Medical Policy

Subject:	Autologous Cell Sheet-Based Gene Therapy for Treatment of Dystrophic Epidermolysis Bullosa		
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Description/Scope

This document addresses the use of autologous cell sheet-based gene therapy for the treatment of wounds caused by recessive dystrophic epidermolysis bullosa (RDEB), for example prademagene zamikeracel (Zevaskyn™ [formerly pz-cel and EB-101], Abeona Therapeutics, Inc., Cleveland, OH).

Note: Please be aware that use of bioengineered autologous skin-derived products (for example, SkinTE®, MyOwn Skin™) are not addressed in this document. See the following related documents for additional information:

- CG-SURG-127 Products for Wound Healing and Soft Tissue Grafting: Medically Necessary Uses
- SURG.00011 Products for Wound Healing and Soft Tissue Grafting: Investigational

Position Statement

Investigational and Not Medically Necessary:

Use of autologous cell sheet-based gene therapy for wounds caused by recessive dystrophic epidermolysis bullosa (RDEB), for example, prademagene zamikeracel is considered **investigational and not medically necessary**.

Rationale

Prademagene zamikeracel is an ex vivo autologous gene-corrected epidermal skin graft product designed to correct a defect in the COL7A1 gene for individuals with RDEB. Mutation of COL7A1 prevents individuals with recessive RDEB from producing Type VII collagen. As a result, this often-fatal condition is characterized by severe blisters and non-healing wounds, especially on sites with a high probability of sheering or friction. Prademagene zamikeracel was granted Regenerative Medicine Advanced Therapy, Breakthrough Therapy, Orphan Drug, Priority Review and Rare Pediatric Disease designations by the U.S. Food and Drug Administration (FDA). On April 29, 2025, the FDA approved the therapeutic use of prademagene zamikeracel as an autologous cell sheet-based gene therapy indicated for the treatment of wounds with RDEB, in both adults and children (FDA Product Information [PI Label], 2025).

In 2016, Siprashvili and colleagues evaluated the safety and efficacy of prademagene zamikeracel in individuals with RDEB. This single-center, phase 1 clinical trial (NCT01263379) enrolled 4 individuals diagnosed with severe RDEB and wounds measuring at least 100 cm^2 that were suitable for grafting. Autologous keratinocytes were isolated from two 8 mm biopsy samples and were transduced with retrovirus carrying full-length human COL7A1. These were then assembled into epidermal sheet grafts. Type VII collagen gene-corrected grafts (approximately 35 cm^2) were transplanted onto 6 wounds in each of the 4 enrolled individuals (a total of 24 grafts). The primary safety outcomes were recombination competent retrovirus, cancer, and autoimmune reactions. Molecular correction was assessed as type VII collagen expression measured by immunofluorescence and immunoelectron microscopy.

Wound healing was assessed using serial photographs taken at 3, 6, and 12 months after grafting. The 4 participants (mean age, 23 years [range, 18-32 years]) were all born male with an estimated affected body surface area with recessive RDEB ranging from 4% to 30%. All 24 grafts were well tolerated without serious adverse events. Type VII collagen expression at the dermal-epidermal junction was demonstrated on the graft sites in 9 of 10 biopsy samples (90%) at 3 months, in 8 of 12 samples (66%) at 6 months, and in 5 of 12 samples (42%) at 12 months, including correct type VII collagen localization to anchoring fibrils. Wounds with recombinant type VII collagen graft sites displayed 75% or greater healing at 3 months (21 intact graft sites of 24 wound sites; 87%), 6 months (16/24; 67%), and 12 months (12/24; 50%) compared with baseline wound sites. The authors concluded that, while there was wound healing in some type VII collagen gene-corrected grafts, the response was variable among participants and among grafted sites with declining healing over 1 year. They recommended further investigation, in particular with respect to graft durability.

In 2019, Eichstadt and colleagues published additional results from NCT01263379 evaluating 2-year efficacy and safety outcomes of prademagene zamikeracel in 7 individuals with recessive RDEB, including the 4 individuals for whom 1-year outcomes were reported by Siprashvili as described above. As in the pilot study, the gene-corrected autologous epidermal sheets were grown to 35 cm^2. Grafts were transplanted onto 6 wound sites in each of the 7 adult participants (a total of 42 grafts). The mean age of the cohort was just under 29 years (range 18-45). Graft recipients were followed for 2 to 5 years. No serious graft-related adverse events were reported during this time. Wound healing of 50% or greater (measured via Investigator Global Assessment) was present in 95% (36 of 38) of treated wounds versus 0% (0 of 6) of untreated control wounds at 6 months ($p<0.0001$). At year 1, 68% (26 of 38) of treated wounds had 50% or greater healing compared with 17% (1 of 6) of control wounds ($p=0.025$). At year 2, 71% (27 of 38) of treated wounds had 50% or greater healing compared with 17% (1 of 6) of control wounds ($p=0.019$). Sustained expression of corrected type VII collagen persisted up to 2 years after treatment in 2 participants. Wounds with 50% or greater healing demonstrated improvement in reported pain and itchiness. Wounds that were very large (> 100 cm^2) and/or very old (16 years or older) were less likely to demonstrate successful molecular correction. Wounds in areas difficult to protect from shearing demonstrated less ability to heal. All 7 participants reported satisfaction with the treatment and expressed interest in undergoing additional therapy.

In 2022, So and colleagues published results of continued follow-up from NCT01263379. The cohort of 7 adult participants continued to be followed for a mean of 5.9 years (range 4-8 years). At year 5, 70% (21/30) of treated sites demonstrated ≥ 50% wound healing compared to baseline. No sites with ≥ 50% wound healing were painful or pruritic, compared to 67% (6/9) of sites with < 50% wound healing ($p<0.001$) at year 5. Grafts continued to be well-tolerated, and no serious adverse events related to treatment were reported. No persistent systemic autoimmunity against type VII collagen or replication-competent retrovirus infections were identified, and no participants developed squamous cell carcinomas related to treatment during long-term follow-up. Measurement of expression of full-length collagen type VII within grafts was not performed beyond year 2. The authors concluded that prademagene zamikeracel "appears safe and efficacious, and produces long-term improvements in wound healing, pain, and itch for RDEB patients." Further investigation in the setting of a randomized clinical trial is warranted.

In 2020, a phase 3 randomized trial, VIITAL trial, commenced and enrolled participants 6 years of age and up (n=11) with follow-up through 24 weeks (NCT04227106). Participants were qualified for inclusion if the following study criteria were met:

- Age 6 years or older;
- Positive expression of the non-collagenous region 1 of the type VII collagen protein (NC1+) in the skin;
- Two confirmed recessive DEB type VII collagen mutations with recessive inheritance patterns (or confirmation that parents don't have any evidence of dominant disease);
- At least 40 cm^2 areas of chronically wounded area on the trunk and/or extremities suitable for prademagene zamikeracel graft application;
- Able to undergo adequate anesthesia during graft application;
- At least two matched, eligible wound sites (one pair);
    - Wound sites must:
        - Have an area $\geq$ 20 cm^2,
        - Present for $\geq$ 6 months, and
        - Stage 2 wound;

Clinical trial study participants were also required to verify absence of the following exclusion criteria:

- The presence active severe infection or immune compromise (e.g., human immunodeficiency virus [HIV] or hepatitis B or hepatitis C)
- Evidence of immune response to type VII collagen by indirect immunofluorescence (IIF);
- Current evidence or a history of squamous cell carcinoma (SCC) in the area targeted for graft application;
- Hypersensitivity to vancomycin or amikacin;
- Receipt of chemical or biological study product for the specific treatment of recessive DEB in the past 3 months.

The VIITAL trial (NCT04227106) reached primary completion in 2022 with results reported to ClinicalTrials.gov and the FDA PI Label (2025). The results have not yet been published. The data reported show that the study enrolled 11 individuals (86 wounds [43 treated wounds; 43 control wounds]) with a median age of 21 and an age range of 6 to 40 years. The pediatric population in this study consisted of 2 participants, ages 6 and 16. The study was conducted at 2 independent academic medical centers. The first primary outcome of this study was to evaluate wound healing, specifically focusing on the percentage of RDEB wound sites achieving at least 50% healing from the baseline in wounds treated with prademagene zamikeracel compared to those receiving standard care. Investigators assessed wound healing 24 weeks after treatment. Out of 43 prademagene zamikeracel treated wounds, 35 (81%) experienced over 50% healing. In contrast, only 7 (16%) of the 43 wounds treated with standard care showed more than 50% healing ($p<0.0001$). Another primary outcome of this study was an assessment of how pain decreased during wound dressing changes. This was measured by comparing the average difference in scores on the Wong-Baker FACES scale between wounds that received the treatment and those managed with standard care. Pain reduction was evaluated by comparing the level of pain felt 24 weeks after treatment to the initial pain levels before treatment began. The Wong-Baker FACES scale ranges from 0 to 10, with higher scores indicating more pain, as reported by participants. The study reported that pain during dressing changes for treated wounds fell by an average of 3.07 (standard deviation [SD] 3.19), whereas for wounds treated with standard care, the reduction was only 0.9 (SD 2.73) ($p=0.0002$). Some secondary outcomes showed significant improvement in the wounds treated with the proportion completely healed from baseline to Month 3 (6 vs. 0; $p=0.032$) and the proportion completely healed at Month 6 (7 vs. 0; $p=0.016$). The median number of sheets administered was 6 (range 3-6). The most common adverse reactions (over 5% of participants) were procedural pain (n=3) and pruritis (n=1). Serious adverse events were experienced by 2 of the 11 participants. These included 3 wound infections, 1 occurrence of squamous cell skin cancer, and 1 toe amputation. These results have not yet been published in a peer-reviewed journal and are predominantly limited to outcomes reported up to 24 weeks after treatment. The investigators report

an intention to monitor outcomes annually for up to 15 years and the label indicates lifelong monitoring for malignancies is warranted. FDA approval was based on the pivotal phase 3 VIITAL trial.

Warnings, Precautions, Dosage and Administration,

Warnings and precautions from the FDA PI Label (2025) include the following:

- Retroviral vector-mediated insertional oncogenesis may occur after treatment with prademagene zamikeracel; lifelong monitoring of graft recipients for the development of malignancies is recommended
- Transmission of infectious agents may occur because prademagene zamikeracel is manufactured using human-and bovine-derived reagents prademagene zamikeracel the risk cannot be completely eliminated; despite testing, (FDA PI Label, 2025)

Dosage and administration guidance from the FDA PI Label (2025) include the following:

- The recommended dose is based on the surface area of the wound(s); one sheet of prademagene zamikeracel covers an area of 41.25 cm^2
- Up to 12 prademagene zamikeracel sheets may be manufactured from an individual's biopsies for potential use

Therapeutic application of prademagene zamikeracel begins with harvesting grafts from 2, 8mm punch biopsy sites from healthy, non-blistered areas on affected individuals. Local anesthesia is typically administered. The biopsied skin cells are genetically corrected then expanded for grafting back onto the individual's wound sites. This process spans a period of 3 to 4 weeks. Once the sheets are ready for application, the individual undergoes an operation under general anesthesia which typically lasts between 5 to 7 hours. Graft recipients remain in the hospital for about 1 week to receive supportive care and monitoring for signs of complications.

In May of 2023, the FDA approved the in vivo *topical* gene-based therapy beremagene geperpavec (Vyjuvek®, Krystal Biotech, Inc.). Bermagene geperpavec is formulated with a modified herpes virus. It is applied as a topical gel to directly treat wounds in individuals 6 months of age and older with dystrophic epidermolysis bullosa (DEB) with mutations in the COL7A1 gene. This treatment does not require any surgical procedures. Beremagene geperpavec has wider application than prademagene zamikeracel, with treatment indications including both the recessive and dominant forms of DEB. Beremagene geperpavec is typically applied in an outpatient setting or at home on a weekly basis (FDA PI Label, 2023). Beremagene geperpavec was approved based on results from a double-blind intrapatient randomized placebo-controlled trial that enrolled 31 individuals. At 6 months, 67% of treated wounds achieved complete healing (primary outcome), compared to 22% of placebo wounds (p=0.002). The DEB genotype of the enrolled population was 97% RDEB (n=30) and 3% dominant DEB (n=1). No serious, treatment-related events were reported. The most common adverse events were pruritis, chills and squamous-cell carcinoma of the skin, each of which occurred at a rate of 10% (n=3, each) (Guide, 2022).

Summary

The long-term clinical benefit of gene-corrected epidermal skin graft products as a treatment for RDEB is still under investigation. Although early results are encouraging in limited number of patients, the durable effectiveness

of this treatment has not yet been demonstrated outside of a research setting. Additionally, the safety profile and sustained efficacy compared to less invasive gene-based therapy treatments (for example, topical Vyjuvek) warrants consideration and investigation.

Background/Overview

Recessive dystrophic epidermolysis bullosa (RDEB) is an 'ultra-rare' (3.5–20.4 per million), severe, inherited blistering skin disease caused by the absence of a protein known as type VII collagen. It is potentially fatal as a result of wound complications. There is no approved curative treatment for RDEB; only supportive care is currently possible through the prevention of new blisters along with wound care.

Prademagene zamikeracel uses a retroviral vector to integrate collagen type VII alpha 1 chain (COL7A1) into the dividing target cell genome for long-term gene expression. To begin the therapy, each graft is harvested from 2 8mm biopsy sites from affected individuals and genetically corrected then expanded for grafting back onto the individual's wound sites.

In May of 2023, the FDA approved a topical gene therapy (Vyjuvek) formulated with a modified herpes virus for the treatment of wounds in individuals 6 months of age and older with dystrophic epidermolysis bullosa (DEB) with mutation(s) in the COL7A1 gene. In December of the same year, the FDA approved another topical therapy (Filsuvez), a botanical drug product containing birch triterpenes for the treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis in individuals 6 months of age or older.

Definitions

Autologous cell therapy (ACT): A medical treatment involving the transplantation of various types of cells harvested from the individual and then returned to them in a unique manner. This treatment may involve one or several types of cells and has been proposed for a wide variety of conditions.

Regenerative therapy: A cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products that intends to modify, treat, reverse, or cure a disease or condition by contributing, inducing or promoting tissue healing. Regenerative therapies purport to promote the growth and division of repair cells or mediate the inflammatory process associated with an injury or disease, or produce a regenerative effect via their direct incorporation into injured tissue and adjacent tissue.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
For the following procedure codes, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

17999	Unlisted procedure, skin, mucous membrane and subcutaneous tissue [when specified as application of prademagene zamikeracel, genetically engineered autologous cell therapy]

HCPCS

C9399	Unclassified drugs or biologicals [when specified as prademagene zamikeracel]
J3590	Unclassified biologics [when specified as prademagene zamikeracel]

ICD-10 Procedure

XHR0XGA	Replacement of head and neck skin with prademagene zamikeracel, genetically engineered autologous cell therapy, external approach, New Technology Group 10
XHR1XGA	Replacement of chest skin with prademagene zamikeracel, genetically engineered autologous cell therapy, external approach, New Technology Group 10
XHR2XGA	Replacement of abdomen skin with prademagene zamikeracel, genetically engineered autologous cell therapy, external approach, New Technology Group 10
XHR3XGA	Replacement of back skin with prademagene zamikeracel, genetically engineered autologous cell therapy, external approach, New Technology Group 10
XHR4XGA	Replacement of right upper extremity skin with prademagene zamikeracel, genetically engineered autologous cell therapy, external approach, New Technology Group 10
XHR5XGA	Replacement of left upper extremity skin prademagene zamikeracel, genetically engineered autologous cell therapy, external approach, New Technology Group 10
XHR6XGA	Replacement of right lower extremity skin with prademagene zamikeracel, genetically engineered autologous cell therapy, external approach, New Technology Group 10
XHR7XGA	Replacement of left lower extremity skin with prademagene zamikeracel, genetically engineered autologous cell therapy, external approach, New Technology Group 10

ICD-10 Diagnosis

	All diagnoses, including but not limited to
Q81.2	Epidermolysis bullosa dystrophica

References

Peer Reviewed Publications:

1. Eichstadt S, Barriga M, Ponakala A, et al. Phase 1/2a clinical trial of gene-corrected autologous cell therapy for recessive dystrophic epidermolysis bullosa. JCI Insight. 2019; 4(19):e130554.
2. Guide SV, Gonzalez ME, Bağcı IS, et al. Trial of beremagene geperpavec (B-VEC) for dystrophic epidermolysis bullosa. N Engl J Med. 2022; 387(24):2211-2219.
3. Siprashvili Z, Nguyen NT, Gorell ES, et al. Safety and wound outcomes following genetically corrected autologous epidermal grafts in patients with recessive dystrophic epidermolysis bullosa. JAMA. 2016; 316(17):1808-1817.
4. So JY, Nazaroff J, Iwummadu CV, et al. Long-term safety and efficacy of gene-corrected autologous keratinocyte grafts for recessive dystrophic epidermolysis bullosa. Orphanet J Rare Dis. 2022; 17(1):377.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Abeona Therapeutics, Inc. Phase 3, Open-label Clinical Trial of EB-101 for the Treatment of Recessive Dystrophic Epidermolysis Bullosa (RDEB) (VIITAL Trial; NCT04227106). Updated December 05, 2022. Available at: https://clinicaltrials.gov/study/NCT04227106. Accessed on April 29, 2025.
2. Filsuvez Product Information Label (Chiesi USA, Inc. Cary, NC.) December 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/215064s000lbl.pdf. Accessed on January 23, 2024.
3. Vyjuvek Approval Summary (Krystal Biotech, Inc., Pittsburg, PA). No: BL 125774/4. May 19, 2023. Available at: https://www.fda.gov/media/168356/download?attachment. Accessed on April 29, 2025.
4. Vyjuvek Product Information Label (Krystal Biotech, Inc., Pittsburg, PA). May 19, 2023. Available at: https://www.fda.gov/vaccines-blood-biologics/vyjuvek. Accessed on April 29, 2025.
5. Zevaskyn Product Information Label (Abeona Therapeutic, Inc., Cleveland, Oh). April 30, 2025. Available at: https://d1io3yog0oux5.cloudfront.net/_97c62242a52d17e584a3147d26ed2790/abeonatherapeutics/files/ZEVASKYN_Final_Label_30Apr2025.pdf. Accessed on May 13, 2025.

Websites for Additional Information

1. American Academy of Dermatology Association. Epidermolysis Bullosa: Overview. Available at: https://www.aad.org/public/diseases/a-z/epidermolysis-bullosa-overview#:~:text=Dystrophic%20epidermolysis%20bullosa%20causes%20blistering,also%20develop%20fatal%20skin%20cancers. Accessed on April 29, 2025.
2. National Institute of Arthritis and Musculoskeletal and Skin Disease. Epidermolysis Bullosa. Last Reviewed: September 2023. Available at: https://www.niams.nih.gov/health-topics/epidermolysis-bullosa. Accessed on April 29, 2025.

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Zevaskyn

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
New	05/08/2025	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development.
Preliminary Discussion	02/15/2024	MPTAC pre-FDA approval review.