GEM-3: Phase 3 Safety and Immunogenicity Results of Beremagene Geperpavec (B-VEC), an Investigational, Topical Gene Therapy for Dystrophic Epidermolysis Bullosa (DEB)

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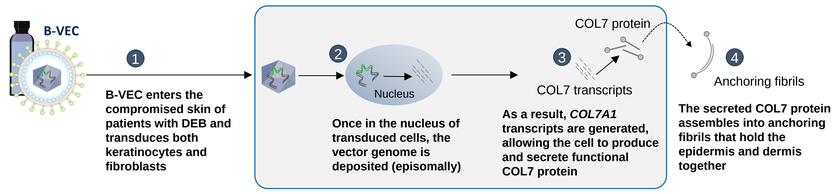
Introduction

- Dystrophic epidermolysis bullosa (DEB) is a serious, ultra-rare genetic blistering disease caused by mutations in the *COL7A1* gene that lead to skin fragility and wounds[1-3]
  - DEB affects ≈9000 people globally, including ≈3000 people in the United States and ≈3000 people in Europe[4]
  - Patients with DEB require proactive management and care due to an increased risk of aggressive squamous cell carcinoma (SCC) and a wide range of other serious secondary complications, regardless of wound size or chronicity[5-7]
  - Current management of DEB is limited to supportive care, such as ameliorating symptoms, palliative wound care, and managing secondary complications[8,9]
- Beremagene geperpavec (B-VEC) is an investigational herpes simplex virus type 1 (HSV-1)–based, topical, redosable gene therapy designed to restore type VII collagen (COL7) protein by delivering the *COL7A1* gene[10] (**Figure 1**)
  - B-VEC utilizes a differentiated HSV-1 vector platform that allows for episomal delivery, high payload capacity, tropism for the skin, and evasion of the immune system, enabling repeat delivery[10]

Figure 1. B-VEC mechanism of action

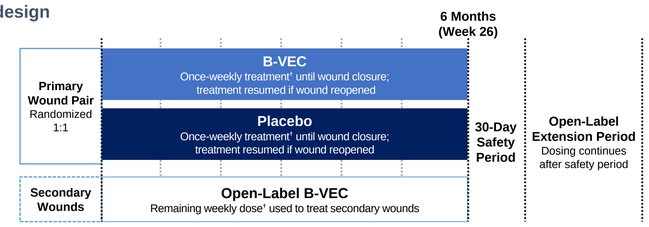


B-VEC, beremagene geperpavec; COL7, type VII collagen; *COL7A1*, collagen type VII alpha 1 chain gene; DEB, dystrophic epidermolysis bullosa.

Methods

- GEM-3 (NCT04491604) is a phase 3, multicenter, double-blind, placebo-controlled intra-patient–randomized study evaluating the efficacy and safety of B-VEC in patients with DEB (**Figure 2**)
- Serum samples before (screening or Week 1) and after (Week 26) B-VEC treatment were collected from patients and evaluated for anti-drug antibodies
  - Anti–HSV-1 specific antibodies were evaluated using a validated plaque reduction neutralization test (PRNT), which determines the percent reduction in B-VEC–mediated plaque formation in the presence of serially diluted patient sera (1:80 to 1:5120) and is reported as PRNT50 (defined as the serum dilution at which a ≈50% reduction in plaques is observed)
  - Immunoglobulin G antibodies against human COL7 were evaluated using a commercially available anti-COL7 enzyme-linked immunosorbent assay (EA 1947-4801 G, EUROIMMUN, Lübeck, Germany), which qualitatively determines anti-COL7 serostatus

Figure 2. GEM-3 study design



†Maximum weekly dose (PFU/week) was based on patient's age and unit dose (PFU/wound) was determined based on wound area at baseline. *Complete wound healing defined as 100% wound closure from exact wound area at baseline, specified as skin re-epithelialization without drainage.
B-VEC, beremagene geperpavec; COL7, type VII collagen; DEB, dystrophic epidermolysis bullosa; HSV-1, herpes simplex virus type 1; PFU, plaque-forming unit.

Results

Patient Disposition

- The intent-to-treat (ITT) population, used for all primary and secondary efficacy analyses, included 31 randomized patients, each with a primary wound pair (**Table 1**)
- The safety population, used for all safety analyses, was the same as the ITT population
- Of 31 randomized patients, 3 withdrew from the study for nondrug-related reasons

Table 1. Baseline demographics and clinical characteristics

Patient demographics/characteristics	Total patients (N=31)	
Age, years		
Mean (SD)	17.2 (10.7)	
Range	1-44	
Age category, n (%)		
≤12 years	10 (32.3)	
>12-≤18 years	9 (29.0)	
>18 years	12 (38.7)	
Male sex, n (%)	20 (64.5)	
Race, n (%)		
White	20 (64.5)	
Asian	6 (19.4)	
American Indian or Alaska native	5 (16.1)	
Genotype, n (%)		
Dominant DEB (DDEB)	1 (3.2)	
Recessive DEB (RDEB)	30 (96.8)	
Primary wound	**B-VEC (N=31)**	**Placebo (N=31)**
Wound area by size, cm²		
Mean (SD)	14.4 (12.7)	15.6 (12.1)
Range	2.3-57.3	2.3-51.5
Wound area by size category*, n (%)		
<20 cm²	23 (74.2)	22 (71.0)
20-<40 cm²	6 (19.4)	8 (25.8)
40-60 cm²	2 (6.5)	1 (3.2)

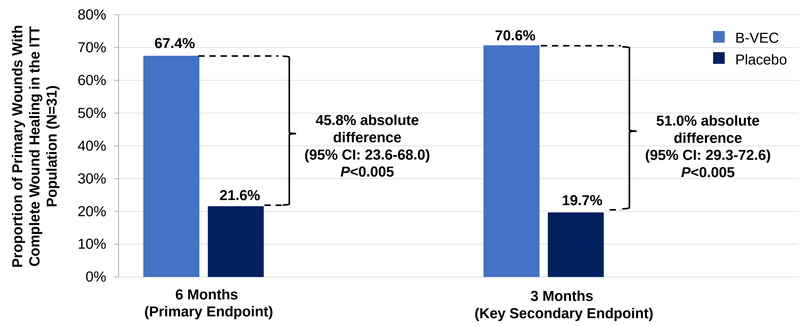
*In a small number of patients, the predefined threshold values for wound area by size category fell in between the size of the 2 wounds. B-VEC, beremagene geperpavec; DEB, dystrophic epidermolysis bullosa; SD, standard deviation.

Results (cont.)

Efficacy

- The proportion of primary wounds with complete wound healing was significantly greater with B-VEC than placebo at both the 3- and 6-month timepoints (*P*<0.005; **Figure 3**)
  - In the patient with DDEB, the primary endpoint of complete wound healing at 6 months was achieved by the B-VEC–treated wound, but not by the placebo-treated wound
- Pain and health-related quality of life assessments demonstrated improvement consistent with a wound healing response

Figure 3. Proportion of primary wounds with complete healing at 6 and 3 months of B-VEC or placebo treatment



Data as of database lock on November 19, 2021; data in figure based on ITT population (imputed); *P* values and CIs are based on exact McNemar's test.
B-VEC, beremagene geperpavec; CI, confidence interval; ITT, intent to treat.

Safety

- The majority of adverse events (AEs) were mild or moderate; no AEs led to treatment discontinuation or death (**Table 2**)
- One AE, mild erythema, was considered possibly related to study drug as assessed by the investigator
- Three patients experienced a total of 5 serious AEs during the study: anemia (2 events) cellulitis, diarrhea, and positive blood culture (1 event each)
  - None were considered related to study drug
- The most frequently reported AEs were pruritus, chills, and SCC (3 patients each)
  - All 3 reports of SCC occurred at sites that were not directly exposed to B-VEC or placebo and were deemed not related to study drug

Table 2. Safety summary

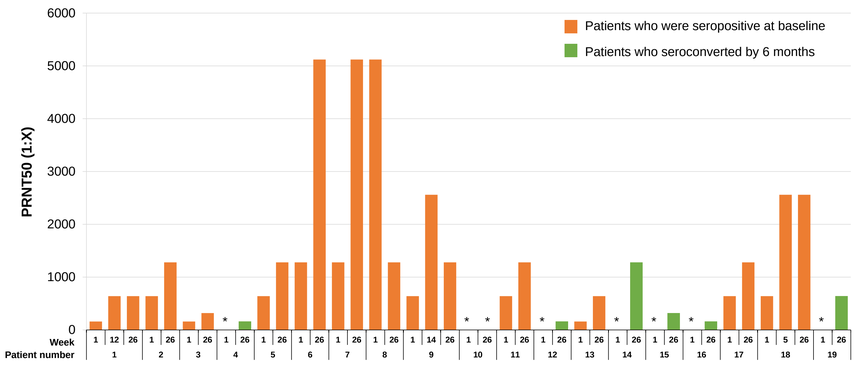
	Total patients (N=31)
Total number of AEs	45
Patients with ≥1 AE, n (%)	18 (58.1)
Mild AE	15 (48.4)
Moderate AE	3 (9.7)
Severe AE	2 (6.5)
Serious AE	3 (9.7)
Drug-related AE	1 (3.2)
AE leading to treatment discontinuation	0 (0)
Death	0 (0)
AEs reported in ≥5% of patients by System Organ Class and Preferred Term*, n (%)	
Skin and subcutaneous disorders	
Pruritus	3 (9.7)
Erythema	2 (6.5)
Rash	2 (6.5)
General disorders and site conditions	
Chills	3 (9.7)
Neoplasms benign, malignant, and unspecified	
Squamous cell carcinoma of the skin	3 (9.7)
Respiratory, thoracic, and mediastinal disorders	
Cough	2 (6.5)
Rhinorrhea	2 (6.5)

*AEs were coded using MedDRA version 24.1. At each level of summarization, a patient was counted once if the patient reported ≥1 event.
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.

Antibody Responses

- 22 of 31 patients (71.0%) provided a serum sample at baseline due to the difficulty of blood draws owing to skin fragility; 19 of the 22 patients (86.4%) also had matched serum samples at 6 months
- At baseline, 14 of the 22 patients (63.6%) were anti–HSV-1 antibody seropositive and 8 were seronegative, in agreement with seropositivity rates of the general US population[11]; 6 of 8 (75.0%) baseline seronegative patients seroconverted by 6 months
- For baseline seropositive patients, where quantitative differences at study completion could be calculated, antibody responses were variable (**Figure 4**), and none were determined to be meaningful, as defined by a >4-fold sustained increase in anti–HSV-1 antibody titer

Figure 4. Anti–HSV-1 antibodies in pre- and post-treatment patient serum samples

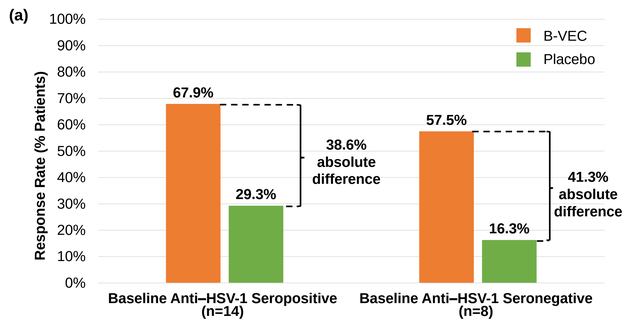


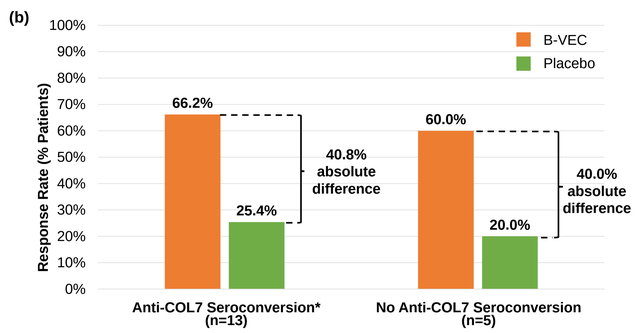
*Below limit of detection.
Seroconversion defined as seronegative at baseline but seropositive at 6 months.
HSV-1, herpes simplex virus type 1; PRNT, plaque reduction neutralization test; PRNT50, the serum dilution at which a ≈50% reduction in B-VEC–mediated plaques is observed.

Results (cont.)

- At baseline, 1 of 22 patients (4.5%) was positive for anti-COL7 antibodies
- 13 of 18 patients (72.2%) with matched serum samples seroconverted by 6 months; no clinically significant immunologic reactions or differences in treatment response were seen
- Post hoc analysis of response rates in primary wound pairs at 6 months suggested equivalent efficacy regardless of baseline anti–HSV-1 antibody status (**Figure 5a**)
- At 6 months, post hoc analysis of treatment response to B-VEC was consistent regardless of anti-COL7 seroconversion (**Figure 5b**)
  - A responder was defined as meeting the primary endpoint of complete wound healing at 6 months

Figure 5. B-VEC response rate at 6 months according to (a) baseline anti–HSV-1 serostatus and (b) anti-COL7 seroconversion





*Seroconversion defined as seronegative at baseline but seropositive when tested at 6 months. Data in figure based on post hoc analysis using imputation.
B-VEC, beremagene geperpavec; COL7, type VII collagen; HSV-1, herpes simplex virus type 1.

Conclusions

- **B-VEC treatment demonstrated a durable and statistically significant improvement in complete wound healing at 3 and 6 months compared with placebo**
- **B-VEC was generally well tolerated, with no treatment-related discontinuations**
- **No clinically significant immunologic reactions were reported during the study**
- **Treatment response to B-VEC was not associated with anti–HSV-1 serostatus at baseline or with anti-COL7 seroconversion**
- **An ongoing open-label extension study (NCT04917874) is investigating the long-term efficacy and safety of B-VEC in patients with DEB, regardless of prior enrollment in GEM-3**

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Disclosures

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