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FOOD AND DRUG ADMINISTRATION
Center for Biologics Evaluation and Research
Office of Therapeutic Products
Office of Pharmacology/Toxicology

BLA NUMBER: STN #125832.000

DATE RECEIVED BY CBER: 25-OCT-2024 (Nonclinical Module), 16-DEC-2024 (Clinical Module), 27-DEC-2024 (Chemistry, Manufacturing, and Controls [CMC]/Product Quality Module)

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PRODUCT: PAPZIMEOS (zopapogene imadenovec; PRGN-2012)

APPLICANT: Precigen, Inc.

PROPOSED INDICATION:

(b) (4)

PHARM/TOX REVIEWER: Valerie Myers
PHARM/TOX TEAM LEADER: Margaret Benny Klimek
PHARM/TOX BRANCH CHIEF: Abigail Shearin
PRODUCT (CMC) REVIEWERS: Sukyoung Sohn, Jianyang Wang, Joydeep Ghosh, Anurag Sharma
CLINICAL REVIEWERS: Prateek Shukla
PROJECT MANAGER: Hawa Camara
DIVISION DIRECTOR: Allen Wensky
OFFICE DIRECTOR: Vijay Kumar

EXECUTIVE SUMMARY:

PAPZIMEOS (zopapogene imadenovec; PRGN-2012) is a non-replicating adenoviral vector-based immunotherapy indicated for the treatment of patients with recurrent respiratory papillomatosis (RRP) (b) (4)

PAPZIMEOS is comprised of a non-replication competent gorilla adenoviral vector (GC46) expressing a fusion antigen of selected regions of HPV6/11 peptide segments. The drug product (DP) is provided as a single dosage suspension in a 2 milliliter (mL), self-standing (b) (4) vial for subcutaneous (SC) injection. PAPZIMEOS

administration results in presentation of the HPV6/11 peptide segments by antigen presenting cells (APCs) on the human leukocyte antigen (HLA)/major histocompatibility complex (MHC). This elicits a cytotoxic CD8⁺ T cell response directed against HPV6- or HPV11-infected cells expressing HPV-associated proteins in RRP patients. The recommended dosing regimen consists of four peripheral SC injections at 5×10^{11} particle units (PU) over a 12-week period on Weeks 1, (b) (4) 6, and 12.

The nonclinical development program evaluated a (b) (4) nonclinical lot of PAPZIMEOS, referred to as PRGN-2012 in the nonclinical studies. PRGN-2012 was produced in the Precigen research and development facility. The only process changes made between PRGN-2012 and PAPZIMEOS (b) (4).

In vitro assessment of transduction efficiency of the GC46 adenovirus was evaluated in (b) (4) from healthy control or RRP patient peripheral blood mononuclear cells (PBMCs) and demonstrated mean transduction efficiencies above 80% in all cell populations indicating effective expression of the target antigens for activation by the immune system.

Antigenicity of PRGN-2012 was evaluated in two separate co-culture studies. CD3⁺ T cells were isolated from healthy (n=3) or RRP subjects positive for infection with HPV6 (n=2) or HPV11 (n=3). PBMC-derived Mo-DCs were transduced with either PRGN-2012, (b) (4) empty GC46 (GC46.empty), (b) (4) T cells from healthy and RRP subjects stimulated by multiple rounds of PRGN-2012-transduced Mo-DCs expanded to a greater extent and produced higher levels of interferon-gamma (IFN- γ), granzyme-B, and granulocyte-macrophage colony-stimulating factor (GM-CSF) at all timepoints assessed compared to the controls where the fusion antigen, PRGN-2012, was not expressed. Transduction of Mo-DCs with PRGN-2012 increased net total cytokine production by both CD8⁺ and CD4⁺ T cells isolated from RRP patients compared to the healthy control donor.

Immunogenicity of PRGN-2012 was evaluated ex vivo using T cells isolated on Day 14 from (b) (4) immunized via SC injection with PRGN-2012 or empty vector on Days 0 and 7. T cells from both immunized groups (b) (4) IFN- γ , a T-cell inflammatory cytokine, was subsequently assessed. Mice immunized with PRGN-2012 demonstrated a marked, HPV antigen-specific IFN- γ response compared to mice immunized with empty vector alone. In a second study of healthy wildtype animals (C57BL/6 mice), T cells were isolated on Day 14 and 21 from mice immunized via SC injection with either PRGN-2012, GC46.empty vector, or FFB on Day 0. Activation of ex vivo isolated T cells and APCs from immunized mice was assessed by direct stimulation with OP from both HPV6 E6 and HPV11 E6 on Day 14 or individual E6/E7 peptides on Day 21. The HPV-specific peptides activated ex vivo isolated Day 14 and 21 T cells from PRGN-2012 immunized animals compared to control as measured by IFN- γ and also by induction of the chemokines, Regulated on Activation, Normal T cell Expressed and Secreted (RANTES) and (b) (4) which were assessed on Day 21 only.

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

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

Repeat administration of a dose level approximately 5-fold higher than the intended clinical dose, assuming a 60-kilogram adult of 5×10^{11} PU (1×10^{10} VP/mouse/dose) of PRGN-2012 once weekly on Days 0, 7, and 14 was well tolerated in WT C57BL/6 mice with no safety findings reported at termination after 21 Days.

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

PHARMACOLOGY/TOXICOLOGY RECOMMENDATION:

There are no nonclinical deficiencies identified in this BLA submission (STN #125832). There are no outstanding requests for additional nonclinical testing for PAPZIMEOS. The nonclinical information provided in the BLA supports approval of the licensure application.

Formulation and Chemistry:

PAPZIMEOS is a non-replicating adenoviral vector-based immunotherapy designed to express a fusion antigen comprising regions of HPV6 and HPV11 proteins.

PAPZIMEOS has a concentration of 5×10^{11} PU/mL and is provided in single-dose, self-standing (b) (4) vials, each of which contains a minimum extractable volume of 1 mL and excipients of: Tris base (10 millimolar [mM]), sodium chloride (75 mM), magnesium chloride hexahydrate (1 mM), polysorbate 80 (0.019 mM), and trehalose dihydrate (146 mM) and is a clear to slightly opalescent to opalescent colorless liquid.

Abbreviations

Ad	Adenovirus
APC	Antigen Presenting Cells
BD	Biodistribution
(b) (4)	
CBC	Complete Blood Count
CD	Cluster of Differentiation
(b) (4)	
DC	Dendritic Cells

(b) (4)	
DNA	Deoxy Ribonucleic Acid
DP	Drug Product
ECOG	Eastern Cooperative Oncology Group
(b) (4)	
ELISpot	Enzyme-Linked Immunospot
FFB	Final Formulation Buffer
GC46	Gorilla Adenoviral Vector
GM-CSF	Granulocyte Colony Stimulating Factor
HLA	Human leukocyte Antigen
HPV	Human Papillomavirus
HSC	Hematopoietic Stem Cell
IFN- γ	Interferon-gamma
LIGHT	LT-related Inducible ligand that competes for Glycoprotein D binding to Herpesvirus entry mediator on T cells
(b) (4)	
MHC	Major Histocompatibility Complex
MIP ^{(b) (4)}	Macrophage Inflammatory Protein ^{(b) (4)}
mL	Milliliter
mM	Millimolar
Mo-DCs	Monocyte-derived Dendritic Cells
MOI	Multiplicity of Infection
NK	Natural Killer
OP	Overlapping Peptides
PBMCs	Peripheral Blood Mononuclear Cells
PU	Particle Unit
RANTES	Regulated on Activation, Normal T cell Expressed and Secreted
RRP	Recurrent Respiratory Papillomatosis
SC	Subcutaneous
TNF- α	Tumor Necrosis Factor α
VP	Viral Particles
WT	Wild Type

Related File(s)

IND 26884 (primary), A Phase I Study of Adjuvant PRGN-2012 in Adult Patients with Aggressive Recurrent Respiratory Papillomatosis; Precigen, Inc.

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INTRODUCTION

RRP is a rare and chronic disease caused by infection with HPV type 6 or 11. Patients with RRP have persistent HPV infection and recurrent growth of exophytic neoplasms (i.e., squamous papilloma) anywhere in the upper and lower respiratory tract, but most commonly, the larynx^{1,2}. 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, respiratory failure and in rare instances, malignant transformation^{3,4}. The disease burden is significant, with patients often undergoing dozens of repeated surgical procedures over their lifetime that can result in permanent hoarseness⁵. This is associated with considerable economic and emotional burden^{6,7,8} resulting in a significant loss of quality of life and increased depression scores^{9,10,11}. Currently, there are no guidelines or best practices for clinical management of RRP because there is poor evidence upon which to base the current therapies. The variable expression and rarity of RRP have made large-scale studies and the development of reliable outcome measures challenging.

¹ Benedict PA, Ruiz R, Yoo M, Verma A, Ahmed OH, Wang B, Dion GR, Voigt A, Merati A, Rosen CA, Amin MR, Branski RC. Laryngeal distribution of recurrent respiratory papillomatosis in a previously untreated cohort. *Laryngoscope*. 2018 Jan;128(1):138-143. doi: 10.1002/lary.26742. Epub 2017 Jul 17. PMID: 28714564.

² Carifi M, Napolitano D, Morandi M, Dall'Olio D. Recurrent respiratory papillomatosis: current and future perspectives. *Ther Clin Risk Manag*. 2015 May 5;11:731-8. doi: 10.2147/TCRM.S81825. PMID: 25999724; PMCID: PMC4427257.

³ Schraff S, Derkay CS, Burke B, Lawson L. American Society of Pediatric Otolaryngology members' experience with recurrent respiratory papillomatosis and the use of adjuvant therapy. *Arch Otolaryngol Head Neck Surg*. 2004 Sep;130(9):1039-42. doi: 10.1001/archotol.130.9.1039. PMID: 15381589.

⁴ Dedo HH, Yu KC. CO(2) laser treatment in 244 patients with respiratory papillomas. *Laryngoscope*. 2001 Sep;111(9):1639-44. doi: 10.1097/00005537-200109000-00028. PMID: 11568620.

⁵ Scatolini ML, Labedz G, Cocciaglia A, Pérez CG, Nieto ME, Rodríguez D Áquila M, Rodríguez HA. Laryngeal sequelae secondary to surgical treatment for recurrent respiratory papillomatosis in children. *Int J Pediatr Otorhinolaryngol*. 2020 Mar;130:109815. doi: 10.1016/j.ijporl.2019.109815. Epub 2019 Dec 14. PMID: 31846823.

⁶ Loizou C, Laurell G, Lindquist D, Olofsson K. Voice and quality of life in patients with recurrent respiratory papillomatosis in a northern Sweden cohort. *Acta Otolaryngol*. 2014 Apr;134(4):401-6. doi: 10.3109/00016489.2013.867457. Epub 2014 Jan 17. PMID: 24433057.

⁷ Montaña-Velázquez BB, Nolasco-Renero J, Parada-Bañuelos JE, García-Vázquez F, Flores-Medina S, García-Romero CS, Jáuregui-Renaud K. Quality of life of young patients with recurrent respiratory papillomatosis. *J Laryngol Otol*. 2017 May;131(5):425-428. doi: 10.1017/S0022215117000354. Epub 2017 Feb 14. PMID: 28193306.

⁸ San Giorgi MRM, de Groot OSD, Dikkers FG. Quality and readability assessment of websites related to recurrent respiratory papillomatosis. *Laryngoscope*. 2017 Oct;127(10):2293-2297. doi: 10.1002/lary.26521. Epub 2017 Feb 24. PMID: 28233911; PMCID: PMC5638064.

⁹ Loizou C, Laurell G, Lindquist D, Olofsson K. Voice and quality of life in patients with recurrent respiratory papillomatosis in a northern Sweden cohort. *Acta Otolaryngol*. 2014 Apr;134(4):401-6. doi: 10.3109/00016489.2013.867457. Epub 2014 Jan 17. PMID: 24433057.

¹⁰ Montaña-Velázquez BB, Nolasco-Renero J, Parada-Bañuelos JE, García-Vázquez F, Flores-Medina S, García-Romero CS, Jáuregui-Renaud K. Quality of life of young patients with recurrent respiratory papillomatosis. *J Laryngol Otol*. 2017 May;131(5):425-428. doi: 10.1017/S0022215117000354. Epub 2017 Feb 14. PMID: 28193306.

¹¹ San Giorgi MRM, de Groot OSD, Dikkers FG. Quality and readability assessment of websites related to recurrent respiratory papillomatosis. *Laryngoscope*. 2017 Oct;127(10):2293-2297. doi: 10.1002/lary.26521. Epub 2017 Feb 24. PMID: 28233911; PMCID: PMC5638064.

Patients with RRP are thought to have dysfunctional immune responses to HPV infections. Therefore, the applicant developed PAPZIMEOS, a non-replicating adenoviral vector-based immunotherapy which elicits a T cell response in RRP patients directed against HPV6- or HPV11-infected papilloma cells.

NONCLINICAL STUDIES

Reviewer Note: PAPZIMEOS is referred to as PRGN-2012 (research grade lot) in this review memo. There are no differences between the adenovirus and fusion protein in PRGN-2012 compared to the clinical product, PAPZIMEOS.

PHARMACOLOGY STUDIES

Summary List of Pharmacology Studies

The following pharmacology studies were conducted to support the rationale for the administration of PAPZIMEOS to treat RRP caused by HPV6 and HPV11.

In Vitro Studies

Study Number	Study Title / Publication Citation	Report Number
1	Evaluation of the Antigenicity of PRGN-2012 In Vitro Using Patient Cells and Ex Vivo Using Cells Isolated from (b) (4) Transgenic Mice	PREC-2099R-E107
2	In Vitro Evaluation of PRGN-2012 for the Treatment of HPV6 and HPV11-Mediated Disease Using Cells from Infected Patients and Healthy Donors	PREC-2099R-E108

In Vivo Studies

In Vivo Studies in Healthy Animals

Study Number	Study Title / Publication Citation	Report Number
3	Evaluating the Immunogenicity of PRGN-2012 in C57BL/6 Mice	PREC-2099R-A261

In Silico Study using Bioinformatic Modeling

Study Number	Study Title / Publication Citation	Report Number
4	PRGN-2012 Antigen Bioinformatic Analysis	PREC-2099R-E106

Reviewer Note: Study Nos. 1-3 are summarized in this review memo under 'Overview of Pharmacology Studies.' Study No. 4 is summarized under 'Other Safety/Toxicology Studies' in this review memo because it is comprised of an in silico assessment of the potential for off-target antigen reactivity of PRGN-2012.

Overview of Pharmacology Studies

Overview of In Vitro Studies

Study No. 1 (Report No. PREC-2099R-E107)

Evaluation of the Antigenicity of PRGN-2012 In Vitro Using Patient Cells and Ex Vivo Using Cells Isolated from (b) (4) Transgenic Mice

Objective: To evaluate the antigenicity response of PRGN-2012 both ex vivo and in vitro to support the development of PRGN-2012 for the treatment of HPV6 and HPV11 mediated RRP disease.

Methods and Key Results:

Ex vivo: (b) (4)

[Redacted text block]

In vitro: (b) (4)

[Redacted text block]

T cell expansion and cytokine production (i.e. IFN- γ and TNF- α) increased in co-cultures from all three RRP patient Mo-DC populations transduced with PRGN-2012. Both cytotoxic T cells (CD8⁺) and helper T cells (CD4⁺) were activated and produced IFN- γ with the ratio of CD8⁺ T cells: CD4⁺ T cells >1 in all three RRP donor cell populations. However, only one population of RRP donor-derived Mo-DCs had more dual IFN- γ and TNF- α producing CD8⁺ T cells while the other two RRP donor-derived Mo-DCs had more dual IFN- γ and TNF- α producing CD4⁺ T cells. The reason for this variability was not discussed.

Reviewer Conclusions:

(b) (4)

[Redacted text block]

These data provide ex vivo and in vitro evidence that an antigenic response is generated in T cells after co-culture with APCs from PRGN-2012 immunized mice or PRGN-2012 transduced RRP donor-derived Mo-DCs. These data are supportive of the proposed mechanism of action of PRGN-2012.

Study No. 2 (Report No. PREC-2099R-E108)

In Vitro Evaluation of PRGN-2012 for the Treatment of HPV6- and HPV11-Mediated Disease Using Cells from Infected Patients and Healthy Donors

Objective:

To evaluate the ability of PRGN-2012 to elicit HPV6- and HPV11-specific T helper type 1 (Th1) cytokine IFN- γ in T cells in response to co-culture with Mo-DCs from healthy and RRP donors in vitro.

Methods and Key Results:

Mo-DCs were generated using PBMCs from healthy (n=3) and RRP (n=5 total; n=3 HPV11 and n=2 HPV6) donors with differing HLA types and transduced with either FFB, GC46.empty, (b) (4) or PRGN-2012. at an MOI of 1×10^4 . Transduced Mo-DCs were (b) (4)

, the following was assessed: 1) Antigen specific production of IFN- γ in supernatants, 2) CD4+ and CD8+ T cell specific IFN- γ production by intracellular flow cytometry, 3) CD8+ T cell production of granzyme B, a cytotoxic serum protease, and 4) CD8+ T cell production of GM-CSF

Antigen-specific production of IFN- γ , granzyme B (CD8+), and GM-CSF (CD8+) increased in supernatants from T cells co-cultured with RRP-donor derived Mo-DCs transduced with PRGN-2012 compared to T cells co-cultured with Mo-DCs derived from healthy donors. IFN- γ was produced from both CD8+ and CD4+ T cells.

PRGN-2012 induced higher IFN- γ levels compared to control vectors in all RRP patients but no differences were observed between PRGN-2012 transduction and controls.

Reviewer Conclusions:

These data provide in vitro evidence that there are antigen-specific increases in IFN- γ , GM-CSF, and granzyme B production in T cells after co-culture with PRGN-2012 transduced Mo-DCs. In addition, previous infection of APCs with HPV primes and increases the T cells IFN- γ response. These data are supportive of the proposed mechanism of action of PRGN-2012.

Overview of In Vivo Studies

In Vivo Studies in Healthy Animals

Study No. 3 (Report No. PREC-2099R-A261)

Evaluating the Immunogenicity of PRGN-2012 in C57BL/6 Mice

Objective:

To evaluate the ability of PRGN-2012 to elicit an HBV6- and HBV11-specific T cell response.

Methods and Key Results:

Three groups of 12 female C57BL/6 mice were administered either FFB, or 1×10^{10} VP of GC46.empty or PRGN-2012 vector via SC injection. On Day 14 six mice per group were sacrificed, examined for gross pathological changes, and spleen was collected and assessed ex vivo for antigen-specific T cell presence via ELISpot after stimulation with HBV6 and HBV11 peptides E6 and E7. On Day 21, six mice per group were sacrificed, examined for gross pathological changes, and assessed for cytokine and chemokine responses to stimulation with HBV6 and HBV11 peptides using ELISpot (cytokine IFN- γ and chemokines RANTES and macrophage inflammatory protein ^{(b) (4)} [MIP ^{(b) (4)}]) and additional cytokines and chemokines by flow cytometry. The E6 peptide pool induced IFN- γ and TNF- α by cytotoxic CD8⁺ T cells at higher frequencies by ELISpot than either the FFB or GC46.empty immunized mice as expected. Three peptides in the E6 peptide pool and one peptide in the E7 peptide pool elicited antigen-specific IFN- γ , RANTES and MIP ^{(b) (4)} production in PRGN-2012 immunized mice.

Reviewer Conclusions:

These data provide evidence that PRGN-2012 immunization leads to an HPV6 and HPV11 antigen specific response, CD8⁺ T cell production of cytokines, and production of effector T cell recruiting chemokines in vivo. These data are supportive of the proposed mechanism of action of PRGN-2012.

SAFETY PHARMACOLOGY STUDIES

Safety Pharmacology studies were not conducted.

PHARMACOKINETIC STUDIES (Biodistribution/Shedding)

Per the applicant, BD/shedding studies were not conducted based on the similarity of the GC46 adenoviral platform to human (b) (4)

Reviewer Comment:

- *Shedding analyses were not required for nonclinical studies for this product as mice are generally an unreliable species for adenoviral shedding studies to compare to human shedding. Please see the clinical review regarding analyses of shedding in the clinical study.*

(b) (4)

- *This reviewer agrees that BD assessments would likely not provide any added shedding information given the predictable BD profile of adenoviral vectors that is consistent between vector serotypes and referenced above.*

TOXICOLOGY STUDIES

Summary List of Toxicology Studies

The following toxicology study was conducted to evaluate the safety of PRGN-2012 following SC administration in WT mice.

Toxicology Studies:

Study Number	Study Title / Publication Citation	Report Number
5	PRGN-2012 Repeat Administration Study PREC-2099R-A252 V2.0 In Vivo Research Report	PREC-2099-A252

Study No. 5

Report Number		PREC-2099-A252
Date Report Signed		18-AUG-2020
Title		PRGN-2012 Repeat Administration Study PREC-2099R-A252 V2.0 In Vivo Research Report
GLP Status		No
Testing Facility		Precigen, Inc. 20358 Seneca Meadows Parkway Germantown, MD 20876
Objective(s)		Evaluate the safety and tolerability of repeat SC administration of PRGN-2012 in WT mice.
Study Animals	Strain/Breed	C57BL/6
	Species	Mouse
	Age	6 weeks
	Body Weight	Male: 20.20 to 24.00 grams Female: 16.20 to 19.00 grams
	#/sex/group	6
	Total #	36
Test Article(s)		PRGN-2012, Lot No. 19038, diluted to 1×10^{10} VP/0.1 mL in FFB FFB used for test article dilution, Lot No. (b) (4)
Control Article(s)		GC.empty, Lot No. (b) (4), diluted to 1×10^{10} VP/0.1 mL in FFB FFB used for control vector dilution, Lot No. (b) (4)
Route of Administration		SC
Description of the Disease/Injury Model and Implant Procedure		N/A
Study Groups and Dose Levels		Group 1a – Male mice, 1×10^{10} VP of PRGN-2012 Group 1b – Female mice, 1×10^{10} VP of PRGN-2012 Group 2a – Male mice, 1×10^{10} VP of GC.empty Group 2b – Female mice, 1×10^{10} VP of GC.empty Group 3a – Male mice, FFB Group 3b – Female mice, FFB

Dosing Regimen	Once weekly for three weeks, a total of three administrations on Days 0, 7, and 14 for all groups.
Randomization	Yes
Description of Masking	N/A
Scheduled Sacrifice Time Points	Day 21

Key Evaluations and Assessments:

- Body weights and clinical observations immediately prior to and 24 ± 2 hours following each weekly administration, and at termination.
- Injection site observations were performed 3 ± 1 and 24 ± 4 hours following each administration, in all animals.
- Blood was collected via cardiac puncture at terminal euthanasia on Day 21 for clinical chemistry and complete blood count (CBC) analyses.
- Liver, duodenum, kidney, brain, heart, lungs, spleen, draining lymph nodes (inguinal and axillary), spinal cord (thoracic section), right gastrocnemius, and skin at injection site from all animals in the study were collected on Day 21 for gross pathology and histological evaluation.

Key Results:

- There were no test article-related findings reported.

Reviewer Conclusions:

The dose level assessed in this non-GLP toxicology study provides a 5-fold safety factor for the clinical dose level with the caveat that the processing and binding sequences in wildtype mice is likely different than the peptides recognized by human T cells. The lack of safety findings in this definitive repeat administration safety study conducted in mice provide limited support for the safety of the clinical route of administration and clinical dose level.

Developmental and Reproductive Toxicology Studies:

Per the applicant, studies were not conducted to evaluate this safety endpoint because the GC46 adenoviral vector of PRGN-2012 belongs within the human species C category of adenovectors and is most like human (b) (4). Locally administered adenovectors (SC or intramuscular) have a well-defined and predictable BD profile that is consistent despite differences in vector serotypes, transduction methods, payload, and manufacturing processes; thus, PRGN-2012 is expected to behave similarly to human (b) (4).

Reviewer Comment:

This reviewer agrees with the rationale provided by the applicant for not conducting developmental and reproductive toxicology studies.

Genotoxicity Studies:

Per the applicant, studies were not conducted to evaluate genotoxicity of PRGN-2012 for the following reasons:

- PRGN-2012 is non-integrating by nature and replicates as a linear, extra-chromosomal deoxy ribonucleic acid (DNA) element in the nucleus.
- The PRGN-2012 genome has been rendered replication incompetent through deletions of specific regions.
- PRGN-2012 does not rely on host cell genome integration for expression of the transgene, thus, it has a reduced genotoxic risk and will not result in insertional mutagenesis or position-effect variation.

Reviewer Comment:

This reviewer agrees with the rationale provided by the applicant for not conducting genotoxicity studies.

Carcinogenicity/Tumorigenicity Studies:

Per the applicant, studies were not conducted to evaluate carcinogenicity as adenovectors are non-integrating. Therefore, the risk for insertional mutagenesis is not a major concern. In addition, previous data indicates adenovirus has not demonstrated a significant risk for tumorigenicity in humans.

Reviewer Comment:

This reviewer agrees with the rationale provided by the applicant for not conducting carcinogenicity/tumorigenicity studies.

Other Safety/Toxicology Studies

Study Number	Study Title / Publication Citation	Report Number
6	PRGN-2012 Antigen Bioinformatic Analysis	PREC-2099R-E106

Study No. 6 (Report No. PREC-2099R-E106)

Antigen Bioinformatic Analysis

Objective:

To evaluate the antigen expressed by PRGN-2012 for potential off-target response.

Methods and Key Results:

Bioinformatics analysis was performed to assess the sequence homology of the antigen expressed by PRGN-2012, which is a fusion of selected regions of HPV6 and HPV11 proteins expressed in HPV-infected cells. The PRGN-2012 antigen was compared to (b) (4) protein sequences in the National Center for Biotechnology Information's non-redundant protein database using the (b) (4) search tool. (b) (4)

(b) (4)

Reviewer Conclusions:

This study demonstrated specificity of the PRGN-2012 antigen against HPV-6 and HPV-11, as designed, and indicated a low potential for off-target reactivity to endogenous human peptides/proteins.

Publications Cited

The following publications were provided by the applicant and are not summarized in this review memo; they are primarily in silico evaluations, in vitro methods, published research studies, or assay development reports for analytical testing methods used for serum, plasma, and liver tissue samples from the nonclinical studies. These studies were reviewed but are not directly relevant for informing the safety and activity of PAPZIMEOS.

Study Number	Publication Citation	Summary
6	Ahn J, Peng S, Hung CF, Roden RBS, Wu TC, Best SR. Immunologic responses to a novel DNA vaccine targeting human papillomavirus-11 E6E7. Laryngoscope. 2017 Dec;127(12):2713-2720. doi: 10.1002/lary.26737. Epub 2017 Jul 17. PMID: 28714529; PMCID: PMC5687988.	Administration of an HPV11 vaccine against E6E7 peptides to WT c57/BL6 mice via electroporation elicited an immune response specific to HPV11. HPV11 vaccination of mice inoculated with an HPV11 E6E7 expressing tumor cell line resulted in slowed tumor growth.
7	(b) (4)	(b) (4)
8	Andersen MM, Larsen J, Hansen M, Pedersen AE, Gad M. Development of an In Vitro Assay to Assess Pharmacological Compounds and Reversion of Tumor-Derived Immunosuppression of Dendritic Cells. Immunol Invest. 2021 Jul;50(5):527-543. doi: 10.1080/08820139.2020.1778024. Epub 2020 Jun 23. PMID: 32573300.	Development of an in vitro model in MoDCs for assessing maturation and T cell activation and differentiation.
9	Apte SM, Vadhan-Raj S, Cohen L, Bassett RL, Gordon IO, Levenback CF, Ramirez PT, Gallardo ST, Patenia RS, Garcia ME, Iyer RB, Freedman RS. Cytokines, GM-CSF and IFN γ administered by priming and post-chemotherapy cycling in recurrent ovarian cancer patients receiving carboplatin. J Transl Med. 2006 Apr 7;4:16. doi: 10.1186/1479-5876-4-16. PMID: 16603073; PMCID: PMC1457001.	SC administration of GM-CSF and IFN- γ before and after carboplatin in recurrent epithelial ovarian cancer patients stimulated and activated monocytes/macrophages and resulted in increased numbers of myeloid cells, platelets, and total activated monocyte populations.
10	Bangari DS, Shukla S, Mittal SK. Comparative transduction efficiencies of human and nonhuman adenoviral vectors in human, murine, bovine, and porcine cells in culture. Biochem Biophys Res Commun. 2005 Feb 18;327(3):960-6. doi: 10.1016/j.bbrc.2004.12.099. PMID: 15649439.	Assessment of cross-neutralization of human, porcine, and bovine adenovirus serotypes.
11	Chen W, Lv X, Liu C, Chen R, Liu J, Dai H, Zou GM. Hematopoietic stem/progenitor cell differentiation	Assessment of the role of the cytokine lymphotoxin (LT) like-related inducible

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14	Gigante M, Ranieri E. In vitro/ex vivo generation of cytotoxic T lymphocytes. <i>Methods Mol Biol.</i> 2014;1186:13-20. doi: 10.1007/978-1-4939-1158-5_2. PMID: 25149300.	Description of a protocol for generation of cytotoxic T lymphocytes against target antigens presented by MO-DCs.
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16	Limbach K, Stefaniak M, Chen P, Patterson NB, Liao G, Weng S, Krepiy S, Ekberg G, Torano H, ETTYREDDY D, Gowda K, Sonawane S, Belmonte A, Abot E, Sedegah M, Hollingdale MR, Moormann A, Vulule J, Villasante E, Richie TL, Brough DE, Bruder JT. New gorilla adenovirus vaccine vectors induce potent immune responses and protection in a mouse malaria model. <i>Malar J.</i> 2017 Jul 3;16(1):263. doi: 10.1186/s12936-017-1911-z. PMID: 28673287; PMCID: PMC5496260.	Evaluation of the seroprevalence, immunogenicity, and activity of three newly identified gorilla adenoviruses, GC44, GC45, and GC46 as potential malaria vaccine vectors.
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	Lung Cancer. 2005 Mar;47(3):361-71. doi: 10.1016/j.lungcan.2004.07.046. PMID: 15713519.	cell subsets were identified by assessing a combination of cell surface markers.
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21	Tatsis N, Fitzgerald JC, Reyes-Sandoval A, Harris-McCoy KC, Hensley SE, Zhou D, Lin SW, Bian A, Xiang ZQ, Iparraguirre A, Lopez-Camacho C, Wherry EJ, Ertl HC. Adenoviral vectors persist in vivo and maintain activated CD8 ⁺ T cells: implications for their use as vaccines. Blood. 2007 Sep 15;110(6):1916-23. doi: 10.1182/blood-2007-02-062117. Epub 2007 May 17. PMID: 17510320; PMCID: PMC1976365.	Demonstration of proof-of-concept of adenoviral-based vector vaccine persistence and CD8 ⁺ T cell activation in vivo.
22	Teng SE, Dion GR, Sin DN, Hiwatashi N, Benedict PA, Amin MR, Branski RC. Imiquimod Injection to Rabbit Vocal Folds: A Preliminary, Preclinical Investigation. Otolaryngol Head Neck Surg. 2017 Apr;156(4):702-705. doi: 10.1177/0194599816689585. Epub 2017 Feb 7. PMID: 28171734.	Assessment of injection of a toll-like receptor 7 agonist (Imiquimod) into rabbit vocal fold mucosa was well-tolerated with no laryngeal edema, histopathologic changes to vocal fold structure, and with only transient increases in serologic IFN α levels.
23	Vetskova EK, Muhtarova MN, Avramov TI, Stefanova TR, Chalakov IJ, Nikolova MH. Immunomodulatory effects of BCG in patients with recurrent respiratory papillomatosis. Folia Med (Plovdiv). 2013 Jan-Mar;55(1):49-54. doi: 10.2478/folmed-2013-0005. PMID: 23905487.	Clinical assessment of combination of immunotherapy Calgevax (BCG) and CO2 surgery in RRP patients. Antiviral response in RRP patients dependent on cytokine background.
24	Xu Q, Rangaswamy US, Wang W, Robbins SH, Harper J, Jin H, Cheng X. Evaluation of Newcastle disease virus mediated dendritic cell activation and cross-priming tumor-specific immune responses ex vivo. Int J Cancer. 2020 Jan 15;146(2):531-541. doi: 10.1002/ijc.32694. Epub 2019 Nov 1. PMID: 31584185.	Ex vivo assessment of Newcastle disease virus induced maturation of monocyte-derived immature dendritic cells (iDCs). iDCs promoted an antigen-specific T cell response ex vivo

APPLICANT'S PROPOSED LABEL

Subsections 8.1-8.3 ('Use in Specific Populations') should be revised to reflect available nonclinical/clinical data and comply with 21 CFR 201.56(d)(1), 201.57(c)(9), and 201.57(c)(14), as applicable.

Section 13 ('Nonclinical Toxicology') should be removed as it does not contain necessary information from the nonclinical studies necessary for the safe and effective use of the product.

CONCLUSION OF NONCLINICAL STUDIES

Review of the nonclinical studies did not identify any safety concerns that could not be adequately addressed in the label. The nonclinical data support approval of the license application.

KEY WORDS/TERMS

Non-replicating adenoviral vector-based immunotherapy, immunotherapy, non-replicating adenoviral vector, PAPZIMEOS, zopapogene imadenovec, PRGN-2012, recurrent respiratory papillomatosis, human papillomavirus type 6, human papillomavirus type 11.