

I concur with this review memo. A. Wensky. 3/20/2025

I concur with this review memo. A. Shearin. 4/1/2025

FOOD AND DRUG ADMINISTRATION
Center for Biologics Evaluation and Research
Office of Therapeutic Products
Office of Pharmacology/Toxicology
Division of Pharmacology/Toxicology 1
Pharmacology/Toxicology Branch 1

BLA NUMBER:	STN #125807.000.005.024.025.031.057
DATE RECEIVED BY CBER:	September 25, 2023
DATE REVIEW COMPLETED:	April 1, 2025
PRODUCT:	ZEVASKYN (prademagene zamikeracel)
APPLICANT:	Abeona Therapeutics, Inc.
PROPOSED INDICATION:	Recessive dystrophic epidermolysis bullosa (RDEB)
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CLINICAL REVIEWER:	Chinwe Okoro
PROJECT MANAGER:	Hawa Camara

EXECUTIVE SUMMARY:

This memorandum summarizes the review of three human toxicological risk assessments (TRAs) of extractable and leachable (E&L) chemicals associated with ZEVASKYN drug substances (DS) and drug product (DP). The first study concerns the (b) (4) a collection device used in the production of (b) (4) DS and the (b) (4) container-closure system (CCS). The second and third studies concern a (b) (4) used in the production of the (b) (4) [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] to ZEVASKYN. E&L chemicals from the (b) (4) and DP P1 were analyzed using (b) (4)

(b) (4) (b) (4)
 (b) (4) methods per reports provided in the original BLA submission (Submission Tracking Number [STN#] 125807.000). Validated (b) (4) methods were utilized in E&L reports provided in the BLA re-submission (STN#125807.057). Review of these TRAs did not identify any significant safety concerns with use of the (b) (4) (hereafter referred to as (b) (4) CCS (hereafter referred to as 'RVV CCS'), (b) (4) (b) (4) or ZEVASKYN P1.

PHARMACOLOGY/TOXICOLOGY RECOMMENDATION:

Based on the review of human TRAs associated with the (b) (4) RVV CCS, (b) (4) (b) (4) and ZEVASKYN P1, there were no deficiencies identified. These data provide sufficient support for the suitability of the listed materials in the manufacture and storage of ZEVASKYN.

Formulation and Chemistry:

ZEVASKYN consists of (b) (4)

The ZEVASKYN DP consists of one autologous gene-modified cell sheet affixed to one unit of petrolatum gauze (7.5 x 5.5 centimeter [cm]) with titanium ligation clips. Up to 12 ZEVASKYN DPs may be applied topically to debrided RDEB wounds (cell sheet in contact with the wound bed) per patient³. The petrolatum gauze surface of ZEVASKYN is marked with a single, non-absorbable suture to assist qualified medical professionals in placement of the product. ZEVASKYN is a combination product; the petrolatum gauze and titanium clips are classified as medical devices.

Abbreviations:

>	Greater than
µg	Micrograms
(b) (4)	(b) (4)
(b) (4)	(b) (4)
BLA	Biologics License Application
CASRN	Chemical Abstracts Service Registry Number
CCS	Container closure system
cm	Centimeter

¹ Detects volatile organic compounds.

² Detects semi-volatile and non-volatile organic compounds.

³ Affixed with absorbable suture. 240 cm² wound coverage per patient.

(b) (4)	(b) (4)
<i>COL7A1</i>	Human type VII collagen gene
(b) (4)	(b) (4)
(b) (4)	(b) (4)
DP	Drug product
DS	Drug substance
E&L	Extractables and leachables
(b) (4)	(b) (4)
(b) (4)	(b) (4)
HDE	Maximum human daily exposure
(b) (4)	(b) (4)
hrs	Hours
HV	Healthy volunteers
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
(b) (4)	(b) (4)
IPA	Isopropyl alcohol
(b) (4)	(b) (4)
(b) (4)	(b) (4)
LOQ	Limit of Quantitation
LTR	Long terminal repeat
LZRSE-COL7A1	(b) (4)
ml	Milliliter
mm	Millimeter
(b) (4)	(b) (4)
MOS	Margin of safety
(b) (4)	(b) (4)
No.	Number
°C	Degrees Celsius
(b) (4)	(b) (4)
P1	Primary packaging
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
PDE	Permissible human daily exposure
RDEB	Recessive dystrophic epidermolysis bullosa
RVV	Retroviral vector
(b) (4)	(b) (4)
(b) (4)	(b) (4)
STN#	Submission tracking number
TDI	Tolerable daily intake

TI	Tolerable intake
TRA	Toxicological risk assessment
TTC	Toxicological threshold of concern
V	Volume
(b) (4)	(b) (4)
WT	Wild-type

INTRODUCTION:**DS (LZRSE-COL7A1 RVV):**

(b) (4)

DP (ZEVASKYN):

Each ZEVASKYN DP unit is aseptically packaged in a (b) (4) (b) (4) clamshell assembly. The clamshell assembly is (b) (4) (b) (4) (b) (4) within a (b) (4) capacity (b) (4) (b) (4). These three items comprise ZEVASKYN's P1. The applicant provided E&L analysis and human TRA of ZEVASKYN P1 in their original BLA submission and BLA re-submission.

Reviewer comment: All E&L analyses were conducted by (b) (4) and performed according to (b) (4)

NONCLINICAL STUDIES:

(b) (4)

Study Number (No.) ⁵	Study Title	Maximum ZEVASKYN exposure (units/subject)	Report No.	BLA STN#
1	Toxicological Human Risk Assessment from Potential Leachable Impurities in RVV Supernatant following Use of (b) (4) During Manufacture and Storage; September 20, 2023	15	RCD-EXT-000013	125807.000
2	Toxicological Human Risk Assessment from Potential Leachable Impurities in Drug Product EB-101 (WT Drug Product: (b) (4) following Use of Container Closure (device) Materials During Manufacture and Storage; September 20, 2023	15	RCD-EXT-000010	125807.000
3	Toxicological Human Risk Assessment for Potential Leachable Impurities in Drug Product EB-101/PZ (PRADEMAGENE ZAMIKERACEL) packaged for (b) (4) July 12, 2024	12	RCD-EXT-000034	125807.057

Study No. 1:

Analysis of extractables from the (b) (4) and RVV CCS was performed by (b) (4) under Study Nos. 23B0089R-A04 and 23B0089R-A05 using (b) (4)

(RVV CCS) for (b) (4) and (b) (4) analysis of extracts is described in Abeona Therapeutics Study Report No. DEV-000062.

Analysis of leachables present in RVV supernatant was performed by (b) (4) under Study Nos. 23B0089R-A05 and 23B0089R-A07. Leachables were detected in RVV supernatant (b) (4)

(b) (4) respectively. No volatile, semi-volatile, or non-volatile organic compounds were detected in extracts of either material via (b) (4) (b) (4) detected (b) (4) greater than (>) limit of quantification (LOQ) in RVV supernatant extracts of the (b) (4) and RVV CCS, respectively. All metals detected were present at levels below the permissible daily human exposure (PDE) for a parenterally administered product per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline Q3D (R1) Step 5. Risk of harm is further reduced by RVV manufacturing not reflective of exaggerated extraction conditions and absence of direct patient exposure to the RVV.

⁵ Study Nos. 1, 2, and 3 were conducted by: (b) (4)

⁶ Detects metals and inorganic compounds in water extracts only. All E&L (b) (4) analyses were conducted using validated methodology.

(b) (4)

Study No. 2:

Analysis of extractables from the (b) (4) and ZEVASKYN P1 was performed by (b) (4) under Study Nos. 23B0097R-A04, 23B0097R-A05, 23B0097R-A06, and 23B0097R-A07. Extractions were performed using (b) (4)

analysis of extracts is described in Abeona Therapeutics Study Report No. DEV-000060.

Analysis of leachables from (b) (4) or WT DP ± P1 was performed by (b) (4) under Study Nos. 23D0029-A04 and 23D0029R-A09. Leachables from WT (b) (4) or WT DP ± P1 were detected following (b) (4) (b) (4) detected (b) (4) DP (Table 1).

Table 1: Organic leachables detected in (b) (4) of WT DP + P1 via (b) (4)

Chemical Abstracts Service Registry Number (CASRN)	Chemical Name	Quantity Extracted (µg/DP + P1)	Toxicological Threshold of Concern (TTC) ¹⁴	Tolerable Intake (TI) ¹⁵	Maximum Human Daily Exposure (HDE) ¹⁶	Margin of Safety ¹⁷ (MOS)
(b) (4)						

⁹ ZEVASKYN P1 and (b) (4)

¹⁰ Clamshell assembly and (b) (4) bag

¹¹ (b) (4) (b) (4)

¹² Clamshell assembly and (b) (4) bag

¹³ Control for chemical impurities that may be present in human skin prior to ZEVASKYN manufacture.

¹⁴ TTC is defined by ICH M7 (R2) as ‘an acceptable intake for any unstudied chemical that poses a negligible risk of carcinogenicity or other toxic effects.’ The methods upon which TTC is based are generally considered to be very conservative since they involve a simple linear extrapolation from the dose giving a 50% tumor incidence (TD50) to a 1 in 10⁶ incidence, using TD50 data for the most sensitive species and most sensitive site of tumor induction. TTC is a concept that refers to the establishment of a level of exposure for all chemicals, whether or not there are chemical-specific toxicity data, below which there would be no appreciable risk to human health. The concept proposes that a low level of exposure with a negligible risk can be identified for many chemicals, including those of unknown toxicity, based on knowledge of their chemical structures.

¹⁵ TI = Tolerable Daily Intake (TDI); used by the International Program on Chemical Safety to describe exposure limits of chemicals. Level of daily intake of a toxic substance that does not produce an adverse health effect. TIs are based on No-Observed-Adverse-Effect-Levels but are not considered an absolute physiological threshold. Rather, they are based on safety factors that reflect variations in a population.

¹⁶ HDE=(µg extracted/DP)(Maximum of 15 DP units applied/subject).

¹⁷ MOS=TTC/HDE

¹⁸ ICH M7 Guidance for daily limit of a mutagenic compound when administered daily for a duration of ≤ 30 days = 120 µg/day or a total in 30 days of 3600 µg. This criterion was used as the TTC for all mutagenic compounds.

(b) (4) detected (b) (4) > LOQ in the WT DP + P1 extracts. All metals detected in WT DP + P1 water extracts were below the PDE per ICH Q3D (R1) Step 5.

(b) (4) detected (b) (4) organic compounds in the water extract of WT DP + P1 in (b) (4) (b) (4) respectively (Table 2). Of all detected compounds, only (b) (4) (b) (4) fall within the established limit of (b) (4) levels differed between (b) (4)

Table 2: Organic leachables detected in water extract of WT DP + P1 via (b) (4)

CASRN	Chemical Name	Quantity Extracted (µg/DP) Positive ion mode	Quantity extracted (µg/DP) Negative ion mode	TTC (µg/day) ²⁰	TI (µg/day) ²¹	HDE (µg/day) ²²	MOS ²³
(b) (4)							

(b) (4)

²⁰ Unless otherwise indicated

²¹ Unless otherwise indicated

²² HDE=(µg/DP) (b) (4)

²³ MOS=TI/HDE or TTC/HDE, depending on the data available for an extracted compound

²⁴ ICH M7 Guidance for daily limit of mutagenic compound when administered daily for a duration of ≤ 30 days = 120 µg/day or a total of 3600 µg in 30 days. This criterion was used as the TTC for all mutagenic compounds.

(b) (4)

Study No. 3:

Analysis of leachables from (b) (4) (cell sheet) ± (b) (4) and WT DP ± device materials²⁶ was performed by (b) (4) under Study Nos. RCD-EXT-000026, RCD-EXT-000027, and RCD-EXT-000033. Leachables were detected in (b) (4) (b) (4) solvents at (b) (4) for (b) (4) Validated (b) (4) (b) (4) and (b) (4) analysis of extracts is described in Abeona Therapeutics Study Report No. DEV-000063. The human toxicological risk of leachables from WT DP ± device materials is described in Study Report No. RCD-EXT-000034.

(b) (4) detected no unique peaks in the (b) (4) in the (b) (4) (b) (4) of WT DP + device materials, respectively. (b) (4) detected (b) (4) (b) (4) of WT DP and WT DP + device materials > LOQ, respectively. All metals detected were present at levels acceptable for elemental impurities per ICH Q3D (R1) Step 5.

(b) (4) demonstrated (b) (4) of WT DP + device materials (Table 3). These are the only biologically relevant impurities detected, as (b) (4) and (b) (4) solvents are incompatible with ZEVASKYN manufacturing. All organic leachables were evaluated as potential mutagens with a maximum PDE of (b) (4) All leachable organic compounds detected were present at levels far below this PDE (as a single unit, and as a cumulative total of (b) (4)

Table 8: Organic leachables detected in (b) (4) WT DP + device materials via (b) (4)

²⁵ Per the applicant's response to P/T IR No. 2, 'existing data for these compounds suggest that they would be beneficial; non-pharmacologic effects have not been cited in the literature. These compounds are assumed to have no adverse effects in humans.' The applicant also notes that these impurities were likely present in ZEVASKYN utilized in the BLA-enabling clinical trial (VIITAL) given a conserved manufacturing process.

²⁶ Device materials = P1 (b) (4)

(b) (4)

²⁹ Additional information regarding 100% IPA and (b) (4) leachables is provided in TRA Study Report No. RCD-EXT-000034.

(b) (4)

Conclusion of Risk Assessment:

The toxicological risk assessment is acceptable and supports the use of 12 ZEVASKYN units per subject under the proposed conditions and duration of clinical use.

³⁰ CASRN unavailable for these compounds

³¹ HDE=(μ g/DP extracted)(maximum 12 DPs per subject)

³² MOS= PDE/HDE