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Our STN: BLA 125832/0

**LATE-CYCLE
MEETING MEMORANDUM**

Precigen, Inc.
Attention: Amy Lankford, PhD
SVP, Head of Clinical Operations & Reg Affairs
20358 Seneca Meadows Parkway
Germantown, MD 20876

Attached is a copy of the memorandum summarizing your June 12, 2025, Late-Cycle Meeting with CBER. This memorandum constitutes the official record of the meeting. If your understanding of the meeting outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER in writing as soon as possible.

Please include a reference to the appropriate Submission Tracking Number (STN) in future submissions related to the subject product.

If you have any questions, please contact the Regulatory Project Manager, Helen Sansone at (240) 549-2276 or by email at Helen.Sansone@fda.hhs.gov.

Sincerely,

Mara Miller, MA
Director
Division of Review Management and Regulatory Review 2
Office of Review Management and Regulatory Review
Office of Therapeutic Products
Center for Biologics Evaluation and Research

Late-Cycle Meeting Summary

Meeting Date and Time: June 12, 2025; 1:00 PM – 2:00 PM ET
Meeting Location: In-Person at White Oak, Building 75, Room 1535/1540
Application Number: BLA 125832/0
Product Name: zopapogene imadenovec [PAPZIMEOS]
Proposed Indications: For the Treatment of Adults with Recurrent Respiratory Papillomatosis.
Applicant Name: Precigen, Inc.
Meeting Chair: Sukyoung Sohn, PhD
Meeting Recorder: Helen Sansone

FDA ATTENDEES

Natalya Ananyeva, PhD, CBER/OTP/OPPT
Marie Anderson, PhD, CBER/OCBQ/DBSQC
Colleen Caldwell, MS, MPH, CBER/OTP/ORMRR
Yang Chang, PhD, PharmD, CBER/OTP/OCE/DCEGM
Char-Dell Edwards, BS, CBER/OCBQ/DIS
Shelby Elenburg, MD, CBER/OTP/OCE/DCEGM
Alifiya Ghadiali, PhD, CBER/OCBQ/DMPQ
Joydeep Ghosh, PhD, CBER/OTP/OGT
Christine Harman, PhD, CBER/OCBQ/DMPQ
Jana Highsmith, CBER/OCBQ/DMPQ
Alicia Howard, CBER/OCBQ/DBSQC
Wei Liang, PhD, CBER/OTP
Philip Olivares, PhD, CBER/OTP/OPPT
Joseph Quander III, CBER/OCBQ/DMPQ
Helen Sansone, CBER/OTP/ORMRR
Andrey Sarafanov, PhD CBER/OTP/OPPT
Zuben Sauna, PhD, CBER/OTP/OPPT
Seth Schulte, MS, CBER/OCBQ/DBSQC/LMIVTS
Muhammad Shahabuddin, PhD, CBER/OCBQ/DBSQC
Kanaeko Sharpe, MS, SBB (ASCP), CBER/OCBQ/DIS
Anurag Sharma, PhD, CBER/OTP/OGT
Prateek Shukla, MD, CBER/OTP/OCE/DCEGM
Ramani Sista, PhD, CBER/OTP/ORMRR
Sukyoung Sohn, PhD, CBER/OTP/OGT
Mara Miller, MA, CBER/OTP/ORMRR
Lori Peters, CBER/OCBQ/DMPQ
Jianyang Wang, PhD, CBER/OTP/OGT
Yakun Wang, PhD, CBER/OBPV/DB
Frances Wong, CBER/OTP/ORMRR
Kerry Welsh, CBER/OBPV/DPV
Nhu-Hac Truong, CBER/OBPV/DPV

APPLICANT ATTENDEES

Doug Brough, Senior Vice President, Head of Research
Bryan Butman, Senior Vice President, Head of CMC
Shanti Ghosh, Executive Director, Regulatory Affairs
PJ Kelley, Manager, Regulatory Affairs
Amy Lankford, Senior Vice President, Head of Clinical Operations & Regulatory Affairs
Jacob Pattasseril, Executive Director, Gene Therapy Manufacturing
Helen Sabzevari, President and Chief Executive Officer
Roshanak Semnani, Executive Director, Translational Research
Khyati Shah, Associate Director, Regulatory Affairs
Rutul Shah, Chief Operating Officer
Ramya Supraneni, Director, Pharmacovigilance
James Wong, Executive Director, Quality Control

BACKGROUND

BLA 125832/0 was submitted on December 27, 2025, for zopapogene imadenovec-drba.

Proposed indication: For the Treatment of Adults with Recurrent Respiratory Papillomatosis.

PDUFA goal date: August 27, 2025

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on June 2, 2025.

DISCUSSION

1. Discussion of Substantive Review Issues

Chemistry, Manufacturing, and Controls (CMC)

- Insufficient information for in-use stability and device compatibility: As we communicated through an IR sent on May 20, 2025, and teleconference held on May 28, 2025, the in-use stability and device compatibility data provided in the BLA is not sufficient to support product preparation and administration instructions in the USPI. We acknowledge that you plan to submit additional in-use and device compatibility data to the BLA by June 27, 2025. The adequacy of the submitted data will be a review issue.
- Higher dose used in the clinical study: As we communicated through an IR sent on May 12, 2025, (b) (4) drug product (b) (4) was used in your clinical study PRGN-2012-201 and the subjects received a 15% higher dose (5.75E+11 particle units (PU)/injection) than the intended commercial dose of 5.0E+11 PU/injection. To address this issue, the acceptance criterion for PU concentration for commercial lot release should be tightened by raising the lower limit. Based on your PU assay validation and batch analysis data from the lots manufactured using the intended commercial manufacturing process (i.e., post-change lots), we expect you to raise the lower limit from (b) (4)

Clinical

- Efficacy data submitted under amendment 125832.31 (Module 2.7.3 Summary of Clinical Efficacy - Duration of Response Update) provides additional information related to treatment durability from the ongoing Phase 1/2 study. In light of the submitted data, the review team is discussing the appropriate pathway for review (i.e., accelerated vs. traditional approval).

Meeting Discussion:

FDA conveyed the substantive review issues for CMC and Clinical. Precigen acknowledged the review issues.

2. Additional Applicant Data

Meeting Discussion:

Precigen submitted a slide deck on June 10, 2025, along with three questions for FDA. Precigen presented their proposed plans to address CMC Discussion Item #1 regarding insufficient information to support in-use conditions to be included in the USPI. Precigen provided an overview of the three studies for in-use stability and device compatibility and proposed a maximum hold time of 60 minutes at room temperature based on the data from Study #1 and Study #2. Precigen plans to submit the final reports for Study #2 and Study #3 by June 27, 2025. Precigen also confirmed that PRGN-2012 samples used for these studies were exposed to laboratory light during testing, which is consistent with the in-use condition described in the proposed USPI. Precigen confirmed that none of the

test samples underwent the commercial labeling process at (b) (4). FDA suggested to include an instruction to not shake the vial in the USPI Section 2. This will be communicated as part of the labeling negotiation process. FDA thanked Precigen for providing additional information and stated that determination regarding the adequacy of the additional in-use stability and device compatibility data to support the commercial in-use conditions will be made upon review of the information provided in the BLA by June 27, 2025.

To address CMC Discussion Item #2 regarding the higher dose used in the clinical study, Precigen agreed to raise the lower limit of the drug product (DP) PU concentration for commercial lot release from (b) (4). FDA thanked Precigen for accepting the recommendation.

In addition, Precigen appreciated the consideration regarding the appropriate pathway for review (i.e., accelerated vs. traditional approval).

Precigen had three questions for FDA:

1. Launch Lot: Precigen plans to use (b) (4) as a launch lot. Precigen confirmed that the (b) (4) vials have not been labeled yet. Regarding the lot release protocol (LRP), FDA stated that Precigen's proposal for using the current draft LRP for the launch lot is not acceptable. FDA recommended Precigen to wait for the LRP template to be finalized before submitting the LRP for the launch lot to FDA. The commercial DS and DP specifications are yet to be finalized (pending information request (IR; dated June 6, 2025) response). FDA clarified that the LRP review for CBER lot release will take approximately 30 days.
 2. The Acceptance Criterion for (b) (4) for Commercial Lot Release (IR 35, response due June 17, 2025): Precigen stated that they plan to raise the lower limit of the acceptance criterion (AC) for the (b) (4) Assay from (b) (4) (FDA had recommended it to be raised to (b) (4)). FDA stated that they have additional questions on the (b) (4) assay and will send an IR by Friday (June 13, 2025). FDA will make their final decision on the proposed revised lower limit for the AC (i.e., (b) (4)) after they review all responses, including the one to be sent on Friday (June 13, 2025).
 3. Viral Shedding: Precigen requested an informal meeting to address the viral shedding approach if the product is approved under a traditional pathway. FDA acknowledged this request and will take into consideration as FDA continue to discuss the appropriate regulatory pathway internally.
3. Discussion of established Pharmacologic Class
- a. Non-replicating adenoviral vector-based immunotherapy

Meeting Discussion:

No discussion during the meeting.

4. Information Requests

- a. IR #31 (Biostatistics) sent on May 21, 2025, pending responses by June 4, 2025
- b. IR #32 (DBSQC) sent on May 28, 2025, pending responses by June 11, 2025
- c. IR #33 (CMC) sent May 29, 2025, pending responses by June 3, 2025 and June 27, 2025 (In-use stability/device compatibility, labeling/shipping validation)
- d. IR #34 (CMC) sent June 2, 2025, pending responses by June 6, 2025
- e. IR #9 (CMC) sent February 27, 2025, pending responses by June 13, 2025 (revalidation report for (b) (4) adventitious agent testing), and
- f. Late Component (CMC), additional long-term stability data by June 27, 2025.

Meeting Discussion:

FDA acknowledged Precigen's responses to IRs #31, 32, 33, and 34, and the review is still ongoing. However, responses from Precigen are still pending for IR #9 dated February 27, 2025, for the revalidation report for (b) (4) adventitious agent testing. Precigen clarified that the revalidation report for (b) (4) adventitious agent testing was submitted along with IR#28 response in Amendment SN0038 submitted on May 30, 2025. After the meeting, FDA confirmed the receipt of this submission.

The CMC Late Component with additional long-term stability data is pending submission by June 27, 2025. FDA reminded Precigen to assess the shelf life per draft ICH Q1 guideline on "*Stability Testing of Drug Substances and Drug Products*" i.e., linear regression analysis with 95% confidence limits for stability-indicating attributes, when they submit the stability data. The determination regarding the adequacy of the stability data to support a commercial shelf life will be made upon review of the information provided in the BLA. FDA also asked to reassess the stability AC using the additional data and provide justification of specifications.

Not listed in the agenda, an IR #35 was sent to Precigen on June 6, 2025, pending a response by June 17, 2025, regarding the DS and DP release specifications.

5. Discussion of Upcoming Advisory Committee Meeting

- a. An Advisory Committee meeting is not planned.

Meeting Discussion:

No discussion during the meeting

6. Risk Management Actions (e.g., REMS, the ability of adverse event reporting and CBER's Sentinel Program to provide sufficient information about product risk)

- a. There is no anticipation of a REMS at this time.

Meeting Discussion:

No discussion during the meeting.

7. Postmarketing Requirements/Postmarketing Commitments

a. We have identified the following PMCs:

- i. Final report for the DP PPQ including (b) (4) additional PPQ runs.
- ii. Final report for the (b) (4) assessment in the DP.
- iii. Reassessment of the acceptance criteria for commercial DP release after manufacturing additional lots.
- iv. PMC to complete the ongoing phase 1/2 study PRGN-2012-201.
- v. PMC to assess viral shedding.

Meeting Discussion:

FDA conveyed the PMCs to Precigen and provided two new additional PMCs:

1. Reassessment of the AC for commercial DS release after manufacturing additional lots (conveyed in CMC IR#15 sent on June 10, 2025)
2. DP (b) (4) study (agreed upon in Amendment 37 dated May 30, 2025)

8. Major Labeling Issues

- a. As we communicated through an IR sent on May 20, 2025 and teleconference held on May 28, 2025, your proposed PI does not include a description of an in-use period and storage conditions, and you did not provide sufficient in-use stability information in your BLA. We will review the additional in-use stability and device compatibility information once it is submitted by June 3, 2025 and June 27, 2025, respectively.

Meeting Discussion:

No discussion during the meeting.

9. Review Plans

- a. Review of the BLA is on-going. We will continue sending IRs as necessary to get clarification on any submitted information.
- b. Communicate Anticipated PMRs: July 16, 2025
- c. Communicate PMCs: July 28, 2025
- d. Start Labeling Negotiations: July 28, 2025
- e. PDUFA Date: August 27, 2025

10. Applicant Questions

Meeting Discussion:

Applicant questions were discussed under Additional Applicant Data (refer to item 2 above). Precigen did not have additional questions.

11. Wrap-up and Action Items

- a. The Late Cycle Meeting Summary will be sent by July 12, 2025

Meeting Discussion:

No discussion during the meeting.

This application has not yet been fully reviewed by the signatory authorities, Division Directors and Review Committee Chair and therefore, this meeting did not address the final regulatory decision for the application.