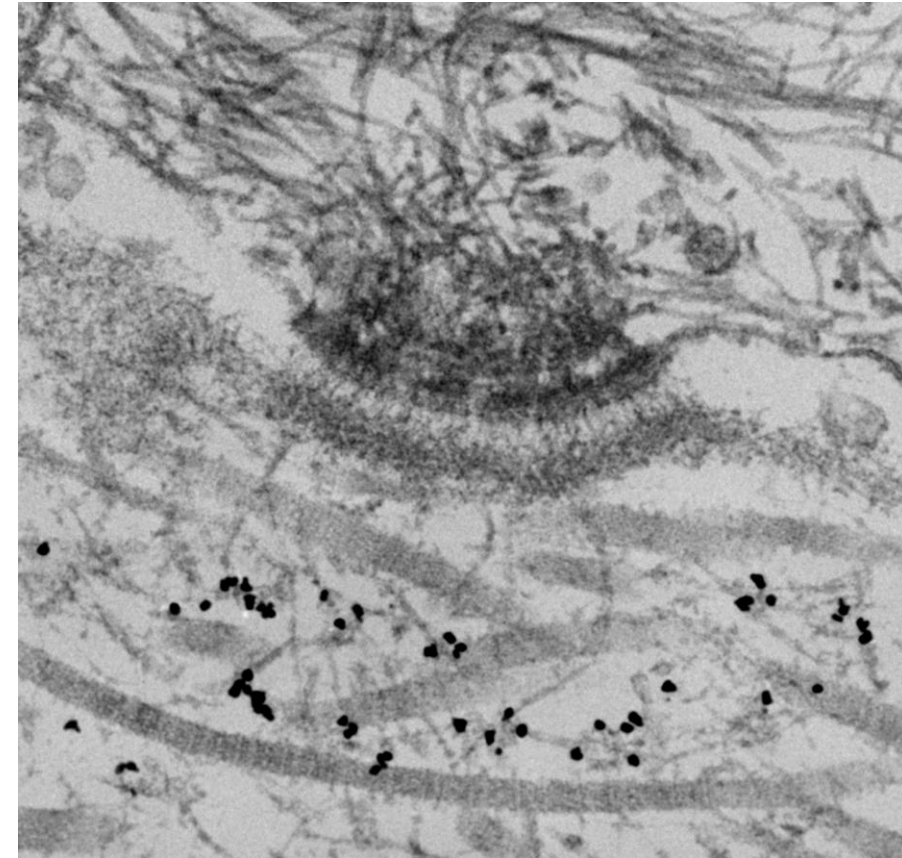
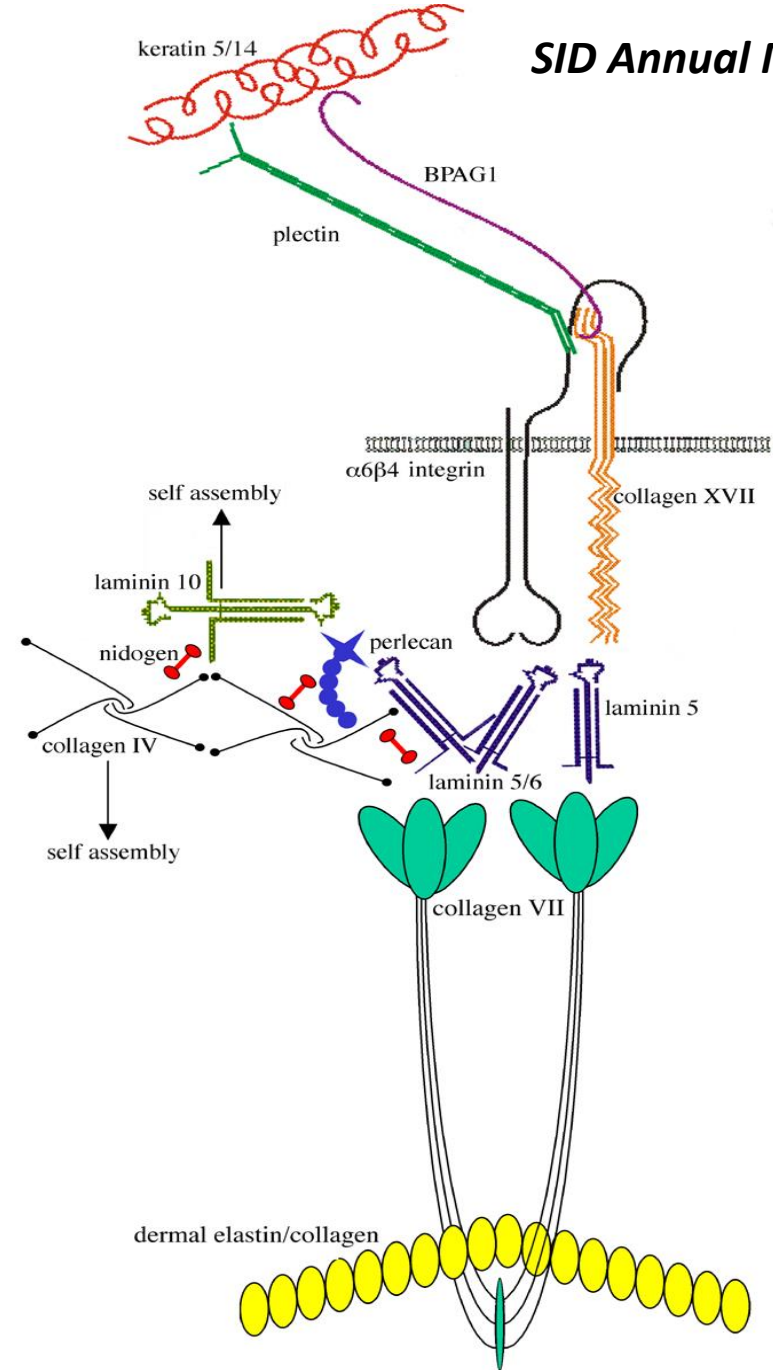


# In Vivo Gene Replacement Therapy for Dystrophic Epidermolysis Bullosa

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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



Produces debilitating scarring to hands and other parts of the body

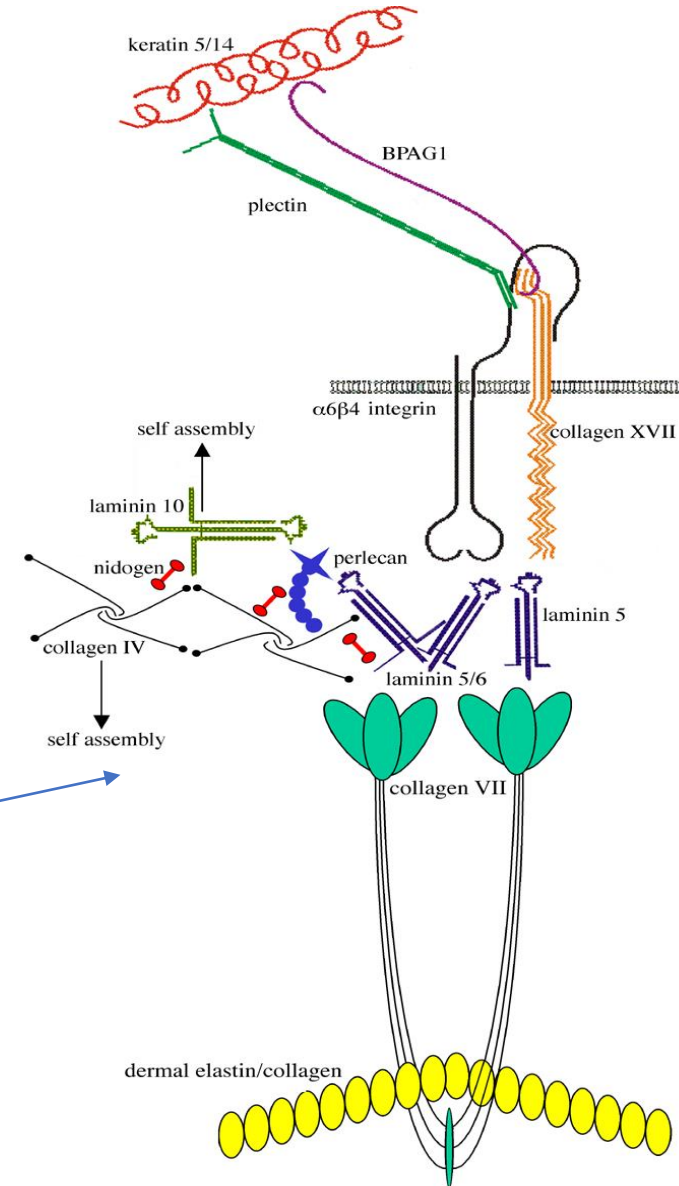


Up to 125,000 people are affected by DEB worldwide

The incidence of DEB is 6.5 per million births in the US<sup>2</sup>

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

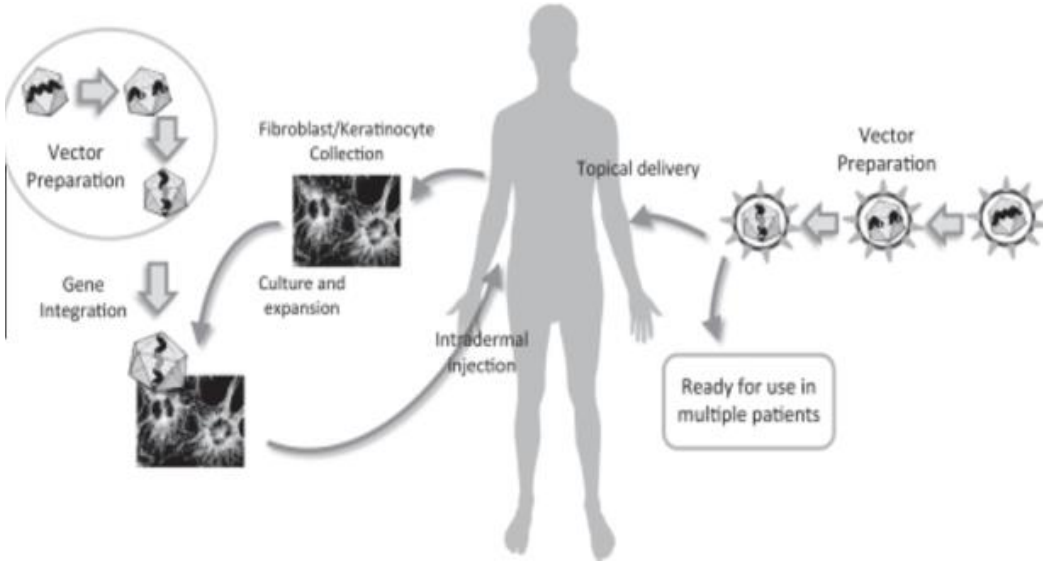


**There are no approved corrective treatments for DEB**

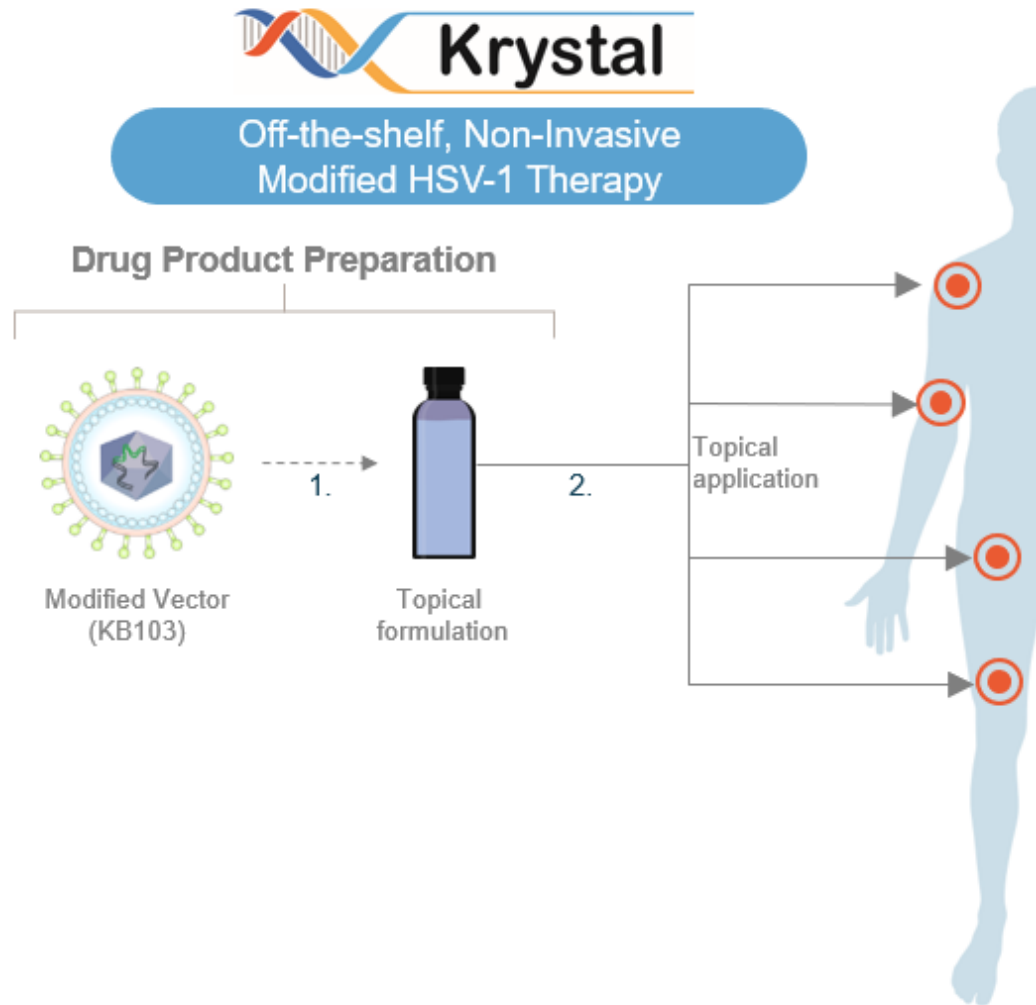
Existing therapies limited to expensive and time-consuming palliative treatments

Palliative treatments cost \$200k – \$400k annually

# In vivo versus ex vivo gene therapy



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



## Competitive Approaches:

### 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

Modified Vector

Fibroblast OR Keratinocyte

Drug Product Preparation

# Summary of Study Design

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- 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

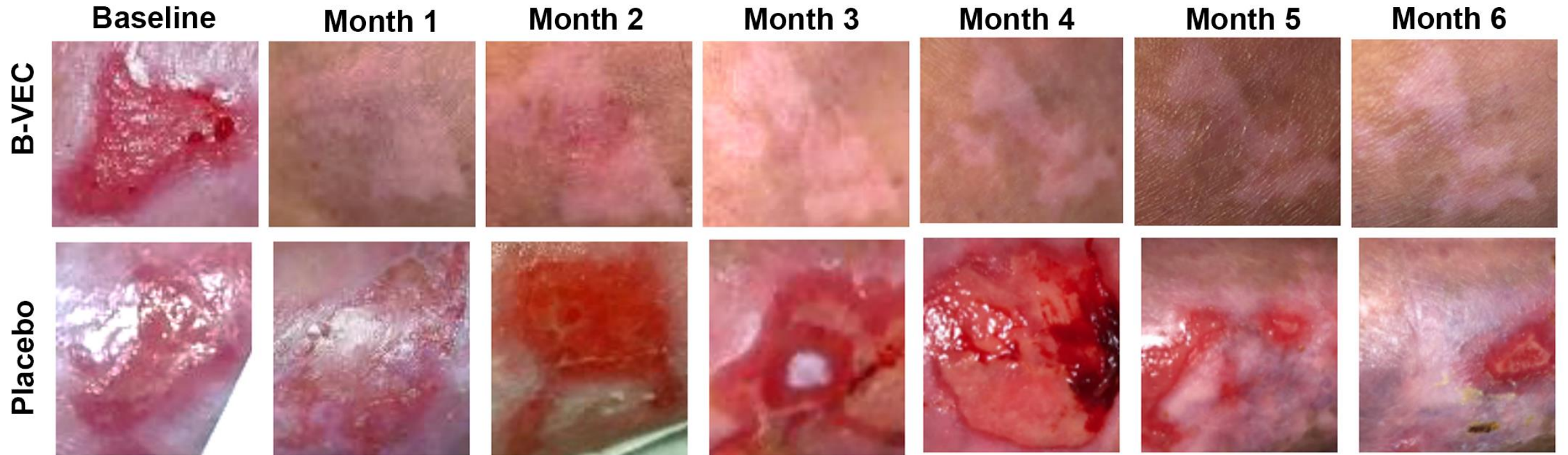
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## Summary

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 9



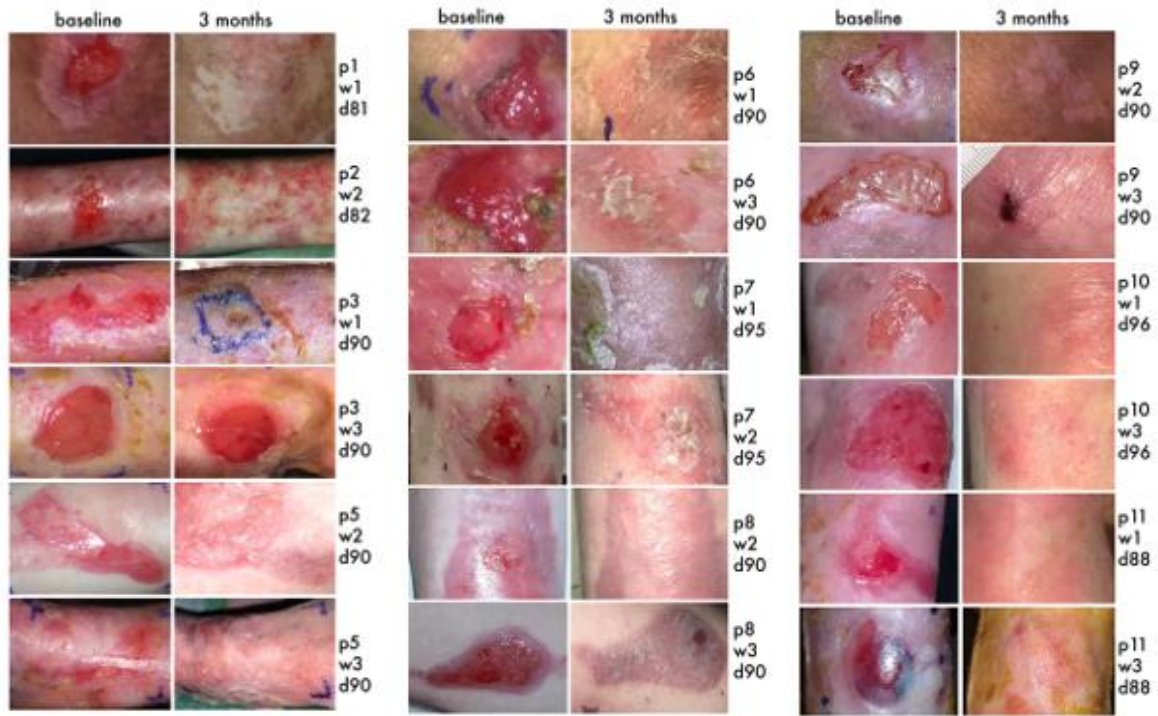


# B-VEC Study: Patient 3

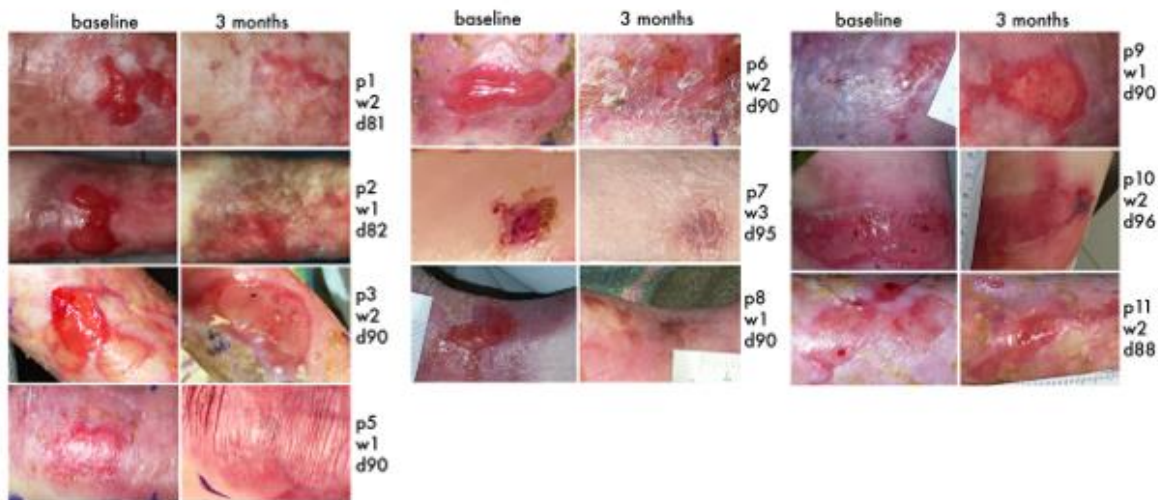


# Effect of BVEC on first 11 patient wounds

## A. B-VEC treated wounds



## B. Placebo treated wounds

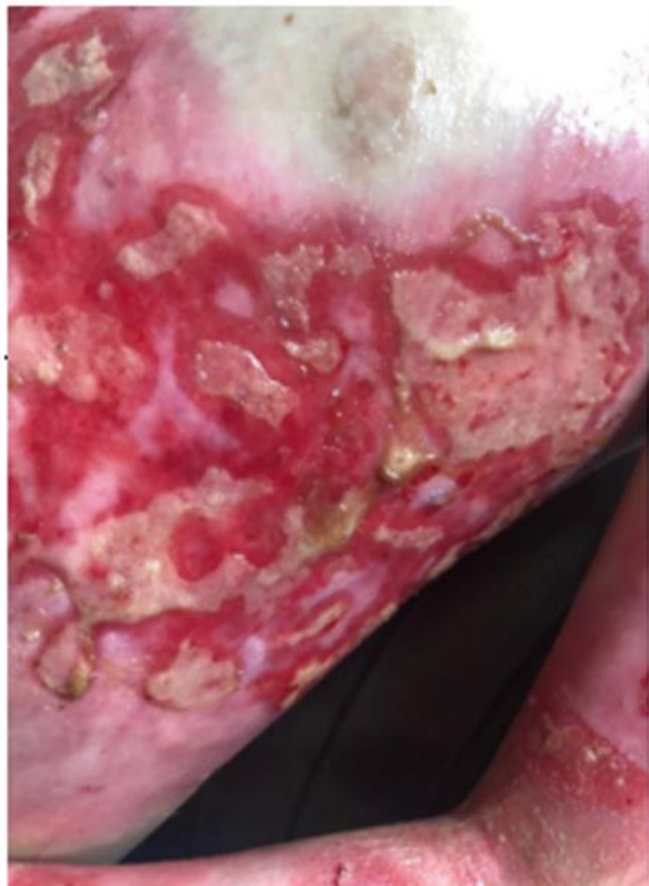


Resistance of treated wounds to blister extension



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

**~1yr. prior to baseline**



**Baseline**



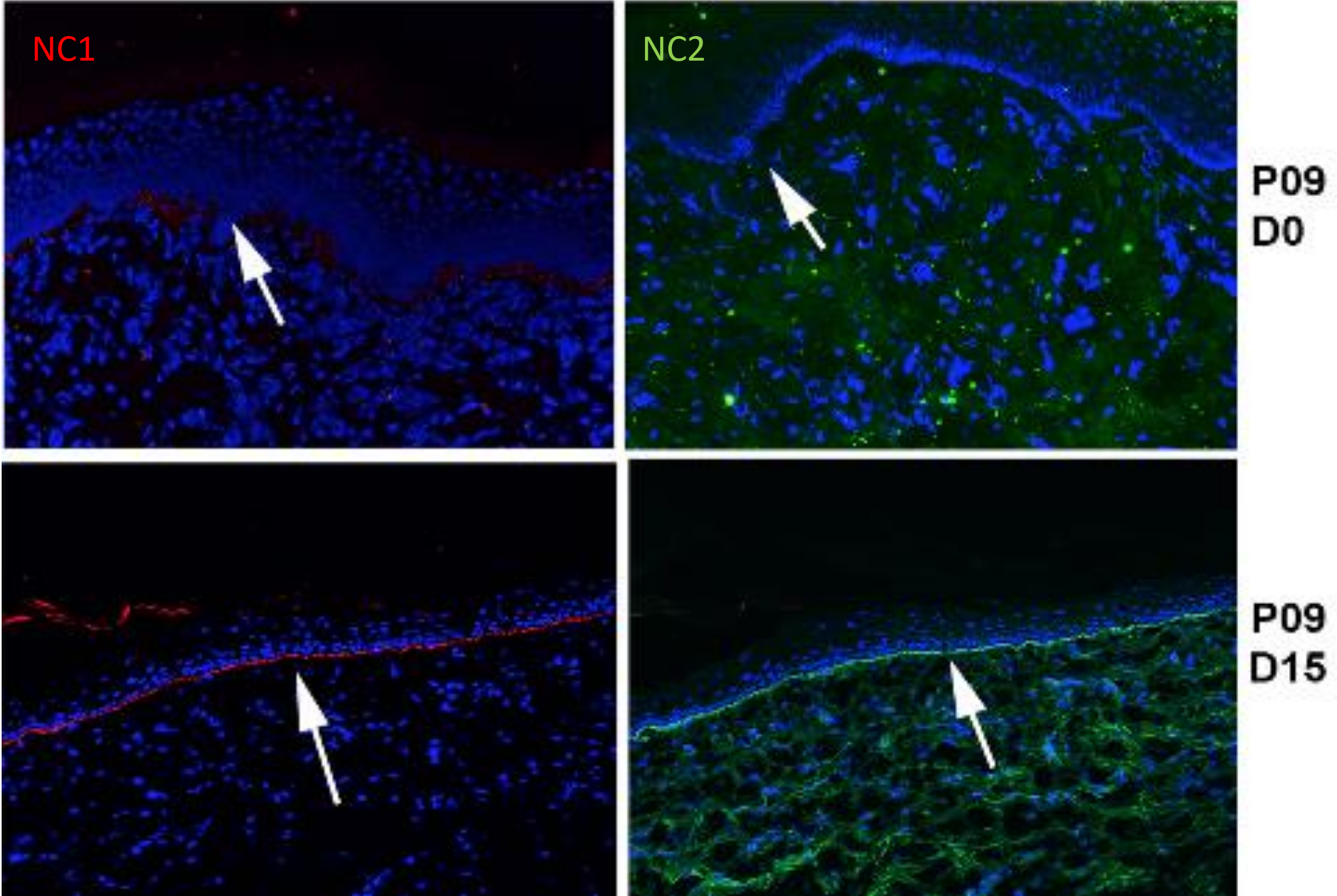
**Day 84**



# 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

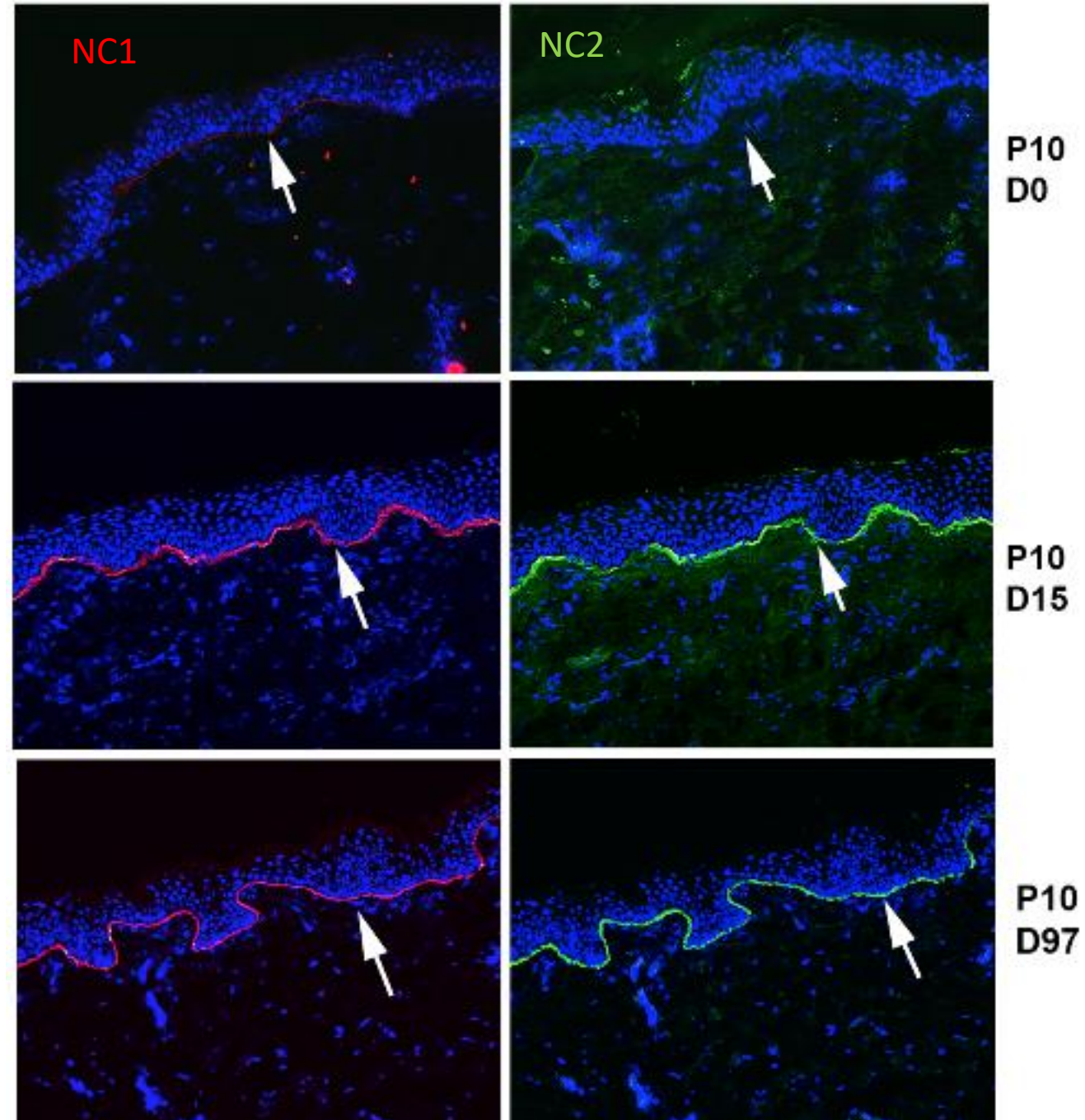
Arrows indicate basement membrane zone



# Linear full-length collagen VII expression following B-VEC therapy: Pt. 10

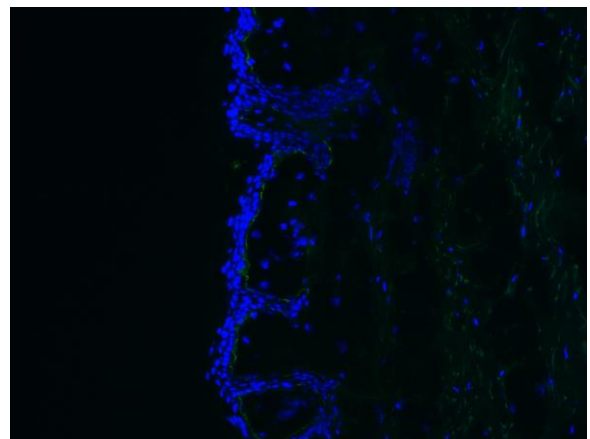
Baseline, Days 15 and 97 collagen VII expression using NC1 and NC2 specific antibodies

Arrows indicate basement membrane zone

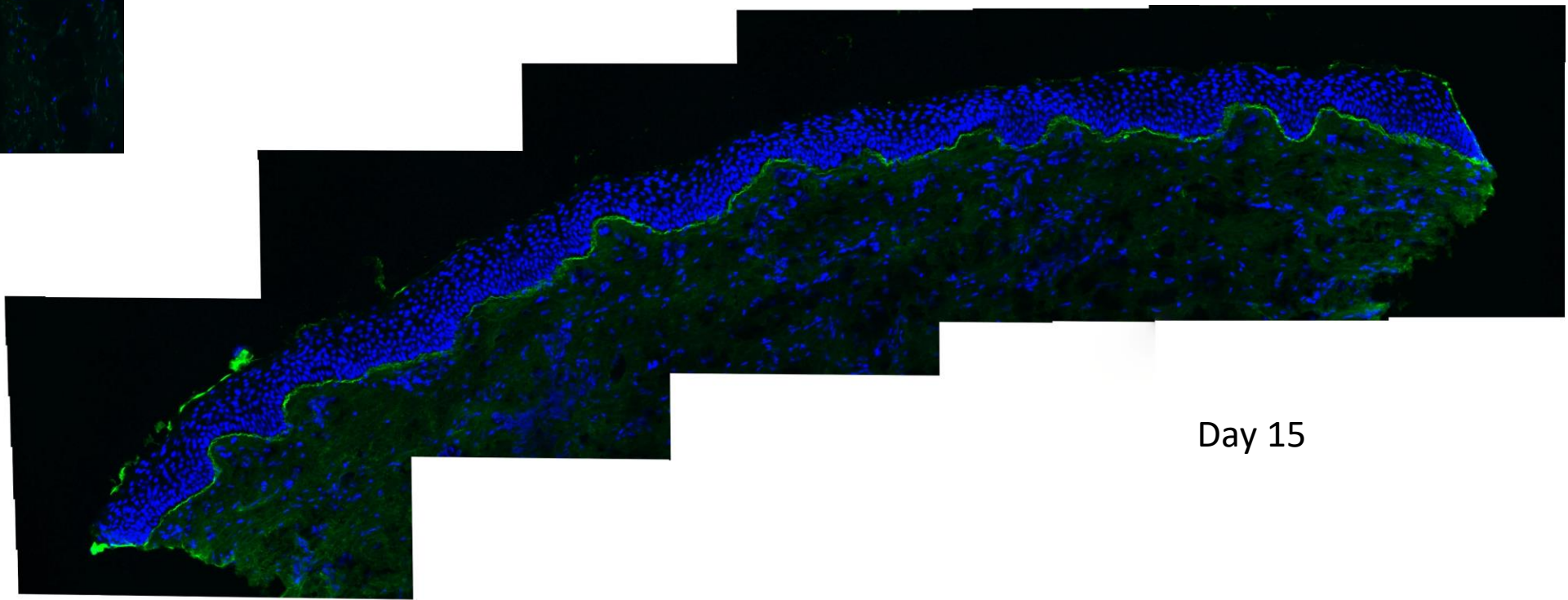


# Tile analysis demonstrates long stretches of linear full-length collagen VII expression following B-VEC therapy: Pt. 10

Baseline and Day 15 collagen VII expression using NC2 specific antibodies

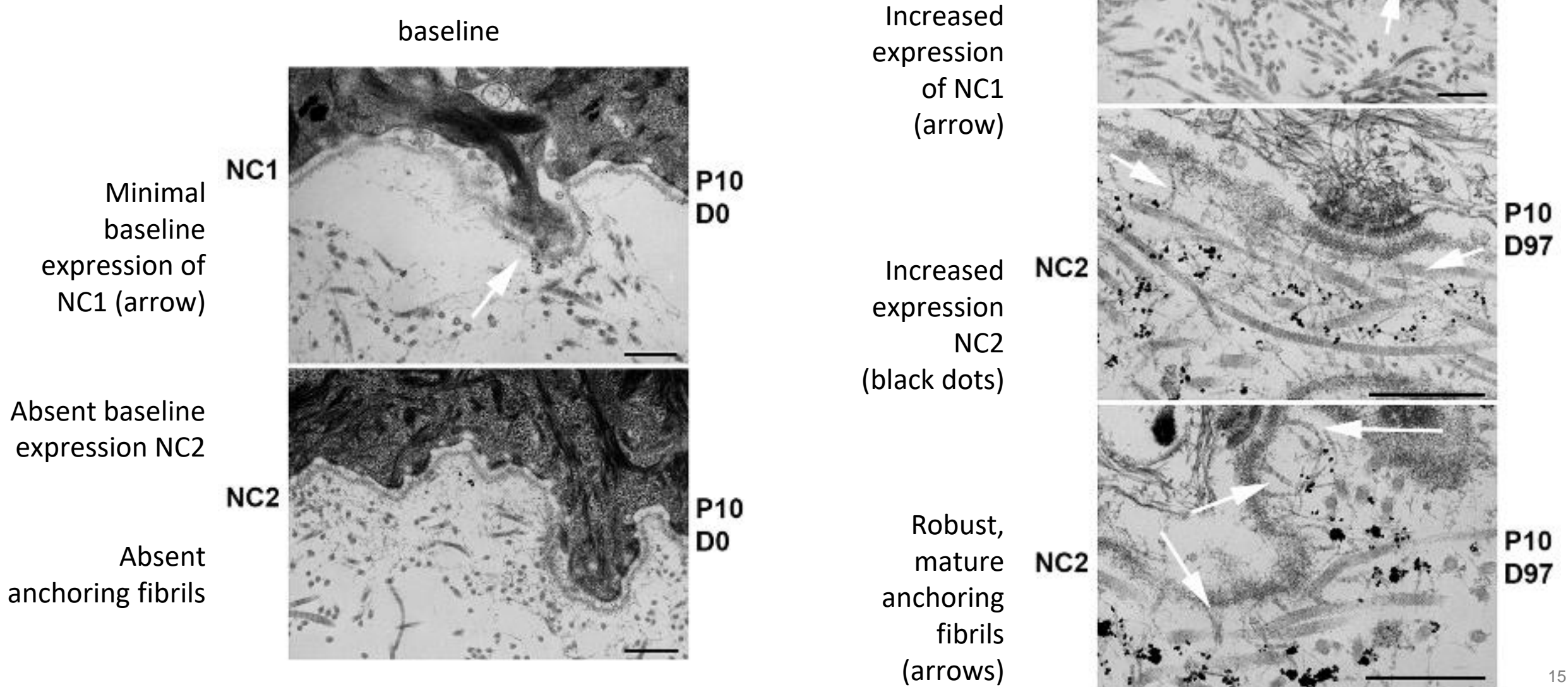


baseline

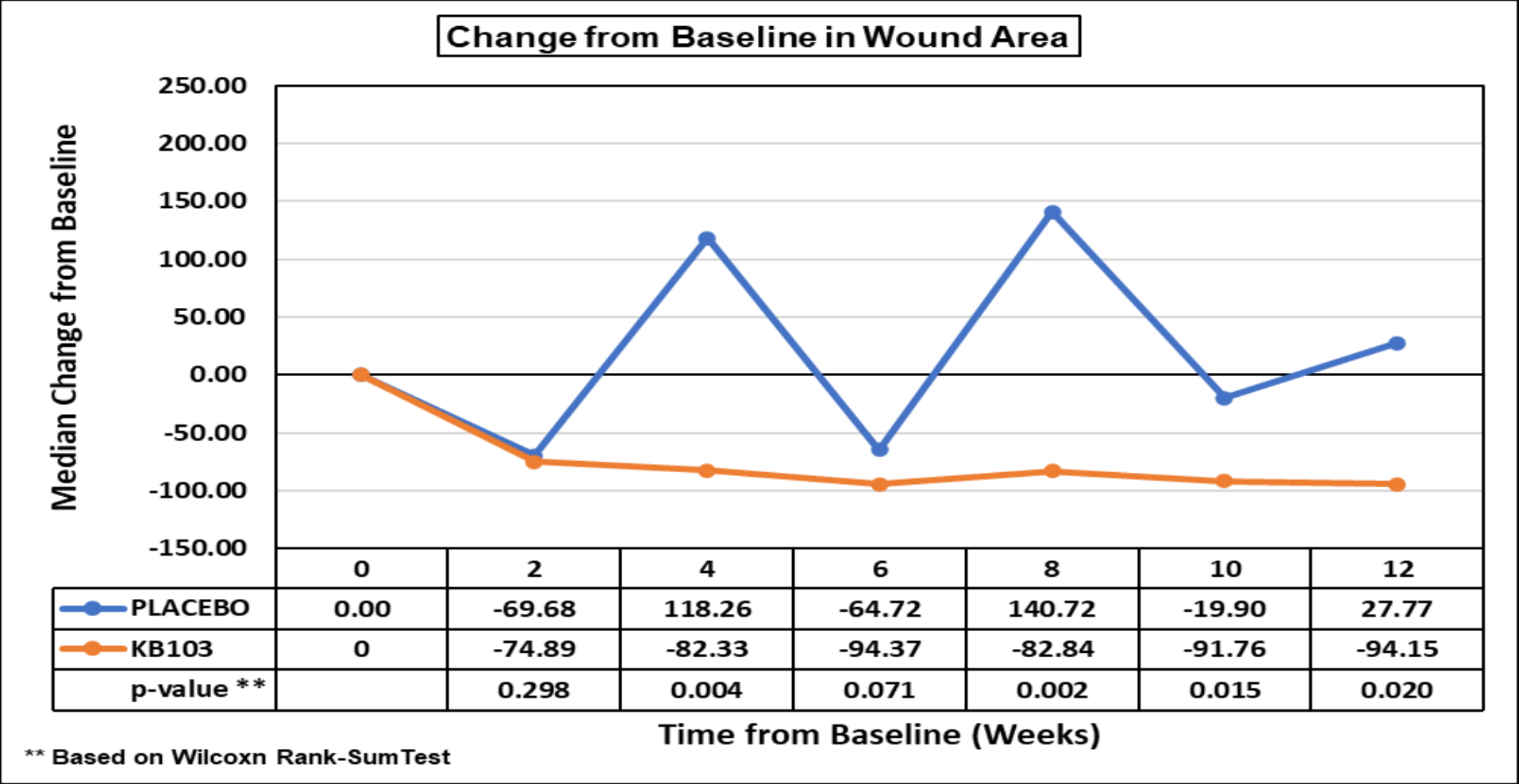


Day 15

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



# Median change in wound area



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



# In summary

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- 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