



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

**PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM**

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**To:** Sukyoung Sohn, PhD  
Chair of the Review Committee  
Office of Therapeutic Products

**Through:** Kerry Welsh, MD, PhD  
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**Subject:** Review of Pharmacovigilance Plan

**Sponsor:** Precigen, Inc.

**Product:** PAPZIMEOS (zopapogene imadenovec)\*

**Application Type / Number:** BLA / STN 125832/0

**Proposed Indication:** Treatment of adults with recurrent respiratory papillomatosis (RRP)

**Submission Date:** December 27, 2024

**Action Due Date:** August 27, 2025

\*This product is referred to as PRGN-2012 throughout this memorandum.

## **1 OBJECTIVE**

The purpose of this review is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) submitted under the original BLA 125832/0 based on the clinical safety database and safety profile of PAPZIMEOS (zopapogene imadenovec). Our review will determine whether any safety-related studies such as Post-Marketing Requirements (PMRs) are warranted and/or if there will be agreed-upon safety-related studies as Post-Marketing Commitments (PMCs), or if Risk Evaluation and Mitigation Strategies (REMS) are required for PRGN-2012, should the indication for this product be approved. Please refer to the Appendix for the complete list of materials reviewed for this memorandum.

## **2 BACKGROUND**

Recurrent respiratory papillomatosis (RRP) is a rare disease of the upper and lower respiratory tracts characterized by growth of benign tumors (papillomas) on the vocal cords, trachea, and lung caused by chronic infection from two types of human papilloma viruses (HPV): HPV6 and HPV11. The incidence has been estimated at 4.5 per 100,000 children and 1.8 per 100,000 adults in the United States. Although typically benign, extensive morbidity arises from papillomatous obstruction of the larynx leading to complications including airway occlusion, loss of lung volume, and post-obstructive pneumonia. In addition, while rare, papillomatous lesions can undergo aggressive malignant transformation<sup>1</sup>. The clinical course of RRP is further complicated by immune dysfunction in affected individuals leading to long-term inadequate T-cell responses against HPV-infected cells<sup>2,3</sup>.

The current standard of care management for RRP is surgical removal of visible papillomas, usually involving microlaryngeal surgery to debulk the lesions. Adjuvant therapies have been tested in clinical trials, including systemic interferon alpha, targeted light source therapy (photodynamic therapy and pulsed-dye laser therapy), and local injection of anti-viral and antiangiogenic agents. However, study results have been inconsistent, and no single adjuvant approach has been widely adopted for the treatment of RRP<sup>4</sup>. PRGN-2012 (zopapogene imadenovec) is a replication incompetent gorilla adenovirus (GC46)-based immunotherapy designed to express antigen-selected regions of HPV6/11 proteins under the control of a cytomegalovirus (CMV) promoter for targeted T-cell response and elimination of HPV-infected papilloma cells.

## **3 PRODUCT INFORMATION**

### **3.1 Product Description**

Per the sponsor's draft U.S. Package Insert (USPI) Section 11, "PAPZIMEOS (zopapogene imadenovec) is a non-replicating adenoviral vector-based [therapy] designed to express a fusion antigen comprising selected regions from several human papilloma virus (HPV) type 6 (HPV6) and 11 (HPV11) proteins". The product is dispensed as single-dose vials with suspensions concentrated at an extractable and recommended dose of  $5 \times 10^{11}$  PU/mL. It is administered as a 4-dose series of subcutaneous injections over a 12-week interval. Each single-dose vial contains the following excipients: Tris base (10mM), sodium chloride (75mM),

magnesium chloride hexahydrate (1 mM), polysorbate 80 (0.019 mM), and trehalose dihydrate (146 mM).

*Reviewer comment: The sponsor's Pharmacology Written Summary indicates that in-vitro and ex-vitro animal model studies showed PRGN-2012 activation of an immune response with increased production of cytokines, such as interferon-gamma (IFN-γ), but transduced antigen-presenting cells (APCs) and targeted T-cell response promotion specifically against HPV6 and HPV11 antigens in HPV-infected cells.*


### **3.2 Proposed Indication**

The sponsor's proposed indication statement as submitted to the original BLA 125832/0 is as follows: "PAPZIMEOS is an adenoviral vector-based immunotherapy indicated for the treatment of recurrent respiratory papillomatosis in adults". OBPV defers to product office on the final language for the indication statement. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon indication after FDA review.

## **4 PERTINENT REGULATORY HISTORY**

This is an original BLA submission, and no patients have been treated with PRGN-2012 in the post-market/commercial setting. On December 16, 2022, nadofaragene firadenovec-vncg (ADSTILADRIN®) was licensed as the first FDA approved non-replicating adenoviral vector-based gene therapy for the treatment of adult patients with high-risk Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer. Adstiladrin's U.S. Package Insert (USPI) indicates labeled adverse events related to the target organ system the product was designed to interrogate (e.g. intravesical toxicity in bladder-directed gene therapy). It additionally cites a background risk of low-level vector shedding and provides labeled precautionary measures including delayed administration during concurrent times of illness and avoidance in immunocompromised individuals susceptible to disseminated viral infection<sup>7</sup>.

Numerous non-human adenoviral vectors, including gorilla adenovirus vector, have increasingly emerged in use for recombinant vaccine and immunotherapy development, such as (b) (4)



## **5 DESCRIPTION OF PRGN-2012 CLINICAL TRIAL SAFETY DATABASE**

### **5.1 Clinical Studies**

The clinical study safety data reviewed are from the Clinical Overview, Summary of Clinical Safety and PRGN-2012-201 Clinical Study Report submitted to 125832/0. OBPV defers to the product office on final review of the clinical database, including safety and efficacy outcomes, which will inform the final language in the USPI. Below is our *focused* review of the sponsor data initially submitted to the BLA, to inform decisions

pertaining to pharmacovigilance planning, should this BLA 125832/0 be approved. Please refer to the package insert for the final clinical safety data.

The sponsor submitted data from the ongoing PRGN-2012-201 study, which is considered the pivotal study supporting the request for accelerated licensure approval. This is a single arm, non-randomized, open label Phase I/II study conducted in the United States assessing the safety (including tolerability and recommended Phase II dose) and efficacy of PRGN-2012 in a total of 38 patients divided into the following cohorts by study phase:

- Phase I: 15 adult patients with RRP, with or without pulmonary involvement, and requiring  $\geq 2$  surgeries within 12 months prior to enrollment
- Phase II: 23 adult patients with RRP, with or without pulmonary involvement, and requiring  $\geq 3$  surgeries within 12 months prior to enrollment

The primary endpoints established as criteria for safety evaluation are defined as follows:

- Incidence and severity of dose-limiting toxicities (DLTs) within 28 days of the first dose of PRGN-2012
- Incidence and severity of adverse events (AEs) within 12 months of the last dose of PRGN-2012
- Incidence and severity of immune-related AEs (irAEs)
- Incidence and severity of serious AEs (SAEs)
- Clinical parameters assessment including vital signs, laboratory results, and physical examination findings

The majority of enrolled patients had previous exposure to other lines of treatment and/or procedures, including common unapproved therapies such as bevacizumab and cidofovir, HPV vaccines, and scope-guided biopsies. All study participants underwent standard of care surgical debulking, defined as laryngotracheal papilloma removal to establish minimal residual disease (MRD), prior to starting study treatment with PRGN-2012. The study treatment was given subcutaneously in 4 doses over a 12-week period on Days 1, 15, 43, and 85. Patients are followed for a 12-month period of short-term follow-up upon study treatment completion, after which eligible participants may enter a 2-year period of long-term follow-up for a total of 36 months of follow-up.

Phase I of the study was designed as a dose-escalation study to assess the safety, tolerability, and recommended Phase II dose (RP2D). In this part of the study, two dose levels were administered and evaluated utilizing a “standard 3+3 dose escalation design”, setting  $1 \times 10^{11}$  particle units (PU) and  $5 \times 10^{11}$  PU as the starting and maximum doses, respectively. Of the 15 patients enrolled in Phase I of the study, 3 participants received 4 doses of the starting dose level (dose level 1; DL1) of  $1 \times 10^{11}$  PU (cumulative dose of  $4.0 \times 10^{11}$  PU) and 12 participants received 4 doses of the maximum dose level (dose level 2; DL2) of  $5 \times 10^{11}$  PU (cumulative dose of  $20 \times 10^{11}$  PU). Following demonstrated tolerability at both dose levels and primarily mild (Grade 1 to 2) treatment-emergent adverse events (TEAEs), the dose of  $5 \times 10^{11}$  PU was established as the RP2D.

Phase II of the study was designed as a dose-expansion study to assess the safety and efficacy of PRGN-2012 in patients treated with the RP2D of  $5 \times 10^{11}$  PU. As of the data cut-off date of August 28, 2024, all enrolled patients have completed study treatment by receiving all 4 doses of PRGN-2012. All but one of the total enrolled participants completed short-term follow-up (the missing individual is the one reported case of death discussed further in Section 5.2), with 84.2% of patients remaining in the ongoing long-term follow-up portion of the study and 13.2% of patients having completed the entire 36-month follow-up period. The overall median duration of follow-up after study treatment is 24 months.

The sponsor additionally references the Phase III confirmatory study, PRGN-2012-301, that is currently ongoing in enrollment and designed to establish the efficacy of PRGN-2012 by evaluating the complete response rate; the sponsor later cites this study as an ongoing measure to further elaborate on the product's long-term safety profile as part of their proposed PVP, discussed in Section 7 of this memorandum.

**Table 1. Summary of Clinical Studies Supporting the Safety of PRGN-2012\***

| Study Identifier (Status)  | Study Title   | N  | Study Population and Dose Level Characteristics   | Description  | Interim Data Cut-off Date for Ongoing Studies |
|--|---|----|---|--|---|
| PRGN-2012-201<br>Pivotal Phase 1 (study ongoing; enrollment and treatment completed) | A Phase 1/2 Study of Adjuvant PRGN-2012 in Adult Participants with Recurrent Respiratory Papillomatosis | 15 | Adult patients with RRP requiring $\geq 2$ surgeries in 12 months prior, with or without pulmonary involvement<br><br>Dose escalation (3+3)<br><br>Dose Level 1 ( $1 \times 10^{11}$ PU), N=3<br><br>Dose Level 2 ( $5 \times 10^{11}$ PU; RP2D), N=12. | Dose-escalation study to determine safety, tolerability, and RP2D of PRGN-2012 | August 28, 2024                               |
| PRGN-2012-201  | A Phase 1/2 Study of  | 23 | Adult patients with RRP   | Dose expansion   |   |

|   |  |  |  |  |                 |
|---|--|--|--|--|-----------------|
| Pivotal Phase 2 (study ongoing; enrollment and treatment completed) | Adjuvant PRGN-2012 in Adult Participants with Recurrent Respiratory Papillomatosis |  | requiring $\geq 3$ surgeries in 12 months prior, with or without pulmonary involvement | study to evaluate safety and efficacy of PRGN-2012 in patients treated at the RP2D (5 x 10 <sup>11</sup> ) | August 28, 2024 |
|---|--|--|--|--|-----------------|

\*Adapted from Table 1, Summary of Clinical Safety, STN 125832/0, Module 2.7.4

*Reviewer comment: The sponsor notes that the inclusion criteria used for the recruitment of participants in Phase I of the study specified a history of  $\geq 2$  surgical interventions for the treatment of RRP within 12 months of enrollment; however, all enrolled Phase I participants had a history of  $\geq 3$  surgical interventions for the treatment of RRP within 12 months of enrollment.*

*Per the sponsor, the rationale for the proposed starting and maximum doses assessed in Phase I of the study was “based on clinical assessment (b) (4)”*

*Enrolled patients who were found to have visible papilloma at Day 43 and 85 of the study were permitted to undergo surgical removal in order to maintain MRD: “Maintenance of a minimal disease burden during treatment allows the T-cells time to expand and prevent them from becoming anergic while the underlying infection is cleared”.*

*PRGN-2012 treatment can be preceded by medical procedures/interventions including the treatment modalities listed above; these procedures/interventions have their own risks independent from the drug product PRGN-2012. In addition, the underlying condition of RRP has many acute and chronic complications.*

## 5.2 Adverse Events

### 5.2.1 Clinical Study PRGN-2012-201

- i) Most common treatment-emergent adverse events (TEAEs): Among all 38 participants who received at least one dose of PRGN-2012, injection site reactions were the most common TEAEs (n=37, 97.4%). Overall, the most common TEAEs occurring in  $\geq 10\%$  of patients were injection site reactions (97.4%), fatigue (73.7%), chills (65.8%), pyrexia (63.2%), oropharyngeal pain (55.3%), myalgia (28.9%), nausea (26.3%), and COVID-19 infection (10.5%). These were also the most commonly reported treatment-related TEAEs with the exception of COVID-19 infection and oropharyngeal pain, which were not considered treatment-related by the investigator and the sponsor. AEs occurring in  $\geq 10\%$  of study participants are shown in Table 2.

**Table 2: Treatment-Emergent Adverse Events Occurring in ≥10% of Participants Following PRGN-2012 Infusion (as of data cut-off August 28, 2024)\***

| <b>Primary System Organ Class Preferred Term</b>            | <b>All Grades n (%)</b> |
|---|-------------------------|
| Number of patients with at least one TEAE                   | 38 (100)                |
| <b>Cardiac disorders</b>                                    | 4 (10.5)                |
| <b>Gastrointestinal disorders</b>                           | 15 (39.5)               |
| Nausea  | 10 (26.3)               |
| <b>General disorders and administration site conditions</b> | 38 (100)                |
| Chills  | 25 (65.8)               |
| Fatigue   | 28 (73.7)               |
| Injection site reaction                                     | 37 (97.4)               |
| Pyrexia   | 24 (63.2)               |
| <b>Infections and infestations</b>                          | 7 (18.4)                |
| COVID-19  | 4 (10.5)                |
| <b>Musculoskeletal and connective tissue disorders</b>      | 12 (31.6)               |
| Myalgia   | 11 (28.9)               |
| <b>Nervous system disorders</b>                             | 7 (18.4)                |
| Headache  | 4 (10.5)                |
| <b>Respiratory, thoracic and mediastinal disorders</b>      | 22 (57.9)               |
| Oropharyngeal pain  | 21 (55.3)               |

\* Adapted from Table 6, Summary of Clinical Safety, STN 125832/0, Module 2.7.4

ii) SAEs: Three patients (7.9%) were reported to have developed a SAE, none of which were considered treatment-related by the investigator and the sponsor: one patient at DL2 with cardiac arrest (detailed further in sub-section iii below), one patient at DL2 with gastrointestinal hemorrhage, and one patient at DL1 with bacterial laryngitis.

The SAE case of gastrointestinal hemorrhage is summarized as follows:

Patient (b) (6) was enrolled in Phase II of the pivotal study and completed all 4 treatment doses at DL2. On (b) (6), the patient underwent standard of care papilloma debulking per protocol with no immediate signs of post-surgical bleeding. A hospital admission was pre-planned given the patient's lack of a post-operative caregiver. Upon admission, the patient received the first dose of PRGN-2012 without complication and approximately 30 minutes thereafter developed hemoptysis. The patient was taken for surgical re-exploration and was found to have an active bleeding site at the inferior pole of the left tonsil. The bleed was cauterized without complication and the patient remained hemodynamically and clinically stable throughout the remainder of the hospitalization course. He was discharged as scheduled for the planned admission. The patient continued in the study and was administered the final dose on (b) (6).

*Reviewer comment: Per FDA request, the sponsor submitted complete blood counts obtained prior to the papilloma cleanout until discharge (Table 25, PRGN-2012-201*

*Clinical Study Report Body) for the patient who developed tonsillar bleeding with all values generally appearing within reasonable range, including normal platelet counts.*

*In an IR response submitted to STN 125832/0.35, the sponsor provided further clinical data confirming the tonsil as the isolated active bleeding site. Additionally, the short latency period between receiving an injection of PRGN-2012 and following debulking surgery (within 30 minutes and 6-8 hours, respectively) corroborate the opinion of the investigator and sponsor of the SAE as being related to the MRD surgery.*

The SAE case of bacterial laryngitis is summarized as follows:

Patient (b) (6) was enrolled in Phase I of the pivotal study and completed all 4 treatment doses at DL1. The final dose was administered on (b) (6) and the patient additionally underwent the last MRD procedure per protocol on the same date. On (b) (6), the patient presented to a local emergency department with sore throat, throat swelling, dysphagia, and was subsequently escalated to intensive care. He received intravenous steroids, which reportedly resulted in improvement in the swelling. He was seen by an otolaryngologist the following day and was found to have erythema of the supraglottic region of the larynx, ultimately diagnosed as bacterial laryngitis. The patient was discharged on the same day with a steroid taper and continued daily intramuscular antibiotic injections in the outpatient setting. He experienced symptomatic improvement within 48 hours and achieved symptomatic resolution upon antibiotic course completion. The patient returned for a protocol follow-up visit on (b) (6) at which time the examination showed normal swallowing and respiratory function, with no recurrence of throat swelling.

The patients who experienced gastrointestinal hemorrhage and bacterial laryngitis were a part of a group of reported Grade 3 TEAEs (n=4, 10.5%), alongside cases of syncope (n= 1, 2.6%) and hypertension (n=1, 2.6%). None of the Grade 3 TEAEs were considered treatment-related by the investigator and the sponsor.

**Reviewer comment:** *Review of the SAE cases potentiate events stemming from surgical complications given the sites of surgical debulking are plausible sources of bleeding and infectious nidus.*

iii) Deaths: One individual, Patient (b) (6) died of cardiac arrest on Day (b) (6) while enrolled in Phase II of the pivotal study and (b) (6) days after receiving the last dose of PRGN-2012. The patient's medical history included coronary artery disease, severe aortic stenosis, severe chronic obstructive pulmonary disease with exertional dyspnea, chronic obstructive bronchitis, colon cancer diagnosed in 2001 with surgical resection, malignant neoplasm in-situ of the colon diagnosed in 2021, and a 40-year tobacco smoking history. Two days prior to the patient's death, he was found to have "severe single-vessel disease which required the placement of two drug-eluting cardiac stents", and severe aortic stenosis and pulmonary hypertension. A transcatheter aortic valve replacement was subsequently recommended, but the patient was discharged without undergoing the procedure. An incidental bladder mass was also



identified during this period of clinical decompensation. This event was not considered treatment-related by the investigator and the sponsor.

*Reviewer comment: Review of the single case of death suggests a fatal outcome likely attributed to pre-existing underlying conditions.*

iv) Adverse events of special interest (AESIs): One irAE case was reported of an individual who experienced peripheral sensory neuropathy while enrolled in the Phase II portion of the study. The event occurred on Day 1 of the study following the first DL2 treatment dose, was mild in severity, and resolved within 8 days of onset. The event did not require any form of intervention and was not considered treatment-related by the investigator and the sponsor.

*Reviewer comment: The sponsor submitted a 120-Day Safety Update to STN 125832/0.27 with no new SAEs, treatment-related AEs, or new safety signals reported during the long-term follow-up. As of the cut-off date of February 20, 2025, 10 additional participants completed the 36-month period of follow-up (n=15, 39.5%) and 22 (57.9%) continue in the long-term follow-up for a median follow-up duration of 27 months.*

One participant in the PRGN-2012-201 pivotal study became pregnant during the short-term follow-up period, approximately 6 months after study treatment completion, and delivered a 40-week full-term female neonate without any reported complications.

*Reviewer comment: An update on the pregnancy case was provided in the 120-Day Safety Update submitted to STN 125832/0.27 and in an IR response submitted to STN 125832/0.18. As of March 27, 2025, the child was 2 years of age and medically assessed as “healthy and has achieved all expected developmental milestones and maintains a standard growth trajectory”. No congenital defects or delivery complications were noted. The patient experienced postpartum preeclampsia attributed to COVID infection contracted during her third trimester, in addition to a history of postpartum preeclampsia in a previous pregnancy requiring management with magnesium, hydralazine, and nifedipine.*

## **6 SPONSOR’S PHARMACOVIGILANCE PLAN**

The sponsor submitted a Risk Management Plan (RMP; BLA 125832/0.4; submitted on January 9, 2025) proposing routine pharmacovigilance (PV) activities and risk minimization activities, including routine risk communication (e.g. “targeted educational materials tailored to specific audiences, including healthcare providers and patient advocacy groups”), the establishment of PRGN-2012 administration only by qualified healthcare professionals within a controlled clinical environment, and the product’s labeling as a risk mitigation tool. The sponsor proposes the long-term follow-up in the ongoing clinical studies, PRGN-2012-201 and PRGN-2012-301, as measures to collect long-term safety data and capture newly identified or delayed adverse events. Sources including patient registries will be utilized to capture a broader treatment population for expansion on the safety profile of PRGN-2012.

*Reviewer comment: The sponsor clarified in an IR response submitted to STN 125832/0.35 that the Coordination of Rare Diseases at Sanford (CoRDS; NCT01793168) was cited to characterize the disease burden of RRP in adult patients but is not intended to be used as a primary data source for safety surveillance in the PVP as the CoRDS is not designed to support PV activities. The sponsor states that the largest U.S. advocacy group, Recurrent Respiratory Papillomatosis Foundation, is planning to implement a new patient registry. Should the registry become available, the sponsor will assess its feasibility and data quality for supplementation to other real-world data sources included in routine PV activities. The sponsor confirms such addition will be incorporated in a revised PVP and RMP as an amendment to the BLA accordingly. Of note, any educational materials planned by the sponsor are a voluntary risk mitigation measure and not being required by FDA under a REMS.*

**Table 3. Sponsor's Pharmacovigilance Plan\***

| Type of Concern | Safety Concern    | Proposed Action  |
|-----------------|-------------------|--|
| Identified      | None              | N/A  |
| Potential       | Thrombotic Events | Routine risk minimization measures <ul style="list-style-type: none"> <li>• Post-market monitoring of potential thrombotic events</li> </ul><br>Routine and/or Additional PV Activity <ul style="list-style-type: none"> <li>• Routine PV</li> <li>• Expedited 15-day reporting of all thrombotic events for 3-years post approval</li> <li>• Trend analysis in periodic safety reports with interval and cumulative data</li> </ul> |
| Missing         | Pregnancy         | Routine risk minimization measures <ul style="list-style-type: none"> <li>• Labeling in USPI Section 8.1 Pregnancy</li> <li>• Prescription-only product</li> </ul>   |

|         |                       |  |
|---------|-----------------------|--|
|         |                       | <p>Routine and/or Additional PV Activity</p> <ul style="list-style-type: none"> <li>• Routine PV</li> <li>• Long-term safety monitoring in ongoing clinical studies PRGN-2012-201 and PRGN-2012-301</li> </ul>   |
| Missing | Lactation             | <p>Routine risk minimization measures</p> <ul style="list-style-type: none"> <li>• Labeling in USPI Section 8.2 Lactation</li> <li>• Prescription-only product</li> </ul> <p>Routine and/or Additional PV Activity</p> <ul style="list-style-type: none"> <li>• Routine PV</li> <li>• Long-term safety monitoring in ongoing clinical studies PRGN-2012-201 and PRGN-2012-301</li> </ul> |
| Missing | Viral Vector Shedding | <p>Routine risk minimization measures</p> <ul style="list-style-type: none"> <li>• Instructions for proper hand hygiene and handling disposal of affected materials to be given to close contacts of the treated individual and adhered to for one month</li> </ul>  |

|  |  |   |
|--|--|---|
|  |  | <ul style="list-style-type: none"> <li>• Prescription-only product</li> </ul> <p>Routine and/or Additional PV Activity</p> <ul style="list-style-type: none"> <li>• Routine PV</li> <li>• Vector shedding is currently being evaluated in ongoing clinical study PRGN-2012-301</li> </ul> |
|--|--|---|

\*Adapted from Tables 12 and 13, Risk Management Plan (Non-REMS), version 3.0, STN 125832/0.46, Module 1.16.1

### 6.1 Enhanced Pharmacovigilance

The sponsor will perform expedited reporting to FAERS regardless of seriousness or label status for thrombotic events for three years post-approval. The sponsor will also include summaries and trend analyses in periodic safety reports using both interval and cumulative data. Please see section 7.2.1 below for a discussion of the Important Potential Risk of thrombotic events.

*Reviewer comment: The sponsor agreed to perform the above enhanced pharmacovigilance activities in the IR response submitted to STN 125832/0.46.*

## 7 ANALYSIS OF SPONSOR'S RISK MANAGEMENT PLAN

### 7.1 Important Identified Risks

Per the sponsor, "there are no risks considered important for inclusion in the list of safety concerns in the RMP".

*Reviewer comment: Based on review of the pivotal Phase I/II study data, the safety profile of PRGN-2012 appears generally tolerable, particularly with regard to severe or life-threatening AEs, SAEs, and deaths. As such, the reviewer is agreeable to accepting the sponsor's lack of identified risks in the proposed RMP. The safety specifications of the PVP may be updated in the future as needed, as we accrue postmarketing experience with the product in the post-approval period, should this product be approved.*

### 7.2 Important Potential Risks

#### 7.2.1 Thrombotic Events

As noted by the sponsor (IR response submitted to STN 125832/0.35), no thrombotic events have been reported in all patients who have been treated with PRGN-2012 and completed up to 3 years of follow-up. Routine hematology and coagulation panels collected from screening through one year of follow-up have not detected any clinically

significant safety concerns. However, the risk of prothrombotic antibody development and emergence of thrombotic microangiopathy have been described following use of adenoviral vector-based products. For example, while not yet well-defined, virtually all affected individuals who received a recombinant, replication-incompetent human adenovirus vaccine had positive platelet-activating anti-platelet factor 4 [PF4] antibody titers, although earliest symptom onset is typically 5 days post-vaccine<sup>8,9</sup>, with candidate mechanisms behind immune-mediated thrombocytopenia with or without thrombosis under consideration in the literature. After discussion, the sponsor agreed with FDA's request to add thrombotic events as an Important Potential Risk to the PVP (IR responses submitted to STN 125832/0.35 and STN 125832/0.46). The sponsor also agreed to FDA's request for enhanced pharmacovigilance activities for thrombotic events, which includes expedited reporting to FAERS regardless of seriousness or label status for three years post-approval and a summary and analysis in periodic safety reports.

*Reviewer comment: The sponsor's revised RMP (version 3.0, dated June 27, 2025) incorporating enhanced pharmacovigilance activities for thrombotic events is acceptable.*

*The sponsor was additionally requested to provide rationale for excluding the following as Important Potential Risks in the Risk Management Plan (RMP) based on potential class effects of adenoviral vectors:*

- *Immunogenicity*
- *Carcinogenicity*
- *Genotoxicity*
- *Complications related to target organ interrogation e.g. locations of papilloma*
- *Viral vector shedding*

*In the IR response submitted to STN 125832/0.35, the sponsor confirmed there have been no reports of adverse events considered related to immunogenicity, including immediate hypersensitivity reactions, laryngeal edema, thrombocytopenia, or severe injection site reactions in treated subjects up to 3 years of follow-up. While positive neutralizing antibody titers were detected in all patients and transient, low levels of seropositivity detected in some about 6-12 weeks after treatment, there was no observation of sustained or increasing development of antibodies nor significantly demonstrated effect on safety.*

*Regarding carcinogenicity and genotoxicity, the sponsor states the vector basis is reliant on the isolate GC46 genome of a gorilla adenovirus with deletions in the E1<sup>(b) (4)</sup>*

*[REDACTED], lead to replication incompetence in transduced cells and reduce the risk of generating replication competent adenovirus. Similarly to other adenovectors, PRGN-2012 does not rely on host cell genome integration for transgene expression, thereby reducing genotoxic risk and insertional mutagenesis or position-effect*

*variegation. There was no observed malignant transformation or development in treated subjects up to 3 years of follow-up.*

*Furthermore, the sponsor states PRGN-2012's administration route is designed as a local subcutaneous injection preceded by debulking surgery to establish minimal residual disease prior to treatment. Per the sponsor, debulking of the site of papillomatous lesions "mitigates the risk of a large cytotoxicity effect triggering an inflammatory response or cytokine storm". Nasopharyngolaryngoscopies performed at interval stages of the study treatment have not demonstrated evidence of laryngeal edema or immune-mediated events in subjects monitored throughout the pivotal clinical trial. In patients who experienced recurrence of papilloma, there was no evidence of atypical location recurrence, altered papilloma morphology, increased growth intensity, or significant changes to surrounding tissue. As such, although excluded as Important Potential Risks from the RMP, the sponsor notes potential adverse events related to the product class will continue to be monitored in the ongoing confirmatory study, PRGN-2012-301, and across routine surveillance and signal detection activities.*

*Based on review of supplemental data in corroboration with safety data submitted in non-clinical, clinical studies, and discussions with the OTP clinical team, routine pharmacovigilance is sufficient to monitor the risk of PRGN-2012 in addition to enhanced pharmacovigilance to monitor for the potential risk of thrombotic events. Please see Section 7.4.2 below for a discussion on viral shedding.*

### **7.3 Important Missing Information**

#### **7.3.1 Pregnancy and Lactation**

No studies have been conducted in pregnant or lactating women, and no reproductive toxicology studies were conducted with PRGN-2012. The sponsor states that potential effects on reproductive health cannot be excluded given the immunomodulatory nature of PRGN-2012.

The sponsor will perform routine PV and long-term safety monitoring in ongoing clinical studies. The sponsor's proposed USPI indicates that no human or animal reproduction data are available to suggest the presence or absence of drug associated risk and provides an estimated background risk of miscarriage and major birth defects.

*Reviewer comment:* *The sponsor's proposed PVP to monitor the missing information of pregnancy and lactation is acceptable.*

#### **7.3.2 Viral Vector Shedding**

The risk of vector shedding and infectious transmission is generally correlated with the mode of administration, with higher risk typically associated with products administered systemically (e.g. intravenous, subretinal, intravesical). While the risk of potential complications from vector shedding is considered low based on PRGN-2012's replication deficiency and local administration route, the sponsor acknowledged that the risk of transmission to untreated individuals cannot be completely excluded at this time.

The sponsor submitted a revised RMP (version 2.0) adding viral vector shedding as Missing Information in the RMP with risk minimization measures including instructions to healthcare providers and close contacts of the treated individual. Viral vector shedding is currently being evaluated by analysis of urine, fecal, skin (site of injection) and nasal swab samples collected at baseline and at interval timepoints (Days 3, 15, 43, 85 and up to at least 6 weeks after the last administration of PRGN-2012) in the ongoing confirmatory study, PRGN-2012-301.

*Reviewer comment: In response to an IR under STN 125832/0.35, the sponsor states that the replication deficient nature of the GC46 vector in combination with an administration route “very similar to the intramuscular administration commonly employed for other vector-based vaccines, which act by inducing an immune response and are associated with a lower risk of shedding and exposure to caregivers” portends a low risk of particle shedding and infectious transmission.*

*However, as the risk of vector shedding and transmission to untreated individuals cannot be excluded, the sponsor submitted a revised RMP (version 2.0, dated May 23, 2025) adding viral vector shedding as Missing Information currently being evaluated in the ongoing confirmatory study, PRGN-2012-301.*

*In an IR response submitted to STN 125832/0.35, the sponsor states that proposed modifications to the precautions will be discussed with the FDA after analysis of vector shedding data is ascertained from the ongoing clinical study. The sponsor’s proposed PVP to monitor the missing information of viral shedding is acceptable.*

## **8 ADDITIONAL REVIEW TEAM SAFETY-RELATED PMR RECOMMENDATION**

As per OTP assessment, the Applicant did not adequately validate the (b) (4) assay for detecting adventitious viral contamination in the (b) (4) specifically:

- There was insufficient information on assay specificity and detection limits for (b) (4) viruses.
- Method Suitability was not verified properly.

OTP made a determination that additional analysis was needed in a post-marketing study that will be required to ensure that the (b) (4) assay is suitable for detecting adventitious viral contamination in the (b) (4)

Claims databases and available data sources in the CBER Biologics Effectiveness and Safety (BEST) System (also referred to as CBER Sentinel Program) are not sufficient to assess the serious risk of patient exposure to adventitious viral contamination in the (b) (4). Sentinel insufficiency provides justification for a sponsor conducted postmarketing requirement (PMR) for a CMC study.

OTP presented this additional CMC study to the CBER safety working group (SWG) on July 10, 2025 and received SWG concurrence for a PMR under 505(o) of Federal Food,

Drug, and Cosmetic Act (FDCA) to conduct a revalidation study for the (b) (4) assay to include:

(b) (4)

Note that OBPV defers to OTP for review of the above study.

## **9 DPV ASSESSMENT**

Review of available clinical trial data and safety update reports from ongoing studies indicate a generally tolerable safety profile and favorable benefit-risk profile with no major important identified risks observed. Based on the non-integrating and replication deficient nature of this non-human adenovirus vector and submitted clinical safety data, the sponsor's proposal of conducting routine and enhanced pharmacovigilance in accordance with 21 CFR 600.80 and monitoring long-term safety through ongoing studies PRGN-2012-201 and PRGN-2012-301 are acceptable. The sponsor confirmed commitment to adhering to enhanced AE reporting requirements for the potential risk of thrombotic events, including expedited 15-day reporting and periodic safety report analyses for three years post-approval.

## **10 DPV RECOMMENDATIONS**

Should the product be approved for the treatment of adults with RRP, the proposed RMP, version 3.0, dated June 27, 2025 is adequate to monitor post-marketing safety for PRGN-2012 with routine and enhanced pharmacovigilance, including adverse event reporting, in accordance with 21 CFR 600.80. The available safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS), and there is no safety-related post-marketing commitment (PMC) study. Of note, OTP has recommended a safety-related postmarketing requirement (PMR) for a CMC study for revalidation of the (b) (4) assay to ensure adequate detection of adventitious viral contamination in the (b) (4) (please see product office review memorandums and July 10, 2025 SWG meeting minutes for details).

Please see the final version of the package insert submitted by the sponsor for the final agreed-upon language for the label.



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**APPENDIX**  
**Materials Reviewed**

**Table A1: Materials reviewed in support of this assessment**

| <b>Date</b>       | <b>Source</b> | <b>Document Type</b> | <b>Document(s) Reviewed</b>                                   |
|-------------------|---------------|----------------------|---|
| October 25, 2024  | Sponsor       | STN125832/0          | Module 2.4 Nonclinical Overview                               |
| October 25, 2024  | Sponsor       | STN125832/0          | Module 2.6.2 Pharmacology Written Summary                     |
| October 25, 2024  | Sponsor       | STN125832/0          | Module 2.6.6 Toxicology Written Summary                       |
| December 13, 2024 | Sponsor       | STN125832/0          | Module 2.5 Clinical Overview                                  |
| December 13, 2024 | Sponsor       | STN125832/0          | Module 2.7.4 Summary of Clinical Safety                       |
| December 13, 2024 | Sponsor       | STN125832/0          | Module 5.3.5.1 Study PRGN-2012-201 Clinical Study Report      |
| January 9, 2025   | Sponsor       | STN125832/0          | Module 1.16.1 Post-approval Pharmacovigilance Plan            |
| January 9, 2025   | Sponsor       | STN125832/0          | Module 1.16.1 Risk Management Plan (Non-REMS)                 |
| March 25, 2025    | Sponsor       | STN125832/0.18       | Module 1.11.3 Clinical Information Amendment                  |
| April 25, 2025    | Sponsor       | STN125832/0.31       | Module 2.7.3 Summary of Clinical Safety 120-Day Safety Update |
| April 25, 2025    | Sponsor       | STN125832/0.27       | Module 2.7.4 Day 120 Safety Update                            |
| May 23, 2025      | Sponsor       | STN125832/0.35       | Module 1.11.4 Multiple Module Information Amendment           |
| May 23, 2025      | Sponsor       | STN125832/0.35       | Module 1.16.1 Risk Management Plan (Non-REMS) version 2.0     |
| June 27, 2025     | Sponsor       | STN125832/0.46       | Module 1.16.1 Risk Management Plan (Non-REMS) version 3.0     |
| June 27, 2025     | Sponsor       | STN125832/0.46       | Module 1.11.4 Multiple Module Information Amendment           |