Topical Application Of Beremagene Geperpavec, An Engineered Herpes Simplex Virus Type I-based Gene Therapy Vector Expressing Type VII Collagen, Is Safe And Efficacious In A Murine Corneal Wound Model

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Beremagene geperpavec (B-VEC) for dystrophic epidermolysis bullosa (DEB)

B-VEC, a non-replicating, engineered herpes simplex virus type I (HSV-1)-based gene therapy vector

- Expresses the human COL7A1 gene, which codes for the COL7 protein
- Formulated for topical application to DEB-associated skin lesions
- Phase I/II clinical trial data showed significant improvement in the healing of DEB-associated skin lesions over placebo and that repeat doses were well tolerated
- B-VEC is currently in Phase III clinical trials for treatment of DEB skin lesions, including chronic wounds

![Diagram of skin layers and B-VEC gene therapy process]

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DEB-associated eye disease and potential ophthalmic use of B-VEC

Eye Disease in Epidermolysis Bullosa (EB) Patients

- EB can result in the development of abrasions, blistering, vascularization, and scarring of the cornea, conjunctiva, and eyelids
- Eye involvement can occur in most types of EB but is most common in RDEB
- Current treatments are limited to ophthalmic lubricants and removal of scar tissue
- Topical B-VEC could be a potential treatment for DEB-associated eye disease

Herpes Stromal Keratitis (HSK)

- Immunopathological condition that can occur after a corneal HSV-1 infection
- Can cause inflammation, irreversible scarring of the cornea, and blindness
- HSK manifests as progressive:
  - Opacity
  - Neovascularization
  - Loss of corneal sensitivity
- Mice can be used to study the development of HSK

Topical B-VEC delivers human COL7A1 to the cornea, but not the underlying sensory nerves, in a murine corneal wound model

- **Corneal wound + Treatment**
- **Harvest TGs and corneas for gene expression**
- **Blinded HSK clinical scoring + Histology**

<table>
<thead>
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<th>Days post infection (DPI)</th>
<th>0</th>
<th>1</th>
<th>10</th>
<th>21</th>
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<tbody>
<tr>
<td><strong>Cornea</strong></td>
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<td><strong>Trigeminal Ganglion (TG)</strong></td>
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<td><strong>Ophthalmic Branch (V1)</strong></td>
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<td><strong>Maxillary Branch (V2)</strong></td>
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<td><strong>Mandibular Branch (V3)</strong></td>
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**Human COL7A1 Transcripts**

- **Vehicle**
- **B-VEC**

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Topical B-VEC application to the wounded murine cornea does not cause pathology

Data analyzed with repeated measures 2-way ANOVAs with Tukey's post tests. **p<0.01; ****p<0.0001, ns: not significant.
Repeated topical B-VEC application to the wounded murine cornea is safe

Data analyzed with repeated measures 2-way ANOVAs with Tukey’s post tests. *p<0.05; **p<0.01; ****p<0.0001, ns: not significant.

*10dpi data not shown as B-VEC did not separate from vehicle control at 10 dpi, as shown in previous results.
Summary

**Efficacy**
- Human COL7A1 was expressed in B-VEC treated corneas, but not the underlying sensory nerves

**Safety**
- B-VEC treated corneas developed little or no pathology
- B-VEC HSK clinical scores were not statistically different from vehicle treated corneas in either single and repeat dose experiments
- KOS/Vector treated corneas developed moderate to severe HSK after a single dose with 190-fold less virus than the B-VEC dose used

**Conclusion**
- B-VEC may be safe for repeated, topical treatment of human DEB corneal manifestations