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

M. Peter Marinkovich,[1] Mercedes E. Gonzalez,[2] Shireen V. Guide,[3] I. Sinem Bagci,[1] Surya Chitra,[4] Brittani Agostini,[5] Hubert Chen,[5] Trevor Parry,[5] Suma Krishnan[5]

[1]Stanford University, Redwood City, CA, USA; [2]University of Miami, Miami, FL, USA; [3]Mission Dermatology Center, Children's Hospital of Orange County, University of California, Irvine, Department of Dermatology, Rancho Santa Margarita, CA, USA; [4]Savio Group Analytics & Statistics, Hockessin, DE, USA; [5]Krystal Biotech, Inc., Pittsburgh, PA, USA

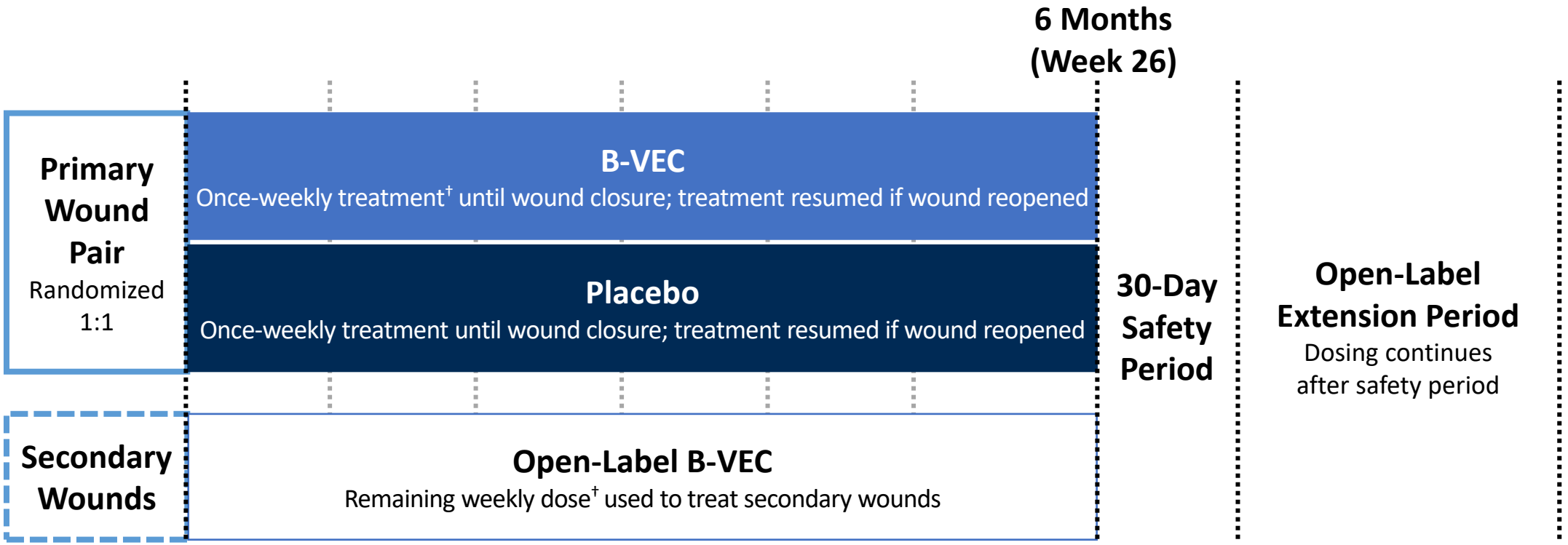
Disclosures

- M. Peter Marinkovich reports the following disclosures:
  - Krystal Biotech (Investigator), Abeona Therapeutics (Investigator), CastleCreek (Investigator), Phoenix Tissue Repair (Investigator), WINGS Therapeutics (Investigator)
- This study was funded by Krystal Biotech, Inc.

GEM-3: Phase 3 Study Evaluating the Efficacy and Safety of B-VEC in Patients with DEB

31 patients enrolled

- Age ≥6 months
- Genetically confirmed DEB
- Two cutaneous primary wounds similar in size, appearance, and anatomical region
- B-VEC dose based on patient age and wound size†



Primary Efficacy Endpoint

– Complete wound healing* at Weeks 22 & 24 or Weeks 24 & 26 (6 months)

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

Secondary Efficacy Endpoints

– Complete wound healing* at Weeks 8 & 10 or Weeks 10 & 12 (3 months)

– Mean change in pain severity associated with wound dressing changes

Safety Endpoints

– Adverse events, vital signs, physical/skin examination, and laboratory evaluations

– Pre- and post-treatment anti-HSV-1 and anti-COL7 antibodies

NCT04491604; †Maximum weekly dose (PFU/week) was based on patient's age and unit dose (PFU/wound) was determined based on wound area at baseline.
B-VEC, beremagene geperpavec; COL7, type VII collagen; DEB, dystrophic epidermolysis bullosa; HSV-1, herpes simplex virus type 1; PFU, plaque-forming unit.

B-VEC was Generally Well Tolerated

- The majority of AEs were mild or moderate; no AEs led to treatment discontinuation or death
- One AE, mild erythema, was considered possibly related to study drug as assessed by the investigator
- The most frequently reported AEs were pruritus, chills, and squamous cell carcinoma (3 patients each)
  - All 3 reports of squamous cell carcinoma occurred at sites that were not directly exposed to B-VEC or placebo and were deemed not related to study drug

	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 (%)	Total patients (n=31)
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.

Anti-HSV-1 and Anti-COL7 Antibody Results

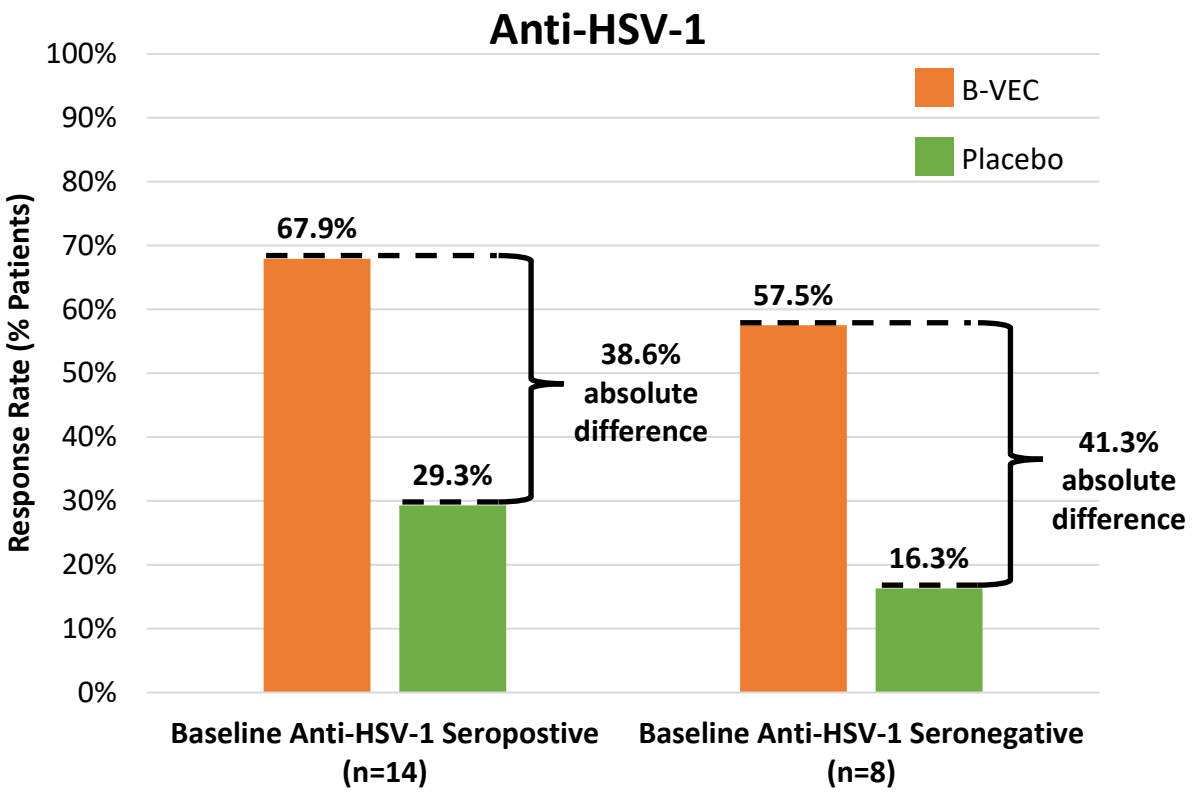
- 22 of 31 patients (71.0%) provided a serum sample at baseline due to the difficulty of blood draws owing to skin fragility
  - 19 of the 22 patients (86.4%) also had matched serum samples at 6 months

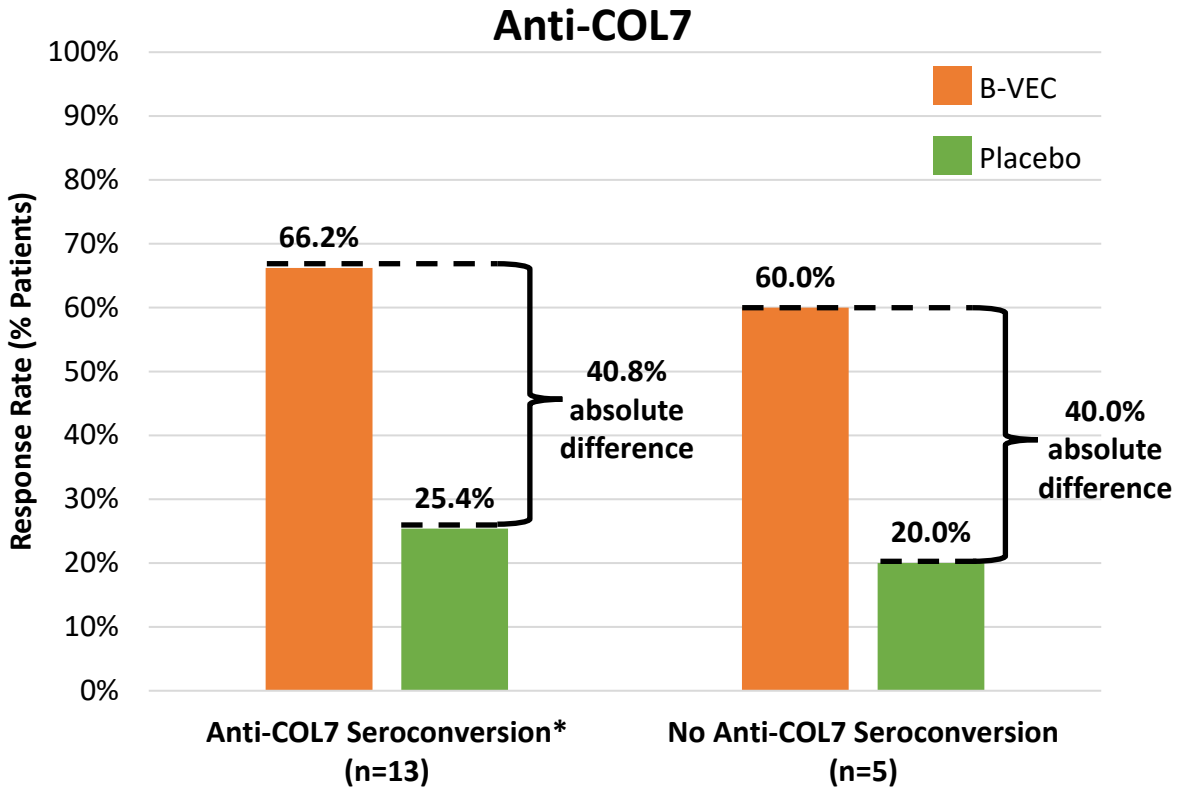
- At baseline, 14 of the 22 patients (63.6%) were anti-HSV-1 seropositive and 8 were seronegative, in agreement with seropositivity rates of the general US population[1]
  - 6 of 8 (75.0%) baseline seronegative patients seroconverted at 6 months
  - For baseline seropositive patients, where quantitative differences at study completion could be calculated, antibody responses were not determined to be meaningful

- 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

1. Xu F, et al. *J Infect Dis*. 2002;185(8):1019-1024.
COL7; type VII collagen; HSV-1, herpes simplex virus type 1.

Treatment Response to B-VEC was Not Associated with Anti-HSV-1 Serostatus at Baseline or with Anti-COL7 Seroconversion





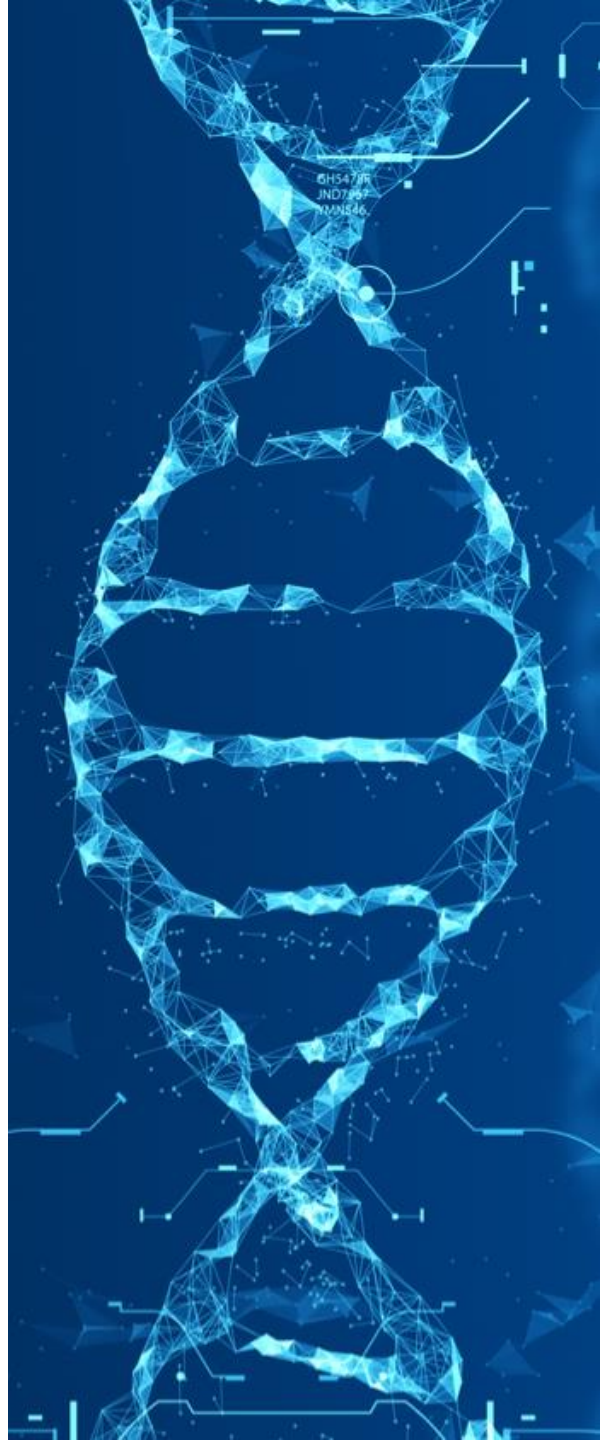
- Response rates in primary wound pairs at 6 months suggested equivalent efficacy regardless of baseline anti–HSV-1 antibody status

- At 6 months, treatment response to B-VEC was consistent regardless of anti-COL7 seroconversion

Data in figures based on post hoc analyses using imputation; a responder was defined as meeting the primary endpoint of complete wound healing at 6 months.
*Seroconversion defined as seronegative at baseline but seropositive when tested at 6 months.
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 is investigating the long-term efficacy and safety of B-VEC in patients with DEB, regardless of prior enrollment in GEM-3



Open-label extension study: NCT04917874
B-VEC, beremagene geperpavec; COL7, type VII collagen; DEB, dystrophic epidermolysis bullosa; HSV-1, herpes simplex virus type 1.