In Vivo Gene Replacement Therapy for Dystrophic Epidermolysis Bullosa

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Conflict of Interest:

Dr. Marinkovich performed research on the preclinical, phase 1-2, and phase 3 studies of B-VEC in dystrophic epidermolysis bullosa, under a sponsored research project funded by Krystal Biotech and overseen by Stanford University’s Research Management Group.
Dystrophic Epidermolysis Bullosa (DEB)

A rare, genetic disease that causes skin to blister from minor trauma

Up to 125,000 people are affected by DEB worldwide

The incidence of DEB is 6.5 per million births in the US\(^2\)

Caused by lack of type VII collagen due to a mutation in *COL7A1*

Without type VII collagen the epidermis does not anchor to the dermis

There are no approved corrective treatments for DEB

Existing therapies limited to expensive and time-consuming palliative treatments

Palliative treatments cost $200k – $400k annually

Produces debilitating scarring to hands and other parts of the body

Produced by lack of type VII collagen due to a mutation in *COL7A1*
In vivo versus ex vivo gene therapy
Topical in vivo gene therapy: Simple, Painless and Easy to Administer

**Benefits of topical in vivo approach to treat DEB**

- “Off-the-Shelf” product ready for use in multiple patients
- Manufacturing and supply chain costs are lower – direct ship to local site
- Therapy can be administered by any dermatologist, primary care physician, care giver, nurse
- No hospitalization needed
- Does not require expensive, invasive, and time-consuming procedures, sophisticated medical teams or travel to specialty centers
Summary of Study Design

- This study was an intra-patient comparison of wounds randomized to receive either topical B-VEC or placebo in patients with generalized recessive dystrophic epidermolysis bullosa.
- In Phase 1 (2 patients) one wound was administered B-VEC and one wound was administered placebo.
- In Phase 2 (6 patients, 4 in Phase 2A and 2 in Phase 2B), 2 wounds were administered B-VEC and one wound was administered placebo.
- Three-month trial plus long-term imaging post-study.
- Dosing range in combined study was 1e8-3e8 pfu/ml.
- Safety was assessed through AEs, including clinically significant changes in laboratory results, vitals, and physical exam findings.
- Viral shedding was analyzed through the collection of blood, urine, and skin swabs, and antibodies to HSV and collagen VII were analyzed through collection of serum.
B-VEC Safety Update in Wounds with Topical Application

Summary

B-VEC continues to be well tolerated to date following repeat dosing

- No treatment-related adverse events (serious or otherwise) were reported.
- No immune response or blistering observed around the sites of administration following first and repeat dose.
- Blood and urine samples collected throughout the study revealed:
  - No systemic viral shedding
  - No adverse events associated with routine labs (chemistry and hematology)
  - Some patients had baseline C7 and HSV1 antibodies which did not impair efficacy or tolerance of therapy
B-VEC Study: Patient 3

1st treatment

Baseline  | Month 1  | Month 2  | Month 3  | Month 4

Baseline  | Month 1  | Month 2  | Month 3  | Month 4

2nd treatment
Effect of BVEC on first 11 patient wounds

Resistance of treated wounds to blister extension
B-VEC Study: Patient 12 (Age 11)

~1yr. prior to baseline  Baseline  Day 84
Linear localization of full-length collagen VII following B-VEC therapy: Pt. 05

Baseline and Day 15 collagen VII expression using NC1 and NC2 specific antibodies
Linear full-length collagen VII expression following B-VEC therapy: Pt. 10

Baseline, Days 15 and 97 collagen VII expression using NC1 and NC2 specific antibodies

Arrows indicate basement membrane zone
Tile analysis demonstrates long stretches of linear full-length collagen VII expression following B-VEC therapy: Pt. 10

Baseline and Day 15 collagen VII expression using NC2 specific antibodies
Full-length collagen VII promotes the formation of mature anchoring fibrils, following B-VEC therapy.

**Minimal baseline expression of NC1** (arrow)

**Absent baseline expression NC2**

**Absent anchoring fibrils**

**Increased expression of NC1** (arrow)

**Increased expression NC2** (black dots)

**Robust, mature anchoring fibrils** (arrows)
Median change in wound area

Statistically Significant (p-value < 0.05) Reduction in Wound Area achieved in Weeks 8, 10 and 12
In summary

• B-VEC is being developed as a topical gel to treat patients with dystrophic epidermolysis bullosa and designed to be applied by a physician, caregiver or nurse.

• B-VEC has received Received regenerative medicine advanced therapy (RMAT) designation from the FDA and Priority Medicines (PRIME) designation awarded by EMA

• Clinical data to date shows that B-VEC separates significantly from placebo between Weeks 8 through 12

• Design of upcoming pivotal study to closely align with the study design in Phase 1/2 clinical trial