The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 15, 2022 VOL. 387 NO. 24

Trial of Beremagene Geperpavec (B-VEC) for Dystrophic Epidermolysis Bullosa

Shireen V. Guide, M.D., Mercedes E. Gonzalez, M.D., I. Sinem Bağcı, M.D., Brittani Agostini, B.S.N., Hubert Chen, M.D., Gloria Feeney, B.S., Molly Steimer, B.S., Binoy Kapadia, B.S., Kunju Sridhar, Ph.D., Lori Quesada Sanchez, B.S., Franshesca Gonzalez, B.S., Matthew Van Ligten, B.S., Trevor J. Parry, Ph.D., Surya Chitra, Ph.D., Lisa A. Kammerman, Ph.D., Suma Krishnan, M.S., and M. Peter Marinkovich, M.D.

ABSTRACT

BACKGROUND

Dystrophic epidermolysis bullosa is a rare genetic blistering skin disease caused by mutations in *COL7A1*, which encodes type VII collagen (C7). Beremagene geperpavec (B-VEC) is a topical investigational herpes simplex virus type 1 (HSV-1)–based gene therapy designed to restore C7 protein by delivering *COL7A1*.

METHODS

We conducted a phase 3, double-blind, intrapatient randomized, placebo-controlled trial involving patients 6 months of age or older with genetically confirmed dystrophic epidermolysis bullosa. For each patient, a primary wound pair was selected, with the wounds matched according to size, region, and appearance. The wounds within each pair were randomly assigned in a 1:1 ratio to receive weekly application of either B-VEC or placebo for 26 weeks. The primary end point was complete wound healing of treated as compared with untreated wounds at 6 months. Secondary end points included complete wound healing at 3 months and the change from baseline to weeks 22, 24, and 26 in pain severity during changes in wound dressing, assessed with the use of a visual analogue scale (scores range from 0 to 10, with higher scores indicating greater pain).

RESULTS

Primary wound pairs were exposed to B-VEC and placebo in 31 patients. At 6 months, complete wound healing occurred in 67% of the wounds exposed to B-VEC as compared with 22% of those exposed to placebo (difference, 46 percentage points; 95% confidence interval [CI], 24 to 68; P=0.002). Complete wound healing at 3 months occurred in 71% of the wounds exposed to B-VEC as compared with 20% of those exposed to placebo (difference, 51 percentage points; 95% CI, 29 to 73; P<0.001). The mean change from baseline to week 22 in pain severity during wound-dressing changes was −0.88 with B-VEC and −0.71 with placebo (adjusted least-squares mean difference, −0.61; 95% CI, −1.10 to −0.13); similar mean changes were observed at weeks 24 and 26. Adverse events with B-VEC and placebo included pruritus and chills.

CONCLUSIONS

Complete wound healing at 3 and 6 months in patients with dystrophic epidermolysis bullosa was more likely with topical administration of B-VEC than with placebo. Pruritus and mild systemic side effects were observed in patients treated with B-VEC. Longer and larger trials are warranted to determine the durability and side effects of B-VEC for this disease. (Funded by Krystal Biotech; GEM-3 ClinicalTrials.gov number, NCT04491604.)

From the Mission Dermatology Center, Department of Dermatology, Children's Hospital of Orange County, University of California Irvine, Rancho Santa Margarita (S.V.G., M.V.L.), the Department of Dermatology, Stanford University School of Medicine, Stanford (I.S.B., K.S., M.P.M.), and the Veterans Affairs Medical Center, Palo Alto (M.P.M.) — all in California; Pediatric Skin Research, Coral Gables, FL (M.E.G., L.Q.S., F.G.); Krystal Biotech, Pittsburgh (B.A., H.C., G.F., M.S., B.K., T.J.P., S.K.); Savio Group Analytics, Hockessin, DE (S.C.); and Kammerman Consulting, Chevy Chase, MD (L.A.K.). Dr. Marinkovich can be contacted at mpm@stanford.edu or at the Department of Dermatology, Stanford University School of Medicine, 455 Broadway St., Redwood City, CA 94063.

Drs. Guide, M. Gonzalez, and Bağcı contributed equally to this article.

N Engl J Med 2022;387:2211-9.
DOI: 10.1056/NEJMoa2206663

A Quick Take is available at NEJM.org

Dystrophic epidermolysis bullosa is a rare genetic blistering disease caused by mutations in *COL7A1*, the gene encoding type VII collagen (C7), which result in absent or dysfunctional anchoring fibrils and which disrupt adhesion of the epidermis to the dermis.[1,2] Extensive skin blistering develops from minor trauma.[3] Over time, repeated blistering and fibrosis can lead to squamous-cell carcinoma, life-threatening infections, and limb deformities.[4-6] No approved corrective therapies for dystrophic epidermolysis bullosa currently exist.

Cell-based treatments for dystrophic epidermolysis bullosa have shown both successes and limitations.[7] Bone marrow transplantation in a small group of patients[8] was associated with 30% mortality. Grafting or injection of ex vivo transduced *COL7A1*-overexpressing autologous dystrophic epidermolysis bullosa keratinocytes[9] (ClinicalTrials.gov number, NCT01263379) or fibroblasts[10] (NCT02493816) to patient skin is being investigated. However, viral insertional oncogenesis risk[11,12] and the long-term durability of molecular correction remain concerns.[9,10,13]

The challenges of in vivo gene therapy for dystrophic epidermolysis bullosa include the difficulty of achieving efficient cutaneous gene transfer, the large viral size required to accommodate the approximately 9-kb *COL7A1* transgene,[9,10] and the limitation of readministering most viral vectors owing to immune reactions.[14-16] To address these limitations, beremagene geperpavec (B-VEC), an investigational herpes simplex virus type 1 (HSV-1)–based, topical gene therapy, was designed to restore functional C7 protein through delivery of *COL7A1*.[17] B-VEC is based on an engineered, replication-defective HSV-1 vector platform allowing delivery into the nucleus without host DNA integration, high payload capacity, tropism for the skin, and evasion of the immune system, which enables repeat dosing.

In a previous open-label, placebo-controlled phase 1–2 trial involving 9 patients with recessive dystrophic epidermolysis bullosa, repeated topical application of B-VEC resulted in full-length C7 protein expression and normalized anchoring fibril formation.[17] Over a period of 3 months, wounds that were exposed to B-VEC were more likely to have closure and remain healed than those exposed to placebo. We conducted a 6-month, phase 3 trial (GEM-3) to evaluate the efficacy and safety of topical B-VEC in patients with dystrophic epidermolysis bullosa.

METHODS

TRIAL DESIGN AND OVERSIGHT

This was a phase 3, double-blind, intrapatient randomized, placebo-controlled trial that evaluated the efficacy and safety of B-VEC in children and adults with dystrophic epidermolysis bullosa. Patients were recruited from three sites in the United States (see the Supplementary Appendix, available with the full text of this article at NEJM.org). This trial used an intrapatient control design suggested by the Food and Drug Administration for studying genetic skin conditions.[18] For each patient, the site investigator selected two wounds of similar size, anatomical region, and appearance (defined as the primary wound pair; see the protocol, available at NEJM.org, for details). The wounds within each pair were randomly assigned in a 1:1 ratio to receive weekly application of either B-VEC or placebo for 26 weeks until wound closure. Additional secondary wounds were selected for open-label B-VEC treatment.

The trial was designed jointly between the primary investigator (the last author) and the sponsor, Krystal Biotech, and conducted by the sponsor in collaboration with the principal investigators. The sponsor provided the active-drug and placebo formulations, collected the data, monitored the trial conduct, and performed the statistical analyses. The first draft of the manuscript was written by the fifth author. All the authors were involved in the preparation and approval of the manuscript. All the authors had confidentiality agreements with the sponsor, and the sponsor could not delay or prevent publication of the trial results. Trial approval was obtained from ethics committees at each site. All the patients or guardians provided written informed consent before participation. The trial was conducted in conformance with International Council for Harmonisation Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and applicable regulatory requirements. Detailed methods are provided in the Supplementary Appendix and protocol.

PATIENTS

Eligible patients were 6 months of age or older presenting with a clinical diagnosis of dystrophic epidermolysis bullosa, characterized by blistering, wounds, and scarring[19] and confirmed by genetic testing. Patients who had participated in the phase 1–2 trial of B-VEC were not excluded

from participation in the current trial, but the trials were conducted separately. (For all the patients in the phase 1–2 trial who were enrolled in the phase 3 trial, there was at least 1 year of washout between the last dose in the phase 1–2 trial and the first visit of the phase 3 trial.) Patients were excluded if they were undergoing current treatment with immunotherapy, chemotherapy, or other investigational products. Wound sites with current evidence or history of squamous-cell carcinoma or active infection were excluded as sites for application of B-VEC or placebo.

TRIAL PRODUCTS

Topically administered B-VEC consists of thawed cryopreserved B-VEC drug product mixed with an excipient gel, Methocel. Placebo was the excipient gel mixed with normal saline at a matched volume to B-VEC drug product. All the patients, investigators, site staff, and the sponsor remained unaware of the trial-group assignments, except for designated personnel, including the pharmacist or authorized designee who handled unblinded B-VEC or placebo and persons required to prepare the randomization schedule.

The topical B-VEC dose ranged from 4×10^8 to 1.2×10^9 plaque-forming units depending on the baseline wound size and remained fixed thereafter for the remainder of the trial. Baseline wound sizes and subsequent complete wound healing were assessed by means of the Canfield 2D/3D iOS System, a three-dimensional imaging system for quantifying wound surface area. A maximum weekly dose was also defined on the basis of age. B-VEC or placebo was applied only to open wounds. Wounds were evaluated weekly to determine continued application of B-VEC or placebo. If a healed wound reopened, application was resumed; if the wound remained closed, application was omitted. Up to four secondary wounds per patient were allowed to be exposed to the excess trial product, defined as the maximum weekly dose minus the primary-wound dose. No formal analyses of secondary wounds were performed.

END POINTS

The primary end point was a binary indicator of primary wounds with complete wound healing at 6 months (weeks 22 and 24 or weeks 24 and 26); only wounds that were healed for at least 2 consecutive weeks were counted as having had a response. Complete wound healing was defined as 100% wound closure from the exact wound area selected at baseline, specified as skin reepithelialization without drainage, as determined by the investigator.

The key secondary end point was a binary indicator of primary wounds with complete healing at 3 months (weeks 8 and 10 or weeks 10 and 12). Other secondary end points were the change from baseline to weeks 22, 24, and 26 in pain severity during changes in wound dressing, assessed with the use of a visual analogue scale (VAS; scores range from 0 to 10, with higher scores indicating greater pain) for patients 6 years of age or older and the Face, Legs, Activity, Cry, and Consolability–Revised (FLACC-R) scale for patients younger than 6 years of age. Changes in general and skin-specific quality of life were assessed as exploratory end points with the use of the EuroQol 5-Dimension 5-Level questionnaire (EQ-5D-5L) and the Skindex-29 questionnaire.

Safety assessments included monitoring of adverse events that emerged or worsened after the first application of B-VEC or placebo, physical examination, vital signs, and clinical laboratory tests. The severity of adverse events was reported and graded by the investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Immunologic evaluation included testing for antibodies against HSV-1 and C7.

STATISTICAL ANALYSIS

The sample size was estimated with the use of McNemar's test and the incidences of response observed in the phase 1–2 trial at weeks 8 through 12. At a power of 90% and a two-sided alpha level of 5%, we calculated that 24 patients (24 primary wound pairs) would show a difference between trial groups if the true incidence of response was 75% for B-VEC and 25% for placebo and if responses for matched pair members were uncorrelated. A 20 to 25% dropout rate was assumed with a target sample size of 30 to 32 patients.

Primary and secondary efficacy analyses and baseline summaries were based on the intention-to-treat population, which included all the patients whose primary wounds underwent randomization, regardless of whether B-VEC or placebo was applied. If the results for the primary end point were significant, the two-sided 5% alpha level was to be passed to the key

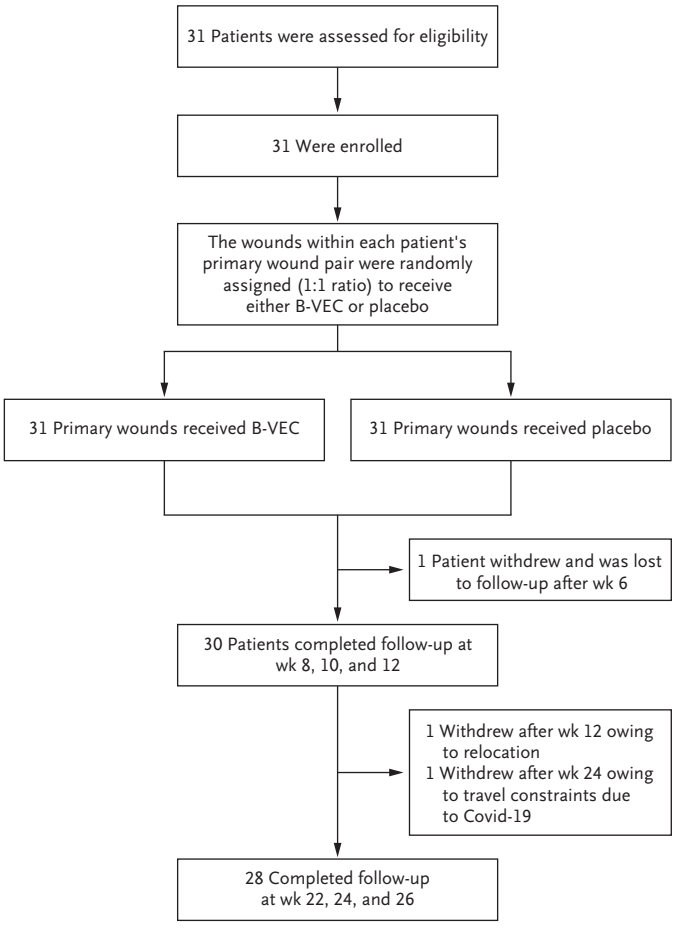

Figure 1. Screening, Randomization, and Follow-up.

A total of 31 patients were enrolled, and 31 primary wound pairs were randomly assigned to receive either B-VEC or placebo. The intention-to-treat and safety populations included all 31 patients. Three patients withdrew from the trial for non–treatment-related reasons. B-VEC denotes beremagene geperpavec, and Covid-19 coronavirus disease 2019.

secondary end point. The widths of confidence intervals for differences between trial groups for all other analyses were not adjusted for multiplicity, and definite conclusions cannot be drawn from these results. The primary and key secondary patient-level end points were binary indicators of wound healing that were summarized within trial groups as percentages. Subgroup analyses for the primary end point were prespecified on the basis of sex and age; a post hoc subgroup analysis was performed on the basis of area or size category of the primary wounds. Supplementary analyses assessed complete wound closure at various time points, including a post hoc assessment of durability of wound healing (confirmed at two consecutive visits 2 weeks apart) at both 3 and 6 months. Safety analyses were based on the safety population, which included all the patients who had received at least one dose of B-VEC or placebo.

To account for the paired nature of the data, an exact McNemar's test was used to analyze primary and key secondary efficacy end points. A multiple imputation approach involving the Markov chain Monte Carlo method under the assumption that all the variables in the imputation model have a joint multivariate normal distribution was used to impute missing data, and the resulting 10 data sets were combined.[20] The 95% confidence intervals were calculated for the percentage of wounds with a response to B-VEC as compared with placebo. Analysis of covariance, with trial product and patient as the fixed effects and baseline pain severity as the covariate, was used to evaluate the difference between B-VEC and placebo in the change from baseline to weeks 22, 24, and 26 in pain severity during wound-dressing changes as measured by VAS and FLACC-R scores. Changes in EQ-5D-5L and Skindex-29 scores were reported with the use of mean values and standard errors. All statistical analyses were performed with the use of SAS software, version 9.4.

RESULTS

PATIENTS

A total of 31 patients were enrolled from August 2020 through April 2021, and the primary wound pairs (62 wounds) were randomly assigned within each patient to receive either B-VEC or placebo (Fig. 1). The intention-to-treat and safety populations included all 31 patients. Five patients had previously been enrolled in the phase 1–2 trial but were treated for different wounds. Three patients withdrew for non–treatment-related reasons (loss to follow-up, relocation, and travel constraints due to coronavirus disease 2019), and therefore imputation of data for the primary end point was required.

The median age of the patients was 16 years (range, 1 to 44), and 61% were 18 years of age or younger (Table 1). All the patients had recessive dystrophic epidermolysis bullosa, except for one who had a dominant form. Primary wounds were similar in size between those exposed to B-VEC

(median area, 10.6 cm^2) and those exposed to placebo (median, 10.4 cm^2) and varied in size among patients (range, 2.3 to 57.3 cm^2). Additional details regarding the patients are provided in Table S1 in the Supplementary Appendix; the representativeness of the enrolled population is based on the limited amount of information available with respect to the overall patient population affected by the disease (Table S2).

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Total Patients (N=31)
Age	
Median (range) — yr	16.1 (1–44)
≤12 yr — no. (%)	10 (32)
>12 to ≤18 yr — no. (%)	9 (29)
>18 yr — no. (%)	12 (39)
Sex — no. (%)	
Male	20 (65)
Female	11 (35)
Race or ethnic group other than Hispanic or Latino — no. (%)†	
White	20 (65)
Black	0
Asian	6 (19)
American Indian or Alaska Native	5 (16)
Native Hawaiian or other Pacific Islander	0
Hispanic or Latino ethnic group — no. (%)†	
Yes	16 (52)
No	15 (48)
Genotype — no. (%)	
Dominant dystrophic epidermolysis bullosa	1 (3)
Recessive dystrophic epidermolysis bullosa	30 (97)
Area of primary wound exposed to B-VEC	
Median (range) — cm^2	10.6 (2.3–57.3)
<20 cm^2 — no. (%)	23 (74)
20 to <40 cm^2 — no. (%)	6 (19)
40 to 60 cm^2 — no. (%)	2 (6)
Area of primary wound exposed to placebo	
Median (range) — cm^2	10.4 (2.3–51.5)
<20 cm^2 — no. (%)	22 (71)
20 to <40 cm^2 — no. (%)	8 (26)
40 to 60 cm^2 — no. (%)	1 (3)

* Percentages may not total 100 because of rounding. B-VEC denotes beremagene geperpavec.
† Race and ethnic group were reported by the patient or the parent or guardian.

EFFICACY

The percentage of primary wounds with complete healing at 6 months was 67% for those exposed to B-VEC and 22% for those exposed to placebo (difference, 46 percentage points; 95% confidence interval [CI], 24 to 68; P=0.002) (Table 2). Complete wound healing at 3 months, the key secondary end point, was observed in 71% of wounds exposed to B-VEC and 20% of those exposed to placebo (difference, 51 percentage points; 95% CI, 29 to 73; P<0.001). Treatment response was evaluated for subgroups with respect to sex, age, and wound size, although statistical power for individual subgroup comparisons was low (Fig. S1 and Table S3). In the patient with dominant dystrophic epidermolysis bullosa, complete wound healing at 6 months occurred in the wound exposed to B-VEC but not in the wound exposed to placebo.

The mean change from baseline to week 22 in pain severity during wound-dressing changes, assessed with the use of a VAS among patients 6 years of age or older, was −0.88 for wounds exposed to B-VEC and −0.71 for those exposed to placebo (adjusted least-squares mean difference, −0.61; 95% CI, −1.10 to −0.13); similar mean changes were observed at weeks 24 and 26 (Table 3). No conclusions could be made about pain severity as assessed with the use of the FLACC-R scale among patients younger than 6 years of age because of the small sample size (four patients). Most patients had improvement by at least one health level or had no change in the EQ-5D-5L dimensions at 6 months as compared with baseline, and Skindex-29 scores were generally the same at follow-up as at baseline (Fig. S2).

Supplementary analyses were conducted to assess the duration of complete wound closure beyond the primary and key secondary end points. A numerically higher percentage of wounds exposed to B-VEC than those exposed to placebo had complete closure across various time points (Table S4). Durability, which was defined as complete wound healing at both 3 and 6 months, was seen in 50% of wounds exposed to B-VEC and 7% of those exposed to placebo (difference, 43 percentage points; 95% CI, 23 to 63). The potential of B-VEC to treat large, chronic wounds was qualitatively explored in secondary wounds.

Table 2. Primary End Point and Key Secondary End Point.*

End Point	Primary Wounds Exposed to B-VEC (N=31)	Primary Wounds Exposed to Placebo (N=31)	Absolute Difference (95% CI)	P Value
	number (percent)		*percentage points*	
Primary end point: complete wound healing at 6 mo†	20.9 (67)	6.7 (22)	46 (24–68)	0.002
Key secondary end point: complete wound healing at 3 mo‡	21.9 (71)	6.1 (20)	51 (29–73)	<0.001

* The primary and key secondary end points were analyzed in the intention-to-treat population. Multiple-imputation methods were used to account for missing data. Fractional counts are due to the multiple-imputation procedure used for analysis. Hypothesis testing was performed with the use of an exact McNemar's test.
† Primary wounds were assessed at weeks 22 and 24 or weeks 24 and 26.
‡ Primary wounds were assessed at weeks 8 and 10 or weeks 10 and 12.

Table 3. Pain Severity during Wound-Dressing Changes.*

End Point	Primary Wounds Exposed to B-VEC	Primary Wounds Exposed to Placebo	Adjusted Least-Squares Mean Difference (95% CI)†
Change from baseline to wk 22 in pain severity during wound-dressing changes			
No. of wounds evaluated	24	24	
Mean change on VAS	–0.88	–0.71	–0.61 (–1.10 to –0.13)
Change from baseline to wk 24 in pain severity during wound-dressing changes			
No. of wounds evaluated	25	25	
Mean change on VAS	–0.64	–0.08	–0.88 (–1.79 to 0.03)
Change from baseline to wk 26 in pain severity during wound-dressing changes			
No. of wounds evaluated	24	24	
Mean change on VAS	–0.63	–0.38	–0.56 (–1.17 to 0.05)

* Shown are data for pain severity (secondary end point) as assessed with the use of a visual analogue scale (VAS; scores range from 0 to 10, with higher scores indicating greater pain) among patients 6 years of age or older. No conclusions could be made about pain severity as assessed with the use of the Face, Legs, Activity, Cry, and Consolability–Revised scale among patients younger than 6 years of age because of the small sample size (four patients).
† Least-squares mean differences were generated from an analysis-of-covariance linear model, with trial product and patient (paired) as the fixed effect and the baseline value as the covariate. The widths of the 95% confidence intervals were not adjusted for multiple comparisons, and no definite conclusions can be drawn from these data.

An illustrative example of a treated secondary wound with an area of more than 100 cm^2 is provided in Figure S3, but this may not be representative of all secondary wounds.

SAFETY

A total of 18 patients (58%) had at least one adverse event (Table 4). The majority of adverse events were mild or moderate in severity, as assessed by the investigators. Five serious adverse events occurred in 3 patients: 1 patient was hospitalized three times, once for diarrhea and twice for severe anemia; 1 patient was hospitalized for treatment of cellulitis; and 1 patient was hospitalized for a positive blood culture related to a hemodialysis catheter. None of the serious adverse events were considered to be related to B-VEC or placebo by the investigators. One adverse event, mild erythema, was considered to be related to B-VEC. No adverse events led to discontinuation of B-VEC or placebo. The most common adverse events were pruritus, chills, and squamous-cell carcinoma of the skin, each of which occurred in 3 patients (10%). All three

cases of squamous-cell carcinoma occurred at wound sites that had not been exposed to B-VEC or placebo.

To determine potential immunogenicity, levels of antibodies against HSV-1 and C7 before and after treatment were assessed. Because of the difficulty of venipuncture in these patients, 22 of 31 patients (71%) had baseline serum samples. Among the patients with baseline samples, 14 of 22 patients (64%) had antibodies against HSV-1, a finding consistent with the prevalence of seropositivity in the U.S. population,[21] and 1 of 22 patients (5%) had antibodies against C7. Among the patients with baseline samples, 19 had samples at both baseline and week 26, including the patient who had antibodies against C7. By week 26, seroconversion had occurred in 6 of 8 patients (75%) with no antibodies against HSV-1 at baseline (Fig. S4) and in 13 of 18 (72%) with no antibodies against C7 at baseline. No clinically significant immunologic reactions were reported. Treatment response to B-VEC was not associated with baseline HSV-1 serostatus (Table S5) or C7 seroconversion (Table S6).

Table 4. Summary of Adverse Events.*

Event	Safety Population (N=31)
Total no. of adverse events	45
Patients with ≥1 adverse event — no. (%)†	18 (58)
Mild	15 (48)
Moderate	3 (10)
Severe	2 (6)
Serious‡	3 (10)
Related to B-VEC or placebo	1 (3)
Leading to discontinuation of B-VEC or placebo	0
Adverse events reported in ≥5% of patients — no. (%)†§	
Skin and subcutaneous disorders	
Pruritus	3 (10)
Erythema	2 (6)
Rash	2 (6)
General disorders and site conditions: chills	3 (10)
Neoplasms: squamous-cell carcinoma of skin	3 (10)
Respiratory, thoracic, and mediastinal disorders	
Cough	2 (6)
Rhinorrhea	2 (6)

* Data are for adverse events that emerged or worsened after the first application of B-VEC or placebo.
† At each level of summarization, a patient was counted once if one or more events occurred.
‡ Five serious adverse events occurred in three patients: one patient was hospitalized three times, once for diarrhea (severe adverse event) and twice for severe anemia (both severe adverse events); one patient was hospitalized for treatment of cellulitis (severe adverse event); and one patient was hospitalized for a positive blood culture related to a hemodialysis catheter (moderate adverse event).
§ Adverse events were classified according to system organ class and preferred term in the *Medical Dictionary for Regulatory Activities*, version 24.1.

DISCUSSION

In this phase 3 trial of topical B-VEC, the percentages of wounds that had complete healing at 3 months and at 6 months were higher for wounds exposed to B-VEC than for those exposed to placebo. There was a numerically greater reduction in pain from baseline with B-VEC than with placebo during wound-dressing changes. Treatment with B-VEC did not result in treatment-related discontinuations or clinically significant immunologic reactions. These results are concordant with those of an open-label phase 1–2 trial of B-VEC, which showed improvement in complete wound closure at 3 months and evidence of molecular correction.[17] However, biopsies to demonstrate molecular correction were not performed in the current trial.

The primary end point in this trial assessed 100% wound closure, requiring that wounds be completely healed for at least 2 consecutive weeks; this represented a high bar for patients who often have recurrent wounds that are prone to reopening quickly.[22] Requiring healing at two time points distinguished the transient closure observed in wounds exposed to placebo from the more durable closure observed in wounds exposed to B-VEC.

In a phase 3 trial of topical birch triterpenes involving patients with epidermolysis bullosa, complete closure of target wounds within 45 days occurred in 41% of the patients who received the active drug and 29% of those who received placebo.[23] Two ex vivo gene-based approaches, which involve viral transfer of *COL7A1* into keratinocytes or fibroblasts that are harvested from patients and are then transplanted back as an epidermal graft or intradermal injection, are under investigation but require cell-manufacturing procedures, anesthesia, and hospitalization.[9,10] The current trial used B-VEC, an in vivo gene-

transfer treatment that can be topically applied on an outpatient basis.

One obstacle of other gene therapies is that they do not allow repeat dosing because of the development of immunity to the vector, which can induce neutralizing antibody responses. By using a modified, replication-defective HSV-1 backbone, B-VEC has inherent immune-evasive properties, which allow repeat dosing, at least for the period used in the trial. This finding is supported by the lack of any clinically significant immunologic reactions or manifestations of active HSV-1 infection despite weekly dosing for 26 weeks.

Our trial has several limitations. Primary wounds were predominantly no larger than 40 cm^2 in area, although a similar response was observed in larger wounds. The small sample size made evaluation of subgroups impractical. Wounds were selected and assessed during the trial by the site investigator. Only one patient with dominant dystrophic epidermolysis bullosa was enrolled. In this patient, the wound that was exposed to B-VEC had complete healing at 6 months, whereas the wound exposed to placebo did not. Preclinical research has indicated that increasing the expression of wild-type C7 in the skin of patients with dominant dystrophic epidermolysis bullosa can be considered to be a valid therapeutic approach.[24] Five patients had previously been enrolled in the phase 1–2 trial, which may have led to potential sources of bias. The intrapatient design limited evaluation of systemic adverse events because all the patients had received both B-VEC and placebo. Minimal evidence of systemic toxic effects was observed. To minimize the manipulation of wounds and the burden to the patient associated with complex wound-dressing changes, formal assessments for wound closure were performed only at key time points during the trial. Thus, analyses of the precise time to wound closure or change in wound size were not possible.

In this trial involving patients with dystrophic epidermolysis bullosa, we found that repeated topical application of B-VEC, an HSV-1–based gene therapy, resulted in a greater likelihood of complete wound healing than the topical application of placebo at up to 6 months. Longer and larger trials are warranted to determine the durability of effect and risks of this approach.

Supported by Krystal Biotech. Dr. Marinkovich reports receiving salary support from the Office of Research and Development, Palo Alto Veterans Affairs Medical Center.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank current or former Krystal Biotech employees Nick Reitze, Nikhil Sarma, Swati Banerjee, and Cheaney Seiler for their assistance in the processing and analyses of clinical samples and Anastasia McManus for editorial support and critical feedback.

REFERENCES

1. Fine JD. Epidemiology of inherited epidermolysis bullosa based on incidence and prevalence estimates from the National Epidermolysis Bullosa Registry. JAMA Dermatol 2016;152:1231-8.
2. Marinkovich MP. Inherited epidermolysis bullosa. In: Kang S, Amagai M, Bruckner AL, et al., eds. Fitzpatrick's dermatology, 9th ed. New York: McGraw Hill, 2019:1011-35.
3. Bruckner AL, Losow M, Wisk J, et al. The challenges of living with and managing epidermolysis bullosa: insights from patients and caregivers. Orphanet J Rare Dis 2020;15:1.
4. Bardhan A, Bruckner-Tuderman L, Chapple ILC, et al. Epidermolysis bullosa. Nat Rev Dis Primers 2020;6:78.
5. Fine J-D, Johnson LB, Weiner M, Li K-P, Suchindran C. Epidermolysis bullosa and the risk of life-threatening cancers: the National EB Registry experience, 1986–2006. J Am Acad Dermatol 2009;60:203-11.
6. Condorelli AG, Dellambra E, Logli E, Zambruno G, Castiglia D. Epidermolysis bullosa-associated squamous cell carcinoma: from pathogenesis to therapeutic perspectives. Int J Mol Sci 2019;20:5707.
7. Marinkovich MP, Tang JY. Gene therapy for epidermolysis bullosa. J Invest Dermatol 2019;139:1221-6.
8. Wagner JE, Ishida-Yamamoto A, McGrath JA, et al. Bone marrow transplantation for recessive dystrophic epidermolysis bullosa. N Engl J Med 2010;363:629-39.
9. 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;316:1808-17.
10. Lwin SM, Syed F, Di WL, et al. Safety and early efficacy outcomes for lentiviral fibroblast gene therapy in recessive dystrophic epidermolysis bullosa. JCI Insight 2019;4:e126243.
11. Knight S, Collins M, Takeuchi Y. Insertional mutagenesis by retroviral vectors: current concepts and methods of analysis. Curr Gene Ther 2013;13:211-27.
12. Gene therapy needs a long-term approach. Nat Med 2021;27:563.
13. 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.
14. Verdera HC, Kuranda K, Mingozzi F. AAV vector immunogenicity in humans: a long journey to successful gene transfer. Mol Ther 2020;28:723-46.
15. Shirley JL, de Jong YP, Terhorst C, Herzog RW. Immune responses to viral gene therapy vectors. Mol Ther 2020;28:709-22.
16. Hamilton BA, Wright JF. Challenges posed by immune responses to AAV vectors: addressing root causes. Front Immunol 2021;12:675897.
17. Gurevich I, Agarwal P, Zhang P, et al. In vivo topical gene therapy for recessive dystrophic epidermolysis bullosa: a phase 1 and 2 trial. Nat Med 2022;28:780-8.

18. Food and Drug Administration. Human gene therapy for rare diseases: guidance for industry. January 2020 (https://www.fda.gov/media/113807/download).
19. Has C, Bauer JW, Bodemer C, et al. Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility. Br J Dermatol 2020;183:614-27.
20. Schafer JL. Analysis of incomplete multivariate data. London: Chapman and Hall, 1997:115.
21. Xu F, Schillinger JA, Sternberg MR, et al. Seroprevalence and coinfection with herpes simplex virus type 1 and type 2 in the United States, 1988–1994. J Infect Dis 2002;185:1019-24.
22. Solis DC, Teng C, Gorell ES, et al. Classification of 2 distinct wound types in recessive dystrophic epidermolysis bullosa: a retrospective and cohort natural history study. J Am Acad Dermatol 2021;85:1296-8.
23. Kern JS, Sprecher E, Fernandez MF, et al. Efficacy and safety of Oleogel-S10 (birch triterpenes) for epidermolysis bullosa — results from the phase 3, randomised, double-blind phase of the "EASE" study. Br J Dermatol 2022 October 20 (Epub ahead of print).
24. Fritsch A, Spassov S, Elfert S, et al. Dominant-negative effects of COL7A1 mutations can be rescued by controlled overexpression of normal collagen VII. J Biol Chem 2009;284:30248-56.