



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

PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM ADDENDUM

From: Sarada Panchanathan, MD, MS
Medical Officer, Pharmacovigilance Branch 3
(PB3), DPV, OBPV, CBER, FDA

To: Bao Nguyen, PhD
Chair of the Review Committee
Office of Therapeutic Products (OTP)

Through: Kerry Welsh, MD, PhD
Branch Chief, PB3

Meghna Alimchandani, MD
Acting Director DPV
OBPV, CBER, FDA

Subject: Review of Pharmacovigilance Plan

Sponsor: Abeona Therapeutics

Product: Prademagene zamikeracel

Application Type / Number BLA / STN 125807/0.57

Proposed Indication Treatment of wounds associated with recessive dystrophic epidermolysis bullosa (RDEB)

Submission Date: October 28, 2024

Action Due Date: April 29, 2025

1 OBJECTIVE

The purpose of this addendum is to review specific safety issues subsequent to, and not addressed by, the original pharmacovigilance memo for prademagene zamikeracel. Please refer to the original BLA memo for review of the Pharmacovigilance Plan (PVP) under STN 125807/0. A new PVP was not included with the additional documents submitted to BLA 125807/0.57.

A post-marketing requirement (PMR) safety study to assess the potential serious risk of insertional oncogenesis and secondary malignancies was discussed at the Safety Working Group on March 14, 2024 and concurrence was obtained. This addendum reviews the revisions to the proposed protocol for the safety study submitted by Abeona, as well as revisions to the PVP.

Please refer to Appendix 1 for the complete list of materials reviewed for this memorandum addendum.

2 MODIFICATIONS TO PHARMACOVIGILANCE PLAN

The following modifications are noted:

- a) Addition of local immune reaction to the Important Identified Risks and removal of immune reaction from Important Potential Risks
- b) Addition of the required post-marketing safety study Pz-cel-RY-401 to the planned post-marketing activities
- c) Addition of enhanced pharmacovigilance activities:
 - i. expedited reporting of all malignancies, regardless of type or location
 - ii. summary and cumulative analysis of all serious adverse events and malignancies in periodic safety reports

Reviewer comment: During the original BLA review, the sponsor was requested to perform enhanced pharmacovigilance activities for post-treatment malignancies including expedited reporting to FAERS and a summary and analysis in periodic safety reports. However, the sponsor did not add these activities to the PVP. The PVP also did not include information on the postmarket long term follow-up study. The sponsor submitted a revised PVP (version 3) incorporating enhanced pharmacovigilance activities and the postmarket long term follow-up study in an IR response submitted to STN125807/0.64. However, the revised PVP only specified enhanced pharmacovigilance activities for cutaneous malignancies and in the context of the postmarket safety study. It was also noted in the revised PVP that the sponsor added “local immune reactions” as an Important Identified Risk, but did not include a risk characterization or mitigations. The sponsor was requested to specify enhanced pharmacovigilance activities for all spontaneous reports of post-treatment malignancies and for more information on “local immune reactions” as an Important Identified Risk. The sponsor submitted a revised PVP (version 4) to STN125807/0.66. In version 4 of the PVP, the enhanced pharmacovigilance activities included expedited reporting only

for three years following use of prademagene zamikeracel. Given the potential long latency for development of secondary malignancies, three years is not a sufficient amount of time for adequate characterization of this risk. In a response to an IR, a revised PVP (version 5) was submitted to STN 125807/0.68, where it was clarified that expedited reporting will not be terminated at three years. This PVP (version 5) is acceptable.

3 SAFETY-RELATED POST-MARKETING REQUIREMENT (PMR) STUDY

Title: Study Pz-cel-RY-401 A Long-Term Safety Follow-up Registry for Patients Who Received Treatment with Prademagene Zamikeracel for Recessive Dystrophic Epidermolysis Bullosa (RDEB) in the Post-Marketing Setting

Objectives:

1. To evaluate the long-term safety profile of prademagene zamikeracel (pz-cel)
2. To evaluate the wound healing durability of pz-cel
3. To assess the occurrence of all malignancies after treatment with pz-cel, regardless of type or location, in individuals who received pz-cel treatment for RDEB in the post-marketing setting.

Population: Patients who received surgical application of pz-cel for the treatment of RDEB wound sites in the post-marketing setting. Patients treated with other approved products for dystrophic epidermolysis bullosa such as Vyjuvek will be allowed to enroll.

Safety Outcome Endpoints:

1. Number and incidence of new cases of treatment-related malignancies
2. Number and incidence of treatment-emergent SAEs, including systemic and wound-specific SAEs
3. Number and incidence of treatment-related SAEs related to pz-cel, including systemic and wound-specific SAEs
4. Number and incidence of positive replication-competent retrovirus (RCR) testing results required for AEs and SAEs where retroviral infection is a consideration.

Data Collection:

In addition to routine clinic visits, data collected from the electronic data capture system, and patient/caregiver direct reports into a patient-facing portal, the following procedure will be followed to obtain specific data regarding malignancies or retroviral presence:

- 1) HCPs will notify the Sponsor and/or designated safety service provider of any malignancy within 72 hours, and a request for biopsy and whole blood sample will be made. In the event of death from a disease potentially associated with a retrovirus or malignancy within 15 years following product administration, a biopsy sample or pertinent autopsy tissue will be assayed for detection of retroviral presence.
- 2) A Sponsor-designated laboratory will receive all tissues and whole blood samples. Genomic DNA will be isolated from biopsy tissue for testing for

detection of proviral genome sequences. If this is positive, insertion site analysis will be performed for integration frequency and clonal abundance. Whole blood samples will be tested for RCR.

- 3) In addition to malignancy, specific symptoms to monitor that would trigger RCR testing include:
- a. New-onset or unexplained neurological deficits
 - b. Seizures of unknown etiology or increase in frequency or severity of seizures
 - c. Cognitive or behavioral changes not associated with any psychiatric dysfunction

The sponsor proposed the following milestones:

- Final protocol submission: 06/30/2025
- Study completion date: 07/31/2045
- Final study report (FSR) submission: 07/31/2046

Reviewer comment: The initial proposal for this study was reviewed in the Division of Pharmacovigilance memorandum under STN125807/0, including the Sentinel sufficiency assessment, noting this study is a Postmarketing Requirement, and the presentation to the Safety Working Group. The sponsor was not notified of the PMR during the initial BLA review.

In response to an IR dated January 17, 2025 submitted to STN 125807/0.61 on February 7, 2025, the protocol was amended (version 2) to include testing for all malignancies, regardless of type or location. In addition, specific genomic testing for proviral DNA and whole blood RCR assay for adverse events or symptoms suggestive of possible retrovirus-associated disease. Additional symptoms that would trigger RCR testing include new-onset or unexplained neurological deficits, seizures of unknown etiology or increase in frequency or severity of seizures, and cognitive or behavioral changes not associated with any psychiatric dysfunction. These revisions are acceptable.

A PMR notification letter was sent to the Sponsor on February 28, 2025.

4 ANALYSIS OF SPONSOR'S PHARMACOVIGILANCE PLAN (Version 4)

4.1 Important Identified Risks

4.1.1 Risk 1: Wound Infection

The risk of wound infection is innate to the disease process as well as a risk related to the product. The recommendation will be for any patient with a wound infection to be treated per standard of care using topical or systemic antibiotics as determined by bacterial culture and clinical judgment. In addition to routine pharmacovigilance activities and routine communication of safety information and risks, the Sponsor proposes to follow all patients in both the LTFU studies and the post-marketing registry.

4.1.2 Risk 2: Procedural Pain

Procedural pain is associated with both the surgical procedure and wound dressing changes. The recommendation is to manage pain per standard of care. Routine pharmacovigilance activities and communication of safety information and risks will be performed.

4.1.3 Risk 3: Pruritus

Pruritus is commonly seen as the wounds heal and should be managed according to standard of care. Communication of this effect will be including in the prescribing information, instructions for use, and packaging and labels. Routine pharmacovigilance activities will be performed.

4.1.4 Risk 4: Local Immune Reaction

This risk refers to local erythema and spontaneous blistering within the treated area, caused by anti-C7 antibodies (C7 refers to collagen protein 7 which is the corrected gene in the new keratinocytes). Though there have been some patients with documented circulating anti-C7 antibodies, these have resolved spontaneously and have not been associated with systemic signs of immune rejection. The Sponsor recommends evaluation of areas of inflammation with routine biopsy and (b) (4) as well as direct immunofluorescence which is standard for any inflammatory wound in a patient. Immunologic rejection should initially be treated with potent topical steroids or other immune-modulating topical treatments. If systemic immune reaction occurs, there may be a need for immune suppression. The Sponsor proposes monitoring with routine pharmacovigilance activities, evaluation of the risk in ongoing LTFU studies up to 15 years post treatment, and through providing communication of important safety information.

Reviewer Note: This Important Identified Risk is new in the pharmacovigilance plan. The proposed pharmacovigilance activities are acceptable in evaluating this risk.

4.2 Important Potential Risks

4.2.1 Risk 1: Insertional Oncogenesis

Insertional oncogenesis is a recognized class effect of gene therapies. If a malignancy is identified, the recommendation will be made to remove it surgically and collect a sample for isolation of genomic DNA for detection of proviral genome sequences. This will enable determination if the malignancies are related to Zevaskyn or, in the case of squamous cell carcinoma, to the underlying RDEB disease process. In addition to routine pharmacovigilance activities and expedited reporting, as well as analysis in the periodic safety reports, this risk will be further assessed in the PMR described above.

Reviewer Note: Insertional oncogenesis has not been identified in the clinical trials but not all squamous cell carcinoma samples in the clinical studies were tested for proviral DNA and not all patients with squamous cell carcinoma were tested for replication-competent retrovirus. The proposed enhanced pharmacovigilance activities and the PMR are acceptable for evaluation of this risk.

4.2.2 Risk 2: Anemia exacerbation

Routine pharmacovigilance activities, routine evaluation in the ongoing LTFU studies, and communication of this risk in prescribing information will be performed. The recommendation will be to manage anemia according to standard of care.

4.2.3 Risk 3: Postoperative hemorrhage

Routine pharmacovigilance activities, routine evaluation in the ongoing LTFU studies, and communication of this risk in prescribing information will be performed. The recommendation will be to manage postoperative hemorrhage according to standard of care.

4.2.4 Risk 4: Vomiting

Routine pharmacovigilance activities, routine evaluation in the ongoing LTFU studies, and communication of this risk in prescribing information will be performed. The recommendation will be to manage vomiting according to standard of care.

4.2.5 Risk 5: Risk associated with general anesthesia

Zevaskyn will only be administered in select qualified sites to ensure an experienced anesthesiologist will be available to administer general anesthesia.

4.2.6 Risk 6: Risk associated with commercially available drugs for biopsy

A recommendation will be communicated to avoid drugs known to cause irritation, sensitization, or severe skin irritations based on prior medical history.

4.3 Important Missing Information

4.3.1 Missing Information 1: Use in pregnant or breastfeeding women

Routine pharmacovigilance activities will be performed, including evaluation of pregnancy and/or breastfeeding cases. The lack of safety information in this population will be communicated in the prescribing information.

Reviewer comment: The specified pharmacovigilance activities in combination with the PMR patient registry with long term follow up of 15 years, enhanced pharmacovigilance activities (expedited reporting and analysis in periodic safety reports) are acceptable to assess the risks of use of Zevaskyn. The specific potential risks of insertional oncogenesis of Zevaskyn will be evaluated in the PMR described above.

5 DPV ASSESSMENT

This product is the first topical gene therapy with an integrating viral vector. The Sponsor has described that the resulting keratinocytes have stem-cell like properties. There is an unknown potential for insertional oncogenesis in this patient population with an existing elevated risk of aggressive squamous cell carcinoma. For this reason, it is essential to differentiate any malignancies as to whether they arise from the underlying disease process or from treatment with prademagene zamikeracel.

6 DPV RECOMMENDATIONS

Should the prademagene zamikeracel be approved for the indication of treatment of (b) (4) wounds in patients with recessive dystrophic epidermolysis bullosa, the proposed PVP, version 5 dated March 6, 2025 is adequate to monitor post-marketing safety, with the PMR registry study to assess for the serious risk of insertional oncogenesis and secondary malignancies, enhanced pharmacovigilance including expedited reporting and summary/analysis in periodic safety reports for post-treatment secondary malignancies, and routine pharmacovigilance in accordance with 21 CFR 600.80. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon language for the label.

APPENDIX

Table 1: Materials reviewed in support of this addendum

Date	Source	STN	Document(s) Reviewed
Apr 15, 2024	FDA	125807	Pharmacovigilance Review Memo as of CR decision
Jun 18, 2024	FDA	125807	Pharmacovigilance Review Memo Addendum
Oct 28, 2024	Sponsor	125807/0.57	Module 5.2 Tabular listing of Clinical Studies v2
Oct 28, 2024	Sponsor	125807/0.57	Module 5.3.5.4 EB-101-RY-401 Long-Term Safety Follow-up Registry Study Protocol v0.9
Feb 7, 2025	Sponsor	125807/0.61	Module 1.11.3 Response to IR of Jan 17, 2025 Module 5.3.5.4 16.1.1 Study Protocol version 2
Feb 24, 2025	Sponsor	125807/0.64	Module 1.11.3 Response to IR of Feb 11, 2025 Module 1.16 Risk Management Plan version 3
Mar 4, 2025	Sponsor	125807/0.66	Module 1.11.3 Response to IR of Feb 25, 2025 Module 1.16 Risk Management Plan version 4
Mar 6, 2025	Sponsor	125807/0.68	Module 1.16 Risk Management Plan version 5