Summary Basis for Regulatory Action

Date:	April 28, 2025
From:	Bao-Ngoc Nguyen, PhD, Review Committee Chair Office of Cell Therapy and Human Tissues (OCTHT) Office of Therapeutic Products (OTP)
BLA STN:	BLA 125807/0
Applicant:	Abeona Therapeutics Inc.
Submission Receipt Date:	Resubmission: October 28, 2024 Original submission: September 25, 2023
PDUFA* Action Due Date:	April 29, 2025
Proper Name:	prademagene zamikeracel
Proprietary Name:	ZEVASKYN
Indication:	Treatment of wounds in adult and pediatric patients with recessive dystrophic epidermolysis bullosa (RDEB).

***** PDUFA = Prescription Drug User Fee Act

Recommended Action: The Review Committee recommends approval of this product.

Director, Office Of Therapeutic Products

Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (Product Office and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Bao-Ngoc Nguyen, PhD, OTP/OCTHT/DCT2 Joshua Kufera, PhD, OTP/OGT/DGT2 Mo Liu, PhD, OTP/OGT/DGT2 Ileana Marrero-Berrios, PhD, OTP/OCTHT/DCT2 Carolina Panico, MD, PhD, OTP/OCTHT/DCT2 Brianna Davis, CBER/OCBQ/DBSQC Alicia Howard, PhD, CBER/OCBQ/DBSQC Marie Anderson, MS, PhD, CBER/OCBQ/DBSQC Sang Hyuk Lee, PhD, CBER/OCBQ/DBSQC Ou Ma, PhD, CBER/OCBQ/DMPQ Iryna Zubkova, PhD, CBER/OCBQ/DMPQ
Clinical • Clinical (OCE/DCEGM) • Postmarketing safety Pharmacovigilance review (OBPV/DE) • BIMO	Chinwe Okoro, MD Sarada Panchanathan, MD Haecin Chun, MS, CBER/OCBQ/DIS
Statistical • Clinical data (OBPV/DB)	Tanbin Rahman, PhD
Non-clinical/Pharmacology/Toxicology Pharmacology/Toxicology (Product Office)	Amanda Szucsik, DVM, MS
Clinical Pharmacology	Yang Chang, PhD
Labeling • Promotional (OCBQ/APLB) • Regulatory (CBER/OTP/OCE)	Oluchi Elekwachi, PharmD, MPH (PNR) Teresa Vu, PharmD Afsah Amin, MD, MPH
Other Review(s) not captured above categories, for example: Consults for Extractables/Leachables	Andrey Sarafanov, PhD

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I. Introduction

Abeona Therapeutics Inc. (the Applicant) submitted a Biologics License Application (BLA), STN 125807, for licensure of prademagene zamikeracel, with the proprietary name ZEVASKYN. ZEVASKYN is an autologous cell sheet-based gene therapy in which ex vivo expanded autologous keratinocytes are transduced with the LZRSE-Col7A1 RVV, a replication-incompetent retroviral vector (RVV) carrying a transgene encoding human collagen type VII alpha 1 chain (COL7A1).

A complete response letter (CRL) was issued for the original BLA submission on April 16, 2024, due to Chemistry, Manufacturing, and Controls (CMC) concerns, including observations made during the pre-license inspection, that were inadequately addressed. These CMC concerns included an inadequate sterility assurance plan for the final drug product (DP), insufficient information to support the validation of the (b) (4) (b) (4) methods used to release the LZRSE-Col7A1 RVV, deficient validation of the (b) (4) method used for LZRSE-Col7A1 RVV release, lack of DP identity assay for the final DP, inadequate validation of visual assays used for product lot release, inadequate assessment of an incoming raw material, insufficient validation of (b) (4) tests performed on incoming reagents, inadequate validation of (b) (4) and deficient container closure integrity testing performed for the (b) (4) and DP container closures. In response to the FDA concerns, the applicant implemented adequate quality and compliance improvements at their product manufacturing facility to address the CRL deficiencies. All CRL items were satisfactorily addressed in the October 28, 2024, resubmission.

This document summarizes the basis of approval of ZEVASKYN for treatment of wounds in recessive dystrophic epidermolysis bullosa (RDEB). Substantial evidence of effectiveness is established based on data from a single adequate and well-controlled clinical study VIITAL (EB-101-CL-301), and confirmatory evidence from an open-label, proof of concept study. EB-101-CL-301 was a multicenter, open-label, randomized, intra-subject-controlled, 24-week study of ZEVASKYN that evaluated wound healing and pain reduction in subjects with genetically confirmed (*COL7A1* variant) RDEB aged 6 years and older (mean age: 22.5 years). EB-101-CL-301 comparing ZEVASKYN treated wounds than control wounds from baseline to week 24, demonstrated both a higher proportion of ZEVASKYN treated wounds achieved >50% healing wounds and a higher pain reduction compared to control. The submitted evidence considered together supports a favorable benefit-risk determination for the use of ZEVASKYN in RDEB across the entire age range. The final indication is supported by evidence in the studied population of subjects 6 years and older and extrapolation of findings from the studied population to patients younger than 6 years old with RDEB.

The safety evaluation was based on 18 subjects with RDEB aged 6 to 45 years treated with ZEVASKYN across 3 clinical trials (Phase 1/2a trial: 14563/31095 EB-101, Phase 3 trial VIITAL: EB-101-CL-301 and long-term follow-up (LTFU) study: EB-101-LT-001). There was no observable difference in risks from ZEVASKYN treatment in the pediatric and adult population. And although the safety database was relatively small, (n=18 with 85 ZEVASKYN treated wounds), it was acceptable considering the seriousness and rarity of the condition, the substantial evidence of effectiveness, and the observed safety

profile of ZEVASYKN. Per FDA's request, the Applicant agreed to conduct a long-term safety study as a Post Marketing Requirement (PMR) in a registry of ZEVASYKN treated patients to address concerns of insertional oncogenesis associated with ZEVASYKN integrating viral component.

The review team recommends approval of this BLA with one (1) PMR related to collecting long-term safety data in a registry of ZEVASYKN and two (2) CMC Post Marketing Commitments (PMCs) related to the acceptance criteria of the LZRSE-Col7A1 RVV and (b) (4) studies.

1. Background

Epidermolysis bullosa (EB) is a heterogeneous group of inherited mechanobullous cutaneous disorders caused by mutations in genes that encode structural proteins in the skin. There are 3 major subtypes: simplex EB (EBS), junctional EB (JEB) and dystrophic EB (DEB). DEB is divided into two major types, an autosomal dominant, milder type (DDEB) and an autosomal recessive, severe type (RDEB). Both forms are caused by pathogenic mutations in the *COL7A1* gene, which encodes type VII collagen (Col7), a structural component of anchoring fibrils (AF) which hold the epidermis and dermis together and are essential for maintaining the integrity of the skin.

Clinical manifestations of skin fragility in DEB include blistering with minimal trauma that heals with milia and scarring. Blistering and erosions affecting the whole body may be present in the neonatal period. Diagnosis of DEB can be established by clinical presentation supported by molecular genetic testing showing pathogenic mutation(s) in the *COL7A1* gene. Direct immunofluorescence (IF) and/or electron microscopy on skin biopsy can establish the diagnosis in the absence of genetic testing.

Before May 2023, RDEB treatment was limited to supportive therapy: wound care, avoidance of trauma, and screening for squamous cell carcinoma (SCC) beginning in the second decade of life. In May 2023, VYJUVEK, a novel HSV-1 vector-based gene therapy product was approved for treatment of wounds in subjects 6 months of age and older with DEB. In December 2023, FILSUVEZ (birch triterpenes), a botanical topical gel was approved for the treatment of wounds associated with dystrophic and junctional EB in adult and pediatric subjects six months of age and older.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
IND submission	May 12, 2008
Orphan Drug designation granted	May 24, 2017
Rare Pediatric Disease designation granted	May 25, 2017
Breakthrough Therapy designation granted	August 16, 2017
Regenerative Medicine Advanced Therapy designation granted	January 26, 2018
Pre-BLA meeting	August 25, 2023
BLA 125807/0 submission	September 25, 2023
BLA filed	November 21, 2023
Mid-Cycle communication	January 25, 2024
Late-Cycle meeting	March 21, 2024
Complete Response Letter	April 16, 2024
Re-submission after Complete Response	October 28, 2024
Action Due Date	April 29, 2025

2. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

This BLA includes an adequate description of the manufacturing process of ZEVASKYN. The CMC review team concludes that the manufacturing material, process, and controls can yield ZEVASKYN with consistent quality attributes. Thus, the CMC review team recommends approval with two (2) PMCs as outlined below.

Product Description

ZEVASKYN is a device/biologic combination product intended for treatment of RDEB. ZEVASKYN consists of autologous cells obtained from a skin biopsy that have been genetically modified via *ex vivo* transduction with the LZRSE-Col7A1 RVV. Transgene integration into the host cell genome allows for constitutive COL7A1 expression by transduced cells. Three Col7 alpha protein chains trimerize to form a collagen VII fibril, facilitating wound healing in patient who receive the product. ZEVASKYN is manufactured starting with an autologous skin biopsy. The autologous cells are transduced with the LZRSE-Col7A1 RVV and then grown into 41 cm² sheets. Each sheet is secured to sterile petrolatum gauze using sterile ligation clips, where the gauze, petroleum jelly, and ligation clips are considered the device constituents of the combination product. Up to 16 ZEVASKYN sheets may be manufactured per autologous skin biopsy, of which up to 12 may be topically administered. ZEVASKYN sheets are topically applied to the wound beds using absorbable sutures and covered with additional wound dressings and gauze.

Manufacturing Summary

To manufacture ZEVASKYN, cells from an autologous skin biopsy sample from patients with RDEB are obtained. These cells are then transduced (b) (4) with the LZRSE-Col7A1 RVV, which is manufactured at Abeona Therapeutics, to generate cells that are gene-modified to express Col7 protein trimer. After transduction, cells are (b) (4)

The assembly of ZEVASKYN involves

(b) (4) attaching them to a petrolatum gauze with titanium ligation clips. ZEVASKYN is then visually inspected for holes or tears before being packaged in a custom-made clamshell container, which is placed inside a sterile (b) (4) bag containing excipient media. Channels within the clamshell container allow for the excipient media to move through the clamshell container to maintain the viability of cells in the ZEVASKYN product. The (b) (4) bag acts as the sterile barrier packaging. After release of the ZEVASKYN product, the DP is hand delivered to the appropriate health care setting for administration to the skin wounds of patients with RDEB.

The LZRSE-Col7A1 RVV is a replication-incompetent (b) (4) (b) (4) vector which is (b) (4) and carries a COL7A1 transgene under control of the (b) (4) promoter. The LZRSE-Col7A1 RVV is manufactured at Abeona Therapeutics using (b) (4)

The manufacturing control strategy includes: (1) procedures to establish and maintain chain of identity and chain of custody (COI/COC), (2) raw material and reagent qualification programs, (3) in-process monitoring and control testing, (4) validation of manufacturing process, and (5) release testing.

ZEVASKYN is manufactured in a closed system from raw materials and reagents that meet acceptable quality standards. Human- and animal-derived raw materials are appropriately controlled to ensure absence of microbial and viral contaminants. Samples for lot release testing are collected at the following stages during manufacture to accommodate the testing limitations on the assembled DP and its short shelf-life: samples for potency testing are taken (b) (4) mycoplasma testing sample is taken on the day of final product assembly; final product endotoxin and (b) (4) test samples are taken on the day of assembly from P1 packaging (b) (4) bag containing the clamshell tray with the final DP); final product rapid sterility testing and (b) (4) sterility testing is taken from P1 packaging (b) (4) after assembly (with results available (b) (4) after release); visual testing and visual contour testing are conducted on a quality control (QC) DP sample prior to release as well as again on each DP (i.e., cell sheet) at the clinical site prior to administration onto subjects. All assays are adequately validated and the manufacturing process produces product of acceptable quality.

Risk mitigating measures include aseptic operations throughout the DP manufacturing process under an ISO (b) (4) biosafety cabinet with ISO (b) (4) background. Adequate operator

training and use of personal protective equipment, use of sterile single use materials, validated cleaning procedures, and environmental monitoring are being performed.

Comparability

During the BLA review, comparability of (b) (4) different LZRSE-Col7A1 RVV manufacturing processes was assessed. The process was first changed in 2020 during the Phase 3 clinical study. Notable changes were made to the facility (from (b) (4) (b) (4) (b) (4) to Abeona Therapeutics), (b) (4) (b) (4) (b) (4) step. Although statistical equivalence in pre- and post-change critical quality attributes (CQAs) was not established, the change resulted in process improvements, no detriment to DP quality or clinical efficacy, and improved clinical safety. The process was next changed in 2022 after the Phase 3 clinical study and before process performance qualification. Notable changes were made to the (b) (4) strategy, as well as the establishment of a (b) (4) All changes were justified or supported by characterization data which reflected minimal differences in vector CQAs. Clinical data was considered appropriate to be pooled from DP manufactured using all (b) (4) LZRSE-Col7A1 RVV manufacturing processes to support the BLA.

Process Validation

The applicant validated the manufacturing process at the Abeona Therapeutics commercial manufacturing site, 6555 Carnegie Ave, Cleveland, OH 44103, using (b) (4) process performance qualification (PPQ) batches. The process validation was supported by reliable and consistent manufacture of ZEVASKYN batches which met established release acceptance criteria. Stability of the final product was established using PPQ and clinical batches.

Manufacturing Risks, Potential Safety Concerns, and Management

There is a theoretical risk of insertional oncogenesis after treatment with ZEVASKYN, which may arise from LZRSE-Col7A1 RVV integration into the host cell genome. There was no evidence of insertional oncogenesis or preference for specific integration sites in limited *in vitro* studies. In clinical trials of ZEVASKYN, no cases of insertional oncogenesis have been reported, but there is a limited safety database. There is a PMR for a follow-up registry to monitor for insertional oncogenesis.

Transmission of infectious diseases is controlled by reagents and control of the manufacturing process.

ZEVASKYN is an autologous product. As such, product mix-up of autologous lots would result in risks, including infection and graft versus host disease. The COI/COC ensures that the patient receives their autologous lot. COI/COC is established at the point of skin biopsy collection, checkpoints are indicated throughout the manufacturing process, and patient identifiers are confirmed prior to administration with identifiers printed on the product label. The COI/COC is maintained throughout with digital and readable identifiers present on all labels.

The risk mitigation measures include segregation of activities during the manufacturing process, use of closed manufacturing processes (when possible), performing all aseptic

operations in a (b) (4) in a (b) (4) clean room, operator training and use of personal protective equipment, use of sterile single use materials, validated cleaning procedures, and environmental monitoring.

Stability and Shelf Life

Stability data supports a (b) (4) shelf-life at (b) (4) for the LZRSE-Col7A1 RVV. Real-time stability studies determined that ZEVASKYN is stable for 84 hours at room temperature (15-25°C).

CMC PMCs

The CMC team recommends two (2) PMCs. The rationale for the PMCs is described below, and the PMC agreements are detailed in section 9c of this document:

1. There was limited data available for LZRSE-Col7A1 RVV lots manufactured using the intended commercial manufacturing process and tested with the commercial lot release methods at the time of release. Since only (b) (4) LZRSE-Col7A1 RVV lots were used to set the commercial release acceptance criteria (AC), final commercial AC are subject to a PMC to re-evaluate the AC when data from (b) (4) total commercial lots have been manufactured.

2. The (b) (4) validation studies included a (b) (4) study for the media and buffers made in-house. However, (b) (4) study provided did not include an appropriate (b) (4) positive control (b) (4) as the study result showed that the (b) (4) under the testing conditions used.
(b) (4)

b. Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for the ZEVASKYN DP were found to be adequate for their intended use.

The final product commercial release specifications are shown in Table 2.

Table 2. Final Product Commercial Release Specifications

Attribute	Test Parameter	Method	Final Acceptance Criteria
Potency-Related	(b) (4)		
Potency-Related			
Potency-Related			
Potency-Related			
-	Cell Viability	(b) (4)	(b) (4)
Safety	Endotoxin	(b) (4)	(b) (4)
Safety	(b) (4)		
Safety	(b) (4)	(b) (4)	(b) (4)
Safety	Mycoplasma	(b) (4)	No mycoplasma detected
Safety	(b) (4)	(b) (4)	(b) (4)
Safety	DP Rapid Sterility using excipient media from packaging – results available (b) (4) (b) (4) after release	(b) (4)	No Growth
Safety	Sterility using excipient media from packaging – results available (b) (4) after release	(b) (4)	No growth
Identity	Identity by (b) (4)	(b) (4)	(b) (4)
Identity	Vector Detection	(b) (4)	Detected
Appearance	(b) (4)	(b) (4)	(b) (4)
Appearance	Visual Inspection	Assess for uniformity, holes, contaminants	Uniform intact sheet; Confluent, no holes, no contamination

c. CBER Lot Release

An exemption has been granted from CBER Lot Release testing, including no requirement for submission of product samples to CBER. The basis for this decision is that ZEVASKYN is an autologous product, as such each lot will treat a single patient. Failure of a single lot will have minimal potential impact on public health.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of prademagene zamikeracel are listed in Table 3. The activities performed and inspectional histories are noted in the table below.

Table 3. Manufacturing Facilities for Prademagene Zamikeracel (ZEVASKYN)

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification /Results
Abeona Therapeutics Inc. 6555 Carnegie Ave Cleveland, OH 44103 DS and DP Manufacturing	3008334517	080315442	PLI	CBER/DMPQ February 2024 VAI
(b) (4)	(b) (4)	(b) (4)	Waiver	OII (b) (4) VAI
(b) (4)	(b) (4)	(b) (4)	Waiver	OII (b) (4) NAI
(b) (4)	(b) (4)	(b) (4)	Waiver	OII (b) (4) NAI

Abbreviations: DS, drug substance; DP, drug product; NAI, No Action Indicated; VAI, Voluntary Action Indicated; PLI, Pre-license Inspection; OII, Office of Inspections and Investigations

CBER conducted the Abeona Therapeutics facility PLI from February 19 – March 1, 2024, and a Form FDA 483 list of observations was issued. All inspectional issues have been resolved, and the inspection was classified as VAI.

Inspection of the (b) (4) facility was waived. This facility was last inspected in (b) (4) by OII, and a Form FDA 483 list of observations was issued. All inspectional issues have been resolved, and the inspection was classified as VAI.

Inspection of the (b) (4) facility was waived. This facility was last inspected in (b) (4) by OII, and no Form FDA 483 was issued; the inspection was classified as NAI.

Inspection of the (b) (4) facility was waived. This facility was last inspected in (b) (4) by OII, and no Form FDA 483 was issued; the inspection was classified as NAI.

e. Container/Closure System

Each ZEVASKYN cell sheet is enclosed within a clear, sterile protective case (clamshell) inside an aseptically sealed opaque polyvinyl chloride (PVC) pouch filled with nutrition media. A sterile dispensing pin is added to the pouch to allow for the filling and withdrawal of media samples. DP primary packaging components are summarized in the table below:

Table 4. Prademagene Zamikeracel (ZEVASKYN) DP Container Closure System

Component	Description and Material	Manufacturer	Sterility Control	DMF or Standard Applied
Clamshell - Lid	(b) (4) clear lid with (b) (4) coating.	(b) (4)	Sterilized by (b) (4)	(b) (4)
Clamshell - Tray	(b) (4) clear tray with (b) (4) coating		Sterilized by (b) (4)	(b) (4)
(b) (4) Bag	(b) (4)		Sterilized by (b) (4) by vendor	Pre-amendment approval*
Luer Lock Dispensing Pin			Sterilized by vendor	510(k) # (b) (4) and (b) (4)

*A pre-amendment device was in commercial distribution before May 28, 1976, the enactment date of the Medical Device Regulation Act or Medical Device Amendments of 1976.
Abbreviations: (b) (4)

Container closure integrity testing (CCIT) was performed by (b) (4) in the (b) (4) (b) (4) facility using the (b) (4) test method; all acceptance criteria were met.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

II. Nonclinical Pharmacology/Toxicology

In vitro pharmacology studies demonstrated that human keratinocytes obtained from healthy donors and donors with RDEB transduced with the RVV and vectors similar to the RVV expressed Col7 protein. In vivo pharmacology studies were conducted with a nonclinical product representative of ZEVASKYN comprised of vector (the RVV, or vectors similar to the RVV)-transduced human keratinocytes (cells alone or cells grown into sheets) affixed to a block of human acellular dermal matrix or (b) (4) dermis. Nonclinical products were then implanted into excisional wounds generated in (b) (4) (b) (4) mice. RVV-transduced keratinocytes remained localized within explanted nonclinical products, and RVV-mediated expression of Col7 was detected for up to 12-months post-implantation. Histological evaluation of explanted nonclinical products revealed normal epidermal differentiation, localization, and assembly of Col7 protein trimer.

In the toxicology and biodistribution (BD) study, nonclinical products representative of ZEVASKYN comprised of human acellular dermal matrix and RVV-transduced human keratinocytes (cells alone) were implanted into excisional wounds generated in (b) (4) (b) (4) mice for 4- or 8-weeks. COL7A1 transgene DNA was detected in explanted nonclinical products at both sacrifice time points. RVV level

was below the limit of detection in all other tissues assessed. There were no gross or histopathological findings in any tissue assessed, including the explanted nonclinical products.

Integration site analysis (ISA) was performed on RDEB keratinocytes (n=6 donors) transduced with RVV. ISA did not indicate clonality at 6-days post-keratinocyte transduction. There was no evidence of RVV preference to integrate near genes associated with malignancy.

Developmental and reproductive toxicity (DART) studies of ZEVASKYN were not conducted due to the BD of RVV remaining confined to representative nonclinical products. Carcinogenicity and tumorigenicity studies of ZEVASKYN were not conducted due to absence of neoplastic features on histology, low risk of insertional oncogenesis, and frequent SCC screening recommended for all subjects with RDEB.

3. Clinical Pharmacology

ZEVASKYN consists of a patient's own cells that have been gene-modified through LZRSE-Col7A1 RVV transduction to express the *COL7A1* gene to produce Col7 protein. The gene-modified cells are formed into cellular sheets for topical application onto wounds.

The major clinical pharmacology findings from Phase 1/2a study (14563/31095 EB-101), Phase 3 study (VIITAL: EB-101-CL-301) and LTFU study (EB-101-LT-001) are summarized in the following sections:

a. Pharmacokinetics (PK) Assessment

There were no pharmacokinetic assessments performed.

b. Pharmacodynamics (PD) Assessment

In the Phase 1/2a study (n=7), the NC2 domain of Col7 protein and anchoring fibrils were detected in biopsies from 6 treated subjects at 3 months and in 5 treated subjects at 6 months. At 1-year post-treatment, 3 subjects tested positive for either NC2 or anchoring fibrils. At 2 years post-treatment, 2 out of 3 subjects with available biopsies were positive for either NC2 or anchoring fibrils.

c. Immunogenicity Assessment

In the Phase 1/2a study, circulating anti-Col7 antibodies were detected in two out of seven subjects, which resolved without intervention by 1 year after treatment. Tissue-bound antibodies beyond trace staining were detected in four subjects which resolved in three subjects at 1 year follow-up.

In the Phase 3 study, all tested subject biopsies were negative for Col7 immune complexes at screening, three months, and six months. No systemic immunologic responses were reported during the study.

Because of the small sample size, there is limited data to determine the effect of anti-Col7 antibodies on the pharmacodynamics, safety, and efficacy.

d. Replication Competent Retrovirus (RCR) testing

All subjects tested negative for RCR across the 3 clinical trials.

4. Clinical and Statistical Assessment
a. Clinical Program

The Phase 3 study (VIITAL: EB-101-CL-301, Study 1) provided the primary evidence of ZEVASKYN's safety and effectiveness. Study 1 was a multicenter (U.S.-based), randomized, intra-subject-controlled clinical trial of ZEVASKYN in subjects with genetically confirmed RDEB (with mutations in the *COL7A1* gene) aged 6 years and older. For each subject, suitable wound pairs were identified for randomization and treatment. The maximum wound pairs in any one subject were 5. Each pair of wounds was assigned either treatment with ZEVASKYN or with standard of care (SOC) which are wound dressings categorized under the following: foams, hydrogels, alginates, hydrofibers, modified absorbent pads and contact layer, biosynthetic cellulose and lipidcolloid dressings. Each SOC assigned wounds were treated with topical antibiotic as well.

The co-primary endpoints were wound healing and pain reduction at Week 24. Randomized wound pairs were compared for ≥50% healing from baseline at Week 24 and pain reduction was assessed by the mean difference in scores of the Wong Baker FACES Scale between randomized wound pairs at Week 24.

The primary efficacy analysis was based on a comparison of intra-subject wound healing between the 43 wounds randomized to ZEVASKYN treatment, versus the 43 wounds randomized to SOC. In addition, the two secondary efficacy endpoints were the proportion of randomized wound pairs with complete wound healing (defined as re-epithelialization with no drainage or erosion and presence of only minor crusting) at Week 12 and Week 24 compared to baseline as determined by direct assessment of the principal investigator using digital photograph.

Clinical Efficacy Findings:

In Study 1, 11 subjects were randomized, and all completed the study. There were four males and seven females aged 6 – 40 years with clinical manifestations and genetic confirmation of RDEB. Table 5 summarizes the primary efficacy analysis. At week 24, a higher proportion of ZEVASKYN treated wounds (81.4%) achieved ≥50% healing from baseline compared to control wounds (16.3%; $p<0.0001$). In addition, mean pain reduction from baseline to Week 24 was higher in ZEVASKYN treated wounds (3.07) than in control wounds (0.90; $p=0.0002$) with a mean (95% confidence interval) pairwise difference across wound pairs (n=42) of 2.14 (1.07, 3.21). Furthermore, a higher proportion of ZEVASKYN treated wounds (Week 12: 14.0%, $p=0.0316$; Week 24: 16.3%, $p=0.0160$) completely healed at Weeks 12 and 24 from baseline compared with control wounds (0% at both time points).

Table 5: Efficacy Results for VIITAL Study (N=86 wounds)

Efficacy Endpoint	ZEVASKYN (N=43 wounds)	Control (N=43 wounds)	P value
Proportion of randomized wound pairs healed ≥50% from baseline at Month 6[a] n (%)	35 (81%)	7 (16%)	<0.0001
Mean pain reduction from baseline at Month 6[b] Mean (SD)	-3.07 (3.19)	-0.90 (2.73)	0.0002
Proportion of randomized wound pairs completely healed from baseline at Month 3 n (%)	6 (14%)	0 (0%)	0.0316
Proportion of randomized wound pairs completely healed from baseline at Month 6[a] n (%)	7 (16%)	0 (0%)	0.0160

Complete wound healing is defined as re-epithelialization with no drainage or erosion and presence of only minor crusting.
[a] The proportion of wounds achieving success criteria at Month 6 must have been confirmed at least 2 weeks later.
[b] One wound (n=42) was excluded from the control group due to missing baseline value.
Abbreviations: N, total number of observations; SD, Standard deviation; %, percentage

Study 2: Phase 1/2a Study

Study 2 was a single-center, open-label, single-arm, proof-of-concept study to evaluate the efficacy and safety of ZEVASKYN in the treatment of subjects aged 13 years and older with RDEB. This study consisted of 3 parts: 52-week study primary endpoint assessment duration, a 5-year long-term yearly in-clinic monitoring and a 10-year annual phone/questionnaire follow-up. Study 2 enrolled 7 subjects, comprising 5 males and 2 females aged 18 – 45 years of age. Forty-eight (48) wounds (38 chronic, 4 induced and 6 control chronic wounds) were treated and analyzed. Out of the 48 wounds, 44 wounds (38 chronic and 6 chronic control wounds) were assessed for efficacy based on the proportion of wounds with ≥50% healing at end of follow up. A higher percentage of healing were noted in the ZEVASKYN treated wounds compared to the unmatched control wounds at 3 months (94.7% versus 33.3%), 6 months (94.7% vs 0%), and 12 months (68.4% vs 33.3%) post treatment.

The efficacy and PD findings in Study 2 (also see Clinical Pharmacology Section), although exploratory in nature, are supportive of the observed treatment effect demonstrated in Study 1 and are used as confirmatory evidence.

Efficacy Conclusions

ZEVASKYN resulted in greater healing and in greater pain reduction when applied to wounds of subjects with RDEB as compared to wounds treated with standard-of-care therapy in the pivotal study. These results are both clinically and statistically significant and provide the primary evidence of effectiveness for the product. ZEVASKYN activity was evident in biopsies of treated wound by detection of the NC2 domain of the Col7 protein and anchoring fibrils. The Phase 1/2a study provides supportive evidence of the treatment effect and serves as confirmatory evidence.

a. Based on the current understanding of this monogenic disease (RDEB) for treatment of the target population with ZEVASKYN, the following considerations were used to support the use of pediatric extrapolation in review of this BLA.The pathophysiology and molecular mechanism of RDEB as a single-gene disorder is well-defined and expected to be similar across all ages. Similarly, we expect that RDEB-associated wounds observed in children

will respond to treatment with ZEVASKYN in a similar way to those observed in adults with RDEB.

b. The product dose is based on wound surface area as it is topically administered. Dosing is independent of age, weight, or body surface area. Therefore, no differences in dosing are expected across different ages.
c. Efficacy assessments were the same in the adult treated population as the pediatric population. There are no different considerations in assessing efficacy in younger children (younger than 6 years old) as compared to older children and adults.
d. No serious safety signals were identified in dosed subjects (children over 6 years old and adults) that warrants additional safety measures in younger children.

Therefore, it is appropriate to extrapolate the efficacy and safety in dosed subjects in the trials to subjects of all ages with the disease.

b. Pediatrics

ZEVASKYN has orphan drug designation for the treatment dystrophic EB and is exempt from Pediatric Research Equity Act (PREA) pediatric study requirements. However, the safety and effectiveness of ZEVASKYN have been established in pediatric patients and the product is labeled for the treatment of adult and pediatric patients with RDEB.

c. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

BIMO inspection assignments were issued for the Applicant and two clinical investigator study sites that participated in the conduct of Protocol EB-101-CL-301 (VIITAL). The inspections did not reveal significant issues that impact the data submitted in this original Biologics License Application (BLA).

5. Safety and Pharmacovigilance

The risks of ZEVASKYN are characterized based on a safety database of 18 subjects aged 6 to 45 year in both the Phase 3 and Phase 1/2a studies. There were 2 deaths in the Phase 1/2a study which were ruled as unrelated to ZEVASKYN. There were a total of 16 serious adverse events (SAEs) in 6 subjects. None of the SAEs was considered related to ZEVASKYN. There were no study discontinuations due to adverse reactions. The most observed adverse events included wound infection, pruritus, immune local reaction and procedural pain (Table 6). Due to the small number of subjects enrolled in the studies for ZEVASKYN, and the frequency of single AEs, a 10% incidence rate was chosen to accurately capture commonly occurring AEs with EB-101.

Table 6: Adverse Reactions (Incidence ≥10%) Following Treatment With ZEVASKYN

Adverse Reactions	Subjects n (%), (n=18)
Any adverse reaction	10 (55.6)
Local reaction	3 (16.7)
Procedural pain	7 (38.9)
Pruritus	2 (11.1)
Wound infection	3 (16.7)

The combined safety analysis of these studies shows that ZEVASKYN treatment in this population is well tolerated with a favorable benefit/risk profile.

The Applicant's pharmacovigilance plan (PVP) includes the important identified risks of wound infection, procedural pain, pruritus, and local immune reaction. Important potential risks include insertional oncogenesis, anemia exacerbation, postoperative hemorrhage, vomiting, risk associated with general anesthesia, and risks associated with commercially available drugs used for biopsy. Areas of missing information include safety in pregnant or breastfeeding women. The proposed PVP is adequate.

The Applicant will conduct routine pharmacovigilance with adverse event reporting in accordance with 21 CFR 600.80 for all adverse events. Enhanced pharmacovigilance for secondary malignancies, regardless of seriousness or relatedness to the product, will be performed by submission of expedited (15-day) reports for spontaneous reports, and inclusion of a summary and analysis in periodic safety reports.

In addition, to evaluate the potential serious risk of secondary malignancy and insertional oncogenesis, the Applicant will conduct a post-marketing observational study as a PMR with 15 years of follow-up. This prospective, observational study will characterize the risk of secondary malignancies and long-term safety of prademagene zamikeracel . This study is in alignment with FDA Guidance Long Term Follow-up After Administration of Human Gene Therapy Products (January 2020) available at https://www.fda.gov/media/113768/download. The available safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS).

6. Labeling

The proposed proprietary name, ZEVASKYN, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on February 27, 2024, and was found acceptable. CBER communicated the acceptability of the proprietary name to the Applicant on December 27, 2024.

APLB reviewed the proposed prescribing information and package and container labels on March 25, 2025, and found them acceptable from a comprehension, readability, and promotional perspective.

The Office of Clinical Evaluation (OCE) labeling review team, together with the relevant discipline review teams, reviewed and revised the proposed prescribing information to ensure that it meets regulatory/statutory requirements, is consistent with current labeling practice, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the product, and provides clear and concise information for the healthcare providers. With the agreed revisions, the prescribing information is acceptable.

7. Advisory Committee Meeting

This application was not referred to an Advisory Committee meeting because the review of information submitted in the application did not raise concerns or controversial issues that required discussion at an Advisory Committee.

8. Other Relevant Regulatory Issues

ZEVASKYN received orphan drug, rare pediatric disease, Regenerative Medicine Advanced Therapy, and Breakthrough Therapy designations for the treatment of

dystrophic EB. The BLA received priority review, and the Applicant received a Rare Pediatric Disease Priority Review Voucher.

9. Recommendations and Benefit/Risk Assessment

A. Recommended Regulatory Action

Substantial evidence of effectiveness for ZEVASKYN in the treatment of wounds in RDEB is established based on evidence from a single adequate and well-controlled Phase 3 study and confirmatory evidence from a Phase 1/2 study. The demonstrated clinical benefit of ZEVASKYN on healing and pain reduction in wounds caused by RDEB outweigh the observed risks of procedural pain, wound infection, and pruritus (seen in a minority of treated subjects) and those can be mitigated through labeling and post-marketing routine pharmacovigilance activities. The potential serious risk of insertional oncogenesis (given the chemical nature and mechanism of the product) will be further evaluated through a long-term, post-marketing observational study as a PMR.

The review team recommends approval of ZEVASKYN for the indication of treatment of wounds in adults and pediatric patients with RDEB.

B. Benefit/Risk Assessment

The overall benefit/risk assessment of ZEVASKYN is favorable based on comprehensive review of the efficacy and safety data contained in the BLA.

The Phase 3 pivotal study demonstrated that more ZEVASKYN treated wounds achieved healing after 24 weeks of follow up compared to control wounds and that pain was reduced in subjects whose wounds were treated with ZEVASKYN compared to those treated with SOC (control). The Phase 1/2 study provides confirmatory evidence substantiating the observed treatment effects shown in Study 1.

There were no serious risks related to the product that were observed in the ZEVASKYN clinical program and the observed adverse events were related to procedural pain, wound infection, and pruritus. No cases of cancer were observed. The potential of insertional oncogenesis associated with ZEVASKYN'S integrating viral component will be evaluated through a safety PMR to conduct a long-term safety study in ZEVASKYN treated patients.

C. Recommendation for Postmarketing Activities

The Applicant will be required to conduct the following postmarketing safety study as a PMR:

1. A postmarketing, prospective, observational study to assess and characterize the risk of secondary malignancies after treatment with prademagene zamikeracel and to assess long-term safety of prademagene zamikeracel (Study Pz-cel-RY-401). The study will include 100 patients with recessive dystrophic epidermolysis bullosa who receive prademagene zamikeracel, and each enrolled patient will be followed for 15 years after product administration.

   Final Protocol Submission: June 30, 2025

Study Completion Date: July 31, 2045

Final Report Date: July 31, 2046

The Applicant agreed to the following two (2) CMC PMCs:

1. Abeona Therapeutics commits to re-evaluate the acceptance criteria (AC) for release testing of the LZRSE-Col7A1 retroviral vector based on manufacturing experience when data from (b) (4) total commercial batches are available and revise the AC, if appropriate. AC will be re-evaluated for the (b) (4) release tests. The re-evaluation report will be submitted as a "PMC Submission-Final Study Report."

   Final Report submission: June 30, 2027

2. Abeona Therapeutics commits to providing the results of an updated (b) (4) (b) (4) study in a Final Study Report Submission by October 29, 2025.

   Study Protocol Submission: July 29, 2025

   Final Study Report Submission: October 29, 2025