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Application Type	Original Biologics License Application
STN	BLA 125832/0
CBER Received Date	December 27, 2024
PDUFA Goal Date	August 27, 2025
Division / Office	DCEGM/ OCE/OTP
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Priority Review	Yes
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Applicant	Precigen Inc.
Established Name	zopapogene imadenovec-drba
(Proposed) Trade Name	PAPZIMEOS
Pharmacologic Class	Non-replicating adenoviral vector-based immunotherapy
Dosing Regimen	5 x 10 ¹¹ particle units per injection administered by subcutaneous injection four (4) times over a 12-week interval
Indication(s) and Intended Population(s)	Treatment of adults with recurrent respiratory papillomatosis

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GLOSSARY

AE	Adverse event
BMI	Body mass index
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CI	Confidence interval
CMC	Chemistry, Manufacturing, and Controls
CR	Complete response
CR _{1Y}	Complete response through the first year
CR _{2Y}	Complete response through the first two years
CSR	Clinical study report
DL	Dose level
DLT	Dose-limiting toxicity
EES	Efficacy Evaluable Population
FAS	Full Analysis Population
HPV	Human papillomavirus
ICE	Intercurrent events
IND	Investigational New Drug
IR	Information request
LTFU	Long-term follow-up
Max	Maximum
Min	Minimum
MRD	Minimal residual disease
NIH	National Institutes of Health
ORR	Objective response rate
PCOD	Primary cut-off date
PD	Progressive disease
PEEP	Primary efficacy evaluation period; 1 year post-treatment
PR	Partial response
PU	Particle units
RECIST	Response Evaluation Criteria in Solid Tumors
RMAT	Regenerative Medicine Advanced Therapy
RP2D	Recommended Phase 2 dose
RRP	Recurrent respiratory papillomatosis
RTM	Regression-to-the-mean
SAE	Serious adverse event
SAF	Safety Analysis Population
SAP	Statistical Analysis Plan
SAT	Single-arm trial
SC	Subcutaneous
SCOD	Secondary cut-off date
SD	Standard deviation

SEEP	Secondary efficacy evaluation period; 2 years post-treatment
TEAE	Treatment-emergent adverse event
TTR	Time to recurrence
US	United States
VHI-10	Voice Handicap Index-10

1. EXECUTIVE SUMMARY

The applicant submitted this original Biologics License Application (BLA) for PAPZIMEOS (also referred to as PRGN-2012, zopapogene imadenovec) for the treatment of adults with recurrent respiratory papillomatosis (RRP). PAPZIMEOS is an adenoviral vector-based immunotherapy designed to express a fusion antigen of selected regions of human papillomavirus (HPV) proteins expressed in HPV 6- and HPV 11-infected cells. The efficacy and safety results are based on data from Study PRGN-2012-201.

Data package and study design

PRGN-2012-201 is an ongoing, Phase 1/2, single-arm study where all 38 RRP patients received PAPZIMEOS. Eligibility criteria include receiving three or more surgeries during the 12-month retrospective baseline period. All 38 patients completed the series of 4 injections on Days 1, 15, 43, and 85. Three of these 38 patients received dose level 1 (DL1) at 1×10^{11} particle units (PUs) per injection. The other 35 patients received the recommended Phase 2 dose (RP2D), the proposed dose, at 5×10^{11} PU per injection. All patients underwent a surgery on Study Day 1 before initiation of PAPZIMEOS to remove laryngotracheal papilloma and establish minimal residual disease (MRD). The applicant counted this surgery as a baseline surgery in the eligibility criteria and endpoint analyses. During the treatment period, patients would undergo additional surgical procedures to remove all visible papilloma on Days 43 and 85 to maintain MRD. Patients then entered a 12-month follow-up period after the last treatment injection. The primary efficacy endpoint is absence of any surgery during the 12-month follow-up, i.e., complete response through the first year (CR_{1Y}). Patients would then be followed up for an additional two years, for a total of three years of follow-up post-treatment. The applicant pre-specified study success criterion to be the lower bound of the two-sided 95% confidence interval (CI) on CR_{1Y} exceeding 10%. Because of availability of additional follow-up data while the BLA was under review, we also reviewed complete response through the first two years (CR_{2Y}).

Efficacy

The efficacy database consists of data on the 35 patients treated at the proposed dose level, i.e., efficacy evaluable population (EES). The primary data cut-off date (PCOD) was August 28, 2024, when all patients had been followed up for at least one year, except for one patient who died prior to the one-year visit. The secondary cut-off date (SCOD) was March 21, 2025, for the 120-day safety report submitted to the BLA.

In the EES, median age was 49.0 years (range: 20 to 88), 43% (15/35) were females, and most patients were White (32/35, 91%). Around 2/3 (23/35, 66%) of patients had adult onset. The median number of surgeries during the 12-month baseline period, counting the mandatory Day 1 surgery, was 4 (range: 3 to 10).

Eighteen of the 35 patients in EES achieved CR_{1Y}, the primary efficacy endpoint, resulting in a point estimate on CR_{1Y} of 51% with a 95% CI of (34%, 69%), meeting the study success criterion with the lower bound of the CI exceeding 10%.

We have evaluated the impact of various sources of potential biases associated with this single-arm trial, and corresponding correction/mitigation strategies. As a result, we excluded the Day 1 surgeries from the count of baseline surgeries when considering the acceptability of the null threshold of 10% on CR_{1Y} rate as well as analyses of secondary endpoints related to comparisons of number of surgeries between the baseline and the primary efficacy evaluation period, i.e., one year post-treatment. Although we do not have high confidence that the 10% threshold is adequate, the observed lower bound of the 95% CI, at 34%, is high enough to be robust to uncertainties introduced by these biases. As a result, we conclude that PAPZIMEOS is efficacious based on the primary analysis of CR_{1Y}.

CR_{2Y} was achieved in 15 patients, resulting in a CR_{2Y} rate of 43% (95% CI: 26%, 61%). The lower bound of 26% substantially exceeded the probability of achieving CR_{2Y} in the target population under standard of care. The additional CR_{2Y} result, though not pre-planned, provides highly persuasive evidence on the efficacy of PAPZIMEOS.

Safety

The safety database consists of data on the 38 patients through the SCOD.

Three serious adverse events (SAEs) occurred. One patient who received the proposed dose died of cardiac arrest. Another patient who received DL1 experienced a grade 3 bacterial laryngitis that lasted 5 days starting 11 days after the 4th injection. A third patient who received the proposed dose experienced an SAE of grade 3 upper gastrointestinal hemorrhage within 27 minutes after receiving the first injection (approximately 6-8 hours following surgery). Please see the clinical review memo for a full evaluation of the safety information.

Conclusion and recommendations

PAPZIMEOS is effective in reducing number of surgeries in adult RRP patients. This conclusion is supported by highly persuasive evidence of absence of surgeries lasting at least two years post treatment in 43% of the EES. Although patients with fewer than three surgeries during the baseline period were not included in the study, it is plausible that such patients would benefit similarly from PAPZIMEOS because of the same mechanism of action. Therefore, we recommend approval of the proposed indication of PAPZIMEOS.

2. CLINICAL AND REGULATORY BACKGROUND

This original Biologics License Application (BLA) is a marketing application for PAPZIMEOS (PRGN-2012, zopapogene imadenovec-drba) for the proposed indication of treatment of adults with recurrent respiratory papillomatosis (RRP).

PAPZIMEOS is a non-replicating adenoviral vector-based immunotherapy designed to express a fusion antigen of selected regions of human papillomavirus (HPV) proteins expressed in HPV 6- and HPV 11-infected cells. Delivered via subcutaneous (SC) injections, PAPZIMEOS is intended to generate immune responses directed against the HPV 6- and HPV 11-infected papilloma cells in RRP patients.

2.1 Disease or Health-Related Condition(s) Studied

RRP is a rare, difficult-to-treat, and sometimes fatal neoplastic disease of the upper and lower respiratory tracts that is most commonly caused by chronic infection with HPV type 6 or 11. Patients with RRP have dysfunctional immune responses to HPV infections, resulting in persistence of infections and recurrent neoplastic growth of masses (papilloma) in the upper and lower respiratory tracts. Approximately 1000 new cases of RRP are diagnosed each year in the United States (US).

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

There are no therapeutics approved for the treatment of RRP. The current standard-of-care treatment for RRP is repeated endoscopic debulking with ablation or excision of papillomatous lesions, exposing the patients to anesthetic and surgical risks, along with emotional distress.

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

PAPZIMEOS has not been approved in any country.

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

The clinical development program of PAPZIMEOS is under Investigational New Drug application (IND) 26884. Table 1 provides a summary of the regulatory history.

Table 1 Regulatory History and Official Communications with FDA

Date	Description/Recommendation	Comments/Implementation
October 13, 2020	Original submission of IND 26884	-
March 17, 2021	FDA granted Orphan Drug Designation (DRU-2020-8055) for PAPZIMEOS for treatment of RRP	-

Date	Description/Recommendation	Comments/Implementation
June 7, 2022	FDA (b) (4)	(b) (4)
December 20, 2022	Type C Meeting (CRMTS #14520)	(b) (4) FDA suggested on using Derkey anatomical scoring as objective quantitative criteria for surgical intervention for intra-patient single-arm comparison. <ul style="list-style-type: none"> Precigen proposed patient population of severe, aggressive RRP with ≥ 3 surgeries per year in pre-treatment period.
June 13, 2023	FDA granted Breakthrough Therapy Designation status (b) (4)	(b) (4)
August 18, 2023	FDA center director granted sponsor's Informal Dispute Appeal	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 PAPZIMEOS, as well as a plan for a confirmatory study to confirm the clinical benefit post-marketing, should the product be approved under the accelerated approval pathway.
January 31, 2024	Type B Meeting (CRMTS #15427)	FDA concurred with Precigen that no additional nonclinical studies are required, provided guidance on design of the confirmatory study and drug product stability data package, and confirmed eligibility for rolling review of the planned BLA.

Date	Description/Recommendation	Comments/Implementation
August 29, 2024	Pre-BLA meeting (CRMTS #15245)	FDA provided requests for the BLA submission related to nonclinical, clinical and CMC data packages.
During BLA review	-	Per FDA request during the review of the BLA, the applicant submitted an efficacy update including available long-term follow-up data of the study subjects in the ongoing study PRGN-2012-201, data cutoff date of March 21, 2025 (STN 125832/0.36), and subsequently the source datasets.

BLA = Biologics License Application; FDA = the United States Food and Drug Administration; IND = Investigational New Drug; RRP = recurrent respiratory papilloma; CMC=Chemistry, Manufacturing, and Controls.

Source: Adapted from BLA 125832/0, Clinical Overview, Table 3, p.14.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

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

5.1 Review Strategy

My review focuses on Study PRGN-2012-201, the sole study submitted by the applicant as the primary basis of evidence to support the BLA.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

I have reviewed the following amendments and documents in the applicant's submissions to BLA 125832/0:

- STN 125832/0.17 Module 1.14 Labeling
 - The format of proposed labeling in the original submission was incorrect; replaced per FDA request
- STN 125832/0.1 Module 1.2 Reviewer's Guide
- STN 125832/0.1 Module 2.5 Clinical Overview
- STN 125832/0.1 Module 2.7.3 Summary of Clinical Efficacy
- STN 125832/0.1 Module 2.7.4 Summary of Clinical Safety
- STN 125832/0.1 Module 2.7.6 Synopses of Individual Studies
- STN 125832/0.1 Module 5.2 Tabular Listing of all Clinical Studies
- STN 125832/0.1 Module 5.3 Clinical Study Reports

- STN 125832/0.27 Module 2.7.4 Summary of Clinical Safety (Day 120 Safety Update)
- STN 125832/0.31 Module 1.11.3 Clinical Information Amendment-Response to clinical information request (IR) #2 on April 30, 2025
- STN 125832/0.36 Module 1.11.3 Clinical Information Amendment-Response to clinical IR#3 on May 21, 2025
- STN 125832/0.38 Module 5.3 Clinical Study Reports (updated ADaM dataset with SAS Version 5)
- STN 125832/0.39 Module 1.11.3 Clinical Information Amendment-Response to Biostats IR#1 on May 21, 2025

5.3 Table of Studies/Clinical Trials

Study PRGN-2012-201 is the sole study in the clinical development program conducted to support the BLA. Key features of the study are listed below:

- Study Phase and Design: This is an on-going, Phase 1/2 single-arm study to evaluate the safety and efficacy of PAPZIMEOS for the treatment of adult patients with RRP.
- Patient Population: aged from 20 to < 88 years.
 - Safety population: 3 patients treated at dose level 1; 35 patients treated at dose level 2 (the recommended Phase 2 dose, RP2D).
 - Efficacy population: 35 patients treated at the RP2D.
- Study Location: Single site at National Institutes of Health (NIH)
- Treatment Duration: 12 weeks with SC injections on Days 1, 15, 43, and 85
- Short-term Follow-up Duration: 12 months after last injection with visits scheduled at 6, 12, 24, and 52 weeks
- Long-term Follow-up Duration: an additional 2 years (ongoing)

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study PRGN-2012-201

The PRGN-2012-201 study (NCT04724980) is titled “A Phase 1/2 Study of Adjuvant PRGN-2012 in Adult Participants with Recurrent Respiratory Papillomatosis.” The following are the key dates:

- March 16, 2021: First patient enrolled.
- March 18, 2021: First patient received PAPZIMEOS.
- November 4, 2021: Last Phase 1 patient (N=15) received PAPZIMEOS.
- March 10, 2023: Last patient (N=38) received PAPZIMEOS.
- June 5, 2024: Last patient (N=38) completed the primary follow-up period (12-month visit).
- August 28, 2024: The primary cut-off date (PCOD) for the clinical study report (CSR) supporting the original BLA submission.

- March 21, 2025: The secondary cut-off date (SCOD) for the 120-day safety report submitted to the BLA.

6.1.1 Objectives

Study PRGN-2012-201 consisted of a Phase 1 part and a Phase 2 part. The Phase 1 part was to identify the recommended Phase 2 dose (RP2D) of PAPZIMEOS. Of the Phase 1 part, 3 patients received dose level 1 (DL1) and 12 patients received the RP2D. Patients treated with the RP2D in both the Phase 1 and the Phase 2 parts were to be combined in analyses to address the efficacy objectives below:

Primary efficacy objective

To demonstrate the efficacy of PAPZIMEOS by evaluating the complete response (CR) rate, defined as the percentage of patients with no clinically indicated surgical interventions during the 12-month period following the completion of PAPZIMEOS treatment. For ease of reference, we call this period the primary efficacy evaluation period (PEEP).

Secondary efficacy objectives

1. Determine the objective response rate (ORR), defined as the percentage of patients with a CR or partial response (PR), defined as at least a 50% decrease in the number of surgeries during the PEEP as compared to that during the 12 months prior to PAPZIMEOS treatment initiation (baseline period).
2. Determine the percentage of patients with any decrease in the number of surgeries during the PEEP as compared to that during the baseline period.
3. Determine the absolute and percent change in the number of surgeries during the PEEP as compared to that during the baseline period.
4. Determine the absolute and percent change in the number of surgeries during the 6 months following completion of PAPZIMEOS treatment compared to that during the 6 months prior to PAPZIMEOS treatment initiation.
5. Determine duration in time to first surgical debulking from the completion of PAPZIMEOS treatment.
6. Determine the rate of pulmonary RRP responses (CR and PR) in patients with pulmonary disease.
7. Evaluate changes in Derkey and Voice Handicap Index-10 (VHI-10) scores over time following PAPZIMEOS treatment initiation.
 - a. The VHI-10 is a patient reported outcome instrument that consists of 10 questions that measures the impact of a person's voice disorder on his or her daily activities. Each question is scored on a scale from 0 to 4 with a higher score indicating a greater frequency of problem (0: never, 4: always).

6.1.2 Design Overview

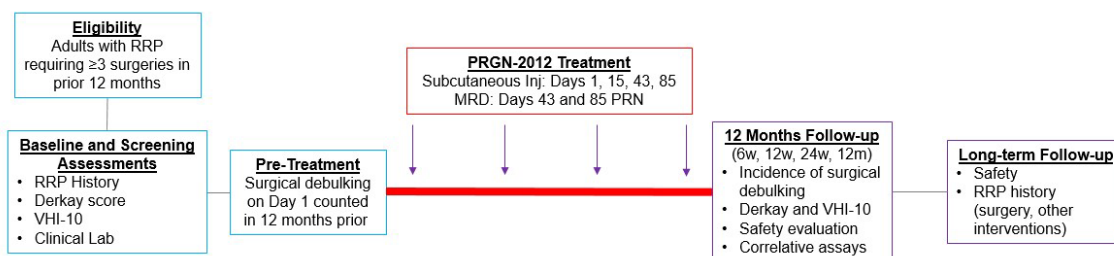
PRGN-2012-201 is an ongoing Phase 1/2 single-arm study. Figure 1 describes the study procedures.

On Day 1, prior to the initiation of the treatment, all patients underwent a standard-of-care surgical debulking procedure to remove laryngotracheal papilloma and establish minimal residual disease (MRD). Patients were then to receive a series of four SC injections of PAPZIMEOS at DL1 (1×10^{11} particle units [PUs] per injection) or the RP2D dose (5×10^{11} PUs per injection) over a 12-week period, on Days 1, 15 ($\pm 2d$), 43 ($\pm 2d$), and 85 ($\pm 7d$). To maintain MRD, on treatment Days 43 and 85, patients would undergo a flexible nasopharynxgolarngoscopy and/or tracheoscopy in the clinic, and a Derkay score would be determined. If the Derkay score was ≥ 1 , indicating visible papilloma, then the papilloma would be removed.

After the last treatment with PAPZIMEOS at Day 85, patients would enter PEEP for safety and efficacy evaluations at clinic visits at 6 (± 1), 12 (± 1), 24 (± 1), and 52 (± 2) weeks. In addition, all endoscopic imaging assessments performed on patients from 12 months prior to the start of treatment (Day 1) and through 12 months following the completion of treatment (Day 85) would be provided for the Derkay scoring by Central Blinded Imaging Review.

Patients would then be contacted by telephone every three months for two additional years (± 14 days) (long-term follow-up, LTFU) to determine incidence of surgical interventions, Derkay score, and/or imaging evaluations.

Figure 1 Study Schematics



Source: Adapted from BLA 125832/0.1, Protocol Amendment 7, Figure 7, p.989.

6.1.3 Population

Male and female patients, aged 18 years and older, with clinical diagnosis of RRP:

- Histological diagnosis of papilloma confirmed by pathology report from a CLIA-certified (or comparable) laboratory
- Presence of laryngotracheal papillomas accessible for endoscopic surgical cleanout (with or without pulmonary RRP)
- A history of ≥ 3 surgical interventions for control of RRP in the last 12 months (prior to and including Day 1)

Among the exclusion criteria:

- A history of surgical debridement of papillomas such that in the opinion of the study team a patient is unlikely to be able to safely have a six-week interval between surgical interventions.

Reviewer's comment

The criterion of “A history of ≥ 3 surgical interventions ...” was revised from “A history of ≥ 2 surgical interventions ...” in protocol version 4.0 (March 30, 2023). At that time, the last patient was already treated (March 10, 2023) and 16 patients had completed the short-term follow-up.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The recommended dose of PAPZIMEOS is 5×10^{11} PUs per injection, with 4 injections over a 12-week period, on Days 1, 15, 43, and 85.

6.1.6 Sites and Centers

The study has been conducted at a single clinical site: the Clinical Center at the Center for Cancer Research in the National Cancer Institute, part of the National Institutes of Health (NIH). IND sponsorship started with NIH and was transferred to Precigen from NIH on April 12, 2022.

6.1.7 Surveillance/Monitoring

Please see Section 6.1.2 Design overview.

6.1.8 Endpoints and Criteria for Study Success

Primary efficacy endpoint

Complete response rate through the first year (CR_{1Y}), defined as the percentage of patients not requiring any clinically indicated surgical intervention during the 12 months following PEEP.

The CR_{1Y} rate will be tested against a null response rate of 10%.

Secondary efficacy endpoints

The secondary efficacy endpoints followed the secondary efficacy objectives described in Section 6.1.1.

Reviewer's comment

The applicant described the primary efficacy endpoint as CR. We introduce the subscript to term it instead as CR_{1Y} , to distinguish it from CR_{2Y} , an additional endpoint we defined and reviewed while the BLA review was underway. We defined CR_{2Y} in a similar way as CR_{1Y} , i.e., absence of any surgeries during the first two years, the extended follow-up period (SEEP). During the BLA review, we determined that the 120-day safety submission contained additional follow-up data that may provide more definite results on efficacy evaluation, and therefore requested updated datasets to evaluate the additional data, including CR_{2Y} .

6.1.9 Statistical Considerations & Statistical Analysis Plan

6.1.9.1 The Applicant's Proposed Statistical Analysis Plan (SAP)

Analysis sets

- Full Analysis Population (FAS): All enrolled patients who met eligibility criteria and signed informed consent. The FAS was to be used for the analysis of demographic and baseline characteristics.
- Efficacy Evaluable Population (EES): All enrolled patients who met eligibility criteria and received any administrations of PAPZIMEOS at the RP2D. The EES was to be used for the primary analysis of CR_{1Y}, the primary efficacy endpoint, and CR_{2Y}, the additional efficacy endpoint we introduced.
- Safety Analysis Population (SAF): All enrolled patients in the study who received at least one dose of PAPZIMEOS. SAF includes EES and those patients who received DL1.

Primary analysis for the primary efficacy endpoint

The primary analysis for the CR_{1Y} rate would be a 95% exact confidence interval (CI), with the lower bound exceeding 10% indicating study success, i.e., the null response rate was set at 10%.

Description of the primary estimand:

- Treatment condition of interest: PAPZIMEOS
- Target study population: adult patients with RRP
- Variable of interest: complete response CR_{1Y} defined as a patient with no surgical intervention during the PEEP
- Population level summary measure: CR_{1Y} rate defined as the percentage of patients with no clinically indicated surgical interventions during PEEP
- Intercurrent events (ICE) and strategies to handle ICEs:

ICE	Strategy
Early discontinuation from study prior to the 12 months follow up visit or discontinuing treatment prior to administration of all 4 doses of PAPZIMEOS	Composite strategy, where data are 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 4 doses of PAPZIMEOS are counted as non-responders.
Death prior to month 12	Composite strategy (non-response)

Analysis plan for secondary efficacy endpoints

Descriptive statistics and informal hypothesis testing were planned.

Reviewer's comment

Some secondary efficacy endpoints compare the number of surgeries between the 12-month baseline period and the PEEP, e.g., ORR. The proposed analysis plan for these surgery-comparison-related endpoints introduces several sources of biases, some easily corrected while others are difficult to address. This will be discussed in some detail in Section 6.1.9.2 "Statistical review team's assessment of the SAP" below. Review of the remaining secondary endpoints, i.e., pulmonary RRP response, Derkay scoring, VHI-10, is deferred to the clinical reviewer.

Additional analyses by the reviewer

For a more comprehensive picture of the treatment effect, we define and review the CR_{2Y} endpoint, as well as examine the treatment effect at an individual level for all patients to assess whether there are potential treatment harms (e.g., increase in surgery frequency after treatment) in non-responders.

Sample size estimation

The study was initiated using the Fleming two-stage design, with the first stage (Phase 1) treating 15 patients and the second stage (Phase 2) potentially treating an additional 23 patients. The study was designed to have a one-sided type I error rate of 0.025 under the null response rate of 10% and a power of 80% under the alternative response rate of 30%. The sponsor planned to stop the study for futility if there were ≤ 2 responses in the first 15 treated patients, and potentially stop early for efficacy if there were ≥ 5 responses. Otherwise, the study would proceed to the Phase 2 part and 23 additional patients would be treated at the RP2D for a total of 35 patients treated at RP2D. The null hypothesis would be rejected if 8 or more responses were observed in these 35 patients, in which case the 95% CI would be (10.4%, 40.1%).

Reviewer's comment

The study was initially planned as an early-phase study with Fleming's two-stage design to assist go/no go decision-making. Following discussion with the FDA after Phase 1 results were available, the study was repositioned to serve as the primary study to support the BLA. The applicant agreed not to stop early for efficacy as planned, but instead to continue through Phase 2. As a result, the two-stage design is no longer applicable. Nonetheless, the initial sample size remained appropriate for the revised design and was used to guide study execution.

6.1.9.2 Statistical review team's assessment of the SAP

This section provides the statistical review team's evaluation of the conduct, analysis, and interpretation of this single-arm trial (SAT). The guiding principle is to identify factors (other than receiving PAPZIMEOS or not) that may lead to dissimilarities between the 12-month baseline period and the 12-month PEEP, and to mitigate such dissimilarities, such that we may attribute the observed treatment difference between these two periods to PAPZIMEOS.

1. The null CR rate of 10%

The applicant did not document a rationale for the proposed null CR_{1Y} rate of 10% in the protocol or SAP. However, this issue was discussed between the FDA and the sponsor during the IND review. At the end of Phase 1, when some of the discussions occurred, the sponsor reported a median number of surgeries during the 12-month baseline period of 5 (range: 3, 10). FDA determined that a 10% null was reasonable for a patient population with null surgery frequencies similar to the reported end-of-phase-1 population.

However, as will be discussed below in Comments #2, #3, and #4, the null CR_{1Y} rate depends on the profile of the patients treated in the SAT, e.g., the true null baseline surgery frequencies and other factors, which could not be completely pre-specified at the design stage by setting the eligibility criterion to be an observed baseline frequency of 3 or more surgeries/year.

2. Counting the surgery on Study Day 1 as a baseline surgery introduces a bias

In the protocol and SAP, though not apparent, Day 1 surgery was counted as a baseline surgery in all analyses. While it is clinically reasonable to mandate a surgery on Study Day 1 for all patients, counting this surgery as a baseline surgery introduces a bias of one more surgery during the baseline period, compared to the PEEP, under the null situation where there is no treatment effect.

Note: This issue was communicated to the applicant during an informal teleconference on May 19, 2025 and was acknowledged by the applicant. The applicant stated that excluding the Day 1 surgery from the baseline count may introduce bias under the alternative where there is a treatment effect. However, multiple simulations by the reviewer have consistently demonstrated the same expected bias, which lead the review team to disagree with the applicant's statement.

- For any baseline-vs-PEEP comparison involving surgery counts, the Day 1 surgery should be excluded from the baseline count to remove this bias. These endpoints include some secondary efficacy endpoints such as ORR.
 - This biased counting also has implication on whether the null CR_{1Y} rate of 10% would be reasonable. For example, under an assumption of a Poisson distribution for surgery counts, a patient with a null frequency of λ surgeries/year would have an $(e^{-\lambda})$ chance of being a CR_{1Y} in the absence of any treatment effect. For $\lambda=2$, this chance is 13.5% while for $\lambda=3$, this chance is 5.0%. This chance decreases to a negligible magnitude when $\lambda \geq 4$. Note that these calculations are based on the null surgery frequencies, a reasonable range of which can be informed by the observed baseline surgery frequency after removing the Day 1 surgery bias, i.e., the sponsor's eligibility criterion of three or more baseline surgeries, in the analyses, becomes two or more. Furthermore, the null CR_{1Y} rate and the null surgery frequency would also be influenced by the additional factors described below.
3. MRD: the PEEP starts with MRD while the baseline period does not, creating a bias

Patients started from a state of MRD at the beginning of PEEP. The MRD status was achieved through the Day 1 surgery and the options of additional surgeries on Days 43 and 85 during the treatment period. In contrast, patients did not start from a state of MRD at the beginning of the baseline period. Since it takes time for a papilloma to grow following MRD, this dissimilarity in MRD status may introduce a bias in favor of the treatment, affecting the interpretation of the analyses of the PEEP CR_{1Y} rate and surgery count-related secondary endpoints. However, this bias is difficult to quantify and address without adequate data on individual disease progression profile and trajectories.

- Empirically, if the baseline period were longer, e.g., three years instead of one year, one might estimate the potential bias due to this factor based on an analysis of timespans between successive baseline surgeries. However, only one year of baseline data was provided in the BLA; some patients had been diagnosed with RRP for only one year before trial entry and therefore only had one year of baseline data.
- Other observations that may provide some insight would be time to the first two surgeries post-treatment in subjects who did not achieve CR_{1Y} (referred to here as non-responders). Specifically, denote Day 1 surgery as Surgery #0, the most recent baseline surgery prior to that as Surgery #-1, and the most recent one prior to Surgery #-1 as Surgery #-2, and so forth. Similarly, denote the post-treatment surgeries sequentially as Surgery #1, Surgery #2, if they occurred. Among the non-responders, the timespan between Surgeries #0 and #1 had a median of 114 days (range: 78, 452), corresponding to 0.31 (range: 0.21, 1.24) years. In contrast, the timespan between Surgeries #1 and #2 had a median of 92 days (range: 23, 608), corresponding to 0.25 (range: 0.06, 1.66) years. The time to the first post-treatment surgery appears to be in general longer than that to the next surgery. However, there is high variability, and it is impossible to know whether this general reduction is due to the MRD or the fact that it takes time for the systemic treatment to take effect, or a combination of both. As an exercise, we examine the hypothetical situation where the MRD would result in a reduction of 0.15 years in time to next surgery, i.e., taking a difference between the two minimums in the timespans to the first two post-treatment surgeries (78-23=55 days). For the CR_{1Y} rate, this would result in a revised PEEP (rPEEP) of 0.85 year from the intended 1 year of PEEP. Therefore, the null CR_{1Y} rate, based on the rPEEP, would be ($e^{-0.85\lambda}$) under a Poisson processes, which may be a reasonable approximation after discounting the MRD bias. This results in a the null CR_{1Y} rate of are 18.2%, 7.8%, 3.3%, for $\lambda=2, 3, 4$, respectively. This chance decreases to a negligible magnitude when $\lambda \geq 5$.

4. Regression to the mean

RRP surgery frequency has high inter-patient and intra-patient variability, and spontaneous remission may occur. This may lead to the regression-to-the-mean (RTM) phenomenon when the SAT enrolled only patients with high numbers of baseline surgeries.

- RTM introduces difficulty in interpreting uncorrected quantitative comparisons in number of surgeries between the baseline and the PEEP periods, e.g. ORR.

Similar to discussions above, it may influence the null CR_{1Y} rate as well to an unknown extent.

- The SAT does not include data, e.g., baseline data for a longer duration, to help evaluate the magnitude and effect of RTM. RTM is discussed further in the efficacy analysis section below.

5. Additional factors that may influence study result interpretation

The following factors may also influence study result interpretation.

- There were substantive changes in the protocol when the trial was well underway after the sponsor and FDA agreed to use this trial to support the BLA. We investigated whether any unexpected changes in study conduct occurred following the protocol revision. Details are provided in Section 6.1.11.1.
- The trial was conducted at a single clinical site, which raises concerns on robustness and generalizability of the trial result. On the other hand, patients were cared for by their respective home physicians, not by the study site, which may mitigate this concern to some extent.
- Timing of surgery may not be completely “objective”, and could probably be done within a time window, whose width may or may not be wide enough to cause concern. To partially assess whether this can be a concern, we compared timespans between Surgery #-1 and Surgery #0, with that between Surgery #-2 and Surgery #-1. There is no systemic difference between these two timespans, e.g., median of difference is 0.5 days, indicating that there is no bias in the timing of Day 1 surgeries.
- Baseline data were collected retrospectively, which may not be as similar to PEEP were the baseline data to be collected prospectively.
- Missing data. There were a substantial amount of missed visits, some caused by a revision in protocol V4.0 to introduce longer follow-up. However, the applicant stated that they were able to identify surgeries by reviewing medical records, therefore this is of little concern.
- Effect of treatment with other products prior to and after PAPZIMEOS treatment. Bevacizumab, a recombinant monoclonal humanized antibody that blocks angiogenesis by inhibiting the human vascular endothelial growth factor A, has been evaluated in a number of studies for treatment of RRP. In the PRGN-2012-201 study, 25/35 (71%) of the EES had received Bevacizumab prior to entering the study. Prior to the initial administration of PAPZIMEOS, a washout of 30 days for prior systemic treatment with bevacizumab was required. For any other systemic treatments for RRP, a washout of 30 days or ≥ 3 half-lives was required. During the study, some patients received bevacizumab after failing to meet the primary endpoint. The clinical reviewer does not believe the way bevacizumab was used before or during the study would have confounded the treatment effect.
- The proposed 10% null threshold on CR_{1Y} rate may not be reasonable if there are a substantial number of patients with low baseline surgery frequencies, i.e., two

surgeries/year after correcting for the Day 1 surgery counting. However, if the 95% CI on the CR_{1Y} rate is substantially higher than 10%, then efficacy of PAPZIMEOS can still be concluded despite a high degree of uncertainty on setting a suitable null response rate. To increase our confidence on the causal interpretation of the trial results, the clinical and statistical teams requested and reviewed additional follow-up data, including the CR_{2Y} endpoint, when these data became available during the BLA review.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The efficacy and safety databases consist of 38 RRP patients treated with PAPZIMEOS: 3 at the dose of 1×10^{11} PUs per injection (DL1), and 35 at the proposed marketing dose of 5×10^{11} PUs per injection (RP2D). Among the 35 patients treated at RP2D, 12 were from the Phase 1 part and 23 were from the Phase 2 part.

6.1.10.1.1 Demographics

Table 2 shows the demographics and selected baseline characteristics, i.e., body mass index (BMIs), of patients in the study. The median age of patients at study entry was 49.5 years (range: 20 to 88 years). Slightly more than half were males (23/38; 60.5%), and the majority were White (33/38; 86.8%) and Not Hispanic or Latino (32/38; 84.2%). Patients were evenly distributed across the BMI weight categories.

Table 2 Demographics and Baseline Characteristics (Full Analysis Population, N=38)

	DL1 (N = 3)	RP2D (N = 35)	RP2D Phase 1 (N = 12)	RP2D Phase 2 (N = 23)	Overall (N = 38)
Age at study entry (years)					
Mean (SD)	56.3 (15.1)	49.4 (15.7)	49.7 (12.8)	49.2 (17.3)	49.9 (15.6)
Median (Min, Max)	63.0 (39, 67)	49.0 (20, 88)	49.5 (30, 73)	49.0 (20, 88)	49.5 (20, 88)
Sex (n (%))					
Male	3 (100)	20 (57.1)	7 (58.3)	13 (56.5)	23 (60.5)
Female	0	15 (42.9)	5 (41.7)	10 (43.5)	15 (39.5)
Race (n (%))					
Asian	1 (33.3)	0	0	0	1 (2.6)
Black or African American	0	1 (2.9)	1 (8.3)	0	1 (2.6)
White	1 (33.3)	32 (91.4)	11 (91.7)	21 (91.3)	33 (86.8)
Other	0	1 (2.9)	0	1 (4.3)	1 (2.6)
Unknown or Not Reported	1 (33.3)	1 (2.9)	0	1 (4.3)	2 (5.3)
Ethnicity (n (%))					
Hispanic or Latino	0	4 (11.4)	0	4 (17.4)	4 (10.5)
Not Hispanic or Latino	3 (100)	29 (82.9)	11 (91.7)	18 (78.3)	32 (84.2)
Unknown or Not Reported	0	2 (5.7)	1 (8.3)	1 (4.3)	2 (5.3)
BMI at Baseline (kg/m2)					
Mean (SD)	25.6 (5.6)	27.8 (6.0)	27.3 (5.0)	28.0 (6.6)	27.6 (6.0)
Median (Min, Max)	23.4 (21.4, 32.0)	26.4 (19.3, 50.2)	26.2 (20.8, 36.7)	26.4 (19.3, 50.2)	25.9 (19.3, 50.2)
Weight categories based on BMI					
Healthy weight (18.5 to 24.9 kg/m2)	2 (66.7)	10 (28.6)	4 (33.3)	6 (26.1)	12 (31.6)
Overweight (25 to 29.9 kg/m2)	0	13 (37.1)	4 (33.3)	9 (39.1)	13 (34.2)
Obesity (≥ 30 kg/m2)	1 (33.3)	12 (34.3)	4 (33.3)	8 (34.8)	13 (34.2)

DL1=dose level 1 at 1×10^{11} PUs/injection; RP2D=recommended Phase 2 dose at 5×10^{11} PUs/injection; max = maximum; min = minimum; SD = standard deviation; BMI= body mass index, calculated as weight (kg)/height (m)². Baseline is defined as the last non-missing value prior to the first dosing of the study drug.
Source: Adapted from BLA 125832/0.1, Clinical Study Report, Table 5, p.52.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 3 shows the disease history and baseline disease characteristics of RRP patients treated in this study. The median time from diagnosis was 15.5 years (range: 1 to 65). Median age at diagnosis was 32.0 years (range: 1 to 68). RRP lesions were more frequently characterized by HPV type 6 (26/38; 68.4%) than type 11 infection (12/38; 31.6%). Notable differences in some baseline characteristics exist between the Phase 1 and Phase 2 patients in the efficacy evaluable population (EES), i.e., those treated with the R2PD:

- More Phase 2 than Phase 1 patients had juvenile onset, at 43.5% (10/23) and 16.7% (2/12), respectively.

- More Phase 1 than Phase 2 patients had higher baseline surgery frequencies, with 50% of Phase 1 patients had ≥ 6 surgeries during the baseline period. For Phase 2 patients, about half (11/23) had 3 baseline surgeries and the rest (12/23) had 4 or 5 baseline surgeries. These counts include the Day 1 surgeries.

Table 3 Recurrent Respiratory Papillomatosis Disease History and Baseline Disease Characteristics (Full Analysis Population, N=38)

	DL1 (N = 3) n (%)	RP2D (N = 35) n (%)	RP2D Phase 1 (N = 12) n (%)	RP2D Phase 2 (N = 23) n (%)	Overall (N = 38) n (%)
Primary Disease Site					
Larynx	2 (66.7)	27 (77.1)	8 (66.7)	19 (82.6)	29 (76.3)
Other	1 (33.3)	8 (22.9)	4 (33.3)	4 (17.4)	9 (23.7)
Number of patients with pulmonary RRP	1 (33.3)	4 (11.4)	1 (8.3)	3 (13.0)	5 (13.2)
Number of years from diagnosis^b					
Mean (SD)	18.7 (20.6)	20.4 (19.0)	13.8 (14.1)	23.9 (20.5)	20.3 (18.8)
Median (Min, Max)	11.0 (3, 42)	20.0 (1, 65)	6.0 (1, 35)	22.0 (1, 65)	15.5 (1, 65)
Age at diagnosis (years)^c					
Mean (SD)	37.7 (19.4)	29.0 (21.4)	35.8 (20.6)	25.4 (21.3)	29.7 (21.1)
Median (Min, Max)	28.0 (25, 60)	35.0 (1, 68)	38.5 (1, 68)	28.0 (1, 64)	32.0 (1, 68)
Adulthood status at disease onset					
Juvenile onset	0	12 (34.3)	2 (16.7)	10 (43.5)	12 (31.6)
Adult onset	3 (100)	23 (65.7)	10 (83.3)	13 (56.5)	26 (68.4)
HPV viral type					
6	2 (66.7)	24 (68.6)	9 (75.0)	15 (65.2)	26 (68.4)
11	1 (33.3)	11 (31.4)	3 (25.0)	8 (34.8)	12 (31.6)
ECOG Performance Status					
0	3 (100)	32 (91.4)	12 (100)	20 (87.0)	35 (92.1)
1	0	3 (8.6)	0	3 (13.0)	3 (7.9)
Number of Surgeries during the 12-month Baseline Period, including the Day 1 Surgeries					
Mean (SD)	6.3 (2.1)	4.5 (2.0)	5.8 (2.8)	3.7 (0.8)	4.6 (2.1)
Median (Min, Max)	7.0 (4, 8)	4.0 (3, 10)	5.0 (3, 10)	4.0 (3, 5)	4.0 (3, 10)
Category Based on Number of Baseline Surgeries					
Low (≤ 25 th percentile, i.e., ≤ 3 surgeries)	0	15 (42.9)	4 (33.3)	11 (47.8)	15 (39.5)
Medium (25th to ≤ 75 th percentile, i.e., >3 surgeries to ≤ 5 surgeries)	1 (33.3)	14 (40.0)	2 (16.7)	12 (52.2)	15 (39.5)
High (>75 th percentile, i.e., >5 surgeries)	2 (66.7)	6 (17.1)	6 (50.0)	0	8 (21.1)

ECOG = Eastern Cooperative Oncology Group; HPV = Human Papillomavirus; max = maximum; min = minimum; RRP = recurrent respiratory papillomatosis; SD = standard deviation; DL1=dose level 1 at 1×10^{11} PUs/injection; RP2D=recommended Phase 2 dose at 5×10^{11} PUs/injection.

^b Number of years from diagnosis = (date informed consent signed - date of diagnosis +1)/365.25.

^c Age at diagnosis = age at study entry - number of years from diagnosis.

Source: Adapted from BLA 125832/0.1, Clinical Study Report, Table 6, p.54.

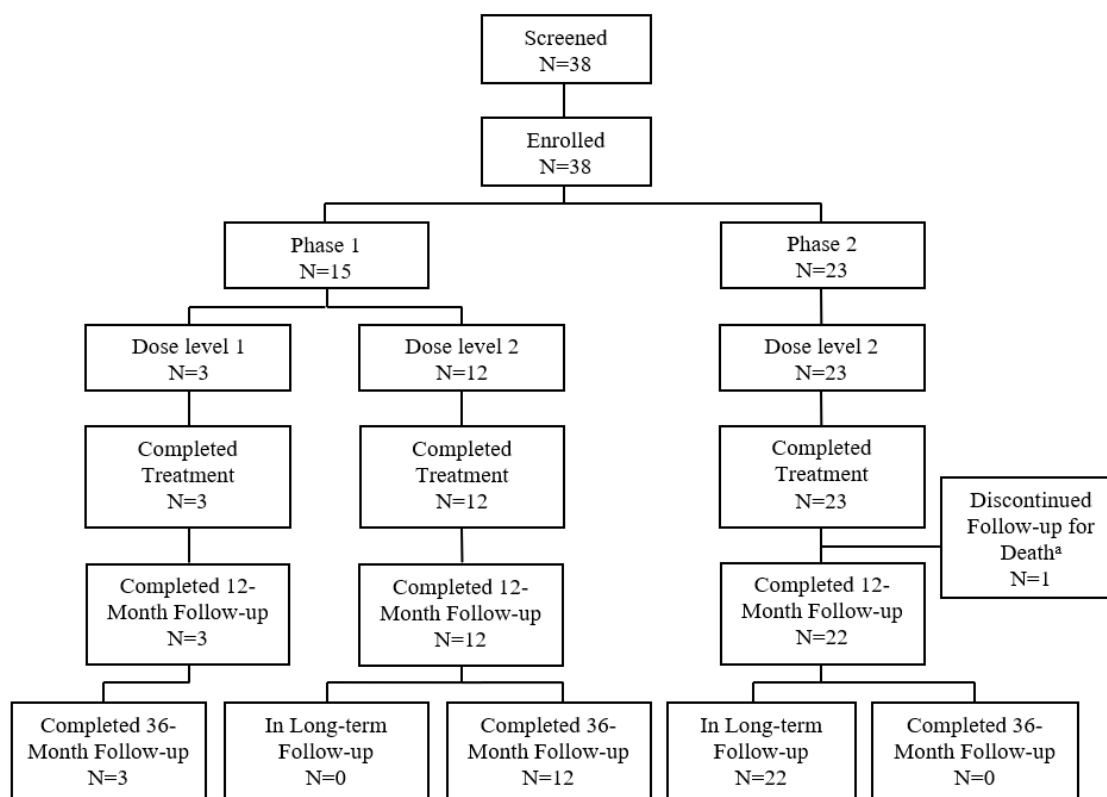
6.1.10.1.3 Patient Disposition

The PCOD for the CSR supporting the original BLA submission was August 28, 2024. The 120-safety report had a SCOD of March 21, 2025.

Figure 2 summarizes patient disposition as of the SCOD. There were no screen failures. All 38 screened patients received all 4 injections in the treatment series and formed the FAS and SAF. Of these, the EES included all 35 patients treated at the RP2D of 5.0×10^{11} PUs per injection, and the remaining 3 patients were treated at DL1 of 1.0×10^{11} PUs per injection.

Table 4 summarizes the duration of follow-up for both the PCOD and the SCOD. As of the SCOD, all DL1 patients were followed-up for the full 36 months. For the EES, 12 (34%) patients completed the 36-month follow-up and 31 (80%) completed the 24-month follow-up. There was no early discontinuation except for one death, which will be described under Section 6.1.12. As of the SCOD, the median follow-up in EES was 30 months (range: 21 to 36 months), excluding the subject who died.

Figure 2 Patient Disposition as of the Secondary Cutoff Date on March 21, 2025



Dose level 2 in this figure is the recommended Phase 2 dose mentioned in the text.

Source: Adapted from BLA 125832/0.1, Clinical Study Report, Figure 2, p.51 and BLA 125832/0.36, Clinical Information Amendment-Response to clinical information request #3, Figure 1, p.9.

Table 4 Duration of Follow-up After Treatment

	DL1 (N = 3) n (%)	RP2D (N = 35) n (%)	RP2D Phase 1 (N = 12) n (%)	RP2D Phase 2 (N = 23) n (%)	Overall (N = 38) n (%)
Primary cut-off date (August 28, 2024)					
Follow-up duration (months)					
(0, 12]	0	2 (6) ^b	0	2 (9)	2 (5)
(12, 24]	0	21 (60)	0	21 (91)	21 (55)
(24, 36)	0	10 (29)	10 (83)	0	10 (26)
36	3 (100)	2 (6)	2 (17)	0	5 (13)
Secondary cut-off date (March 21, 2025)					
Follow-up duration (months)					
(0, 12)	0	1 (3) ^b	0	1 (4)	1 (3)
(12, 24]	0	8 (23)	0	8 (35)	8 (21)
(24, 36)	0	14 (40)	0	14 (61)	14 (37)
36	3 (100)	12 (34)	12 (100)	0	15 (40)

DL1=dose level 1 at 1×10^{11} PUs/injection; RP2D=recommended Phase 2 dose at 5×10^{11} PUs/injection.

^b Patient (b) (6) died of cardiac arrest and had a last follow-up visit at 5 months after treatment.

Source: Adapted from BLA 125832/0.1, Clinical Study Report, Table 4, p.49, and BLA 125832/0.36, Clinical Information Amendment-Response to clinical information request #3, Figure 1, p.9.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

The primary efficacy endpoint was defined as no requirement for surgical intervention in the 12 months after treatment (denoted as CR_{1Y}), for patients in the EES. As shown in Table 5, 18/35 patients achieved CR_{1Y} resulting in a CR_{1Y} rate of 51.4% with a 95% CI of (34.0%, 68.6%). As previously discussed, the 10% null threshold on CR_{1Y} may not be reasonable when considering the various sources of biases and uncertainties with this SAT. However, the lower bound of 34% on the 95% CI on CR_{1Y} is high enough to allow an efficacy conclusion.

The CR_{1Y} rates are comparable for the Phase 1 and Phase 2 patients in the EES. None of the three patients treated at dose level 1 achieved CR_{1Y}.

Of the 18 EES patients achieving CR_{1Y}, 3 patients (17%) received surgeries shortly after 12 months while the remaining 15 patients (83%) continued to not require any surgery through the SCOD. Of these 15 patients continuing CR, 14 had reached at least 2 years of follow-up by the SCOD, and 6 had reached 3 years of follow-up. In response to an FDA information request, the applicant was able to update with additional follow-up that this patient was a CR_{2Y} responder. As a result, The CR_{2Y} rate estimate was 43% with a 95% CI of (26%, 61%).

Table 5 Complete Responses During the First Year (Determined by the Primary Cut-off Date) and During the First Two Years (Determined by the Secondary Cut-off Date)

	DL1 (N = 3) n (%)	RP2D (N = 35) n (%)	RP2D Phase 1 (N = 12) n (%)	RP2D Phase 2 (N = 23) n (%)
Complete Response during the first year (CR_{1Y})				
Number of CR_{1Y}	0	18	6	12
CR_{1Y} Rate (95% confidence interval)	0 (0.0, 70.8)	51.4 (34.0, 68.6)	50.0 (21.1, 78.9)	52.2 (30.6, 73.2)
Complete Response during the first two years (CR_{2Y})				
Number of CR_{2Y}	0	15	6	9
CR_{2Y} Rate (95% confidence interval)	0 (0.0, 70.8)	43% (26%, 61%)	50.0 (21.1, 78.9)	39.1 (19.7, 61.5)

DL1=dose level 1 at 1×10^{11} PUs/injection; RP2D=recommended Phase 2 dose at 5×10^{11} PUs/injection. Except for one patient, all patients' CR_{2Y} status were determined by the secondary cut-off date. The Agency subsequently inquired and was informed that this subject was a CR_{2Y} responder with additional follow-up. Source: Adapted from BLA 125832/0.1, Clinical Study Report, Table 10, p.60, and review team's calculation.

Reviewer comment

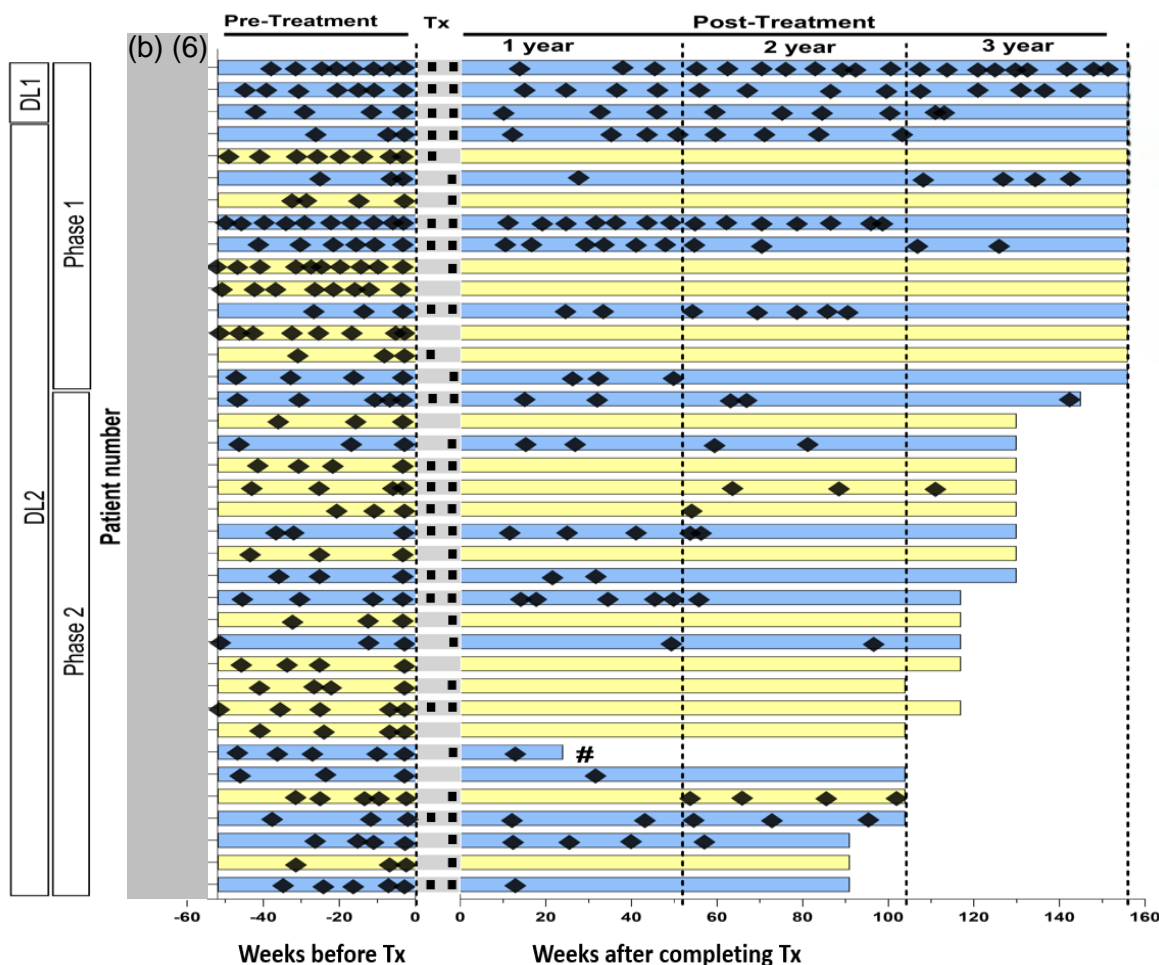
The CR_{2Y} rate estimate was 43% with a 95% CI of (26%, 61%). This is much more persuasive evidence of the efficacy of PAPZIMEOS, compared with the CR_{1Y} result. To illustrate, the lowest number of baseline surgery frequency in this study is two surgeries/year, after excluding the Day 1 surgeries from the baseline counts to correct this bias. Under the null of no treatment effect and a Poisson model, there is only a chance of $e^{-4} = 1.8\%$ to observe CR_{2Y} in any one patient. If we go further to conservatively correct for the potential bias introduced by dissimilarity in MRD status at the beginning of the baseline and the post-treatment follow-up period by subtracting one more surgery from the baseline, then with the lowest number of baseline surgery frequency of one surgery/year, the null probability of CR_{2Y} is $e^{-2} = 13.5\%$. The lower bound on CR_{2Y} of 26% exceeds this most conservative null of 13.5% comfortably.

Figure 3 shows the individual level surgeries (including Day 1 surgeries in the baseline period) during the baseline and post treatment periods. When excluding Day 1 surgeries from the baseline to correct the bias, as discussed previously, we observe the following results:

- Of the 20 patients who did not achieve CR_{2Y} in the EES, there is no evidence that any experienced a material increase in the number of surgeries during the post-treatment follow-up, compared to baseline, by visual inspection and after considering variabilities.
- It is instructive to contrast the EES result with that on the three DL1 patients. It is apparent that PAPZIMEOS was not efficacious at this lower dose level. The

number of surgeries during baseline, Year 1, Year 2, and Year 3 for the three patients were: (7, 3, 8, 9), (6, 4, 4, 5), and (3, 3, 4, 2). This shows within-patient variability over time and a generally stable trend in surgery frequencies across the baseline and post-treatment follow-up period.

Figure 3 Individual-level Surgeries During the Baseline, Treatment Period, and Post-treatment Follow-up (Full Analysis Population, N=38)



Tx: treatment period. Diamonds denote surgeries outside the treatment period. Squares denote surgeries during the treatment period on Day 43 and Day 85 treatment visits to maintain minimal residual disease.
Source: Adapted by the clinical reviewer from BLA 125832/0.36, Clinical Information Amendment-Response to clinical information request #3, Figure 1, p.9.

Additional analyses of factors affecting primary efficacy results

In Section 6.1.9.2, we described the factors that may lead to biases and additional uncertainties beyond statistical variabilities. In view of the substantial PAPZIMEOS treatment effect in CR_{2Y} and CR_{1Y}, we have determined that the influence of most of those factors are not of a magnitude sufficient to change the efficacy conclusion and will not examine them further. In what follows, we will consider the impact on study results of three factors: dissimilarity in MRD, baseline surgery frequency, and time from

diagnosis and its implication on spontaneous remission. Note that the Day 1 surgeries biased counting has already been corrected by not including them in analyses.

1. Dissimilarity in MRD between the starting points of baseline and follow-up period Table 6 and Figure 3 show that 83% (29/35) of the EES patients received surgeries at least once on Day 43 or Day 85 to maintain MRD, with around half of those (14/29) received surgeries on both days.

The applicant suggested that “*there was no relationship between patients having required the MRD procedure and achieving [CR_{1Y}]*,” by quoting that 94% (16/17) of the CR_{1Y} non-responders and 72% (13/18) of the CR_{1Y} responders had received at least one procedure at those two treatment days to maintain MRD, respectively. It is unclear how the data supported this conclusion. However, our concern about potential biases resulting from dissimilarity in MRD at the start of the comparison periods was not about whether MRD would affect CR_{1Y} status, but rather whether they would lead to different time to the next surgery in the absence of any treatment effect, i.e., under the null. There is indication that MRD may prolong the time to the next surgery, when compared to starting follow-up at a random time (i.e., the baseline period), as described in Section 6.1.9.2. In Figure 3, this observation is more evident in patients (b) (6), who had 7 and 6 surgeries during the first year, respectively. In these two patients, on average we would expect the first surgeries to occurred around 1.7 to 2.4 (12/7, 12/6) months during the first-year follow-up if MRD does not have an effect on the time to the next surgery. But the actual time to first post-treatment surgery was 78 and 82 days (2.6 and 2.7 months), respectively.

This potential bias could affect before-and-after comparisons, as well as the null CR_{1Y} rate. However, given the substantial PAPZIMEOS treatment effect, especially when CR_{2Y} rate is considered, this potential bias is of much smaller magnitude and therefore does not affect our conclusion on the treatment effect based on the CR_{2Y} and CR_{1Y} rates. It can nonetheless affect the accuracy on quantitative comparison of surgery frequencies between the baseline and the PEEP.

Table 6 Incidence of MRD Procedures During Treatment (Full Analysis Population)

Parameter	DL1 (N = 3) n (%)	RP2D (N = 35) n (%)	RP2D Phase 1 (N = 12) n (%)	RP2D Phase 2 (N = 23) n (%)
Patients received MRD procedure at Day 43 only	0	2 (6)	2 (17)	0
Patients received MRD procedure at Day 85 only	0	13 (37)	4 (33)	9 (39)
Patients received MRD procedures at Day 43 and Day 85	3 (100)	14 (40)	4 (33)	10 (43)
Total number of patients received MRD procedure	3 (100)	29 (83)	10 (83)	19 (83)
Patients did not have MRD procedure	0	6 (17)	2 (17)	4 (17)

DL1=dose level 1 at 1×10^{11} PUs/injection; RP2D=recommended Phase 2 dose at 5×10^{11} PUs/injection.
MRD = minimal residual disease.

Source: Adapted from BLA 125832/0.1, Clinical Study Report, Table 8, p.58.

2. Baseline surgery frequency

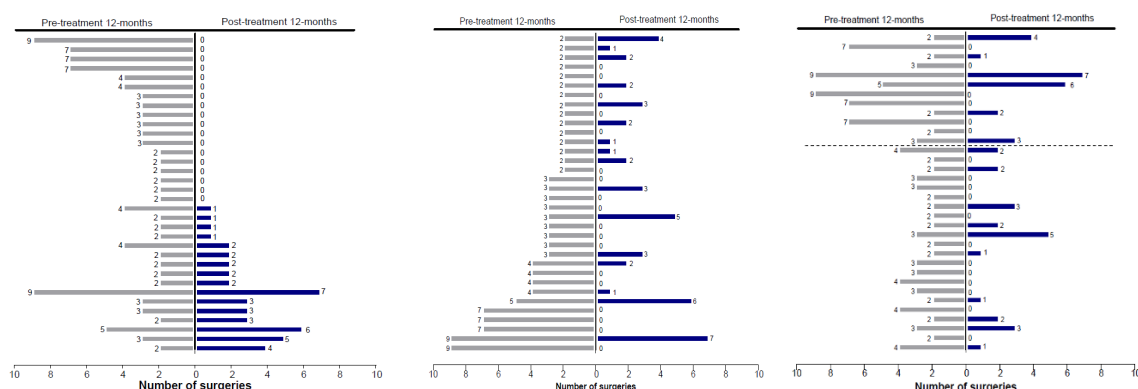
Figure 4 shows the number of surgeries for all EES patients during the baseline and the PEEP. The three graphs show the same data by different ordering: by number of surgeries during PEEP (left panel), or that during baseline (center panel), or the time patients receiving first treatment (right panel). This figure excludes the patient who died, who had a baseline surgery frequency of 4 surgeries/year and was counted as a non-responder, for easier reference. The discussion below will include data on this patient.

The right panel indicates that the Phase 2 part of EES patients have evidently lower baseline surgery frequencies than the Phase 1 part, at a median of 3 (range: 2 to 4) and 4 (range: 2 to 9) surgeries/year, respectively. Protocol Version 4.0 was implemented around the time separating the two phases, after FDA agreed to repurpose this trial to be the primary trial to support a BLA application.

The center panel shows the data ordered by baseline surgery frequencies. The CR_{1Y} rate, for the subgroups with baseline number of surgeries (B) of 2, 3, or 4 to 9, was 40% (6/15), 67% (6/9), and 56% (5/11), respectively. It appears that the B=2 subgroup may have the smallest effect when we would expect a comparatively higher CR_{1Y} rate than the other two subgroups, and indeed 2 of the 9 CR_{1Y} non-responders in this subgroup experienced an increase in surgeries after treatment. However, this may partially reflect the RTM phenomenon; we have no concerns with this subgroup given the totality of the data, especially the data on CR_{2Y}. Hypothetically, if this SAT only has one year of follow-up data and not a sizable number of patients with high baseline surgery frequencies, it would be difficult to set a reasonable null hypothesis on CR_{1Y} which would then lead to less confidence in the interpretation of the study outcome.

The left panel shows that in addition to the convincing evidence of efficacy based on CR endpoints, there do not appear to be detrimental effects in the non-responders. Note that we have not yet taken into account other potential biases and additional uncertainties, but it is reasonable to conclude qualitatively that there is no evidence of harm in the non-responders.

Figure 4 Number of Surgeries During the Baseline and the First Year Post-treatment (Efficacy Evaluable Population Excluding the Death, N=34)



Source: Adapted from BLA 125832/0.39, Clinical Information Amendment-Response to BioStats Information request #1, Figure 1-3, pp.6-8.

3. Time from diagnosis and its implication on spontaneous remission

Given variability of need for surgeries even within a patient over time, it may be reasonable to assume that for patients with a longer time from diagnosis at study entry, the chance of spontaneous remission might be smaller or non-existent.

In the EES, median time since diagnosis was 20 years, with a range of (1, 65) years. Five, three, and one patient had a time since diagnosis of 1, 2, or 3 years, respectively. The remaining 26 patients (74%) all had been 4 or more years since diagnosis. Taken together and considering the large effect size, we determine that spontaneous remissions is unlikely to affect the efficacy conclusion based on the CR rates.

6.1.11.2 Analyses of Secondary Endpoints

Table 7 shows a descriptive summary of the change in number of surgeries between the baseline and the PEEP periods. As discussed in Section 6.1.9.2, other than an adjustment for the bias of the Day 1 surgery in the baseline count (third column), biases due to various other factors (such as MRD and regression to the mean) exist and cannot be quantitatively adjusted. Therefore, caution should be exercised when interpreting the results.

Table 7 Summary of Change of Surgery Numbers from Baseline to the First Year Post-treatment

	Year 1 Results with Day 1 Surgery*	Year 1 Results without Day 1 Surgery
Absolute change in number of RRP surgical interventions		
Mean (SD)	-3.1 (2.6)	-2.1 (2.6)
Median (Min, Max)	-3.0 (-10, 1)	-2.0 (-9,2)
Number of partial responses	5	5
Partial response rate (95% CI)	14.3 (4.8 - 30.3)	14.3 (4.8 - 30.3)
Number of objective responses	23	23
Objective response rate (95% CI)	65.7 (47.8 - 80.9)	65.7 (47.8 - 80.9)
Patients with change in number of RRP surgical interventions		
Increased	2 (5.9)	4 (11.8)
No change	2 (5.9)	6 (17.6)
Decreased	30 (88.2)	24 (70.6)

N=number of patients; CI=confidence interval; SD=standard deviation; Min=Minimum; Max=Maximum.

* For calculation of percentages, the total number of patients used as the denominator was N=34, excluding the death during the 12-month follow-up.

Source: Reviewer's summary

6.1.11.3 Subpopulation Analyses

Table 8 summarizes the subgroup analyses on the CR_{1Y} and CR_{2Y} rates in the EES by sex, race, HPV type, age of onset, and ECOG performance status. The subgroup results are in general consistent with the overall CR_{1Y} rate (51%) and the overall CR_{2Y} rate (43%) in the EES. In general, the sample sizes of the subgroups are too small to conclude material differences between subgroups when there are numerical differences between the results.

Table 8 Subgroup Analysis on Complete Response Rates During the First Year and the First Two Years Post-treatment (Efficacy Evaluable Population, N=35)

	Complete Response during the first year	Complete Response during the first two years
Sex		
Female	7/15 (47%)	4/15 (27%)
Male	11/20 (55%)	10/20 (50%)
Race		
White	16/32 (50%)	12/32 (38%)
Non-White	2/3 (67%)	2/3 (67%)
HPV Type		
HPV 6	14/24 (58%)	11/24 (46%)
HPV 11	4/11 (36%)	3/11 (27%)
Age at onset		
Adult onset	12/23 (52%)	11/23 (48%)
Juvenile onset	6/12 (50%)	3/12 (25%)
ECOG status		
ECOG = 0	16/32 (50%)	12/32 (38%)
ECOG = 1	2/3 (67%)	2/3 (67%)

Source: Reviewer's analysis.

6.1.11.4 Dropouts and/or Discontinuations

One patient died on Day (b) (6). This patient received all study treatment but did not complete the 12-month follow-up period and was included in the efficacy analysis as a non-responder.

6.1.12 Safety Analyses

The safety database consists of safety data on the 38 patients who received PAPZIMEOS in the PRGN-2012-201 study. The three patients who received DL1 were all followed up for 36 months. In the 35 patients who received the RP2D, the median follow-up was 30 months (range: 21 to 36 months).

6.1.12.3 Deaths

One death occurred during the study. Patient (b) (6) died of cardiac arrest on Day (b) (6) days after the last dose of PAPZIMEOS (RP2D). The investigator and the Sponsor determined that the death was not related to the study drug and was most likely related to pre-existing heart-related conditions. The patient was in follow-up and was last seen on (b) (6) days after the last dose.

6.1.12.4 Nonfatal Serious Adverse Events

Three patients (3/38; 7.9%) experienced a total of three serious adverse events (SAEs), including the death described above. The two non-fatal SAEs are listed below.

- Patient (b) (6) (DL1) experienced a grade 3 bacterial laryngitis that lasted 5 days starting 11 days after the 4th PAPZIMEOS injection. The investigator and the Sponsor assessed this SAE as not related to the investigational product, research, surgery, or disease stating that it was most likely related to bacterial infection.
- Patient (b) (6) (RP2D) experienced an SAE of grade 3 upper gastrointestinal hemorrhage within 27 minutes after receiving the first PAPZIMEOS injection (approximately 6-8 hours following surgery). The investigator and the Sponsor assessed this SAE as not related to the investigational product or disease. In the opinion of the investigator and Sponsor, the SAE was related to the surgery.

6.1.12.7 Dropouts and/or Discontinuations

Other than the death summarized above, the applicant reported that no patient discontinued treatment due to a treatment-emergent adverse event (TEAE).

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The applicant submitted this original BLA for PAPZIMEOS for the treatment of adults with RRP. PAPZIMEOS is an adenoviral vector-based immunotherapy designed to express a fusion antigen of selected regions of HPV proteins expressed in HPV 6- and HPV 11-infected cells. The efficacy and safety databases are based on results from Study PRGN-2012-201.

Data package and study design

PRGN-2012-201 is an ongoing, Phase 1/2, single-arm study where all 38 RRP patients received PAPZIMEOS. Eligibility criteria include receiving three or more surgeries during the 12-month retrospective baseline period. All 38 patients completed the series of 4 PAPZIMEOS injections on Days 1, 15, 43, and 85. Three of these 38 patients received dose level 1 at 1×10^{11} PU per injection. The other 35 patients received the proposed dose (RP2D) at 5×10^{11} PU per injection. All patients underwent a surgery on Study Day 1 before initiation of PAPZIMEOS treatment to remove laryngotracheal papilloma and establish MRD. The applicant counted this surgery as a baseline surgery in the eligibility criteria and endpoint analyses. During the treatment period, patients would undergo additional surgical procedures to remove all visible papilloma on Days 43 and 85 to maintain MRD. Patients then entered a 12-month follow-up period after the last treatment injection. The primary efficacy endpoint is absence of any surgery during the 12-month follow-up, i.e., complete response through the first year (CR_{1Y}). Patients would then be followed up for an additional two years, for a total of three years of follow-up post-treatment. The applicant pre-specified study success criterion to be the lower bound of the 95% CI on CR_{1Y} exceeding 10%. Because of availability of additional follow-up data

while the BLA was under review, we also reviewed complete response through the first two years (CR_{2Y}).

Efficacy

The efficacy database consists of data on the 35 patients treated at the RP2D. The primary data cut-off date was August 28, 2024, when all patients had been followed up for at least one year, except for the one patient who died prior to the one-year visit. The secondary cut-off date was March 21, 2025, for the 120-day safety report submitted to the BLA.

In the EES, median age was 49.0 years (range: 20 to 88), 43% (15/35) were females, and most patients were White (32/35, 91%). Around 2/3 (23/35, 66%) of patients had adult onset. The median number of surgeries during the 12-month baseline period, counting the mandatory Day 1 surgery, was 4 (range: 3 to 10).

Eighteen of the 35 patients in EES achieved CR_{1Y}, the primary efficacy endpoint, resulting in a point estimate on CR_{1Y} of 51% with a 95% CI of (34%, 69%), meeting the study success criterion with the lower bound of the CI exceeding 10%.

We have evaluated the impact of various sources of potential biases associated with this single-arm trial, and corresponding correction/mitigation strategies. As a result, we excluded the Day 1 surgeries from the count of baseline surgeries when considering the acceptability of the null threshold of 10% on CR_{1Y} rate as well as analyses of secondary endpoints related to comparisons of number of surgeries between the baseline and the primary efficacy evaluation period, i.e., one year post-treatment. Although we do not have high confidence that the 10% threshold is adequate, the observed lower bound of the 95% CI, at 34%, is high enough to be robust to uncertainties introduced by these biases. As a result, we conclude that PAPZIMEOS is efficacious based on the primary analysis of CR_{1Y}.

As a result, CR_{2Y} was achieved by 15 patients, resulting in a point estimate of CR_{2Y} rate of 43% (95% CI: 26%, 61%). The additional CR_{2Y} result, though not pre-planned, provides highly persuasive evidence on the efficacy of PAPZIMEOS.

Safety

The safety database consists of data on the 38 patients through the SCOD.

Three SAEs occurred. One patient who received the proposed dose died of cardiac arrest. Another patient who received DL1 experienced a grade 3 bacterial laryngitis that lasted 5 days starting 11 days after the 4th PAPZIMEOS injection. A third patient who received the proposed dose experienced an SAE of grade 3 upper gastrointestinal hemorrhage within 27 minutes after receiving the first PAPZIMEOS injection (approximately 6-8 hours following surgery). Please see the clinical review memo for a full evaluation of the safety information.

10.2 Conclusions and Recommendations

PAPZIMEOS is effective in reducing number of surgeries in adult RRP patients. This conclusion is supported by highly persuasive evidence of absence of surgeries lasting at least two years post treatment in 43% of the EES. Although patients with fewer than three surgeries during the baseline period were not included in the study, it is plausible that

such patients would benefit similarly from PAPZIMEOS because of the same mechanism of action. Therefore, we recommend approval of the proposed indication of PAPZIMEOS.