# Dystrophic Epidermolysis Bullosa (DEB)

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



Produces debilitating scarring to hands and other parts of the body
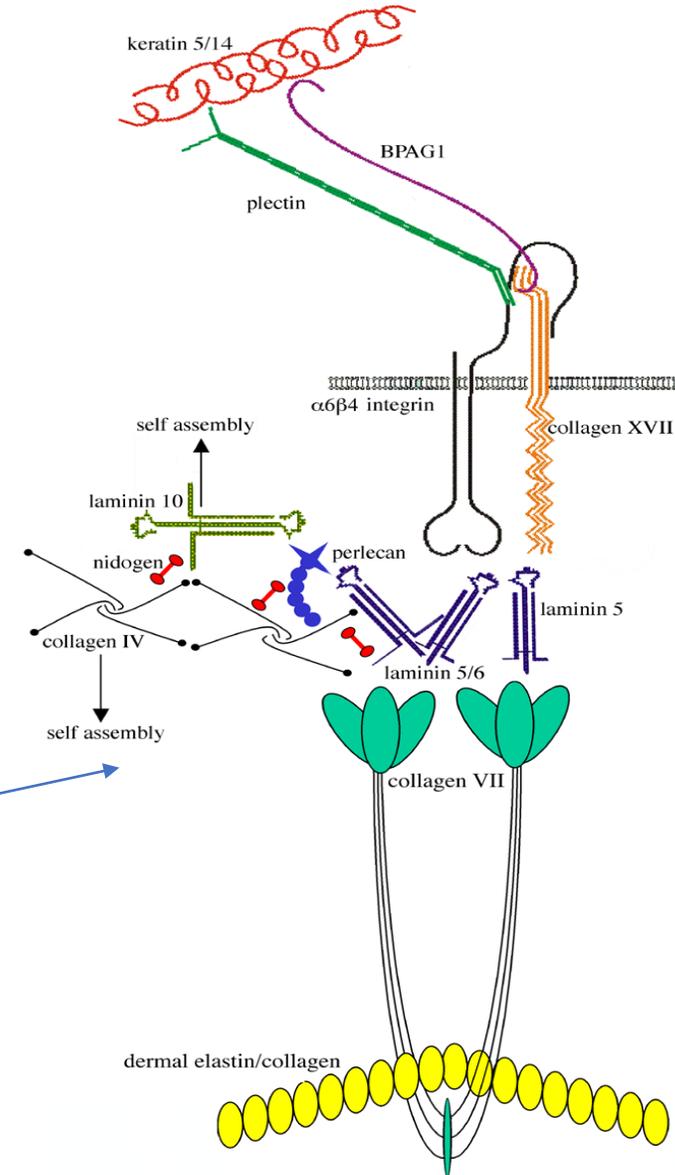


Up to 125,000 people are affected by DEB worldwide

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



keratin 5/14

BPAG1

plectin

self assembly

laminin 10

nidogen

perlecan

collagen IV

self assembly

α6β4 integrin

collagen XVII

laminin 5

laminin 5/6

collagen VII
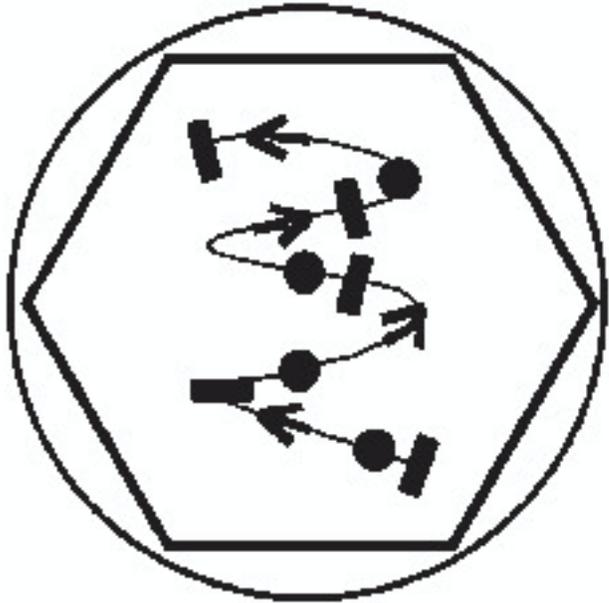
dermal elastin/collagen

**There are no approved corrective treatments for DEB**

Existing therapies limited to expensive and time-consuming palliative treatments

Palliative treatments cost $200k – $400k annually

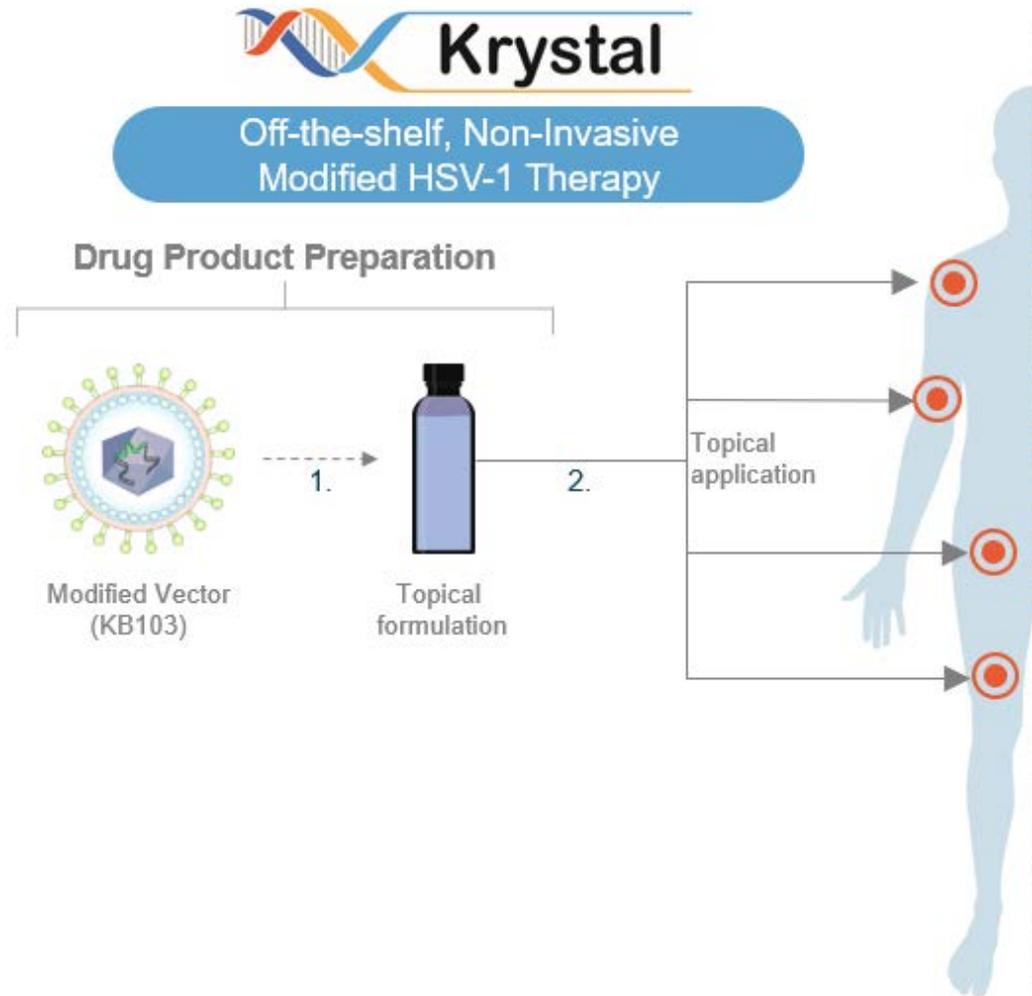# Gene therapy for DEB: a novel approach

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.
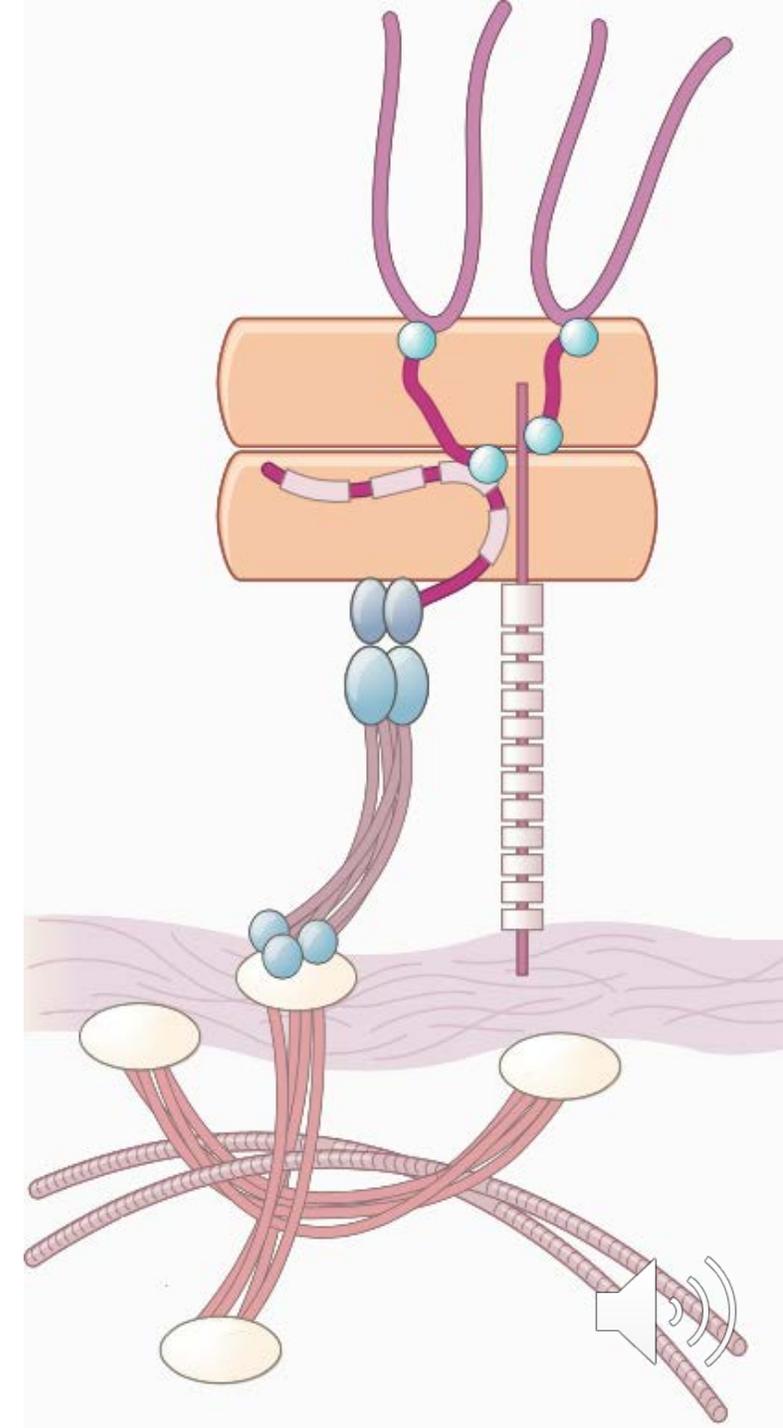
# Topical in vivo gene therapy: Simple, Painless and Easy to Administer



Off-the-shelf, Non-Invasive Modified HSV-1 Therapy

Drug Product Preparation

Modified Vector (KB103) → 1. → Topical formulation → 2. → Topical application

**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 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 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
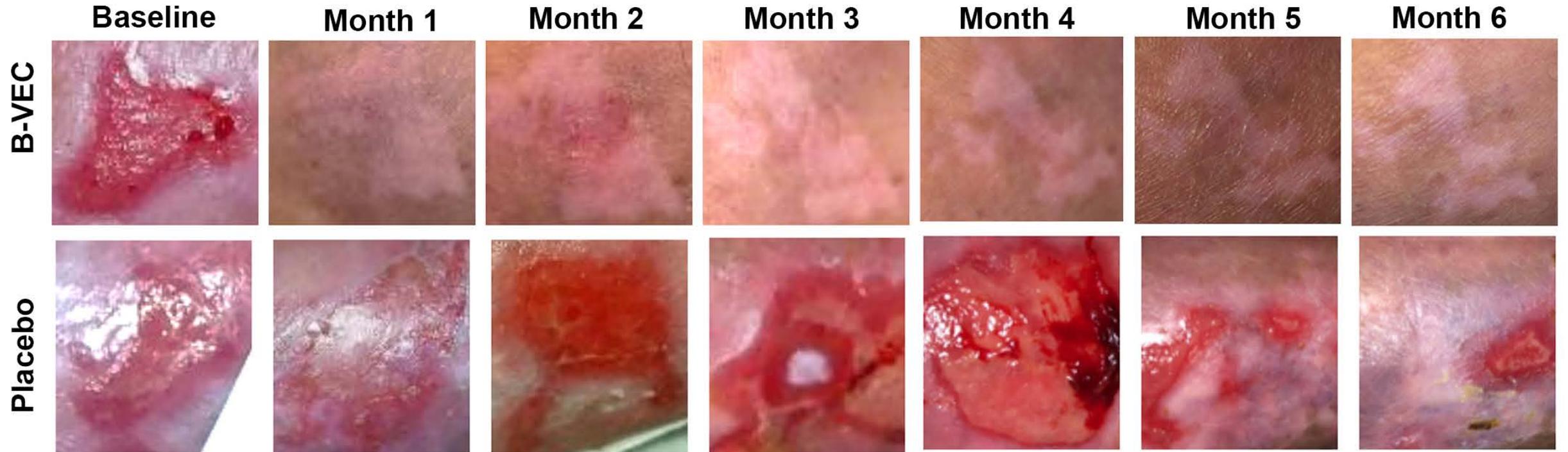
# B-VEC Study: Patient 3

# B-VEC Study: Patient 12 (Age 11)



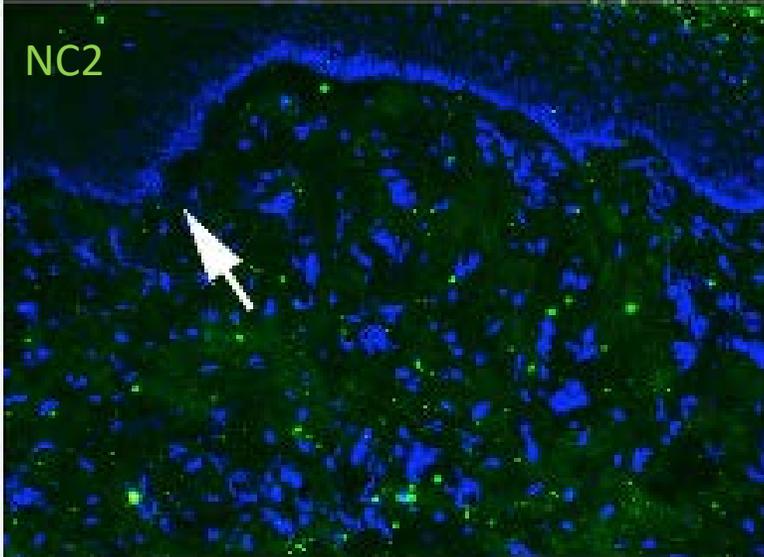~1yr. prior to baseline      Baseline      Day 84

# 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

NC1

NC2
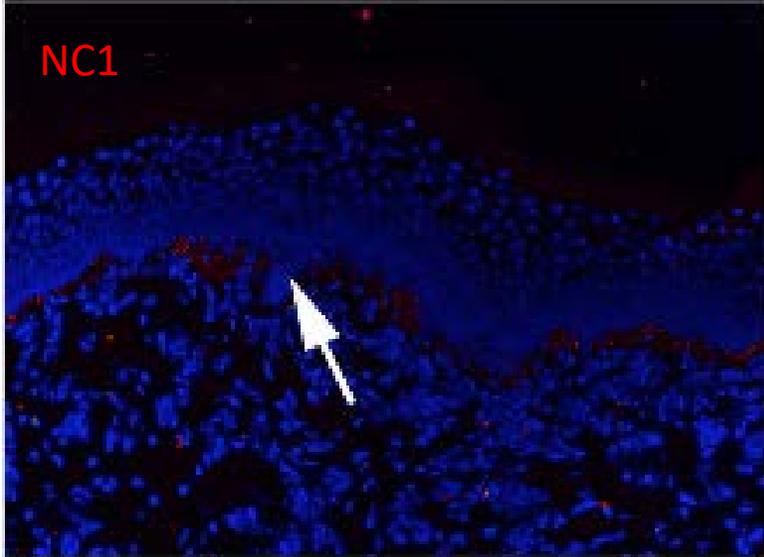
P09 D0

P09 D15

# 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

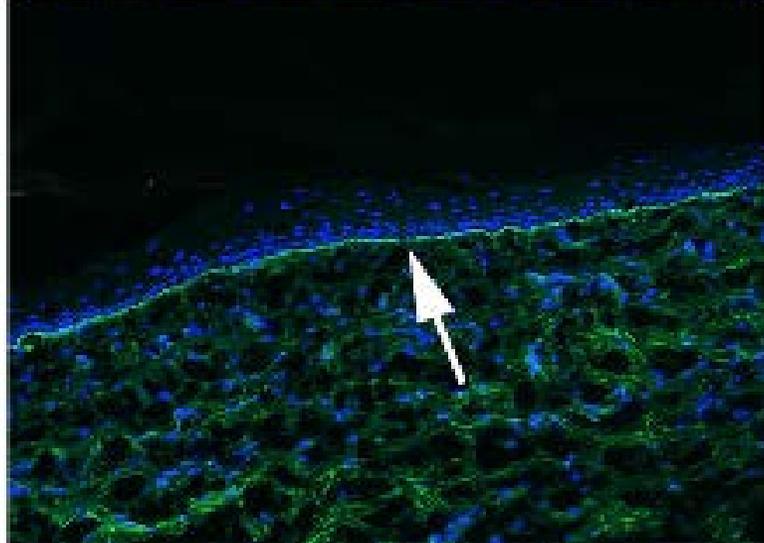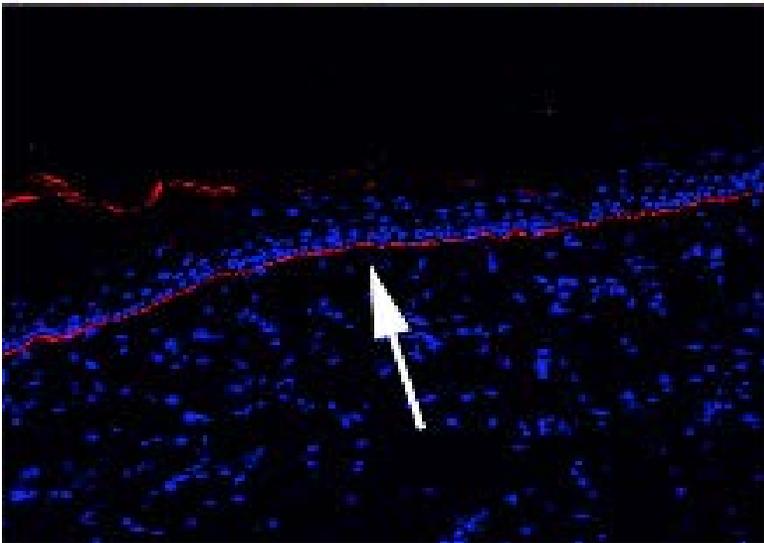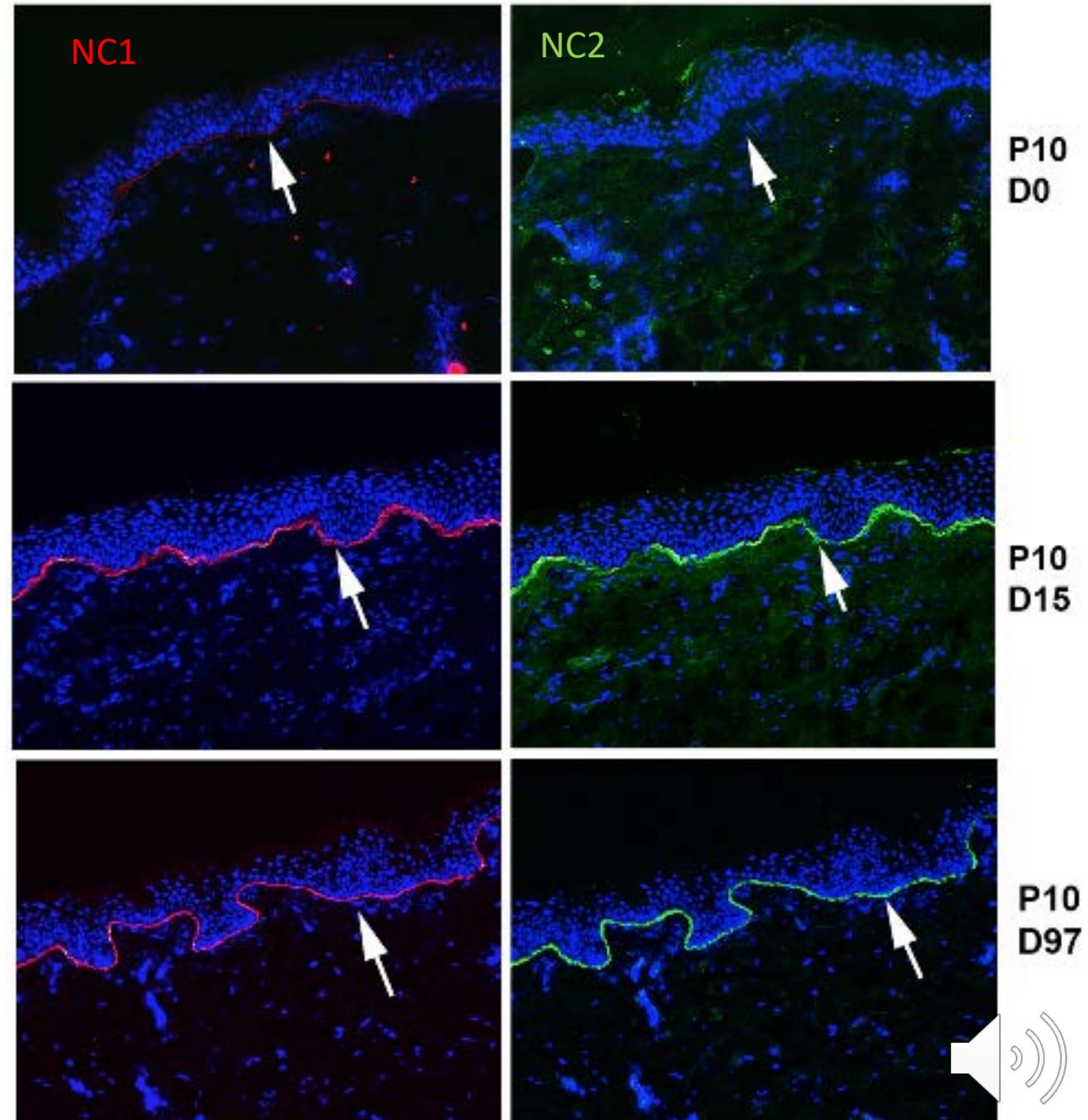# Tile analysis demonstrates long stretches of linear full-length collagen VII expression following B-VEC therapy: Pt. 10



Baseline and Day 15 collagen VII expression using NC2 specific antibodies
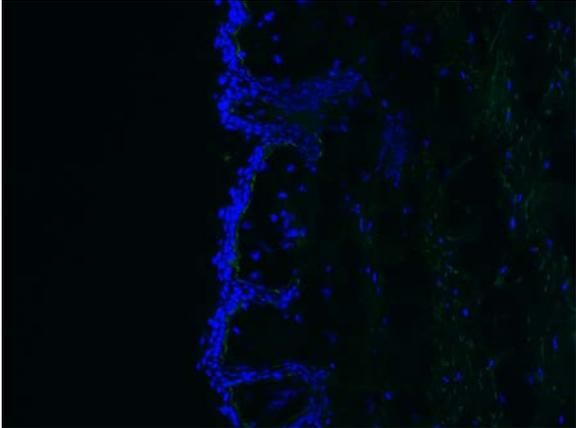
baseline
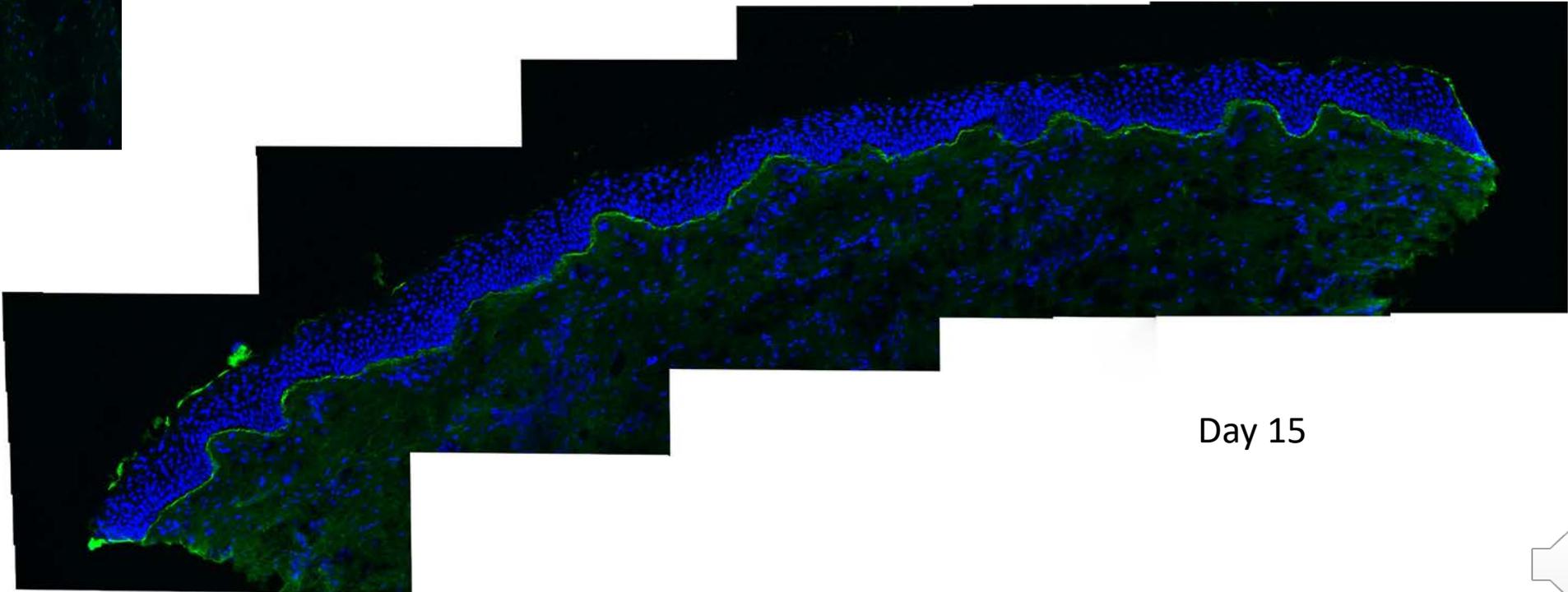
Day 15

# Full-length collagen VII promotes the formation of mature anchoring fibrils, following B-VEC therapy



baseline

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)
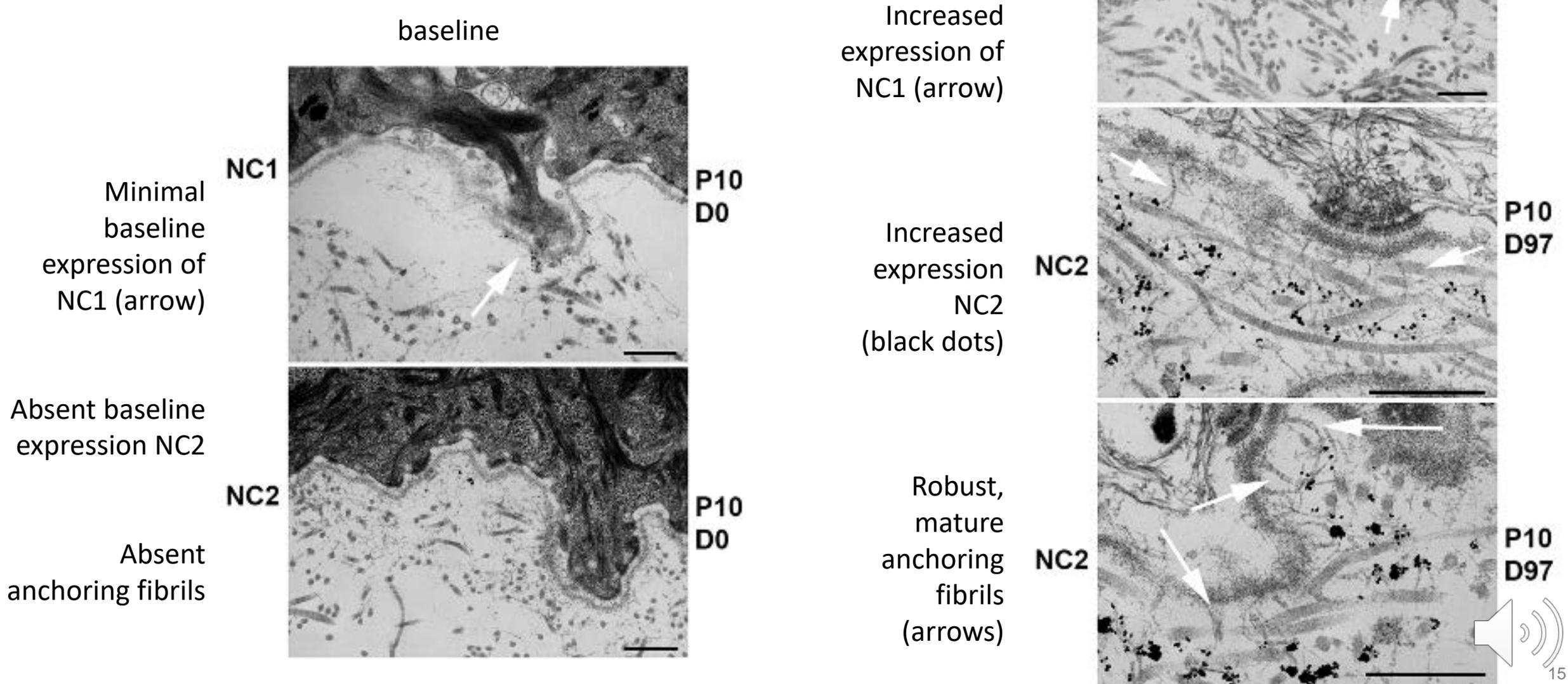
# **B-VEC** Statistical Analysis of Phase 1/2

# Median change in wound area



**Change from Baseline in Wound Area**

| | 0 | 2 | 4 | 6 | 8 | 10 | 12 |
|---|---|---|---|---|---|---|---|
| PLACEBO | 0.00 | -69.68 | 118.26 | -64.72 | 140.72 | -19.90 | 27.77 |
| KB103 | 0 | -74.89 | -82.33 | -94.37 | -82.84 | -91.76 | -94.15 |
| p-value ** | | 0.298 | 0.004 | 0.071 | 0.002 | 0.015 | 0.020 |

**Time from Baseline (Weeks)**

** Based on Wilcoxn Rank-SumTest
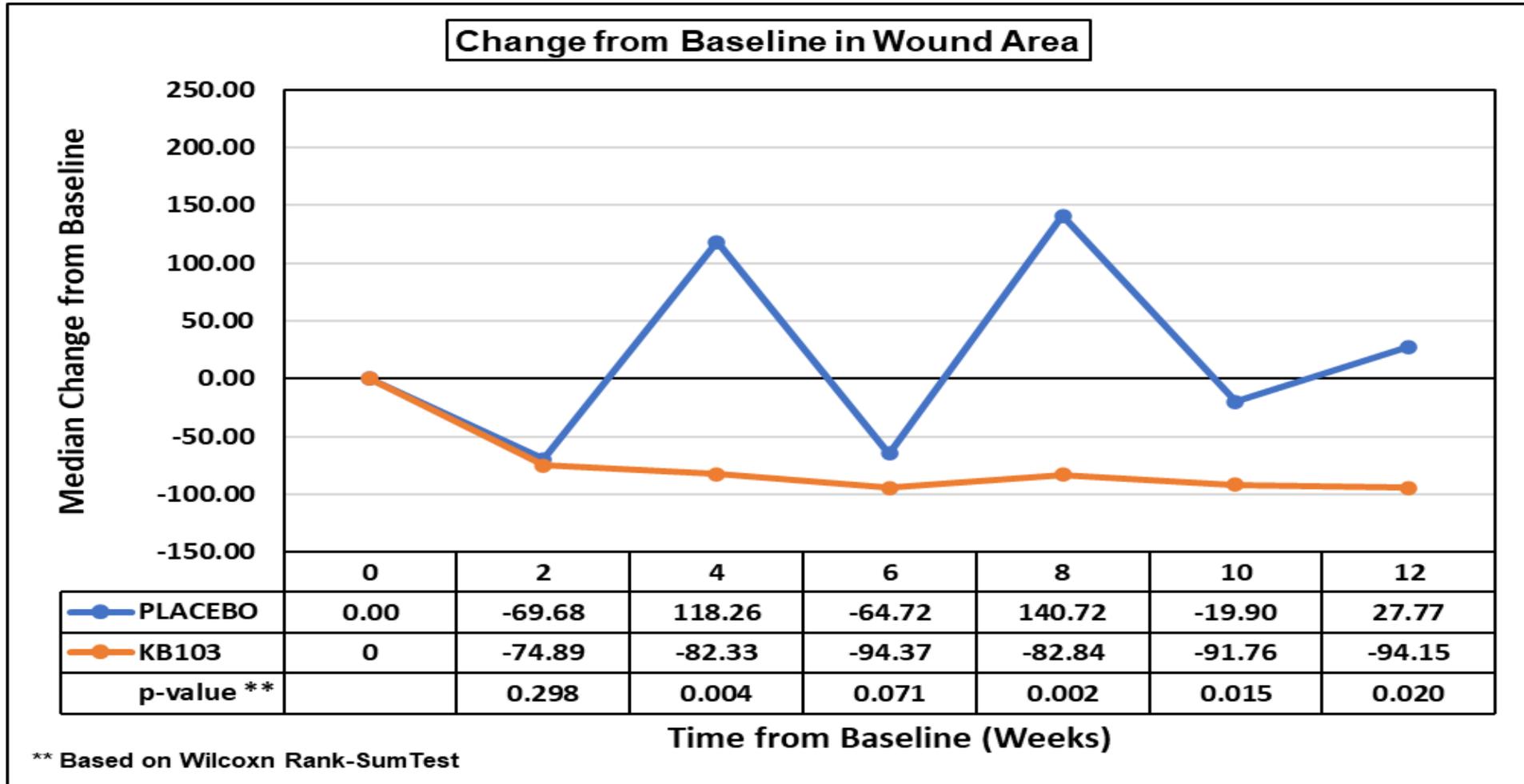
**Statistically Significant (p-value < 0.05) Reduction in Wound Area achieved in Weeks 8,10 and 12**

# Wound closure (≥75% vs ≥90% vs 100%) active vs placebo by week

**Change from Base Line Wound Area = 100%**



| Week | 8 | 12 |
|---|---|---|
| KB103 | 82.4% | 64.3% |
| Placebo | 0.0% | 14.3% |
| p-value | 0.0001 | 0.0348 |

**Change from Base Line Wound Area >= 90%**



| Week | 8 | 12 |
|---|---|---|
| KB103 | 82.4% | 85.7% |
| Placebo | 0.0% | 14.3% |
| p-value | 0.0001 | 0.0019 |

**Change from Base Line Wound Area >= 75%**



| Week | 8 | 12 |
|---|---|---|
| KB103 | 82.4% | 85.7% |
| Placebo | 25.0% | 14.3% |
| p-value | 0.0063 | 0.0019 |
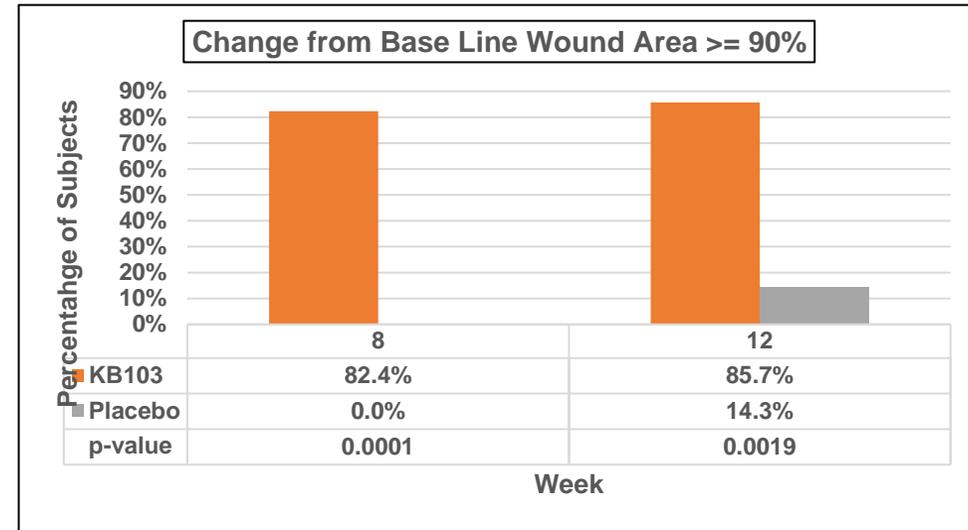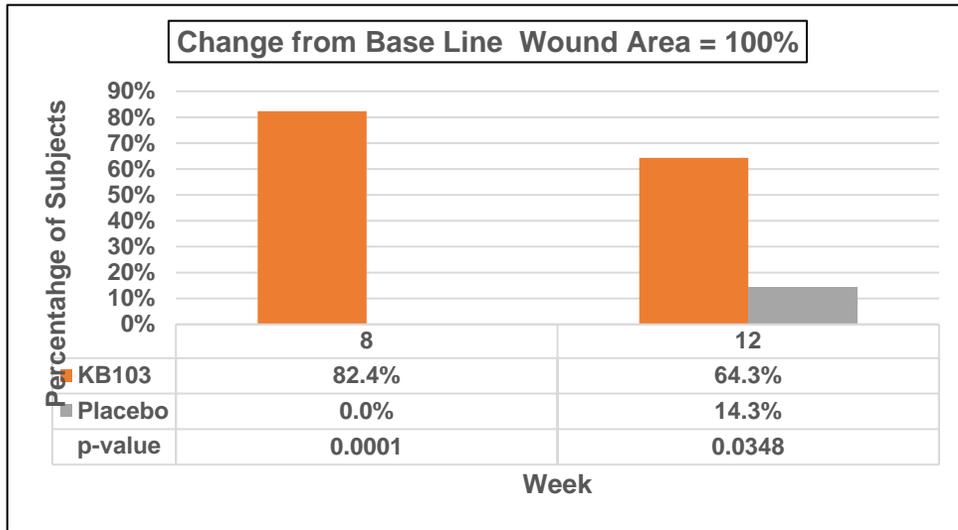
**Wound Closure Response is Statistically Significant (p-value < 0.05) For All The Endpoints**
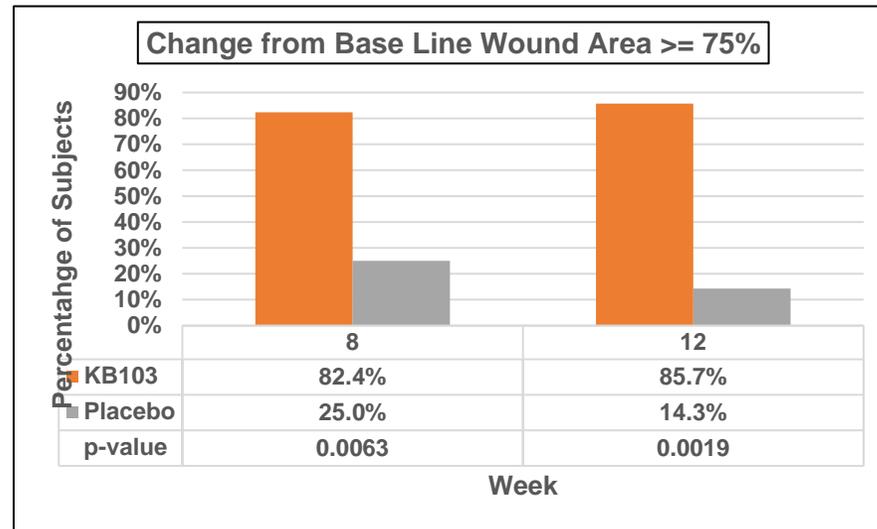
p-values are based on Cochran-Mantel Haenszel (CMH) Test Without Adjusting for Week-to-Week Placebo Variability

# Forest Plot: Wound closure active vs placebo (Week 8 through Week 12)

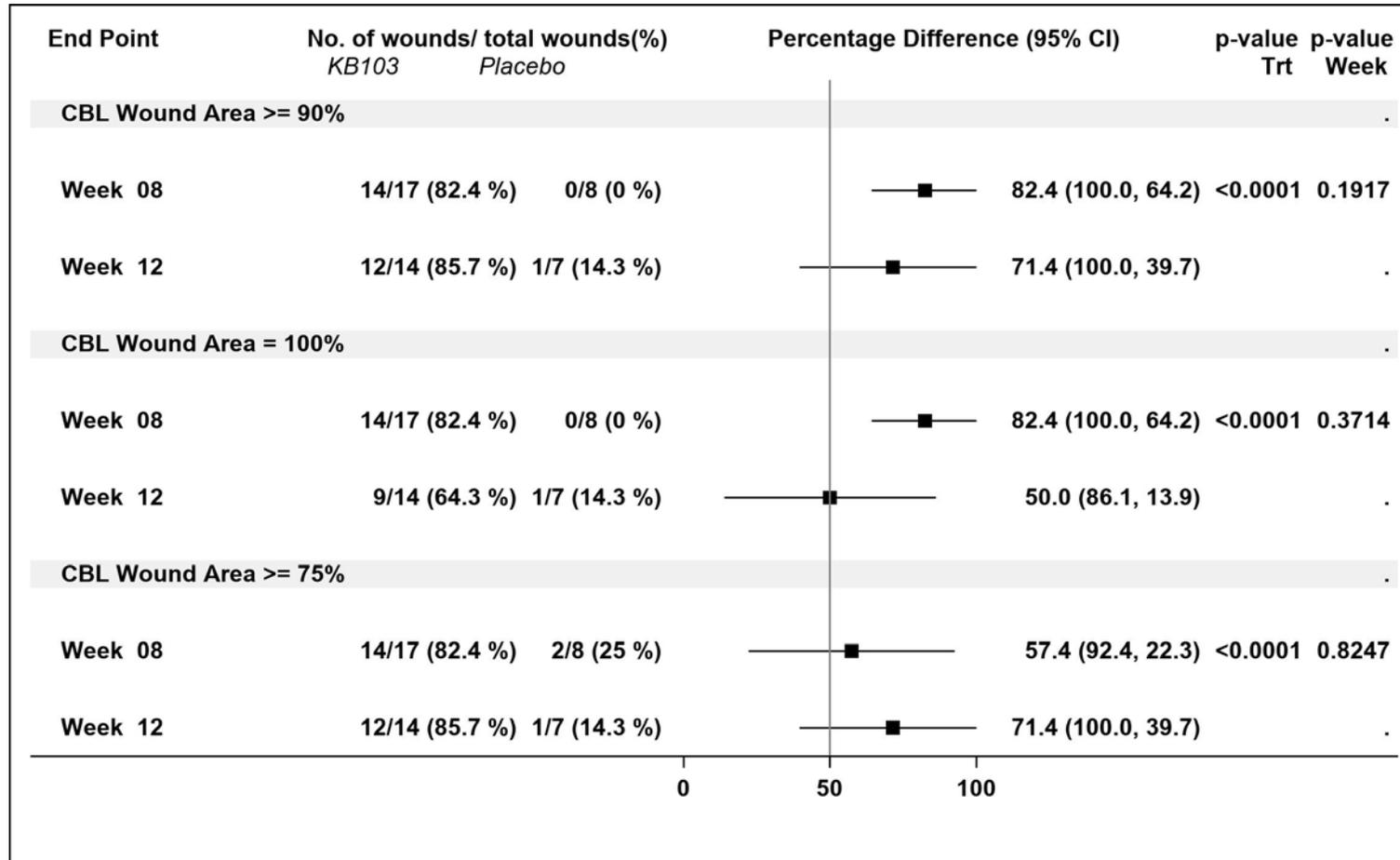| End Point | No. of wounds/ total wounds(%) | | Percentage Difference (95% CI) | p-value Trt | p-value Week |
|---|---|---|---|---|---|
| | KB103 | Placebo | | | |
| **CBL Wound Area >= 90%** | | | | | . |
| Week 08 | 14/17 (82.4 %) | 0/8 (0 %) | 82.4 (100.0, 64.2) | <0.0001 | 0.1917 |
| Week 12 | 12/14 (85.7 %) | 1/7 (14.3 %) | 71.4 (100.0, 39.7) | | . |
| **CBL Wound Area = 100%** | | | | | . |
| Week 08 | 14/17 (82.4 %) | 0/8 (0 %) | 82.4 (100.0, 64.2) | <0.0001 | 0.3714 |
| Week 12 | 9/14 (64.3 %) | 1/7 (14.3 %) | 50.0 (86.1, 13.9) | | . |
| **CBL Wound Area >= 75%** | | | | | . |
| Week 08 | 14/17 (82.4 %) | 2/8 (25 %) | 57.4 (92.4, 22.3) | <0.0001 | 0.8247 |
| Week 12 | 12/14 (85.7 %) | 1/7 (14.3 %) | 71.4 (100.0, 39.7) | | . |



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

**Wound Closure Response is Statistically Robust (p-value < 0.0001) With All The Endpoints After Adjusting for Week-to-Week Placebo Variability by Stratified CMH Test**

# 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

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