (SD)	61.5 (113.3)	11.5 (17.0)
Median (25 th , 75 th percentile)	7.5 (2.5, 90.0)	2.5 (1.0, 17.1)
Min, max	0.6, 422.5	0.8, 47.5

Source: Derived from BLA 125832/0; Module 5.3.5.2, Clinical Study Report and Applicant clinical dataset
a. Best overall response from five individual peptide pools for each patient is used in the summary table
Abbreviations: CR = complete response (no requirement for RRP surgical intervention in 12 months following completion of treatment); HPV 6/11 = human papilloma virus type 6 or type 11; max = maximum; min = minimum; NR = no objective response (<50% reduction from baseline in RRP surgical interventions in the 12 months following completion of treatment); PR = partial response ($\geq 50\%$ reduction from baseline in RRP surgical interventions in the 12 months following completion of treatment); PU = particle units; RRP = recurrent respiratory papillomatosis; SD = standard deviation

The development of NABs to PRGN-2012 following treatment with PRGN-2012 was evaluated in serum samples from Baseline and up to 52 weeks following completion of treatment. NAB were quantitated using a luciferase assay. Prior to treatment, low-level seropositivity was observed in 17 out of 25 patients treated at 5×10^{11} PU per injection. Peak NAB titers were observed by 12 weeks post-treatment with low levels of NAB titers detected in the majority of patients. The NAB expression in PRGN-2012-treated patients did not demonstrate any impact on clinical benefit.

Reviewer Comment:

Induction of HPV 6/11-specific T cells was higher in patients achieving a clinical response to treatment as compared to patients who did not reach an objective clinical response (mean best overall fold change from baseline 164.9 versus 5.1, respectively ; $p < 0.018$). Overall, these data suggest a correlation between induction of HPV 6/11 T cell response and clinical benefit. This finding would be consistent with the hypothesized mechanism of action for PRGN-2012 as previously noted in [Section 4.4 Clinical Pharmacology](#).

Derkey Scoring

In clinical practice, the decision to excise a papillomatous lesion is based on a variety of factors including patient symptoms, lesion size and location, and physician judgement on future impairment caused by the lesion. Understanding that the need for surgical interventions may be subjective, the Derkey staging system has been used to provide an objective criterion for disease state and surgical intervention decision (Derkey et al. 1998). The traditional Derkey scoring system proposed for use in clinical practice includes an assessment of the extent of the disease in the aerodigestive tract as well as

the “patient reported complaint” to decide whether RRP surgery is required. In this study, the Applicant retrospectively assigned modified Derkay scores, which solely utilized the anatomical scoring system to assign scores using still photos retrieved from the medical record. The modified score assigns a numerical score based on anatomical parameters, which is calculated by visualizing each anatomic region in the aerodigestive tract and assigning a score of 0-3 (0=none, 1=surface lesion, 2=raised lesion, 3=bulky lesion) based on the absence or presence of lesions in each region. The total anatomic score is generated by summation of the scores from each affected site ([APPENDIX 2](#)).

The Applicant provided Derkay scores for retrospectively collected endoscopic images obtained by flexible nasopharyngolaryngoscopy or tracheoscopy. Images from the medical record were scored as a means of evaluating appropriateness of surgical intervention prior to excision of papillomatosis lesions. Scoring was performed by both the study site and by blinded central imaging reviewers. Both the study site and the central readers used the same Derkay staging system to provide an objective score based on the number of sites and bulkiness of papilloma within the pharynx, larynx, and trachea. Endoscopic images consisted of those collected by the participants’ home physician during the pre- or post-treatment period and those collected at the study site as per protocol visits (i.e., Days 1, 15, 43 and 85, and at 6, 12, 24 and 52 weeks after completion of PRGN-2012 treatment). At visits conducted during the treatment period (i.e., Days 1, 15, 43, and 85), removal of any visible papilloma (as indicated by a Derkay score ≥ 1) was permitted to maintain MRD.

Out of 156 surgical interventions performed among the 35 patients in the efficacy analysis population, Derkay scores were not determined for 48 interventions (31%). In the overall population, Derkay scores were consistently lower at each post-treatment visit relative to baseline scores. At dose level 2, mean and median Derkay scores were consistently lower than baseline at each posttreatment visit through Week 52. Median changes ranged from -8.0 to -6.0 from baseline to Week 24 and then to -4.0 at Week 52, representing a median percent change of -64.7%. A second, blinded assessment of Derkay scores by a central reader concurred with findings.

Reviewer Comment:

When deciding to perform surgical intervention in RRP, the physician will take into consideration the patient’s clinical symptoms as well as the appearance of papillomatous lesions identified during endoscopic evaluation. Analysis of modified Derkay scores evaluating the anatomical structure of papillomatous lesions was reviewed to ensure that surgical interventions were indicated. Review of Derkay scoring prior to and after treatment does not demonstrate any variation to suggest bias in the decision to perform surgical intervention.

Voice Handicap Index-10 scores

The VHI-10 score is a validated, patient-based, self-assessment questionnaire that consists of 10 questions that measure the impact of a person’s voice disorder on their daily activities (Rosen et al., 2004) ([APPENDIX 3](#)). At all clinic visits, patients completed the VHI-10 self-assessment. Each question was scored on a scale from 0 to 4 with a higher score indicating a greater voice handicap due to RRP. The maximum VHI-10 score is 40, and a total score >11 is considered abnormal. At dose level 2, the post

treatment median VHI-10 score was consistently lower than baseline, with median changes from baseline ranging between -8.0 and -12.0 and maintained through Week 52, where the change from baseline was -11.0.

Reviewer Comment:

Overall, patients reported a lower VHI-10 score following treatment as compared to baseline suggesting an improvement in subjective clinical symptoms.

6.1.12 Safety Analyses

6.1.12.1 Methods

Safety analyses were performed on all 38 patients treated in study PRGN-2012-201. All 38 enrolled patients received complete dosing with PRGN-2012 (i.e., four doses, at their assigned dose level). Three patients enrolled at dose level 1 received four doses at 1×10^{11} PU per injection. The remaining 35 patients enrolled at dose level 2 were treated with four doses at 5×10^{11} PU per injection with a cumulative dose of 20×10^{11} PU. No patient had a missed or partial dose. No patients were withdrawn from treatment during the study.

6.1.12.2 Overview of Adverse Events

No dose-limiting toxicities were reported in the Phase 1 dose-escalation portion of the study. At least one TEAE was reported in all patients, with the majority of TEAEs classified as \leq Grade 2. Of the 343 TEAEs reported, 282 (82.5%) were considered treatment-related by the investigator. Severe (\geq Grade 3) TEAEs were reported in four (10.5%) patients, and none were considered treatment-related by the investigator. Serious adverse events (SAEs) were reported in three (7.9%) patients, and none were considered treatment-related by the investigator. One (2.6%) patient experienced a Grade 1 infusion-related AE of peripheral sensory neuropathy, which occurred after the first dose and resolved prior to the second dose. Similar occurrences were not noted at subsequent dose administration and the patient completed treatment as planned. Although one death did occur during the study, no TEAE resulted in death or treatment discontinuation.

Table 14. Overall Summary of Adverse Events, Safety Analysis Population, PRGN-2012-201

Characteristic	Phase 1 Dose Level 1 1×10^{11} n=3	Phase 1 Dose Level 2 5×10^{11} n=12	Phase 2 Dose Level 2 5×10^{11} n=23	Phase 1/2 Total N=38
All AEs	3 (100) 13	12 (100) 130	23 (100) 202	38 (100) 345
DLTs	0	0	0	0
TEAEs ^a	3 (100) 13	12 (100) 129	23 (100) 201	38 (100) 343
Grade >3 TEAEs	1 (33.3) 1	1 (8.3) 1	2 (8.7) 2	4 (10.5) 4
irAEs	0	0	1 (4.3) 1	1 (2.6) 1
Treatment-related TEAEs ^b	3 (100) 7	12 (100) 109	23 (100) 166	38 (100) 282
SAEs	1 (33.3) 1	0	2 (8.7) 2	3 (7.9) 3

Characteristic	Phase 1 Dose Level 1 1×10^{11} n=3	Phase 1 Dose Level 2 5×10^{11} n=12	Phase 2 Dose Level 2 5×10^{11} n=23	Phase 1/2 Total N=38
Treatment-related SAEs	0	0	0	0
AEs resulting in treatment discontinuation	0	0	0	0
Number of deaths, n(%)	0	0	1 (4.3)	1 (2.6)

Source: Derived from BLA 125832/0; Module 5.3.5.2, Clinical Study Report and Applicant clinical dataset

NOTE: For the calculation of percentages, the number of patients in each column was used as the denominator. AEs or patients were counted once within each category.

a. Any AE that started at or caused worsening of a pre-existing event after the first administration of treatment was considered a TEAE

b. TEAEs were defined as "related" if the relationship to study drug was assessed as "Possibly," "Probably," "Definitely." A missing relationship category was considered as related to the study drug.

Abbreviations: AE = adverse event; DL = dose level; DLT = dose-limiting toxicity; E = number of events; irAE = immune-related adverse event; n = sample size; N = number of patients; SAE = serious adverse event; TEAE = treatment-emergent adverse event

The most common adverse reactions by Preferred Term (occurring in $\geq 5\%$ of patients) were injection site reactions (115 events in 37 [97.4%] patients), fatigue (58 events in 28 [73.7%] patients), chills (37 events in 25 [65.8%] patients), pyrexia (37 events in 24 [63.2%] patients), oropharyngeal pain (24 events in 21 [55.3%] patients), myalgia (11 events in 11 [28.9%] patients), and nausea (13 events in 10 [26.3%] patients) ([Table 15](#)).

Adverse reactions in $< 5\%$ of patients treated with PRGN-2012 included blurred vision, injection-site bruising, dizziness, dyspnea, and pruritus all at 2.6%, or one patient.

Table 15. Adverse Reactions, Safety Analysis Population, PRGN-2012-201

Characteristic	Phase 1 Dose Level 1 1×10^{11} n=3	Phase 1 Dose Level 2 5×10^{11} n=12	Phase 2 Dose Level 2 5×10^{11} n=23	Phase 1/2 Total N=38
Injection site reaction	3 (100)	12 (100)	22 (95.7)	37 (97.4)
Fatigue	0	9 (75.0)	19 (82.6)	28 (73.7)
Chills	0	10 (83.3)	15 (65.2)	25 (65.8)
Pyrexia	0	9 (75.0)	15 (65.2)	24 (63.2)
Myalgia	0	4 (33.3)	7 (30.4)	11 (28.9)
Nausea	0	4 (33.3)	6 (26.1)	10 (26.3)
Headache	0	0	4 (17.4)	4 (10.5)
Tachycardia	1 (33.3)	2 (16.7)	0	3 (7.9)
Diarrhea	1 (33.3)	1 (8.3)	0	2 (5.3)
Hyperhidrosis	0	2 (16.7)	0	2 (5.3)
Vomiting	0	2 (16.7)	0	2 (5.3)

Source: Reviewer table derived from Applicant dataset.

Abbreviations: n = sample size; N = number of patients

6.1.12.3 Deaths

There was one death during this study. Patient (b) (6) was an 89-year-old male with an extensive cardiac history including severe aortic stenosis and pulmonary hypertension in addition to RRP. The patient received all four doses of the study drug per protocol at dosing level of 5×10^{11} PU per injection on Days 1, 14, 43, and 86. He was last seen for study purposes at his Month 6 follow-up.

In October 2023, 10 months after completion of treatment, he presented with dyspnea on exertion and was found to have severe single-vessel disease requiring placement of two drug-eluting stents to the ostial right and mid-right coronary arteries. Two days after placement he had a cardiac event and passed away. The cardiac event is attributed to the patient's pre-existing heart conditions including severe aortic stenosis and ischemic heart disease and was assessed as not related to the investigational product. An autopsy was not performed.

6.1.12.4 Nonfatal Serious Adverse Events

There have been two SAEs to date for this ongoing study.

Patient (b) (6) is a 39-year-old male who completed treatment at a dose level of 1×10^{11} PU per injection on Days 1, 14, 43, and 85. Eleven days after his final treatment dose and last surgical intervention patient presented with grade 3 sore throat, throat swelling, and dysphagia. He was admitted to the intensive care unit and received intravenous steroids with reported improvement in swelling. Otolaryngologist examination the following day identified an erythematous "voice box." The patient was discharged home on a steroid taper and intramuscular antibiotics for a bacterial infection. The event was considered resolved four days later with completion of antibiotic regimen. The patient was noted to have normal swallow and breathing with no return of issues related to throat swelling at subsequent protocol 6-week follow-up visit. The event was classified as a grade 3 laryngitis and was assessed as not related to the investigational product.

Patient (b) (6) is a 41-year-old male who completed treatment at a dose level of 5×10^{11} PU per injection on Days 1, 13, 42, and 89. He received standard-of-care papilloma clean out on Day 1 prior to the first dose of PRGN-2012. He experienced hemoptysis approximately 27 minutes after initial treatment and was subsequently found to have developed a mucosal tear along the inferior pole of the left tonsil, which required cauterization. He did not have any further episodes of upper gastrointestinal bleed following the event and throughout the rest of the AE reporting period. All nasopharyngolaryngoscopy performed after Day 15 and through 12-month follow-up were reported as normal. The patient subsequently completed a four-dose treatment regimen and continues to be followed in this ongoing study. The event was classified as a grade 3 upper gastrointestinal hemorrhage and was assessed as related to complications from nasopharyngolaryngoscopy and not related to the investigational product.

Reviewer Comment:

Individual patient summaries were reviewed for all patients with fatal and non-fatal SAEs as noted above. Additional details and clarifications were submitted in response to IR communications under amendment 46. Upon review of these material, the reviewer agrees with the Applicant's attribution of these events.

6.1.12.5 Adverse Events of Special Interest

Not Applicable

6.1.12.6 Clinical Test Results

Serum chemistry (including thyroid panel), hematology, and coagulation laboratory values were evaluated at each visit. Overall, there were no notable or consistent trends in change from baseline values for clinical laboratory assessments of serum chemistry, hematology, or coagulation. Although some patients experienced fluctuations in individual laboratory values, there were no sustained or prolonged effects observed.

6.1.12.7 Dropouts and/or Discontinuations

All patients completed treatment. To date, there has been one discontinuation from the study due to patient death.

6.1.13 Study Summary and Conclusions

Evaluation of primary and secondary efficacy endpoints for study PRGN-2012-201 demonstrates effectiveness of this product with complete response rate of 51% and an ORR of 71%, respectively. Data from this study also provide evidence of safety with primarily self-limited localized reactions and no SAEs. The Applicant has provided data from a small cohort of 38 patients who have been treated with four doses of PRGN-2012, which is ongoing. Data from the ongoing study suggest durability of treatment effect beyond 12 months.

7. INTEGRATED OVERVIEW OF EFFICACY

No integrated summary of efficacy was submitted, nor was it required since a single pivotal study was submitted. See [Section 6](#) for the efficacy data provided and analyzed in this submission.

8. INTEGRATED OVERVIEW OF SAFETY

No integrated summary of safety was included in the BLA submission, nor was it required as the submission was comprised of a single pivotal study. See [Section 6](#) for the safety data provided and analyzed in this submission.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

No information was collected on the use of PRGN-2012 during pregnancy. One patient became pregnant during the clinical study. The patient is a 36-year-old female who became pregnant approximately six months after the completion of treatment at dose level 2 (5×10^{11} PU per injection). She is a multigravida with a total of four pregnancies and three viable births. She delivered a 40-week full-term female neonate via vaginal delivery without any reported birth complications. The patient experienced post-partum pre-eclampsia attributed to a COVID-19 infection contracted during her third trimester. The child is now two years old and has achieved all expected developmental milestones and maintains a standard growth trajectory. The child has no noted health concerns, and no congenital defects or delivery-related injuries have been reported.

9.1.2 Use During Lactation

No information was collected on the use of PRGN-2012 during lactation.

9.1.3 Pediatric Use and PREA Considerations

This application is exempt from the Pediatric Research Equity Act due to Orphan Drug designation. Clinical studies were conducted exclusively in adult patients.

Reviewer Comment:

RRP affects both adult and pediatric populations, with juvenile-onset RRP and adult-onset RRP sharing the same pathophysiology. The Applicant hypothesizes that pediatric patients may have a different level of immune response compared to adults treated with the same dose level. Furthermore, they note that the lower dose of 1×10^{11} PU per injection was deemed ineffective in the adult population. Therefore, the Applicant will conduct additional safety and efficacy evaluation in pediatric patients with RRP in a future study. They have agreed to conduct this study as a post-marketing commitment with expected final study report by December 31, 2028.

9.1.4 Immunocompromised Patients

There are no available data from PRGN-2012 in immunocompromised patients.

9.1.5 Geriatric Use

There were nine patients (24%) 65 years and older and one patient (3%) 75 years and older in Study PRGN-2012-201. This clinical study did not include sufficient numbers of patients 65 years and older to determine whether age has any effect on treatment outcome.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Viral Vector Shedding

There is a potential risk of complications with PRGN-2012 treatment from vector shedding and transmission to untreated individuals. No vector shedding studies have been conducted with PRGN-2012. The potential risk of viral shedding following PRGN-2012 administration is considered very low. PRGN-2012 utilizes a replication-defective gorilla adenovirus (GC46) vector with deletions in the E1 (b) (4) [REDACTED], which are thought to make the shed particles unlikely to be infectious. Additionally, PRGN-2012 is administered via subcutaneous injection, which is associated with a lower risk of shedding and exposure to caregivers. Furthermore, the potential environmental impact of the approval of this BLA has been reviewed and the review teams agree that approval of this product will not have a significant impact on the quality of the human environment.

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. Additional language describing the potential risk of vector shedding has been added as missing information in the USPI, with risk minimization measures to include instructions to the health care providers for use by patients and caregivers.

10. CONCLUSIONS

PRGN-2012-201 is a single adequate and well controlled study with confirmatory evidence which demonstrates substantial evidence of effectiveness and reasonable assurance of safety to support traditional approval of PRGN-2012 for adults with RRP. The primary evidence of effectiveness is based on the percentage of patients with a complete response, defined as the absence of surgical interventions for RRP in the 12 months following treatment with PRGN-2012. In order to provide an observable difference that would minimize bias and chance, the Applicant evaluated for absence of papilloma in patients who previously demonstrated relatively active disease, requiring three or more surgical interventions in the 12 months prior to treatment. At the proposed dose of 5×10^{11} PU per injection, 18 out of 35 patients did not require surgical intervention in the 12 months following treatment resulting in a complete response rate (95% CI) of 51% (34% to 69%). Furthermore, 15 patients remained surgery free through two years for a 24-month complete response rate (95% CI) of 43% (26% to 61%). In this ongoing study, six patients in the complete response group have completed the 3-year study and remain surgery free. Additional confirmatory evidence to support effectiveness of PRGN-2012 comes from observed higher HPV 6/11-specific T cell responses 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.

Safety analysis from patients exposed to any amount of PRGN-2012 demonstrated primarily localized and self-limited injection site reactions, fatigue, and chills. The study demonstrated that 12 weeks of treatment with PRGN-2012 was well tolerated, with no deaths or SAEs attributed to PRGN-2012, and no AEs leading to withdrawal. The type and frequency of ARs were consistent with the known safety profile of other licensed immunotherapies.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 16. Risk-Benefit Considerations for PRGN 2012

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> RRP is a rare, chronic disease caused by infection with HPV 6/11 anywhere in the upper and lower respiratory tract. Clinical manifestations include dysphonia, stridor, dyspnea, and airway occlusion. Morbidity and mortality are primarily related to papilloma mass effect leading to loss of lung volume, post obstructive pneumonia, or respiratory failure. Malignant transformation in 3% of the population has been reported. There is variable expression of the disease with no identifiable trends in need for surgical interventions over time. There are no large-scale natural history studies characterizing the disease. 	<ul style="list-style-type: none"> RRP is a progressive, life-threatening disease. RRP is a serious condition, based on the chronic morbidity many patients experience. Natural history of RRP is poorly defined due to the rarity of the disease and the fluctuating clinical course
Unmet Medical Need	<ul style="list-style-type: none"> There are no drugs or biologics approved for treatment of RRP infection. Surgical debulking of the papilloma provides symptomatic relief but does not address the causative HPV infection. Frequent surgical procedures to address papilloma recurrence leads to frequent patient exposure to anesthetic and surgical risks. Off label use of adjuvant therapies, including cancer drugs which are directed at limiting HPV viral replication and papilloma growth, have been used in conjunction with surgical intervention to reduce disease burden, but use is limited by a lack of efficacy data and associated toxicities. 	<ul style="list-style-type: none"> There is an unmet medical need for effective treatment of RRP caused by HPV 6/11 infection. Surgical interventions only provide temporary symptomatic relief but also cause significant morbidity Off label adjuvant therapies are not widely used due to efficacy and safety concerns.
Clinical Benefit	<ul style="list-style-type: none"> One well controlled, single arm clinical trial in adults with RRP requiring 3 or more surgical interventions in the 12 months prior to treatment was submitted to support clinical benefit for this rare disease. The Applicant evaluated a complete response, defined as no surgical interventions in the 12 months after treatment, as a clinical endpoint. At 12 months post-treatment, 51% of patients achieved a complete response. The observed results are unexpected when considering limited natural history data for this rare disease. Durability of outcomes beyond 12 months is supported by continued absence of surgical interventions in 15/18 patients evaluated at 2 years and 6/6 patients evaluated at 3 years. Only adults with RRP were enrolled in study PRGN-2012-201. There is no data assessing effectiveness in children. The youngest patient in study PRGN-2012-201 was 20 years old. Sub-analysis evaluating treatment effect did not identify any differences between juvenile and adult onset RRP 	<ul style="list-style-type: none"> Given the observations of clinical benefit and supporting data to suggest durability of treatment effect, PRGN-2012 would allow for a treatment option other than current surgical standard of care. Data suggests that treatment may be beneficial in children with juvenile onset RRP, but definitive conclusions are limited. Further evaluation in a pediatric study is needed. Traditional approval would allow access to treatment for patients with an unmet medical need.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk	<ul style="list-style-type: none"> The most substantial risks of treatment with PRGN-2012 are associated with the inflammation produced at the injection site. Erythema, swelling, and pain were very common. However, most injection site reactions were mild in severity, and they resolved relatively quickly and without sequelae. No other safety signals were apparent in this adult population. There is a potential risk of thromboembolic events based on events observed in other adenoviral products. No viral shedding studies have been performed. The product is a non-replicating viral vector but potential for shedding of replicating virus remains. Exposure of shed virus to individuals not being treated may lead to development of immunogenicity against the vector which would have the potential to decrease treatment efficacy for the bystander. 	<ul style="list-style-type: none"> All the evidence indicates that the risk of treatment with PRGN-2012 is minor. Observed TEAEs related to study drug were limited to Grades 1 or 2. Low potential for viral shedding has not been assessed. Further studies will be needed. Routine pharmacovigilance to include trend analysis to identify unexpected increases in adverse events and their potential relationship to patient subgroups, concomitant medications, or other risk factors. Enhanced pharmacovigilance for identification of potential thrombotic events will be needed to further assess this risk.
Risk Management	<ul style="list-style-type: none"> Injection site reactions were mild and no serious adverse reactions were observed in the clinical study. Viral shedding has not been assessed 	<ul style="list-style-type: none"> Routine measures, such as the package insert and the current pharmacovigilance plan, will be adequate to manage the risks. A PMC evaluating viral shedding will help to assess for the low risk of transmission with this replication incompetent adenoviral vector

Abbreviations: HPV 6/11 = human papillomavirus type 6 or 11; RRP = recurrent respiratory papillomatosis; TEAE = treatment-emergent adverse event

11.2 Risk-Benefit Summary and Assessment

RRP is a serious disorder that results from chronic infection with HPV 6 or 11 leading to recurrent papilloma formation in the respiratory tract. Patients with this disease have significant impairment of breathing and vocalization with disease progression, often leading to respiratory failure. Current standard-of-care treatment is repeated excision of airway papilloma, which has been associated with substantial morbidity. There is a substantial amount of unmet medical need for therapy that can alleviate symptoms and prevent worsening of respiratory function. PRGN-2012 is a non-replication competent gorilla adenovirus-based immunotherapy designed to induce an immune response directed against papilloma cells that have been infected with HPV 6 or HPV 11.

Clinical data from 35 adults with RRP treated with PRGN-2012 in a single-arm, open-label study demonstrate substantial evidence of effectiveness through reduction in surgical interventions required for airway papilloma in the 12 months following treatment when compared to intra-patient/baseline control of the 12 months prior to treatment. Sustained treatment response through two years further reveals clinical benefit through durability of treatment effect.

The observed risks of PRGN-2012 were noted to be mild in nature. The most substantial risks of treatment with PRGN-2012 are associated with the inflammation produced at the injection site. However, most injection-site reactions were mild in severity and resolved relatively quickly and without sequelae. No serious safety signals were apparent in this study in adults with RRP.

Given the severity of RRP and the clinical data supporting the use of PRGN-2012 in adults with RRP, we consider the observed clinical benefits in decreased papilloma recurrence to outweigh the identified and potential risks. Continued evaluation of safety through routine pharmacovigilance will help to ensure the risk-benefit remains favorable in the post-marketing setting.

11.3 Discussion of Regulatory Options

In the original application, the Applicant sought accelerated approval based on an intermediate clinical endpoint of complete response at 12 months. Given the limited duration of follow-up and uncertainty on the durability of effect, the review team agreed with the Applicant's original proposal for accelerated approval rather than traditional approval to permit verification of the clinical benefit in the post-marketing confirmatory study. In the 120-day safety update, the Applicant provided additional efficacy data for all patients through 2 years and 15 patients through end of study at three years enrolled in this ongoing study. Upon review of the additional data, the review team agrees that the Applicant has provided substantial evidence of effectiveness from an adequate and well controlled study to support traditional approval for patients with this rare disease.

The review team also had discussions on whether approval should be limited to patients with three or more surgical interventions in the 12 months prior to treatment. RRP severity has not traditionally been defined by the number of surgical interventions required within a 12-month period due to limited natural history understanding of the disease and data showing that the number of required interventions can fluctuate over time. Based on uncertainties in the ability to accurately define disease severity and the

observed favorable risk-benefit profile in the studied population, the Clinical reviewer recommends traditional approval for adults with RRP.

Regulatory Flexibility

The FDA review of BLA 125832 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 an 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 converting the application from accelerated to traditional approval based on durability data, 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) justified approval with appropriate post-marketing oversight while maintaining scientific rigor.

11.4 Recommendations on Regulatory Actions

Traditional approval for adults with RRP.

11.5 Labeling Review and Recommendations

Several revisions were made to the Applicant's proposed United States Prescribing Information (USPI). Please see [Table 17](#) for a summary of significant changes to the United States Prescribing Information.

Table 17. Summary of Significant Labeling Changes

USPI Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Section 2: Dosage and Administration	-	Section 2.2: Revised to include recommendation on surgical debulking procedure. Revisions were made to this section to use active command language as appropriate.
Section 5: Warnings and Precautions	Only section 5.1 with hypersensitivity reaction warning proposed by the Applicant.	Section 5.2 added to specify the risk of thrombotic events with administration of adenoviral vector-based therapies including PAPZIMEOS.
Section 6: Adverse Reactions (Safety)	-	Information in this section was revised to describe the safety database for PAPZIMEOS. Table 2 was revised to present adverse reactions in descending order of incidence.

USPI Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Section 8.5: Geriatric Use	Clinical studies of PAPZIMEOS did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger patients.	Revised to include the following data on geriatric patients. "There were 9 patients (24%) 65 years of age and older and 1 patient (3%) 75 years of age and older in Study PRGN-2012-201."
Section 12: Clinical Pharmacology	Viral distribution and shedding information included in the proposed draft.	PD: PD data from Study PRGN-2012-201 was added to specify HPV 6 and HPV 11 induction and mean fold-change from baseline in responders and non-responders. PK: Viral distribution and shedding information was omitted as these were not evaluated for PAPZIMEOS.
Section 14: Clinical Studies	Results from exploratory analysis included in the proposed label.	Revised based on current CBER/OTP labeling practice to describe the study design, intervention, population characteristics, and efficacy measures and results, which provided substantial evidence of benefit for PAPZIMEOS. Results from exploratory analysis were deleted as they were not considered substantial evidence.
Section 17: Patient Counseling Information	No information provided in this section.	This section was revised to include important risks listed in section 5 (Warning and Precautions).

Source: FDA Clinical Reviewer and Associate Director of Labeling

Abbreviations: CBER = Center for Biologics Evaluation and Research, FDA = Food and Drug Administration, HPV = human papilloma virus, OTP = Office of Therapeutic Products, PD = Pharmacodynamic, PK = Pharmacokinetic, USPI = United States Prescribing Information

11.6 Recommendations on Postmarketing Actions

The validation of the adventitious viral agent (AVA) testing by (b) (4) method was found to be inadequate during this BLA review. The Applicant will revalidate the AVA testing by (b) (4) method as a CMC post-marketing requirement (PMR).

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: September 30, 2025

Study completion: January 31, 2026

Final study report submission: February 28, 2026

PMC#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

PMC#3: Precigen, Inc. commits to conduct viral shedding studies following administration of zopapogene imadenovec-drba in adult patients with RRP.

Final study report submission: December 31, 2026

PMC#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 RRP.

Final study report submission: December 31, 2028

There are five supplemental CMC PMC studies related to product manufacturing. Please see CMC review for additional details.

APPENDIX 1. ECOG PERFORMANCE STATUS SCALE

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Source: Oken et al., 1982.

The ECOG Performance Status Scale was developed by the Eastern Cooperative Oncology Group (ECOG), now the ECOG-ACRIN Cancer Research Group, and published in 1982 (ecog-acrin.org/scale)

APPENDIX 2. DERKAY SCORING FOR RECURRENT RESPIRATORY PAPILLOMATOSIS

For each site, 0 = none, 1 = surface lesion, 2 = raised lesion, 3 = bulky lesion

Sites:

- Epiglottis – lingual surface
- Epiglottis – laryngeal surface
- Right aryepiglottic fold
- Left aryepiglottic fold
- Right false vocal fold
- Left false vocal fold
- Right true vocal fold
- Left true vocal fold
- Right arytenoid
- Left arytenoid
- Anterior commissure
- Posterior commissure
- Subglottis Trachea – upper one third
- Trachea – middle one third
- Trachea – lower one third
- Right bronchus
- Left bronchus
- Tracheostomy stoma
- Nose
- Pharynx
- Esophagus
- Lungs
- Other

Total Anatomical Score (0-75)

- <20 low risk for adjuvant therapy
- ≥20 high risk for adjuvant therapy

Source: Derkay, 2001; Hester et al., 2003

APPENDIX 3. VOICE HANDICAP INDEX-10

Was the procedure performed? ☐ Yes [1]

☐ No

Reason not performed: [2]

Eval Date [3]

	0 - Never	1 - Almost Never	2 - Sometimes	3 - Almost Always	4 - Always	
My voice makes it difficult for people to hear me.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[4]
People have difficulty understanding me in a noisy room.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[5]
People ask, "What's wrong with your voice?"	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[6]
I feel as though I have to strain to produce voice.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[7]
My voice difficulties restrict my personal and social life.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[8]
The clarity of my voice is unpredictable.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[9]
I feel left out of conversation because of my voice.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[10]
My voice problem causes me to lose income.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[11]
My voice problem upsets me.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[12]
My voice makes me feel handicapped.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	[13]

Total Score [14]

Source: Rosen et al., 2004.