GEM-3: A Phase 3 Study of Beremagene Geperpavec (B-VEC), an Investigational, Topical Gene Therapy, for the Treatment of Dystrophic Epidermolysis Bullosa (DEB)

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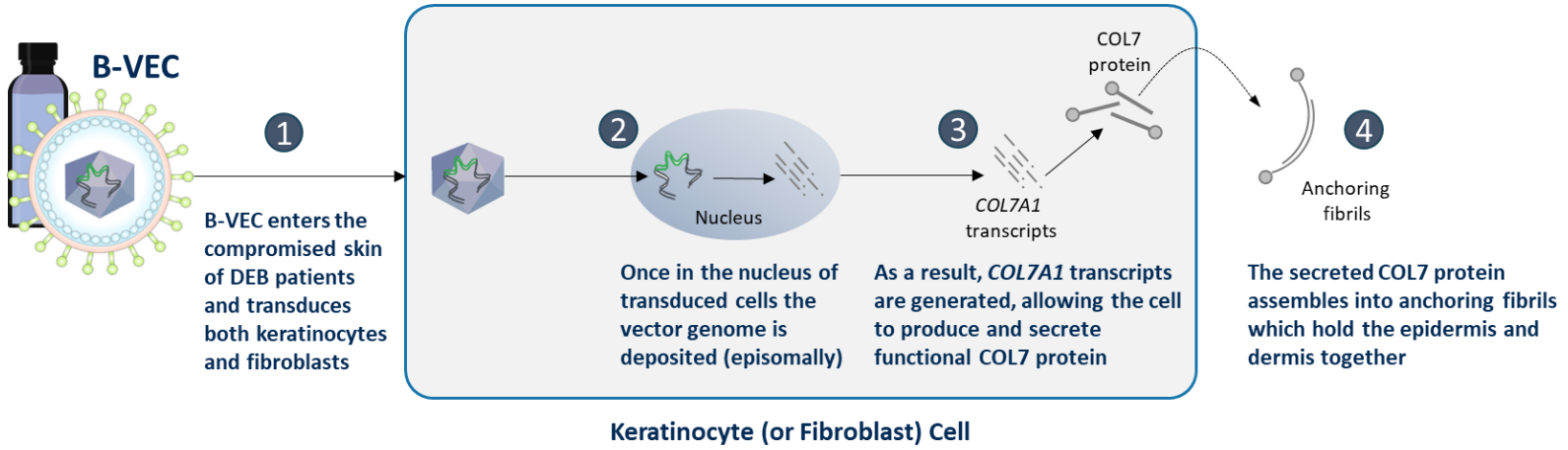
Dystrophic Epidermolysis Bullosa and B-VEC

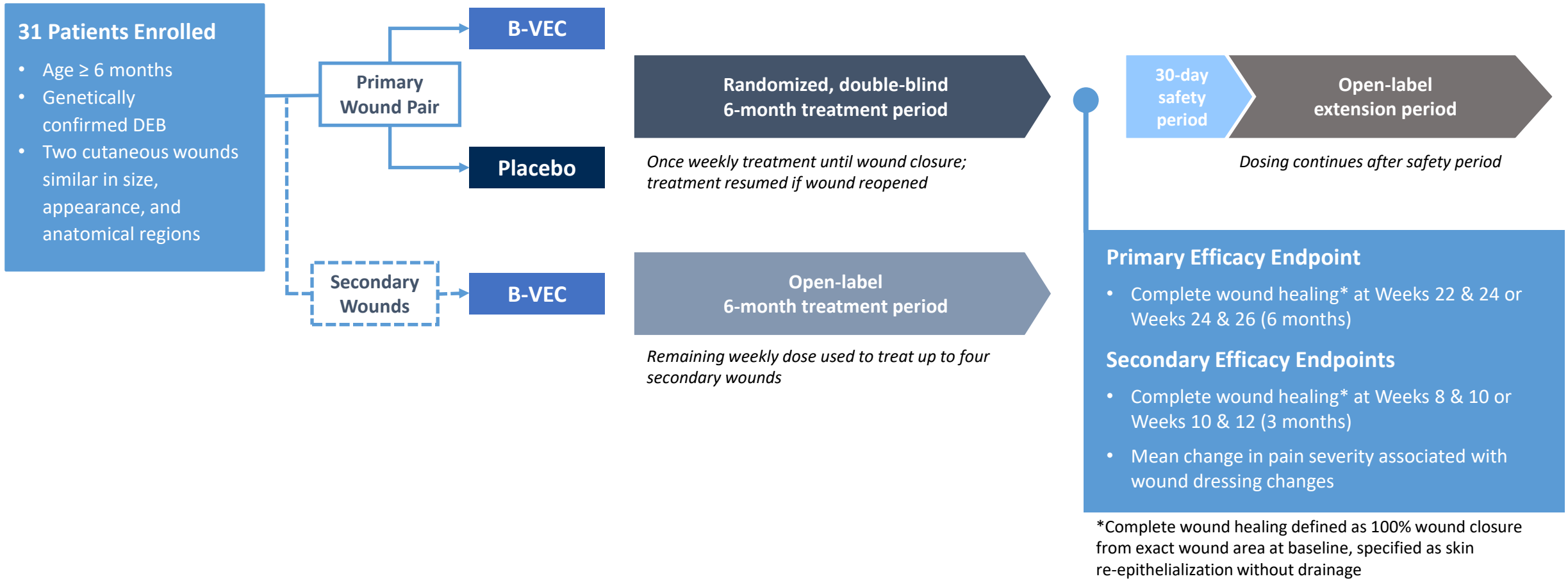
- Dystrophic epidermolysis bullosa (DEB) is a serious, ultra-rare genetic blistering disease caused by mutations in the *COL7A1* gene which lead to skin fragility and wounds[1-3]
  - Patients with DEB are at increased risk for serious complications, including aggressive squamous cell carcinoma[4-6]; management is currently supportive in nature[7,8]
- Beremagene geperpavec (B-VEC) is an investigational HSV-1-based topical, redosable gene therapy designed to restore functional COL7 protein by delivering the *COL7A1* gene
  - B-VEC utilizes a differentiated HSV-1 vector platform that allows for episomal delivery, high payload capacity, tropism for skin cells, and evades the immune system enabling repeat delivery



1. Fine J-D, et al. *J Am Acad Dermatol*. 2014;70(6):1103-1126; 2. Fine J-D. *JAMA Dermatol*. 2016;152(11):1231-1238; 3. Bardhan A, et al. *Nat Rev Dis Primers*. 2020 Sep 24;6(1):78; 4. Condorelli A, et al. *Int J Mol Sci*. 2019;20(22):5707; 5. Montaudié H, et al. *Orphanet J Rare Dis*. 2016;11(1):117; 6. Fine J-D, Mellerio JE. *J Am Acad Dermatol*. 2009;61:367-384; 7. Denyer J, et al. Accessed March 16, 2022. https://www.woundsinternational.com/download/resource/5921; 8. Bruckner AL, et al. *Orphanet J Rare Dis*. 2020;15(1):1.
B-VEC, beremagene geperpavec; COL7, type VII collagen; *COL7A1*, collagen type VII alpha 1 chain; DEB, dystrophic epidermolysis bullosa; HSV-1, herpes simplex virus type 1

GEM-3 Study Design

- GEM-3 (NCT04491604) is a Phase 3, multicenter, randomized, double-blind, placebo-controlled intra-patient study evaluating the efficacy and safety of B-VEC in patients with DEB

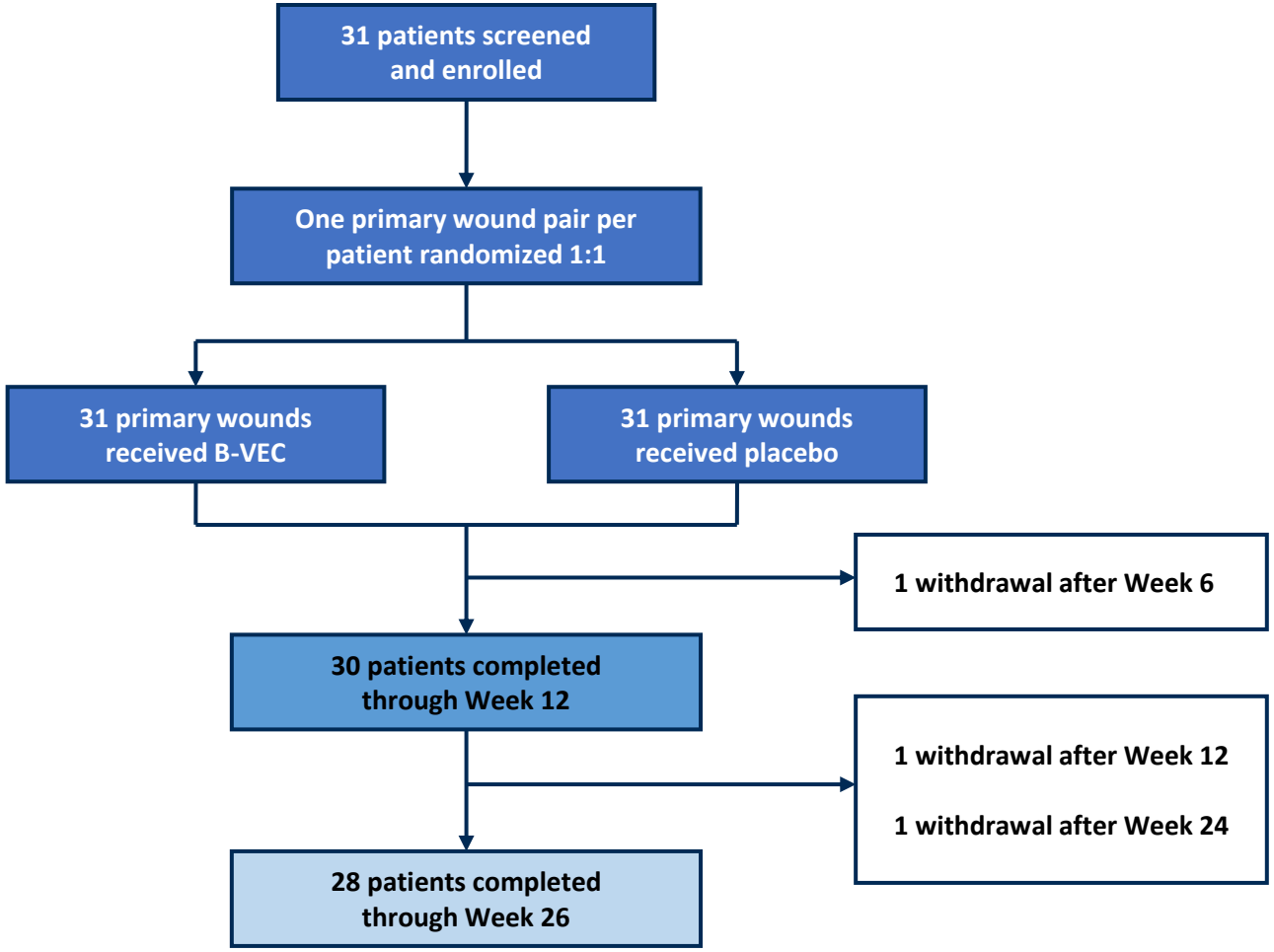


*Complete wound healing defined as 100% wound closure from exact wound area at baseline, specified as skin re-epithelialization without drainage

B-VEC, beremagene geperpavec; DEB, dystrophic epidermolysis bullosa

Patient Disposition

- 31 patients were randomized and made up the intent-to-treat (ITT) population used for all primary and secondary efficacy analyses
- The safety population was the same as the ITT population and used for all safety analyses
- Three patients withdrew from the study for nondrug-related reasons



B-VEC, beremagene geperpavec; ITT, intent-to-treat

Baseline Demographics and Clinical Characteristics

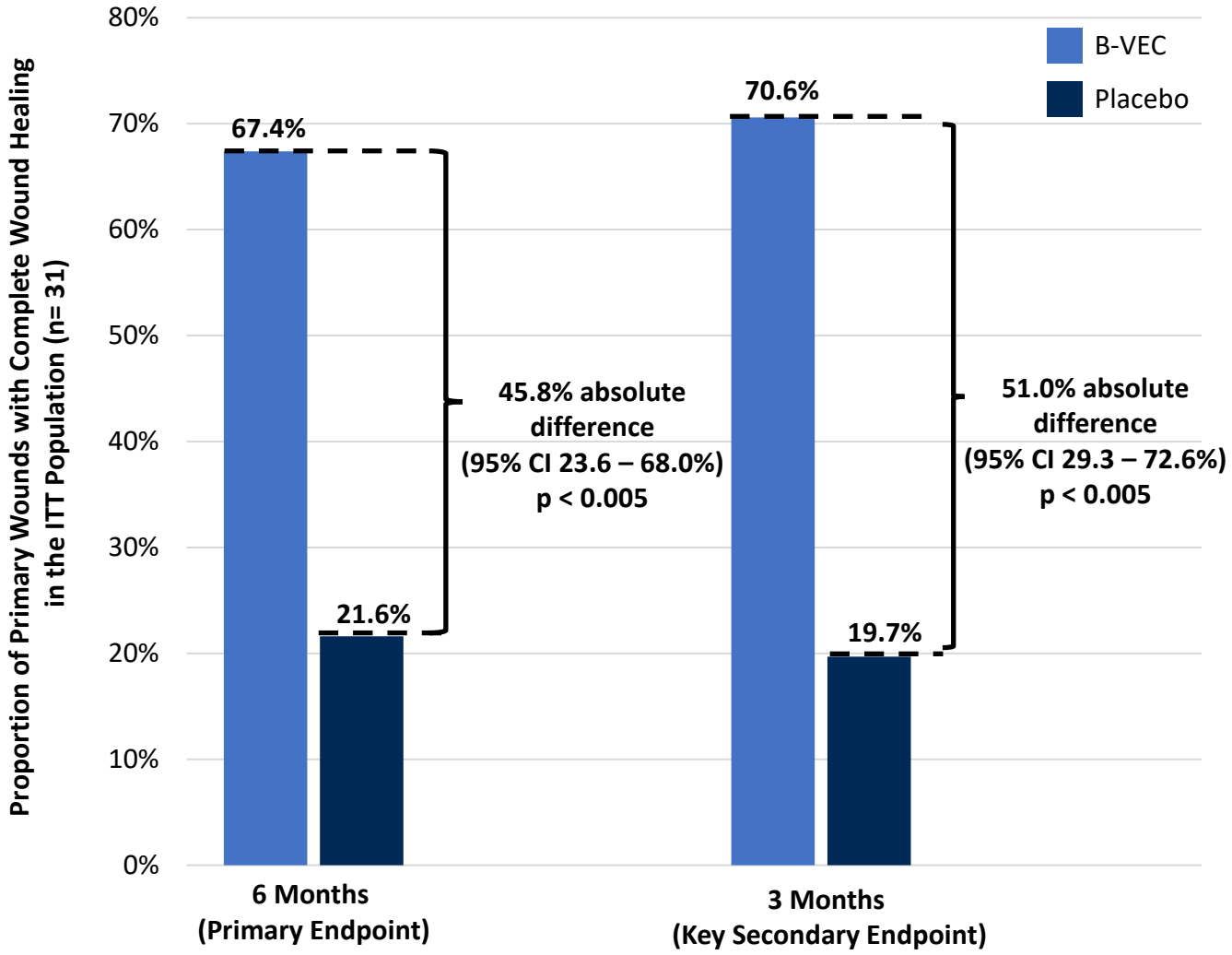
	Total patients (n=31)
Age, years	
Mean (SD)	17.2 (10.7)
Range	1 – 44
Age category, n (%)	
≤12 years	10 (32.3)
>12 and ≤18 years	9 (29.0)
>18 years	12 (38.7)
Sex, n (%)	
Male	20 (64.5)
Female	11 (35.5)
Race, n (%)	
White	20 (64.5)
Asian	6 (19.4)
American Indian or Alaska Native	5 (16.1)

	Total patients (n=31)
Genotype, n (%)	
DDEB	1 (3.2)
RDEB	30 (96.8)

Primary wound	B-VEC (n=31)	Placebo (n=31)
Wound area/size, cm^2		
Mean (SD)	14.4 (12.7)	15.6 (12.1)
Range	2.3 – 57.3	2.3 – 51.5
Wound area/size category*, n (%)		
<20 cm^2	23 (74.2)	22 (71.0)
20 - <40 cm^2	6 (19.4)	8 (25.8)
40 – 60 cm^2	2 (6.5)	1 (3.2)

*In a small number of patients, the pre-defined threshold values for wound area/size category fell in between the size of the two wounds
B-VEC, beremagene geperpavec; DDEB, dominant dystrophic epidermolysis bullosa; RDEB, recessive dystrophic epidermolysis bullosa; SD, standard deviation

Significantly Greater Complete Wound Healing with B-VEC Treatment

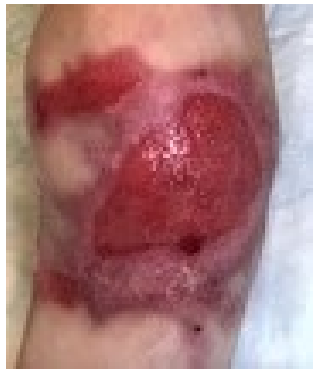
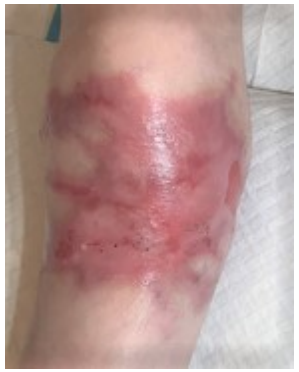
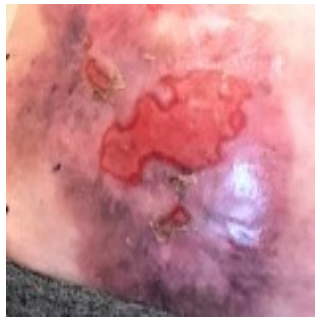
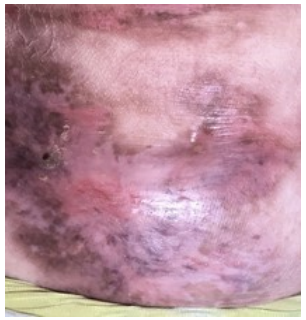
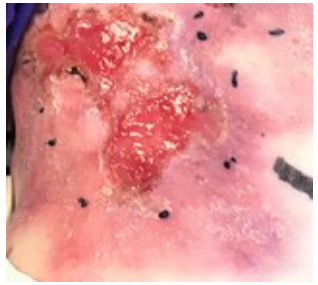
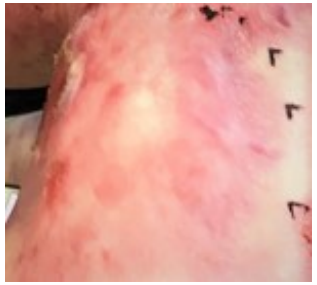


- The proportion of primary wounds with complete wound healing was significantly greater with B-VEC than placebo at both 3- and 6-month timepoints (p <0.005)
- In the patient with DDEB, primary endpoint of complete wound healing at 6 months was achieved by the B-VEC treated wound, but not by the placebo treated wound
- At 6 months, 15 of 17 discordant pairs showed response to B-VEC but not placebo
  - Discordant pair defined as when one wound meets complete wound healing responder definition and other does not

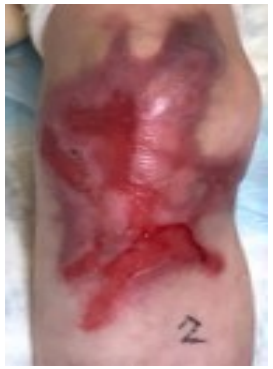
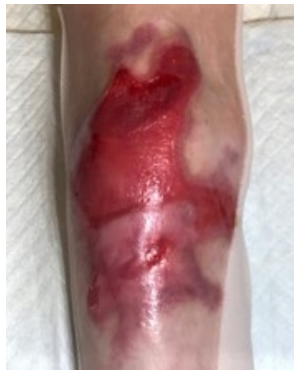
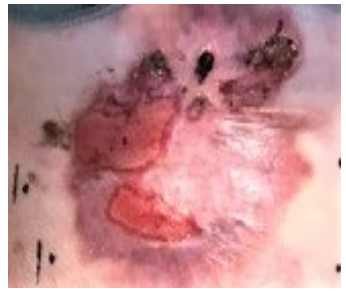
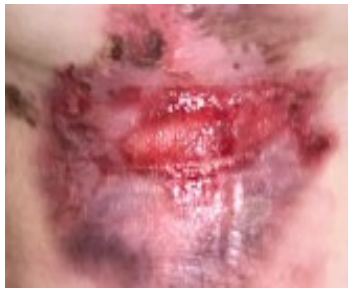
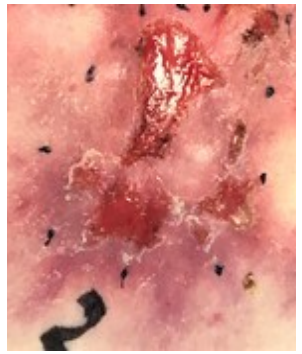
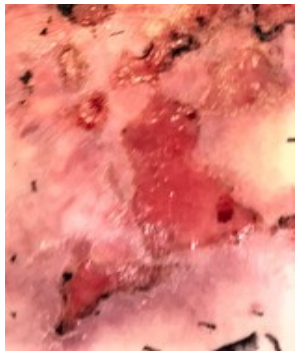
Data as of database lock on 19Nov2021; data in figure based on ITT population (imputed); p-values and CIs are based on exact McNemar's test
B-VEC, beremagene geperpavec; CI, confidence interval; DDEB, dominant dystrophic epidermolysis bullosa; ITT, intent-to-treat

Primary Wound Pairs (15 – 30 cm^2) at Baseline and 6 Months

B-VEC

	Baseline	6 Months
Patient A Knee		
Patient B Lower abdomen		
Patient C Lower trapezius		

Placebo

	Baseline	6 Months
Patient A Knee		
Patient B Sternum		
Patient C Upper paraspinal		

B-VEC, beremagene geperpavec

Treatment with B-VEC Demonstrated Durability of Response

- 49.7% of B-VEC treated wounds compared to 7.1% of placebo treated wounds demonstrated durability of response, defined as wounds that met complete wound healing at both 3 months (key secondary endpoint) and 6 months (primary endpoint)
- Nearly half of all B-VEC treated wounds demonstrated complete wound healing for three consecutive visits

	Responder, n (%)		Absolute Difference, % (95% CI)
	B-VEC (n=31)	Placebo (n=31)	
Durability of response†	15.4 (49.7)	2.2 (7.1)	42.6 (22.6, 62.6)
Complete wound healing			
Weeks 8, 10, and 12	14.8 (47.7)	5.1 (16.5)	31.3 (10.6, 51.9)
Weeks 22, 24, and 26	13.4 (43.2)	2.0 (6.5)	36.8 (19.8, 53.7)

†Durability of response was defined as meeting the responder definition for complete wound healing both at 3 months (Weeks 8 & 10 or Weeks 10 & 12) and at 6 months (Weeks 22 & 24 or Weeks 24 & 26)
Percentages are based on the number of subjects in the intent-to-treat (ITT) population; CIs are based on McNemar's test
Missing endpoint data were imputed assuming the data are missing at random and using multiple imputation methodology

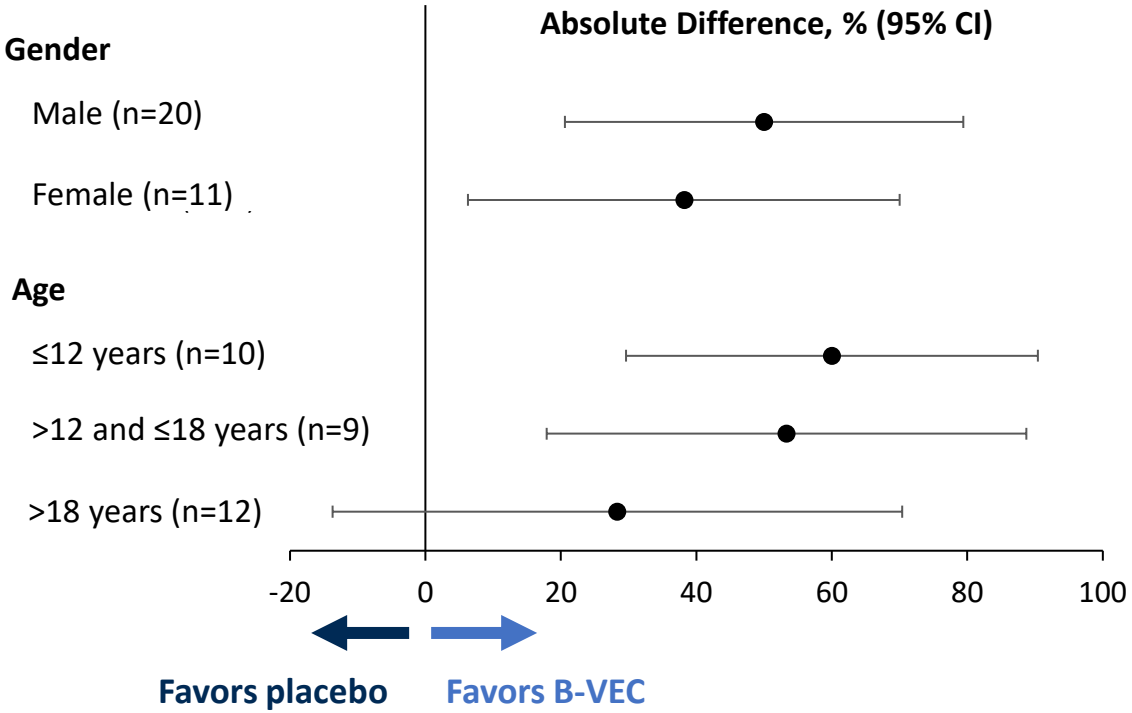
- Of the total B-VEC wounds closed at 3 months, 66.7% (14/21) of B-VEC-treated wounds were also closed at 6 months, as compared to 33.3% (2/6) for placebo treated wounds (p=0.02)

Data as of database lock on 19Nov2021
B-VEC, beremagene geperpavec; CI, confidence interval

Consistent Evidence of a Treatment Response with B-VEC Across Subgroups

- Treatment response was in favor of B-VEC for all gender, age, and wound area/size subgroups, however the individual subgroups were not powered to demonstrate statistical significance

Complete Wound Healing at 6 Months by Gender and Age Subgroups



Complete Wound Healing at 6 Months by Baseline Primary Wound Area/Size Category

Baseline primary wound area/size category*	B-VEC		Placebo	
	N	Complete wound healing at 6 months, n (%)	N	Complete wound healing at 6 months, n (%)
<20 cm²	23	14 (60.9)	22	5 (22.7)
20 - <40 cm²	6	4 (66.7)	8	1 (12.5)
40 – 60 cm²	2	1 (50.0)	1	0 (0)

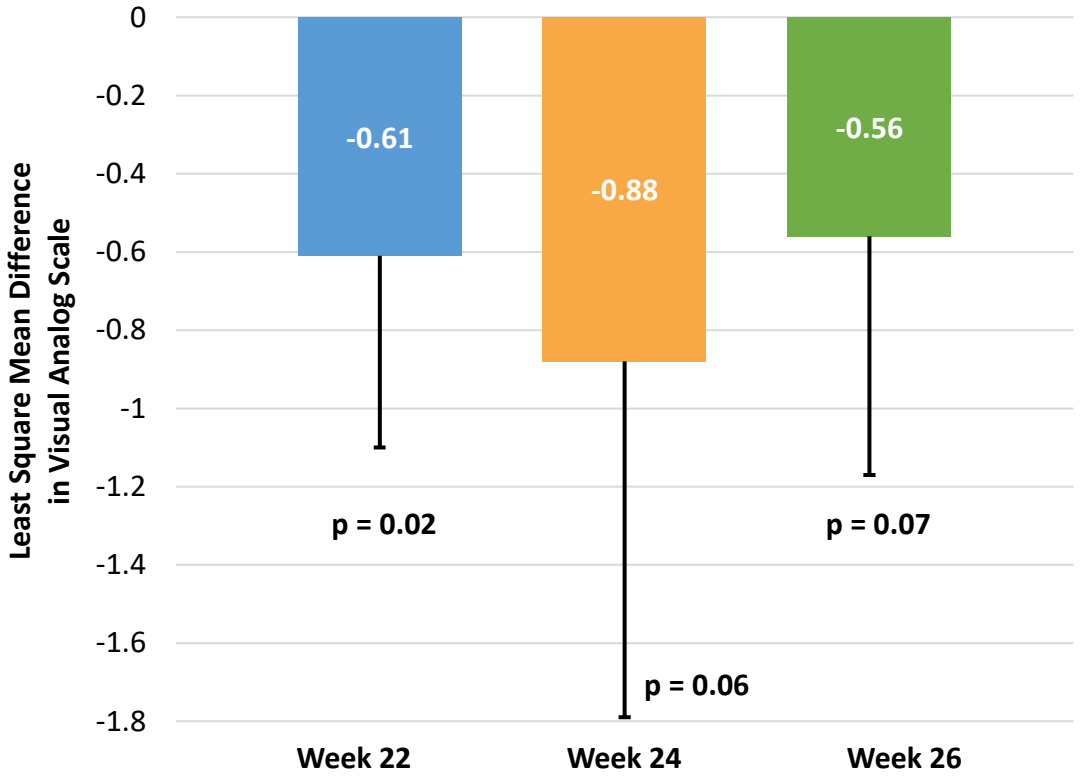
*In a small number of patients, the pre-defined threshold values for wound area/size category fell in between the size of the two wounds

Data as of database lock on 19Nov2021; data in figures based on ITT population (imputed); p-values and CIs are based on exact McNemar's test; gender and age subgroups were pre-specified
B-VEC, beremagene geperpavec; CI, confidence interval; ITT, intent-to-treat

Pain and PRO Assessments Demonstrated Improvement Consistent with a Wound Healing Response

- Baseline VAS score of enrolled patients were approximately 2 to 3 on average
- A trend towards decreased pain in B-VEC treated versus placebo treated wounds was observed across Weeks 22, 24, and 26; improvement in pain was consistent with wound healing
- PRO measures (EQ-5D-5L and Skindex-29) assessed before and after treatment with B-VEC demonstrated improvement across multiple domains directionally, consistent with a wound healing response

Change from Baseline in Pain following B-VEC Treatment



Change from baseline in pain severity associated with wound dressing changes, as measured by Visual Analog Scale, at Weeks 22, 24, and 26 for the ITT population, ages 6 and above
Least square mean difference, 95% CI (shown as error bars), and p values were generated from analysis of covariance linear model with treatment and subject as the fixed effects and the baseline value as the covariate and change from baseline as the dependent variable

Data as of database lock on 19Nov2021
B-VEC, beremagene geperpavec; ITT, intent-to-treat; PRO, patient reported outcomes; VAS, Visual Analog Scale

B-VEC was Generally Well-Tolerated

- The majority of AEs were mild; there were no AEs leading to treatment discontinuation or death
- One AE, mild erythema, was considered possibly related to study drug as assessed by the investigator
- Three patients experienced a total of 5 SAEs during the study: cellulitis, anemia (2 events), diarrhea, and positive blood culture
  - None were considered related to study drug
- No clinically significant immunologic reactions were reported during the study
- Treatment response to B-VEC was not associated with HSV-1 serostatus at baseline or with COL7 seroconversion

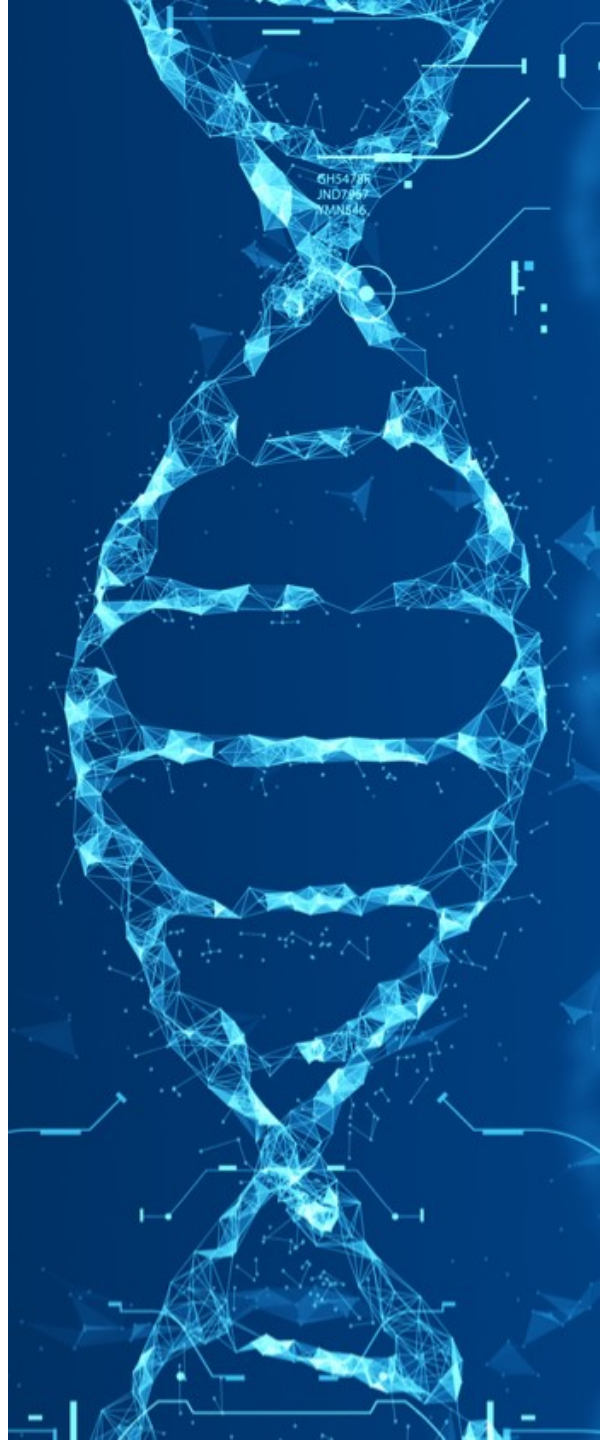
	Total Patients (n=31)
Total number of adverse events (AEs)	45
Patients with ≥ 1 AE, n (%)	18 (58.1)
Serious AEs	3 (9.7)
Severe AEs	2 (6.5)
Drug-related AEs	1 (3.2)
AE leading to treatment discontinuation	0 (0)
Death	0 (0)

Data as of database lock on 19Nov2021
AEs, adverse events; B-VEC, beremagene geperpavec; COL7, type VII collagen; HSV-1; herpes simplex virus type 1; SAEs, serious adverse events

Conclusions

- DEB is a serious, ultra-rare genetic blistering disease caused by mutations in the *COL7A1* gene; no approved therapies are currently available
- B-VEC is an investigational HSV-1-based topical, redosable gene therapy designed to restore functional COL7 protein
- B-VEC treatment demonstrated a durable and statistically significant improvement in complete wound healing at 3 and 6 months compared to placebo
- Pain and PRO assessments showed improvement with B-VEC treatment, consistent with a wound healing response
- B-VEC was generally well-tolerated with no treatment-related discontinuations
- An ongoing open-label extension study is investigating the long-term use of B-VEC in patients with DEB, regardless of prior enrollment in GEM-3

Thank you to the patients, families, investigators, and study staff for their participation in the GEM-3 study



Open-label extension study: NCT04917874
B-VEC, beremagene geperpavec; COL7, type VII collagen; COL7A1, collagen type VII alpha 1 chain; DEB, dystrophic epidermolysis bullosa; HSV-1, herpes simplex virus type 1; PRO, patient reported outcomes