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Gene Therapies for Treatment of Wounds in Dystrophic Epidermolysis Bullosa

Table of Contents
Coverage
Policy Guidelines
Description
Rationale
Coding
References
Policy History

Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of care developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses

as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated, and coverage is not required for non-formulary drugs.

Coverage

Beremagene geperpavec-svdt (Vyjuvek™)

Beremagene geperpavec-svdt (Vyjuvek™) **may be considered medically necessary** for adult and pediatric individuals if they meet criteria 1 through 2:

1. Diagnosis of dystrophic epidermolysis bullosa confirmed by:
   a. Documented mutation(s) in the *COL7A1* gene.
   b. Presence of clinical manifestations of dystrophic epidermolysis bullosa including, but not limited to, chronic and recurring wounds of the skin, blistering of skin, and blistering, ulcerations, and scarring of visceral mucosal tissues.
2. No active infection, active squamous cell carcinoma, or history of squamous cell carcinoma in the targeted wound(s).

Beremagene geperpavec-svdt (Vyjuvek™) **is considered experimental, investigational and/or unproven** for all other non-Food and Drug Administration approved indications.

Prademagene zamikeracel (Zevaskyn™)

Prademagene zamikeracel (Zevaskyn™) **may be considered medically necessary** for the treatment of wounds in adult and pediatric individuals diagnosed with recessive dystrophic epidermolysis bullosa (RDEB) conditions when the following criteria are met.

1. The individual must have wounds associated with recessive dystrophic epidermolysis bullosa (RDEB);
2. **AND ALL** the following:
   a. Documented biallelic pathogenic mutations in the collagen type VII alpha 1 chain (*COL7A1*) gene;
   b. Positive expression of the non-collagenous region 1 of the type 7 collagen protein (NC1+) in the skin;
   c. Presence of at least one chronic wound (e.g., stage 2 wounds that have an area ≥ 20 cm^2) and have been present for at least 3 months;
   d. Presence of clinical manifestations of RDEB, such as extensive skin blistering, skin erosions, or scarring.

Prademagene zamikeracel (Zevaskyn™) **is considered experimental, investigational and/or unproven** for all other non-Food and Drug Administration approved indications.

Policy Guidelines

Beremagene geperpavec-svdt

Recommended Dose

Per the FDA-Label, beremagene geperpavec-svdt should be applied once weekly by a healthcare professional. It may not be possible to apply beremagene geperpavec-svdt to all the wounds at each treatment visit. Beremagene geperpavec-svdt should be applied to wounds until they are closed before selecting new wounds, and previously treated wounds that re-open should be prioritized over new wounds.

PG1. Dosing Recommendations

Age Range	Maximum Weekly Dose (plaque forming units)	Maximum Weekly Volume (mL)*
< 3 years old	2×10^9	1
≥ 3 years old	4×10^9	2

* Maximum weekly volume is the volume after mixing beremagene geperpavec-svdt biological suspension with excipient gel.

Prademagene zamikeracel

Recommended Dose

Per the FDA-label, prademagene zamikeracel is for autologous topical application on wounds only.

- The recommended dose of prademagene zamikeracel 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 twelve prademagene zamikeracel sheets may be manufactured from the patient biopsies and supplied for potential use.

Description

Dystrophic Epidermolysis Bullosa

Dystrophic epidermolysis bullosa is a rare and clinically and genetically heterogeneous skin fragility disorder characterized by blistering of the skin and mucosal membranes that heal with scarring. The onset of symptoms is usually at birth or in early childhood. There may be associated complications, including malnutrition, anemia, infection, and skin cancer. Death may occur prematurely due to multiple causes, including infection, progression of disease, organ failure, and malignancy. (1)

Dystrophic epidermolysis bullosa is caused by variant in the *COL7A1* gene, encoding the alpha-1 chain of type VII collagen. Collagen VII is the main structural constituent of the anchoring fibrils located below the lamina densa of the epidermal basement membrane zone, which hold the epidermis and dermis together and is essential for maintaining the integrity of the skin. It can be inherited in an autosomal dominant or recessive fashion. (2-4) Recessive dystrophic epidermolysis bullosa is more severe than dominant disease variants; however, there is a considerable phenotypic overlap among all types. More than 600 distinct mutations in

the *COL7A1* gene have been identified in dystrophic epidermolysis bullosa. Although a few mutations are recurrent in some populations due to the founder effect, most families carry unique mutations. (5)

The 2020 consensus classification (1) recognizes four major subtypes and several rare, dominant or recessive subtypes of dystrophic epidermolysis bullosa.

1. Localized dominant dystrophic epidermolysis bullosa
2. Intermediate dominant dystrophic epidermolysis bullosa (previously known as generalized dominant dystrophic epidermolysis bullosa)
3. Intermediate recessive dystrophic epidermolysis bullosa (previously known as recessive dystrophic epidermolysis bullosa generalized intermediate, non-Hallopeau-Siemens recessive dystrophic epidermolysis bullosa)
4. Severe recessive dystrophic epidermolysis bullosa (previously recessive dystrophic epidermolysis bullosa generalized severe, Hallopeau-Siemens recessive dystrophic epidermolysis bullosa)

Based on the National Epidermolysis Bullosa Registry in the U.S., the incidence of epidermolysis bullosa was 19.57 per million live births and prevalence of 11.07 per million population over the period from 1986 to 2002. The numbers for recessive dystrophic epidermolysis bullosa was 3.05 per million live births and 1.35 per million population, respectively. (6)

Prior to the Food and Drug Administration (FDA) approval of gene therapies for dystrophic epidermolysis bullosa, there were no FDA-approved treatments for dystrophic epidermolysis bullosa. Disease management was supportive including wound care, pain management, control of infection, nutritional support, and prevention and treatment of complications. FDA previously approved a Humanitarian Devices Exemption for the product, Composite Cultured Skin to be used as a wound dressing in patients with mitten hand deformity due to recessive dystrophic epidermolysis bullosa as an adjunct to standard autograft procedures [i.e., skin grafts and flaps for covering wounds and donor sites created after the surgical release of hand contractions (i.e., “mitten” hand deformities)].

Regulatory Status

In May 2023, beremagene geperpavec-svdt (Vyjuvek; Krystal Biotech) was approved by the FDA for the treatment of wounds in patients 6 months of age and older with dystrophic epidermolysis bullosa with mutation(s) in the *collagen type VII alpha 1 chain (COL7A1)* gene.

In September 2025, the FDA approved a label update for Vyjuvek that expands the Vyjuvek eligible patient population to include dystrophic epidermolysis bullosa (DEB) patients from birth. (10)

In April 2025, prademagene zamikeracel (Zevaskyn™; Abeona Therapeutics) was approved by the U.S. FDA for the treatment of wounds in adult and pediatric patients with recessive dystrophic epidermolysis bullosa.

Rationale

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Gene Therapy for Treatment of Wounds in Dystrophic Epidermolysis Bullosa

Clinical Context and Therapy Purpose

The purpose of gene therapy in individuals with dystrophic epidermolysis bullosa is to provide a treatment option that is an improvement on existing therapies. Prior to the availability of gene therapies, there were no U. S. Food and Drug Administration (FDA)-approved treatments. Disease management was largely supportive including wound care, pain management, control of infection, nutritional support, and prevention and treatment of complications.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population(s) of interest are individuals with dystrophic epidermolysis bullosa *COL7A1* gene.

Interventions

The therapies being considered are beremagene geperpavec-svdt and prademagene zamikeracel.

Beremagene geperpavec-svdt is a live, replication defective herpes-simplex virus type 1 (HSV-1) based vector that has been genetically modified to express the human type VII collagen (COL7) protein. Upon topical application to the wounds, beremagene geperpavec-svdt can transduce both keratinocytes and fibroblasts. Following entry of beremagene geperpavec-svdt into the cells, the vector genome is deposited in the nucleus. Once in the nucleus, transcription of the encoded human *COL7A1* is initiated. The resulting transcripts allow for production and secretion of COL7 by the cell in its mature form. These COL7 molecules arrange themselves into long, thin bundles that form anchoring fibrils. The anchoring fibrils hold the epidermis and dermis together and are essential for maintaining the integrity of the skin. As beremagene geperpavec-svdt is nonintegrating (i.e., its genetic material remains physically separate from the host cell chromosome), it is not anticipated to carry the potential risk of insertional mutagenesis to trigger oncogenesis.

Prademagene zamikeracel is composed of autologous cells isolated from skin punch biopsies of patients with mutations in the *COL7A1* gene and which have been transduced ex vivo with a replication-incompetent retroviral vector containing the full-length *COL7A1* gene. Upon transduction, the *COL7A1* transgene integrates into the host cell genome, resulting in durable expression and formation of anchoring fibrils. Up to twelve sheets may be manufactured from the patient biopsies and supplied for potential use.

Treatment with prademagene zamikeracel is a complex procedure and may require the travel for the biopsy and surgery and stay in the hospital post-procedure for 5-10 days. Moreover, the procedure for general anesthesia is complicated due to the need for extra precautions for fragile skin, difficult airways, difficulty securing intravenous (IV) lines and severe patient anxiety. The number of treatment cycles required per patient depends on patient age, body size, and wound locations. As per the manufacturer, assuming an average affected body surface area of 920 cm^2, and a maximum treated area of 495 cm^2 per administration, the likely maximum potential treatment cycles for adult patients would be two. For pediatric patients who are smaller in size, the maximum potential treatment cycles would likely be one.

Comparators

The following therapies are currently being used to make decisions about dystrophic epidermolysis bullosa: disease management is supportive and includes wound care, pain management, control of infection, nutritional support, and prevention and treatment of complications.

Outcomes

The general outcomes of interest are symptoms, change in disease status, quality of life, treatment-related mortality and treatment-related morbidity. The primary endpoints of interest for trials of wound healing consistent with guidance from the Food and Drug Administration (FDA) for the industry in developing products for the treatment of chronic cutaneous ulcer and burn wounds are as follows: (7)

- Incidence of complete wound closure.
- Time to complete wound closure (reflecting accelerated wound closure).

- Incidence of complete wound closure following surgical wound closure.
- Pain control.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Beremagene geperpavec-svdt

The clinical development program for beremagene geperpavec-svdt is summarized in Table 1. The pivotal phase 3 randomized, double-blinded clinical trial (GEM-3) was the basis for FDA approval of beremagene geperpavec-svdt and is reviewed in detail.

Table 1. Summary of the Clinical Development Program for Beremagene Geperpavec-svdt

Study	Study KB103-001 (GEM-1)	Study B-VEC-03 (GEM-3)	Study B-VEC-EX-02
NCT Number	NCT03536143	NCT04491604	NCT04917874
Phase	1	3	3
Study Population	Individuals 2 years of age or older with genetically confirmed recessive form of dystrophic epidermolysis bullosa	Individuals 6 months of age or older with genetically confirmed dystrophic epidermolysis bullosa	Individuals 2 months of age or older with genetically confirmed dystrophic epidermolysis bullosa
Status	Completed and published (8)	Completed and published (9)	Completed and published (10)
Study Dates	2018-2019	2020-2021	2021-2023
Design	RCT; placebo controlled[a]	DBRCT; placebo-controlled[a]	Open-label single group assignment
Sample Size	9	31	45
Follow-Up	12 weeks	26 weeks	112 weeks

DBRCT: double-blind randomized controlled study; NCT: national clinical trial; RCT: randomized controlled trial.

[a] Each participant serves as his/her own control by contributing a primary size-matched wound pair to be randomized to receive weekly topical application of either gene therapy or the placebo (excipient gel).

Pivotal Randomized Trial

Study characteristics, baseline patient characteristics and results are summarized in Table 2 to 4, respectively. The pivotal GEM-3 study was a 26-week, randomized, double-blind, intra-subject placebo-controlled trial in which 2 comparable wounds in each participant were selected and randomized to receive either topical application of beremagene geperpavec-svdt gel or the placebo (excipient gel) weekly for 26 weeks. The placebo gel and the beremagene geperpavec-svdt gel had the same viscosity and were similar in appearance. The principal investigator at each site was the sole individual who assessed each subject's primary wound pair at all timepoints for primary and secondary endpoints assessment. The principal investigators were blinded for the entire duration of the study. The primary end point was complete wound healing of treated as compared to untreated wounds at 6 months. Efficacy was established on the basis of improved wound healing defined as the difference in the proportion of complete (100%) wound closure at 24 weeks confirmed at 2 consecutive study visits 2 weeks apart, assessed at weeks 22 and 24 or at weeks 24 and 26, between the beremagene geperpavec-svdt gel-treated and the placebo gel-treated wounds. At 24 weeks, complete wound healing occurred in 65% of the wounds exposed to beremagene geperpavec-svdt gel as compared with 26% of those exposed to placebo (difference, 39 points; 95% confidence interval [CI], 14 to 63; p =.012). The most common adverse drug reactions (incidence >5%) were itching, chills, redness, rash, cough, and runny nose. The intra-subject randomization and comparison of dystrophic epidermolysis bullosa wounds confounds the systemic safety evaluation.

Long-term results (beyond 6 months) were reported for 24 rollover individuals from the phase III trial. Out of 24 individuals, 19 were evaluated; data were not available for 5 individuals without consistent follow-up visits. Complete wound closure, reported at month 3, 6, 9 and 12 ranged from 61.1 to 89.5%. (10)

Table 2. Summary of Pivotal Randomized Trial

Study	**Study GEM-3 (NCT04491604) (9)**
Study Type	DBRCT
Country	United States
Sites	3
Dates	2020-2021

Participants	Inclusion
	• 6 months or older
	• Clinical manifestations consistent with dystrophic epidermolysis bullosa
	• Genetically confirmed mutation(s) in the *COL7A1* gene
	• At least 2 cutaneous wounds meeting the following criteria:
	  ○ Location: similar in size, located in similar anatomical regions, and have similar appearance.
	  ○ Appearance: clean with adequate granulation tissue, excellent vascularization, and do not appear infected

	Exclusion • Receipt of chemical or biological study product for the specific treatment of dystrophic epidermolysis bullosa in the past three months
Interventions - Active	Treatment duration • Weekly topical application of beremagene geperpavec-svdt gel for 26 weeks Dose/wound varied by wound area: • For <20 cm^2: 4 X 10^8 PFU • For 20 to 40 cm^2: 8 X 10^8 PFU • For 40 to 60 cm^2: 1.2 X 10^9 PFU Maximum weekly dose varied by age: • For ≥6 months to <3 years: 1.6 X 10^9 PFU • For ≥3 years to <6 years: 2.4 X 10^9 PFU • For ≥6 years: 3.2 X 10^9 PFU
Interventions - Control	Placebo-gel (excipient only)
Follow-Up	26 weeks

COL7A1: collagen type VII alpha 1 chain; DBRCT: double-blind randomized controlled trial; PFU: plaque forming units.

Table 3. Summary of Baseline Demographics and Disease Characteristics in the Pivotal Trial

Characteristic	**Study GEM-3 (N=31) (9)**
Age, median (range), years	16.1 (1-44)
Male, n (%)	20 (65)
Race or ethnic group other than Hispanic or Latino, n (%)	
White	20 (65)
Black	0
Asian	6 (19)
American Indian or Alaska Native	5 (16)
Native Hawaiian or other Pacific Islander	0
Genotype, n (%)	
Dominant dystrophic epidermolysis bullosa	1 (3)
Recessive dystrophic epidermolysis bullosa	30 (97)
Area of primary wound exposed to beremagene geperpavec-svdt, median (range), cm^2	10.6 (2.3–57.3)
Area of primary wound exposed to placebo, median (range), cm^2	10.4 (2.3–51.5)

Table 4. Summary of Key Results in Pivotal Trial

Study GEM-3 (N=31) (9, 11)	**Beremagene geperpavec-svdt**	**Placebo**	**Treatment Difference (95% CI)**	**P value**

Complete Wound Closure, n (%)				
Weeks 22 and 24 or weeks 24 and 26	20 (65)	8 (26)	39% (14 to 63)	.012
Weeks 8 and 10 or weeks 10 and 12	21 (68)	7 (23)	45% (22 to 69)	.003

CI: confidence interval.

The purpose of the study limitations tables (see Tables 5 and 6) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence and provides the conclusions on the sufficiency of evidence supporting the position statement. No major study design or conduct limitations were noted. The size of the safety database and the median duration of exposure for beremagene geperpavec-svdt is inadequate to sufficiently assess harms.

Table 5. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Study Gem-3 (9)	4. Enrolled populations do not reflect relevant diversity (65% White with no Black participants enrolled)				2. Not sufficient duration for harms

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 6. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]

Study GEM-3 (9)						

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Beremagene geperpavec-svdt

Evidence for the use of beremagene geperpavec-svdt for the treatment of wounds in individuals with dystrophic epidermolysis bullosa with mutation(s) in the *COL7A1* gene includes a single RCT. In the pivotal GEM-3 trial (n=31), 2 comparable wounds in each participant were selected and randomized to receive either topical application of beremagene geperpavec-svdt gel or the placebo (excipient gel) weekly for 26 weeks. The primary endpoint was the difference in the proportion of complete (100%) wound closure at 24 weeks confirmed at 2 consecutive study visits 2 weeks apart, assessed at weeks 22 and 24 or at weeks 24 and 26, between the beremagene geperpavec-svdt gel-treated and the placebo gel-treated wounds. At 24 weeks, complete wound healing occurred in 65% of the wounds exposed to beremagene geperpavec-svdt gel as compared with 26% of those exposed to placebo (difference, 39 points; 95% CI, 14 to 63; p =.012). The most common adverse drug reactions (incidence >5%) were itching, neoplasms, chills, redness, rash, cough, and runny nose.

Prademagene zamikeracel

The clinical development program for prademagene zamikeracel is summarized in Table 7. The pivotal phase 3 randomized clinical trial (VIITAL) was the basis for FDA approval of prademagene zamikeracel and is reviewed in detail.

Table 7. Summary of the Clinical Development Program for Prademagene zamikeracel

Study	Protocol 14563	Study EB-101-CL-301 (VIITAL)	Study EB-101-CL-302	Study EB-101-LT-001
NCT No	NCT01263379	NCT04227106	NCT05725018	NCT05708677
Phase	1/2A	3	3	-

Study Population	Individuals 13 years of age or older with genetically confirmed diagnosis of recessive dystrophic epidermolysis bullosa	Individuals 6 years of age or older with genetically confirmed diagnosis of recessive dystrophic epidermolysis bullosa	Individuals 12 months of age or older with genetically confirmed dystrophic epidermolysis bullosa	Individuals who previously received prademagene zamikeracel in a study
Status	Completed and published (12-14)	Completed and unpublished	Ongoing	Ongoing
Study Dates	2013-2019	2020-2022	2023-ongoing	2021-2036
Design	Open-label single group assignment	Open-label single group assignment[a]	Open-label single group assignment[a]	Observational
Sample Size	7	11	12	22
Follow-up	5.9 years	24 weeks	6 months	5 years

NCT: national clinical trial.

[a] Each participant serves as his/her own control by contributing a primary size-matched wound pair to be randomized to receive weekly topical application of either gene therapy or standard of care.

Pivotal Randomized Trial

Study characteristics, baseline patient characteristics and results are summarized in Table 8 to 10, respectively. The pivotal VIITAL study was a 6-month, randomized, intra-subject placebo-controlled trial in which 2 comparable wounds in each participant were selected and randomized to receive either prademagene zamikeracel (up to 6 sheets) or standard of care wound dressings (control treatment). The maximum wound pairs in any one subject were 5. The principal investigator at each site was the sole individual who assessed each subject's primary wound pair at all timepoints for primary and secondary endpoints assessment. The co-primary efficacy end points were 1) proportion of randomized wound pairs with at least 50% healing at month 6 with confirmation of wound healing two weeks later as assessed using baseline digital photography by the investigator, and 2) pain reduction as assessed by the mean differences in patient-reported pain scores using the Wong-Baker FACES scale between randomized wound pairs at month 6. Secondary outcome measures were proportion of randomized wound pairs with complete wound healing defined as reepithelialization with no drainage or erosion and presence of only minor crusting from baseline at month 3 and at month 6 with confirmation of wound healing two weeks later. At 6 months, the proportion of randomized wound pairs healed ≥50% from baseline at 6 months was 81% (35 out of 43) and 16% (7 out of 43) in the treated versus control arm respectively (p-value of <.0001). The mean pain reduction from baseline at month 6 was -3.07 points versus -0.90 points in the treated versus control arm respectively (p-value of <.0002). The most common adverse drug reactions (incidence >5%) were procedural pain and pruritus. The intra-subject randomization and

comparison of dystrophic epidermolysis bullosa wounds confounds the systemic safety evaluation.

Table 8. Summary of Pivotal Randomized Trial

Study	VIITAL (NCT04227106)
Study Type	RCT
Country	United States
Sites	2
Dates	2020-2022
Participants	Inclusion • 6 years or older • Clinical diagnosis of recessive dystrophic epidermolysis bullosa (RDEB) • Positive expression non-collagenous region 1 of the collagen 7 molecule (NC1)+ in the skin • Two confirmed RDEB C7 mutations with recessive inheritance patterns (or confirmation that parents do not have any evidence of dominant disease) • At least 2 matched wounds meeting the following criteria: o An area ≥20 cm^2 o Present for ≥6 months o Stage 2 wound defined as an open skin wound with partial thickness loss of dermis that has not extended through the dermis into subcutaneous tissue Exclusion • Current or history of squamous cell carcinoma at the treatment site
Interventions - Active	Typically, 40 cm^2 keratinocyte sheets for surgical application to cover wounds
Interventions - Control	Standard of care wound dressings[a]
Follow-Up	6 months

Cm: centimeter(s); NCT: national clinical trial; RCT: randomized controlled trial.

[a] Wound dressings were categorized under the following: foams, hydrogels, alginates, hydrofibers, modified absorbent pads and contact layer, biosynthetic cellulose and lipidcolloid dressings. Wounds were treated with topical antibiotic as well.

Table 9. Summary of Baseline Demographics and Disease Characteristics in the Pivotal Trial

Characteristic	**Study VIITAL (N=11)**
Age, median (range), years	21.0 (6, 40)
Male, n (%)	4 (36)
Race or ethnic group other than Hispanic or Latino, n (%)	

White	10 (91)
Other	1 (9)
Number of wounds, median (range)	10 (6, 11)

Table 10. Summary of Key Results in Pivotal Trial

Study VIITAL (N=11, 86 wounds)	Prademagene zamikeracel (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%)	<.0001
Mean pain reduction from baseline at month 6[b], mean (SD)	-3.07 (3.19)	-0.90 (2.73)	.0002
Proportion of randomized wound pairs completely healed from baseline at month 3, n (%)	6 (14%)	0 (0%)	.0316
Proportion of randomized wound pairs completely healed from baseline at month 6[a], n (%)	7 (16%)	0 (0%)	.0160

N: total number of observations; SD: Standard deviation; %: percentage.
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 was excluded from the control group due to missing baseline value.

The purpose of the study limitations tables (see Tables 11 and 12) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence and provides the conclusions on the sufficiency of evidence supporting the position statement. No major study design or conduct limitations were noted. The size of the safety database and the median duration of exposure for prademagene zamikeracel is inadequate to sufficiently assess treatment durability and harms. Although the study and the outcome assessment were not blinded (which could introduce detection and performance biases), the co-primary efficacy endpoint of wound healing is objective and relatively less prone to bias.

Table 11. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Study VIITAL	4. Enrolled populations do not reflect relevant diversity (90% White with no				1. Not sufficient duration for benefits 2. Not sufficient

	Black participants enrolled)				duration for harms

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 12. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Study VIITAL		1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician.				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.

[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Section Summary: Prademagene zamikeracel

Evidence for the use of prademagene zamikeracel for the treatment of wounds in individuals with recessive dystrophic epidermolysis bullosa includes a single RCT. In the pivotal VIITAL trial (n=11), 2 comparable wounds in each participant were selected and randomized to receive either prademagene zamikeracel or standard of care wound dressings. The first co-primary endpoint was the proportion of randomized wound pairs with ≥50% healing from baseline at 6 months. The response rate for the wounds was 81% compared to 16% in the treated versus control arm respectively. The second co-primary efficacy endpoint was pain reduction at 6 months from baseline, assessed by the Wong-Baker FACES Scale. The mean pain reduction from baseline at month 6 was -3.07 points versus -0.90 points in the treated versus control arm respectively. Treatment with prademagene zamikeracel resulted in greater healing and in greater pain reduction as compared to wounds treated with standard-of-care therapy. These results are both clinically and statistically significant and provide the primary evidence of effectiveness. The most common adverse drug reactions (incidence >5%) were procedural pain and pruritus.

Summary of Evidence

For individuals with dystrophic epidermolysis bullosa with mutation(s) in the *COL7A1* gene and who receive beremagene geperpavec-svdt, the evidence includes a single RCT. Relevant outcomes are symptoms, change in disease status, quality of life, treatment-related mortality and treatment-related morbidity. In the pivotal GEM-3 trial (n=31), 2 comparable wounds in each participant were selected and randomized to receive either topical application of beremagene geperpavec-svdt gel or the placebo (excipient gel) weekly for 26 weeks. The primary endpoint was the difference in the proportion of complete (100%) wound closure at 24 weeks confirmed at two consecutive study visits 2 weeks apart, assessed at weeks 22 and 24 or at weeks 24 and 26, between the beremagene geperpavec-svdt gel-treated and the placebo gel-treated wounds. At 24 weeks, complete wound healing occurred in 65% of the wounds exposed to beremagene geperpavec-svdt gel as compared with 26% of those exposed to placebo (difference, 39 points; 95% CI, 14 to 63; p =.012). The most common adverse drug reactions (incidence >5%) were itching, chills, redness, rash, cough, and runny nose. No major limitations were noted. The size of the safety database and the median duration of exposure for beremagene geperpavec-svdt is inadequate to sufficiently assess harms. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are pediatric or adult patients with recessive dystrophic epidermolysis bullosa and who receive prademagene zamikeracel, the evidence includes a single RCT. Relevant outcomes are symptoms, change in disease status, quality of life, treatment-related mortality and treatment-related morbidity. In the pivotal VIITAL trial (n=11), 2 comparable wounds in each participant were selected and randomized to receive either prademagene

zamikeracel or standard of care wound dressings. The first co-primary endpoint was the proportion of randomized wound pairs with ≥50% healing from baseline at 6 months. The response rate for the wounds was 81% compared to 16% in the treated versus control arm respectively. The second co-primary efficacy endpoint was pain reduction at 6 months from baseline, assessed by the Wong-Baker FACES Scale. The mean pain reduction from baseline at month 6 was -3.07 points versus -0.90 points in the treated versus control arm respectively. Treatment with prademagene zamikeracel resulted in greater healing and in greater pain reduction as compared to wounds treated with standard-of-care therapy. These results are both clinically and statistically significant and provide the primary evidence of effectiveness. The most common adverse drug reactions (incidence >5%) were procedural pain and pruritus. No major limitations were noted. The size of the safety database and the median duration of exposure for prademagene zamikeracel is inadequate to sufficiently assess treatment durability and harms. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

European Reference Network for Rare Skin Diseases

The European Reference Network for Rare and Undiagnosed Skin Diseases published expert consensus clinical position statements in 2021 regarding practical recommendations for the management of patients suspected or diagnosed with epidermolysis bullosa covering diagnosis, wound management, oral care and treatment of pain and itch. (3) They also published consensus clinical position recommendations in 2020 to aid decision-making and optimize clinical care by non-epidermolysis bullosa expert health professionals encountering emergency situations in babies, children and adults with epidermolysis bullosa. (15) Both consensus statements were published prior to the Food and Drug Administration (FDA) approval of beremagene geperpavec-svdt.

Dystrophic Epidermolysis Bullosa Research Association

International consensus best practice guidelines on skin and wound care in epidermolysis bullosa were published in 2017. (16) These guidelines were also published prior to the FDA approval of beremagene geperpavec-svdt.

National Instituted for Health and Care Excellence

A technology appraisal guidance titled "Beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa" is currently in the draft stage and is expected to be published in July 2026. (17)

Ongoing and Unpublished Clinical Trials

A currently ongoing or unpublished trial that might influence this policy is listed in Table 13.

Table 13. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date

NCT07016750[a]	A Study Assessing B-VEC Compared to Matching Placebo for the Treatment and Prevention of Corneal Abrasions in Dystrophic Epidermolysis Bullosa	16	Mar 2026
NCT04917887	Long-Term Follow-up Protocol	50	May 2028

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J3389, J3401

*Current Procedural Terminology (CPT®) ©2025 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
06/15/2026	Document updated. The following change was made to Coverage: Added medically necessary language for prademagene zamikeracel (Zevaskyn™): Prademagene zamikeracel (Zevaskyn™) may be considered medically necessary for the treatment of wounds in adult and pediatric individuals diagnosed with recessive dystrophic epidermolysis bullosa (RDEB) conditions when the following criteria are met. 1. The individual must have the following: a. Wounds associated with recessive dystrophic epidermolysis bullosa (RDEB); 2. AND ALL the following: a. Documented biallelic pathogenic mutations in the collagen type VII alpha 1 chain (COL7A1) gene; b. Positive expression of the non-collagenous region 1 of the type 7 collagen protein (NC1+) in the skin; c. Presence of at least one chronic wound (e.g., stage 2 wounds that have an area ≥ 20 cm^2) and have been present for at least 3 months; d. Presence of clinical manifestations of RDEB, such as extensive skin blistering, skin erosions, or scarring. Prademagene zamikeracel (Zevaskyn™) is considered experimental, investigational and/or unproven for all other non-Food and Drug Administration approved indications. Added references 10, 12-14, 17; others updated.
01/01/2026	Document updated. The following change was made to Coverage: Modified conditional coverage statement to remove requirement that patient be ≥6 months of age. No new references added; updated reference 10.
12/15/2025	Document updated with literature review. The following changes were made to Coverage: 1) Modified conditional medical necessity criteria; and 2) Added “non-Food and Drug Administration approved” to experimental, investigational and/or unproven statement. All new references were added. Title changed from “Beremagene geperpavec-svdt”.
12/15/2024	Reviewed. No changes.
11/15/2023	New medical document. Beremagene geperpavec-svdt (Vyjuvek™) may be considered medically necessary for the treatment of dystrophic epidermolysis bullosa (DEB) when ALL of the following criteria are met: individual is aged 6 months or older; individual has documented genetic mutation(s) in the collagen type VII alpha 1 chain (*COL7A1*) gene; and individual has clinical manifestation consistent with DEB. Beremagene geperpavec-svdt (Vyjuvek™) is considered experimental, investigational and/or unproven for all other indications, including but not limited to: current evidence or a history of squamous cell carcinoma in the area that will undergo treatment; individual is actively receiving chemotherapy or immunotherapy; or individual has received a skin graft in the past three (3) months.