In Vivo Correction of Dystrophic Epidermolysis Bullosa by direct cutaneous COL7A1 gene replacement: results of Phase 1/2 trial

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*Relevant Conflict of Interest: Dr. Marinkovich is an Investigator for Krystal Biotech, Inc.
Dystrophic Epidermolysis Bullosa (DEB)

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

Caused by lack of type VII collagen due to a mutation in \textit{COL7A1}

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

Up to 125,000 people are affected by DEB worldwide

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

Produces debilitating scarring to hands and other parts of the body

There are no approved corrective treatments for DEB

Existing therapies limited to expensive and time-consuming palliative treatments

Palliative treatments cost $200k – $400k annually
Gene therapy for DEB: a novel approach

Beremagene geperpavec* (B-VEC, KB103) is a topically administered, replication-deficient HSV-1 vector containing two functional COL7A1 genes applied directly to RDEB patient wounds in an outpatient setting.

Investigators at Stanford University conducted a Phase I/II clinical trial sponsored by Krystal Biotech to evaluate the safety and efficacy of B-VEC in RDEB patients.
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
B-VEC Phase 1/2 Trial
Summary of Study Design

• This study was an intra-patient comparison of wounds randomized to receive either topical B-VEC or placebo.

• 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 $10^8$-$3\times10^8$ 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 first and repeat dose.

- 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 Clinical Mechanistic Data
B-VEC Study: Patient 9

Baseline | Month 1 | Month 2 | Month 3 | Month 4 | Month 5 | Month 6
---|---|---|---|---|---|---
B-VEC | | | | | | 
Placebo | | | | | |
B-VEC Study: Patient 3

1st treatment
Baseline | Month 1 | Month 2 | Month 3 | Month 4

2nd treatment
Baseline | Month 1 | Month 2 | Month 3 | Month 4
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

Arrows indicate basement membrane zone
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 of NC2
- Absent anchoring fibrils
- Increased expression of NC1 (arrow)
- Increased expression of NC2 (black dots)
- Robust, mature anchoring fibrils (arrows)
B-VEC Statistical Analysis of Phase 1/2
Median change in wound area

Statistically Significant (p-value < 0.05) Reduction in Wound Area achieved in Weeks 8, 10 and 12
Wound closure (>75% vs >90% vs 100%) active vs placebo by week

Wound Closure Response is Statistically Significant (p-value < 0.05) For All The Endpoints

p-values are based on Cochran-Mantel Haenszel (CMH) Test Without Adjusting for Week-to-Week Placebo Variability
Forest Plot: Wound closure active vs placebo (Week 8 through Week 12)

The Timepoint (Week) p-values are based on the Breslow-Day for Homogeneity and Cochran-Mantel-Haenszel (CMH) Tests

<table>
<thead>
<tr>
<th>End Point</th>
<th>No. of wounds/ total wounds(%)</th>
<th>Percentage Difference (95% CI)</th>
<th>p-value Trt</th>
<th>p-value Week</th>
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<tbody>
<tr>
<td>CBL Wound Area &gt;= 90%</td>
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<tr>
<td>Week 08</td>
<td>14/17 (82.4 %) 0/8 (0 %)</td>
<td>82.4 (100.0, 64.2) &lt;0.0001 0.1917</td>
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<tr>
<td>Week 12</td>
<td>12/14 (85.7 %) 1/7 (14.3 %)</td>
<td>71.4 (100.0, 39.7)</td>
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<tr>
<td>CBL Wound Area = 100%</td>
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<tr>
<td>Week 08</td>
<td>14/17 (82.4 %) 0/8 (0 %)</td>
<td>82.4 (100.0, 64.2) &lt;0.0001 0.3714</td>
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<td>Week 12</td>
<td>9/14 (64.3 %) 1/7 (14.3 %)</td>
<td>50.0 (86.1, 13.9)</td>
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<tr>
<td>CBL Wound Area &gt;= 75%</td>
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<td>Week 08</td>
<td>14/17 (82.4 %) 2/8 (25 %)</td>
<td>57.4 (92.4, 22.3) &lt;0.0001 0.8247</td>
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<tr>
<td>Week 12</td>
<td>12/14 (85.7 %) 1/7 (14.3 %)</td>
<td>71.4 (100.0, 39.7)</td>
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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 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.
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