

I concur with this review memo. I. Wu 5/4/23

I concur with this review memo. A. Shearin 5/4/23

FOOD AND DRUG ADMINISTRATION
Center for Biologics Evaluation and Research
Office of Therapeutic Products
Office of Pharmacology/Toxicology
Division of Pharmacology/Toxicology 1
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PRODUCT²: VYJUVEK (beremagene geperpavec; B-VEC; KB103)

APPLICANT: Krystal Biotech, Inc.

PROPOSED INDICATION³: Treatment of wounds in patients 6 months and over of age with dystrophic epidermolysis bullosa (DEB)

PHARM/TOX REVIEWER: Cheauyun (Theresa) Chen

PHARM/TOX TEAM LEADER: Abigail Shearin

PHARM/TOX BRANCH CHIEF: Sandhya Sanduja

PRODUCT (CMC) REVIEWERS: Anna Kwilas, Bo Liang, Syed (Rafat) Husain, Jianyang Wang

CLINICAL REVIEWER: Ning Hu

CLINICAL PHARMACOLOGY REVIEWER: Million Tegenge

PROJECT MANAGER: Rommel Maglalang

OFFICE DIRECTOR: Iwen Wu

EXECUTIVE SUMMARY⁴:

VYJUVEK (beremagene geperpavec [B-VEC], previously named KB103) is a gene therapy consisting of a replication-defective, non-integrating, engineered herpes simplex virus type 1 (HSV-1)-based vector expressing human type VII collagen (hCOL7) for the treatment of wounds in patients over 6 months of age with dystrophic epidermolysis bullosa (DEB). The nonclinical data provided to support this biologics licensing application are summarized below.

In vitro pharmacology studies were conducted using human dermal fibroblasts and human dermal keratinocytes (EB-HDF and EB-HDK, respectively) isolated from the skin from patients with epidermolysis bullosa (EB). Transduction with VYJUVEK resulted in a concentration-dependent increase in hCOL7 mRNA and protein expression, downregulation of thrombospondin-1 (TSP-1), upregulation of lysyl hydroxylase 3 (LH3), and increased cell

adhesion to fibronectin and type I collagen. VYJUVEK™ transduction also resulted in expression of hCOL7 protein in the basement membrane zone (BMZ) in a (b) (4) model comprised of EB-HDF and EB-HDK cells.

An *in vivo* pharmacology study evaluated a single intradermal (ID) administration of VYJUVEK to intact skin of healthy BALB/c mice at 4.8×10^6 or 4.8×10^7 pfu/mouse/administration or a single topical application of VYJUVEK mixed with 3% hydroxypropyl methylcellulose (Methocel) excipient gels on a skin wound in BALB/c mice at 4.8×10^7 pfu/application/site. This resulted in a local, transient, dose-dependent increase in vector transduction and hCOL7A1 mRNA transgene expression at the administration site. A significant reduction of vector transduction and transgene expression occurred between Days 3 and 6. Another study in comparing topical application of VYJUVEK mixed with 4% or (b) (4) Methocel gel excipient to a skin wound in BALB/C mice demonstrated similar levels of local vector transduction and hCOL7 mRNA and protein expression.

An *in vivo* pharmacology study was also conducted in type VII collagen hypomorphic mice, a mouse model of EB. In this study, single or repeat ID administration of VYJUVEK in intact skin at 6.4×10^6 or 4.6×10^7 pfu/administration/mouse resulted in local vector transduction and hCOL7A1 mRNA transgene expression at the administration site. Additionally, hCOL7 protein expression was observed in the BMZ and around hair follicles (HF), and local formation of anchoring fibrils (AF) was observed.

VYJUVEK™ was also evaluated in an a human RDEB skin xenograft model in mice in which single topical application of VYJUVEK to a human RDEB skin xenograft at 4.6×10^7 pfu/application resulted in an increase in full-length hCOL7 protein and AF formation in the BMZ compared to the vehicle control. These results support the potential for VYJUVEK-mediated restoration of hCOL7 protein and AF formation in RDEB.

In vivo Good Laboratory Practice (GLP) toxicology studies evaluated 1) single intravenous (IV) administration of VYJUVEK in BALB/c mice at 3.45×10^7 pfu/mouse, 2) five repeat weekly ID administrations of VYJUVEK in BALB/c mice at 6.9×10^6 or 3.45×10^7 pfu/mouse/administration, and 3) single topical application of VYJUVEK mixed with 3% HPMC to wounded skin of BALB/c mice at 3.48×10^7 pfu/application. No VYJUVEK-related adverse findings were observed in these studies VYJUVEK.

Analysis of *in vivo* biodistribution after five weekly repeat ID doses of VYJUVEK in mice at 6.9×10^6 or 3.45×10^7 pfu/dose/mouse resulted in vector detection primarily at the injection site, which declined to baseline by 30 days after the last dose. *In vivo* biodistribution was also evaluated after single topical application of VYJUVEK mixed with 3% HPMC to wounded skin of BALB/c mice at 3.48×10^7 pfu/application/mouse. Vector was present at the administration site 3 days post-administration and was not detected in other analyzed tissues.

Animal reproductive and developmental toxicity (DART) studies were not conducted with VYJUVEK. This is acceptable based on the product characteristics and safety profile.

PHARMACOLOGY/TOXICOLOGY RECOMMENDATION⁵:

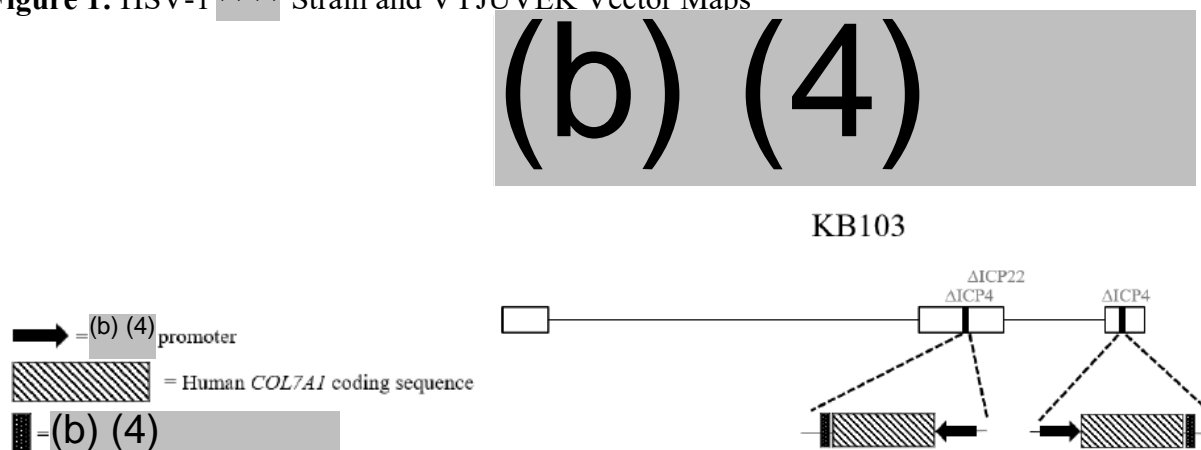
There are no nonclinical deficiencies in the pharmacology-toxicology studies for VYJUVEK, There are no outstanding requests for additional nonclinical data for evaluation of VYJUVEK. The nonclinical data provided in the BLA submission support the approval of this biologics license application.

Formulation and Chemistry⁶:

VYJUVEK (beremagene geperpavec, also named B-VEC, or KB103) drug product (DP) is a replication-defective, non-integrating, engineered HSV-1 based vector expressing hCOL7. The vector is derived from the (b) (4) strain of HSV-1 with deletion of the viral immediate early (IE) genes *ICP4* and *ICP22* and insertion of human *COL7A1* within both copies of deleted ICP4 loci (Figure 1). The copies of human *COL7A1* are each under the control of a (b) (4) promoter and (b) (4) signal.

The topically administered product consists of 1 mL of the VYJUVEK DP in Phosphate Buffered saline (PBS) + 10% glycerol mixed with 1.5 mL of excipient gel, 4.4% HPMC formulated in a buffer solution of PBS and 7.5 mM Tris prior to application.

Figure 1: HSV-1 (b) (4) Strain and VYJUVEK Vector Maps



U_L = unique long; U_S=unique short; TR_L = terminal repeat long; TR_S = terminal repeat short; IR_L = internal repeat long; IR_S = internal repeat short

Source: Page 4 of Module 2.6.1 'Introduction'

Abbreviations

Abbreviation	Definition
A:G Ratio	Albumin: Globulin Ratio
AF	Anchoring Fibril
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
(b) (4)	
BMZ	Basement Membrane Zone
COL7	Type VII Collagen
COL7A1	Collagen Type VII Alpha 1 Chain gene or mRNA
(b) (4)	
(b) (4)	
DEB	Dystrophic Epidermolysis Bullosa
DP	Drug Product
DPBS	Dulbecco's Phosphate-Buffered Saline
DDEB	Dominant Dystrophic Epidermolysis Bullosa
DNA	Deoxyribonucleic Acid
EB	Epidermolysis Bullosa
EB-HDF	Epidermolysis Bullosa – Human Dermal Fibroblast
EB-HDK	Epidermolysis Bullosa – Human Dermal Keratinocyte
G	Gauge
GFP	Green Fluorescent Protein
H&E	Hematoxylin and eosin
hCMV	Human Cytomegalovirus
hCOL7	Human Type VII Collagen
hCOL7A1	Human Collagen Type VII Alpha 1 Chain gene or mRNA
HF	Hair Follicles
HPMC	Hydroxypropyl Methylcellulose
HSK	Herpes Simplex Keratitis
HSV-1	Herpes Simplex Virus Type 1
HDF	Human Dermal Keratinocytes
HDK	Human Dermal Fibroblast
HSV-GFP	Herpes Simplex Virus Vector Expressing Green Fluorescent Protein
ICP	Infected Cell Protein
ID	Intradermal
IE	Immediate Early
IF	Immunofluorescence
IR	Internal Repeat
IRs	Internal Repeat Short
IRL	Internal Repeat Long
(b) (4)	Herpes Simplex Virus 1 Strain (b) (4)
LH3	Lysyl Hydroxylase 3
LN	Lymph Node

mCOL7	Murine Type VII Collagen
mL	Milliliter
mM	Millimolar
MOI	Multiplicity of Infection
mRNA	Messenger Ribonucleic Acid
MT	Microtubule
N-HDF	Normal Human Dermal Fibroblast
N-HDK	Normal Human Dermal Keratinocyte
NOAEL	No adverse effect dose level
PBS	Phosphate-Buffered Saline
PFU	Particle Forming Unit
qPCR	Quantitative Polymerase Chain Reaction
RDEB	Recessive Dystrophic Epidermolysis Bullosa
RT-qPCR	Reverse Transcriptase Quantitative Polymerase Chain Reaction
TG	Trigeminal ganglion
TRL	Terminal Repeat Long
TRs	Terminal Repeat Short
TSP-1	Thrombospondin-1
μl	Microliter
URs	Unique Short
URL	Unique Long
WT	Wild Type

Related File(s)

IND #18100; HSV-1 Vector, Non-Integrating, Replication Incompetent (KB103) Expressing Human Collagen VII (COL7) Protein [Beremagene geperpavec, B-VEC]; Topical; Dystrophic Epidermolysis Bullosa (DEB); Krystal Biotech, Inc.; ACTIVE

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INTRODUCTION

DEB is a clinically and biologically heterogeneous group of dominant and recessive blistering skin disorders caused by mutations in the *COL7A1* gene. In healthy individuals, *COL7A1* encodes wild-type type VII collagen (COL7) that assembles into the anchoring fibrils (AFs) that constitute basement membrane structures and anchor the epidermis and dermis together. Typical morphological findings in the skin of patients with DEB include dermal-epidermal cleavage below the BMZ and abnormal or a structural absence of AFs. The defects in COL7 impair dermal-epidermal cohesion, producing lifelong, widespread, painful blistering and fibrosis starting at birth, accompanied by scarring, susceptibility to infection, and a predisposition to skin cancer.^{1, 2} DEB is divided into two major subtypes depending on inheritance pattern: recessive DEB (RDEB) and dominant DEB (DDEB). The disease, which can present as early as birth, is characterized by skin fragility, separation of the epidermis from the dermis (blister formation), milia, and scarring.³ DEB-associated blisters and erosions affect skin as well as certain mucosa exposed to disruptive external environments, including the oropharynx, esophagus, rectum, genitourinary system, and eyes. Healing of erosions can result in debilitating scarring.

¹ Marinkovich M. Inherited Epidermolysis Bullosa. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, Orringer JS, editors. Fitzpatrick’s Dermatology. 9th ed. New York: McGraw-Hill. 2019; p.1011-1035.

² Has C, et al. (2020) Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility. Br J Dermatol. 183(4):614-627.

³ Intong LR and Murrell DF (2012) Inherited epidermolysis bullosa: new diagnostic criteria and classification. Clin Dermatol. 2012;30(1):70-7.

VYJUVEK is intended to be administered via topical application to transduce both keratinocytes and fibroblasts.

NONCLINICAL STUDIES

PHARMACOLOGY STUDIES

Summary List of Pharmacology Studies⁷

The following pharmacology studies were conducted to support the rationale for administration of VYJUVEK in the proposed population with DEB.

Note: As described in Module 2.4, the VYJUVEK material for the early-phase nonclinical and clinical programs (Phase 1/2) were produced using a (b) (4) production process, while the material in late-phase nonclinical and clinical programs (Phase 3) were produced using a (b) (4) production process.

- To establish comparability of a (b) (4)-produced batch (Lot (b) (4)) versus an (b) (4) produced batch (Lot (b) (4)), an *in vivo* comparability study (Report No. KB103-IVV-010) in immunocompetent mice was conducted. These data were also used to support comparability between batches in early- and late-phase product and clinical development.
- To explore options for alteration of the excipient gel to maximize local containment of VYJUVEK at the treatment site, while not interfering with vector mobilization or transduction of cutaneous skin wounds, *in vivo* nonclinical formulation development studies were undertaken (Report No. KB103-IVV-007, KB103-IVV-FD-009, KB103-IVV-013). Per the applicant, the gel used in the DP formulation of VYJUVEK for topical administration has no appreciable role in dissolution or uptake of the vector by the cells, no impact on the physicochemical characteristics of the DP, and no impact on the uptake of the DP into the wound bed of dosed patients. Therefore, the applicant considers the concentrations of HPMC excipient gel used across the nonclinical and clinical development programs to be functionally equivalent. This reviewer agrees with the applicant's conclusion.
- To support an expanded access request for topical application of VYJUVEK to an RDEB patient's corneal wound, an *in vivo* feasibility study was conducted in an animal model of a scratched cornea. Single (Report KB103-IVV-016) or repeat (Report KB103-IVV-017) instillation of VYJUVEK in a corneal wound in mice did not result in Herpes Simplex Keratitis (HSK)-related clinical signs or microscopic findings compared to control eyes instilled with vehicle.

In Vitro Studies

Study Number	Study Title / Publication Citation	Report Number
1	In Vitro Assessment in Normal and RDEB Cells and Organotypic Cultures	KB103-IVT-001

In Vivo Studies

In Vivo Studies in Healthy Mice With Abraded Skin or Open Wound; or EB Mouse Model

Study Number	Study Title / Publication Citation	Report Number
2	Non-GLP In Vivo Proof-of-Concept Assessments of KB103 in BALB/C Mice	KB103-IVV-001
3	Non-GLP In Vivo Proof-of-Concept Assessments of KB103 in COL7 Hypomorphic And Heterozygous Mice	KB103-IVV-002
4	In Vivo Comparison of COL7 Expression from Topical KB103 Compounded in (b) (4) or HPMC	KB103-IVV-007
5	Short-Term In Vivo Evaluation of KB103 Topical Formulations in BALB/C Mice	KB103-IVV-FD-009
6	Preclinical In Vivo Comparison of Efficacy and Safety of B-VEC GMP (b) (4) and (b) (4) Batches	KB103-IVV-010
7	Short-Term In Vivo Comparison of Expression and Safety of Topical B-VEC Formulated in Different Concentrations of Gel Excipient	KB103-IVV-013
8	Safety Assessment of In Vivo Topical Application of B-VEC in a Mouse Corneal Epithelial Scratch Wound Model	KB103-IVV-016
9	Safety Assessment of Repeated B-VEC Applications to the Scratched Mouse Cornea	KB103-IVV-017
10	Non-GLP Ex Vivo Assessment of KB103 in an RDEB Skin Equivalent Model	KB103-EXV-001

Overview of Pharmacology Studies

Overview of In Vitro Study

Study #1

Title: In Vitro Assessment In Normal And RDEB Cells And Organotypic Cultures

Report No.: KB103-IVT-001

Study Performed by: Thomas Jefferson University

Objectives:

- 1) To evaluate VYJUVEK-mediated hCOL7A1 mRNA and protein expression in human dermal fibroblast (HDF) and human dermal keratinocytes (HDK) from EB subjects (EB-HDF and EB-HDK)
- 2) To evaluate VYJUVEK -mediated activity in EB-HDF and EB-HDK

- 3) To evaluate VYJUVEK-mediated hCOL7 expression in (b) (4) organotypic cultures comprised of EB-HDF and EB-HDK

Methods:

- 1) Expression of hCOL7A1 mRNA and hCOL7 protein in (b) (4) cultures: EB-HDK or EB-HDF cells were transduced with VYJUVEK at different multiplicities of infection (MOI) and cultured for (b) (4) -48 hours. Normal human dermal keratinocytes (N-HDK) or fibroblasts (N-HDF) were included as positive controls. The hCOL7A1 mRNA was determined by qRT-PCR and hCOL7 protein expression was determined by immunofluorescence (IF) and/or Western blot.
- 2) Bioactivity: VYJUVEK-transduced EB-HDF and EB-HDK cells were assessed based on the levels of thrombospondin-1 (TSP-1), LH3, and number of VYJUVEK-transduced cells adhered to (b) (4) plates.

Reviewer's notes:

- *TSP-1 is a negative regulator of angiogenesis*
 - *LH3 is a protein required for deposition and organization of ECM and is reduced in RDEB skin⁴.*
- 3) hCOL7 protein expression in (b) (4) organotypic cultures: EB organotypic skin equivalents constructed with EB-HDF and EB-HDK cells⁵ were transduced with VYJUVEK or untransduced. hCOL7 protein expression was determined by IF. Organotypic skin equivalents that were constructed with N-HDF and N-HDK cells were included as a positive control.

Key Results:

- 1) VYJUVEK-transduced EB-HDK and EB-HDF demonstrated increased hCOL7A1 mRNA and hCOL7 protein expression compared to non-transduced EB-HDK and EB-HDF in (b) (4) culture in a MOI-dependent manner.
- 2) VYJUVEK-transduced cells demonstrated downregulation of TSP-1 expression, upregulation of LH3, and increased cell adhesion to (b) (4) in a plate-based adhesion assay in a MOI-dependent manner.
- 3) VYJUVEK transduced EB organotypic skin equivalents demonstrated increased hCOL7 protein expression in the BMZ compared to non-transduced control.

⁴ Watt SA, et al. (2015) Lysyl hydroxylase 3 localizes to epidermal basement membrane and is reduced in patients with recessive dystrophic epidermolysis bullosa. PLoS One, 10(9): e0137639.

⁵ (b) (4)

Overview of In Vivo Studies

Study #2

Report Number	KB103-IVV-001
Date Report Signed	March 18, 2018
Title	Non-GLP In Vivo Proof-Of-Concept Assessments Of KB103 In BALB/C Mice
Testing Facility	(b) (4)
Objective(s)	To determine local vector transduction and hCOL7 protein expression at the administration site following a single administration via 1) ID injection to intact skin or 2) topical application to abraded skin or an open wound
Animal Model	6-10 week old male BALB/c mice (body weights not specified) with intact skin or wounded (abraded or open wound) skin. <ul style="list-style-type: none"> - Open wound - The open wound was created by removal of a 5-6 mm diameter biopsy of skin using a sharp scissor. - Abraded - The abraded skin was created on the flank region with a mechanical drill followed by superficial perforation with 22G needle.

Study Groups / Study Design:

ID injection

- Test article: VYJUVEK (Lot # (b) (4) , 4.8 x 10⁸ pfu/ml in PBS + 10% glycerol)
- Control article: PBS + 10% glycerol
- ROA: ID administration at two sites/mouse of VYJUVEK or PBS + 10% glycerol to mice with intact skin at Day 1

Topical application

- Test article: VYJUVEK (Lot # (b) (4)) + Excipient gel (3% Methocel (b) (4) 3% Hydroxypropyl methylcellulose [HPMC] formulated in (b) (4)
Note: HPMC is also referred to as 'Methocel'
- Control article: Excipient gel
- ROA: Topical application at two sites/mouse of VYJUVEK/excipient gel mixture (100 µl of VYJUVEK mixed with 20 µl of excipient gel) or excipient gel (120 µl) only to mice with an open wound or abraded skin via a topical 'well' that was adhered to the wounded region using surgical glue at Day 1.
- Study design: Groups 1-3 received single ID administration. Groups 4-6 received single topical administration.
 - Local transduction and hCOL7 expression at the administration sites were determined. The biopsies were used as follows except in Groups 4 and 5*:
 - Half of the biopsy was used for determination of vector transduction by qPCR of hCOL7 DNA) and transgene expression by qRT-PCR of hCOL7A1 mRNA)
 - The remaining half of the biopsy was used for determination of hCOL7 protein expression by IF.

*The entire biopsy for Groups 4 and 5 were assessed by qPCR because it was not feasible to split the wounded tissue.

Group	Test Article/Vehicle	# of Animals	Dose (pfu)/ site	Route	Day 3 Sacrifices	Day 6 Sacrifices	Skin Manipulation
1	100µL ID Vehicle	2	-	ID	1	1	Intact skin
2	100µL KB103 in PBS + 10% Glycerol	6	4.8x10 ⁶	ID	3	3	Intact skin
3		6	4.8x10 ⁷	ID	3	3	Intact skin
4	120µL Gel	4	-	Topical	2	2	Open wound
5	100µL KB103 in PBS + 10% Glycerol + 20 µL Gel	6	4.8x10 ⁷	Topical	3	3	Open wound
6		6	4.8x10 ⁷	Topical	3	3	Abraded Skin

Source: Page 10 of 'KB103 IVV-001 pre-clinical-study-report.pdf' under Module 4.2.1 1 'Primary Pharmacodynamics'

Key Results:

Mice that received single ID administration of VYJUVEK at 4.8 x 10⁶ or 4.8 x 10⁷ pfu/site, or single topical application of VYJUVEK mixed with 3% HPMC excipient gel at 4.8 x 10⁷ pfu/site on wounded skin showed: i) increased vector transduction and hCOL7A1 mRNA expression in a dose-dependent manner and ii) vector presence and hCOL7A1 mRNA expression were transient; between Days 3 and 6 vector transduction decreased more than 25-fold and hCOL7A1 mRNA expression decreased more than 8-fold. Levels of hCOL7 protein expression in the BMZ could not be accurately evaluated because of the presence of endogenous murine COL7 protein in the BMZ.

Reviewer's Conclusion: Single ID administration of VYJUVEK to intact skin or single topical application of VYJUVEK mixed with 3% HPMC excipient gel on wounded skin in BALB/c mice resulted in a local, transient, dose-dependent increase in vector transduction and hCOL7A1 mRNA transgene expression with a significant reduction of vector transduction and transgene expression between Days 3 and 6.

Study #3

Report Number	KB103-IVV-002
Date Report Signed	March 23, 2018
Title	Non-GLP In Vivo Proof-of-Concept Assessments of KB103 in COL7 Hypomorphic and Heterozygous Mice
Testing Facility	Stanford University
Objective(s)	<ul style="list-style-type: none"> To evaluate vector transduction and hCOL7A1 mRNA expression at the injection sites following ID administration in Col7a1^{flNeo} hypomorphic and heterozygous mice To evaluate the formation of AFs in hypomorphic mice administered VYJUVEK

Animal model	<ul style="list-style-type: none"> • Homozygous Col7a1^{flNeo} hypomorphic mice⁶ - murine model of EB that expresses mCOL7 at about 10% of normal levels. Dermal-epidermal separation has been reported in the skin of hypomorphic mice due to a strong reduction of mCOL7 expression. Hypomorphic mice have a normal life span compared to WT mice.⁷ • Heterozygous Col7a1^{flNeo} mice
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This study consisted of three experiments which are described below.

Experiment 1: ID administration of VYJUVEK in hypomorphic mice at the high-dose level 4.6 x 10⁷ pfu/site.

Study Groups/Study Design

- Study animals: Hypomorphic mice (n=3)
- Test article: VYJUVEK
- Control article: HSV-GFP or PBS
- ROA: ID injection to intact skin
- Study design: Each mouse had four injection sites. PBS, HSV-GFP at 4.6 x 10⁷ pfu/site, or VYJUVEK at 4.6 x 10⁷ pfu/site were administered to each site as listed in the table below. Mice 1 and 2 received a single administration on Day 1. Mouse 3 received repeat administrations at each site on Days 1 and 3. Local vector transduction measured by qPCR, hCOL7A1 mRNA expression measured by qRT-PCR, hCOL7 protein expression measured by histology and IF, and AF formation measured by electron microscopy at the injection sites, were determined.

Sample	Mouse	Treatment Day1	Treatment Day 3	Day of Sacrifice
1	1	HSV-GFP	PBS	day 3
2		KB103	-	day 3
3		KB103	-	day 3
4		KB103	-	day 3
5	2	PBS	PBS	day 7
6		KB103	-	day 7
7		KB103	-	day 7
8		KB103	-	day 7
9	3	PBS	PBS	day 7
10		KB103	KB103	day 7
11		KB103	KB103	day 7
12		KB103	KB103	day 7

Source: Page 9 of 'KB103-IVV-002 pre-clinical-study-report.pdf' under Module 4.2.1 1 'Primary Pharmacodynamics'

Key Results:

Hypomorphic mice that received a single ID administration of VYJUVEK at 4.6 x 10⁷ pfu/site/day on Day 1 showed: i) increased vector transduction and hCOL7A1 mRNA

⁶ Fritsch A, et al. (2008) A hypomorphic mouse model of dystrophic epidermolysis bullosa reveals mechanisms of disease and response to fibroblast therapy. J Clin Inv 118:1669-79.

⁷ Natsuga K, et al. (2010) Animal Models of Epidermolysis Bullosa. Dermatol Clin 28:137-42.

expression at the administration sites compared to control mice injected with HSV-GFP or vehicle, ii) a decline in vector transduction and hCOL7A1 mRNA expression from Days 3 to 7, iii) hCOL7 protein expression in the BMZ and around hair follicles (HF) on Day 7, and iv) formation of AF locally at the injection sites on Day 3. Mice that received repeat administration of VYJUVEK on Days 1 and 3 had higher levels of vector transduction and hCOL7A1 mRNA transgene expression on Day 7 compared to mice that received a single administration.

Experiment 2: ID administration of VYJUVEK in hypomorphic mice at the low dose level 6.4×10^6 pfu/site.

Study Groups/Study Design

- Study system: Hypomorphic mice (n=3)
- Test article: VYJUVEK
- Control article: NA
- ROA: ID injection in intact skin
- Study design: Each mouse had 2 or 3 injection sites that were ID injected with VYJUVEK at 6.4×10^6 pfu/site. Mice 1 and 2 received a single administration. Mouse 3 received repeat administrations at each site at Days 1 and 3. Vector transduction and hCOL7A1 mRNA transgene expression was determined at the injection sites for each mouse. hCOL7 protein expression was determined by histology and IF for Mouse 1 only.

Mouse	Treatment Day	# of injection sites	Termination Day
1	1	3	Day 3
2	1	2	Day 3
3	1	2	Day 7

Source: Page 15 of 'KB103-IVV-002 pre-clinical-study-report.pdf' under Module 4.2.1 1 'Primary Pharmacodynamics'

Key Results:

Hypomorphic mice that received single (Day 1) or repeat (Days 1 and 3) ID administration of VYJUVEK at 6.4×10^6 pfu/site showed vector transduction, hCOL7A1 mRNA expression at 2 and 4 days after the last administration, and hCOL7 protein expression in the BMZ and HF when assessed at 2 days following administration.

Experiment 3: ID administration of VYJUVEK at low (6.4×10^6 pfu/site) and high (4.6×10^7 pfu/site) dose levels in heterozygous mice.

Study Groups/Study Design

- Study system: Col7a1^{flNeo} heterozygous mice (n=4)
- Test article: VYJUVEK

- Control articles: HSV-GFP and PBS
- ROA: ID injection in intact skin
- Study design: Each mouse had four injection sites that were ID injected with PBS, HSV-GFP at 4.6×10^7 pfu/site, or VYJUVEK at 4×10^6 pfu/site or 4×10^7 pfu/site. Mice 1 to 3 received a single administration at Day 1. Mouse 4 received repeat administration at the same dose levels at Days 1 and 3. Local vector transduction (by qPCR) and hCOL7A1 mRNA expression (by qRT-PCR) were determined.

Injection Site	Mouse	Treatment Day1	Treatment Day 3	Day of Sacrifice
1	1	PBS	-	Day 3
2		HSVGF	-	Day 3
3		KB103 low	-	Day 3
4		KB103 high	-	Day 3
5	2	PBS	-	Day 5
6		HSVGF	-	Day 5
7		KB103 low	-	Day 5
8		KB103 high	-	Day 5
9	3	PBS	-	Day 7
10		HSVGF	-	Day 7
11		KB103 low	-	Day 7
12		KB103 high	-	Day 7
13	4	PBS	PBS	Day 7
14		HSVGF	HSVGF	Day 7
15		KB103 low	KB103 low	Day 7
16		KB103 high	KB103 high	Day 7

Source: Page 17 of 'KB103-IVV-002 pre-clinical-study-report.pdf' under Module 4.2.1 1 'Primary Pharmacodynamics'

Key Results:

Heterozygous mice that received a single (Day 1) or repeat (Days 1 and 3) ID administration of VYJUVEK at 6.4×10^6 or 4.6×10^7 pfu/site/administration showed: i) a dose-dependent increase in vector transduction and hCOL7A1 mRNA expression at the administration sites, ii) transient hCOL7A1 mRNA expression which declined between Days 3 and 7, and iii) a dose-dependent increase in hCOL7 protein expression in the BMZ and HF on Days 3 and 7.

Reviewer's Conclusion: *Although this study does not include the excipient gel and the topical route of application was not used, the results demonstrate VYJUVEK-mediated hCOL7 protein expression in the BMZ and around HF cells and formation of AF, which hold the epidermis and dermis together and maintain the integrity of the skin. Therefore, these results support the mechanism of action of VYJUVEK.*

Study #4

Report Number	KB103-IVV-007																								
Date Report Signed	December 5, 2018																								
Title	In Vivo Comparison of COL7 Expression from Topical KB103 Compounded in (b) (4) or HPMC																								
Testing Facility	(b) (4)																								
Objective(s)	<p>To compare VYJUVEK that was mixed with 3% HPMC** (VYJUVEK /HPMC) or (b) (4) (VYJUVEK (b) (4)) excipient gel in wounded skin of BALB/c mice via single topical application based on local vector transduction and hCOL7A1 protein expression in VYJUVEK</p> <p>**HPMC (consisting of 3% methocel (b) (4) Hydroxypropyl) is the excipient gel used in the Phase 1 clinical trial. There was a sample containment related challenge when VYJUVEK mixed with 3% HPMC was applied to the skin due to low viscosity.</p> <p>(b) (4) is an alternative excipient which is a (b) (4) compound-based dressing that gels at room temperature or upon application, but liquefies when refrigerated</p>																								
Study Animals	BALB/C mice (6 to 10 weeks old, sex and body weights not specified) with wounded skin. The wounds were created by taking an 8-mm punch skin biopsy.																								
Test Article(s)	VYJUVEK (Lot (b) (4))																								
Test Excipient Gel	<ul style="list-style-type: none">• HPMC• (b) (4)																								
Control Article(s)	Dulbecco’s phosphate-buffered saline (DPBS) + 10% glycerol																								
ROA	Topical application to the wounded region was performed via a topical ‘well’ that was adhered to the wounded region using surgical glue (application volume = 120 µl/site) on Day 1.																								
Study Groups and Dose Levels	<table><tr><th>Group</th><th>N</th><th>Test Article</th><th>Dose/wound</th><th>Excipient</th><th># of sites/animal</th></tr><tr><td>1</td><td>1</td><td>Vehicle</td><td>0pfu</td><td>(b) (4)</td><td>2</td></tr><tr><td>2</td><td>2</td><td>KB103</td><td>1 x 10⁸pfu</td><td>HPMC</td><td>2</td></tr><tr><td>3</td><td>2</td><td>KB103</td><td>1 x 10⁸pfu</td><td>(b) (4)</td><td>2</td></tr></table> <p>Source: Page 10 of ‘KB103-IVV-007 pre-clinical-study-report.pdf’ under Module 4.2.1.2 ‘Secondary Pharmacodynamics’</p> <p>VYJUVEK (100 µl) was mixed with the respective excipient gel (20 µl) before application. VYJUVEK /HPMC and VYJUVEK (b) (4) were designated for Groups 2 and 3, respectively.</p>	Group	N	Test Article	Dose/wound	Excipient	# of sites/animal	1	1	Vehicle	0pfu	(b) (4)	2	2	2	KB103	1 x 10 ⁸ pfu	HPMC	2	3	2	KB103	1 x 10 ⁸ pfu	(b) (4)	2
Group	N	Test Article	Dose/wound	Excipient	# of sites/animal																				
1	1	Vehicle	0pfu	(b) (4)	2																				
2	2	KB103	1 x 10 ⁸ pfu	HPMC	2																				
3	2	KB103	1 x 10 ⁸ pfu	(b) (4)	2																				
Dosing Regimen	Single application per site at two sites per animal																								
Randomization	Not described																								
Description of Masking	Not described																								
Scheduled Sacrifice Time Points	48 hours post-application																								
Study Endpoints	<p>Skin biopsies (8 mm) of the application sites were harvested 48 hours post-application for analysis of:</p> <ul style="list-style-type: none">• Local vector transduction of hCOL7A1 DNA was determined by qPCR using half of the 8 mm skin biopsy.• hCOL7 protein expression was determined by histology/immunofluorescence using the other half of 8 mm skin biopsy.																								

Key Results:

Mice that received topical application of VYJUVEK mixed with HPMC or (b) (4) on the skin wound showed: i) similar increased levels of local vector transduction and ii) similar increased levels of hCOL7 protein expression in the BMZ and around HF's 48 hours post-application.

Reviewer's Conclusion: Single topical application of VYJUVEK mixed with 3% HPMC excipient gels or (b) (4) on wounded skin resulted in similar levels of local vector transduction and hCOL7 protein expression in BMZ and HF's 48 hours post-application.

Study #5

Report Number	KB103-IVV-FD-009																																		
Date Report Signed	March 13, 2020																																		
Title	Short-Term In Vivo Evaluation of B-VEC Topical Formulations in BALB/c Mice																																		
Testing Facility	(b) (4)																																		
Objective(s)	To compare VYJUVEK that was mixed with different excipients (PBS + 10% glycerol, 3% Methocel, 4% Methocel, or 3% Methocel + (b) (4) Poloxamer 407) on wounded skin of BALB/c mice via a single topical application based on local vector transduction and transgene (hCOL7A1 mRNA) expression																																		
Study Animals	BALB/c mice (age and sex not specified) with wounded skin. The wounds of 5-6 mm diameter were created on the back of each mouse via a biopsy punch tool																																		
Test Article(s)	VYJUVEK (Lot # (b) (4) Titer 4.45 x 10 ⁹ PFU/mL)																																		
Test excipient(s)	<ul style="list-style-type: none"> • PBS + 10% glycerol • 3% Methocel • 4% Methocel • 3% Methocel + (b) (4) Poloxamer 407 																																		
Control Article(s)	Not included																																		
Route of Administration	Topical application to the wounded region was via a topical 'well' that was adhered to the wounded region using surgical glue (application volume = 100 µl/site) on Day 1.																																		
Study Groups / Study Design	<table border="1"> <thead> <tr> <th>Group No.:</th><th>N:</th><th>Test Article:</th><th>Excipient Gel:</th><th>Location; No. of Sites:</th><th>Termination (Hours):</th></tr> </thead> <tbody> <tr> <td>1</td><td>3</td><td>KB103</td><td>PBS + 10% glycerol</td><td>Back; 2</td><td>48</td></tr> <tr> <td>2</td><td>3</td><td>KB103</td><td>3% Methocel</td><td>Back; 2</td><td>48</td></tr> <tr> <td>3</td><td>3</td><td>KB103</td><td>4% Methocel</td><td>Back; 2</td><td>48</td></tr> <tr> <td>4</td><td>3</td><td>KB103</td><td>3% Methocel + (b) (4) Poloxamer 407</td><td>Back; 2</td><td>48</td></tr> </tbody> </table> <p>Source: Page 8 of 'KB103-IVV-FD-009 pre-clinical-study-report.pdf' under Module 4.2.1.2 'Secondary Pharmacodynamics'</p> <p>VYJUVEK (50 µl) at 1.1 x 10⁸ pfu was mixed with excipient gel (50 µl) before administration.</p>					Group No.:	N:	Test Article:	Excipient Gel:	Location; No. of Sites:	Termination (Hours):	1	3	KB103	PBS + 10% glycerol	Back; 2	48	2	3	KB103	3% Methocel	Back; 2	48	3	3	KB103	4% Methocel	Back; 2	48	4	3	KB103	3% Methocel + (b) (4) Poloxamer 407	Back; 2	48
Group No.:	N:	Test Article:	Excipient Gel:	Location; No. of Sites:	Termination (Hours):																														
1	3	KB103	PBS + 10% glycerol	Back; 2	48																														
2	3	KB103	3% Methocel	Back; 2	48																														
3	3	KB103	4% Methocel	Back; 2	48																														
4	3	KB103	3% Methocel + (b) (4) Poloxamer 407	Back; 2	48																														
Dosing Regimen	Single application per site at two sites per animal																																		
Randomization	Not specified																																		
Description of Masking	Not specified																																		
Scheduled Sacrifice Time Points	48 hours post-application																																		

Study Endpoints	<p>Skin biopsies (8 mm) of the application sites were harvested 48 hours post-application for analysis of:</p> <ul style="list-style-type: none"> Local vector transduction of <i>hCOL7A1</i> DNA levels by qPCR Local transgene expression of <i>hCOL7A1</i> mRNA by RT-qPCR
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Key Results:

Mice that received topical application of VYJUVEK that was mixed with PBS + 10% glycerol, 3% Methocel, 4% Methocel, or 3% Methocel + (b) (4) Poloxamer 407 on the respective skin wound showed similar local vector transduction and *hCOL7A1* mRNA expression 48 hours post-application.

Reviewer's Conclusion: Topical application of VYJUVEK with different gel excipients (3% Methocel, 4% Methocel, or 3% Methocel + (b) (4) Poloxamer 407) resulted in similar local vector transduction and *hCOL7A1* mRNA expression. The tested gel excipients in this study contain slightly lower concentrations of Methocel compared to the excipient gel for the commercial VYJUVEK product which contains 4.4% Methocel.

Study #6

Report Number	KB103-IVV-010					
Date Report Signed	August 4, 2020					
Title	Preclinical In Vivo Comparison of Efficacy and Safety of B-VEC GMP (b) (4) and (b) (4) Batches					
Testing Facility	(b) (4)					
Objective(s)	To compare VYJUVEK generated from a (b) (4) GMP batch and a (b) (4) GMP batch in BALB/c mice via a single ID administration by local vector transduction and transgene (mRNA and protein) expression.					
Study Animals	Healthy BALB/c mice (age and sex not specified)					
Test Article(s)	<ul style="list-style-type: none"> VYJUVEK (B-VEC (b) (4) (Lot (b) (4)) (manufactured by a (b) (4) process, utilized in the Phase 2 clinical trial, 4.1×10^9 pfu/ml) VYJUVEK (B-VEC KB-GMP) (Lot (b) (4)) (manufactured by the (b) (4) process, utilized in the Phase 3 clinical trial, 7.3×10^9 pfu/ml) <p>The test article was diluted in PBS + 10% glycerol.</p>					
Control Article(s)	PBS + 10% glycerol					
Route of Administration	ID injection to intact skin					
Study Design / Study Groups / Dose level	Group	N	Test Article (TA)	Administration Day and # of sites	Dose (pfu/site)	Termination
	1	3	B-VEC (b) (4) (b) (4)	Day 1, 4 ID	2E8	Day 3
	2	3	B-VEC KB-GMP (b) (4)	Day 1, 4 ID	2E8	Day 3
	3	1	PBS +10% glycerol	Day 1, 4 ID	-	Day 3
	<p>Source: Page 7 of 'KB103-IVV-010 pre-clinical-study-report.pdf' under Module 4.2.1.2 'Secondary Pharmacodynamics'</p> <p>Each mouse had four injection sites.</p>					

Dosing Regimen	Single administration per site on Day 1
Randomization	Not described
Description of Masking	Not described
Scheduled Sacrifice Time Points	Day 3 (48 hours post-administration)
Study Endpoints	<p>Skin biopsies (8 mm) of administration sites were harvested 48 hours post-administration for analysis of:</p> <ul style="list-style-type: none"> Local vector transduction of hCOL7A1 DNA levels by qPCR Local transgene expression of hCOL7A1 mRNA by RT-qPCR Local hCOL7 protein expression by histology/immunofluorescence

Key Results:

Mice that received ID administration of VYJUVEK (Lot (b) (4)) manufactured by the GMP (b) (4) (Lot (b) (4)) used in the Phase 2 clinical trial and VYJUVEK (Lot (b) (4)) that was manufactured by the (b) (4) batches for the pivotal Phase 3 clinical trial, resulted in comparable levels of local vector transduction and hCOL7 protein expression in the BMZ 48 hours post-ID administration. No local microscopic abnormal findings were observed.

Reviewer's Conclusion: The manufacturing process change between the (b) (4) process to the (b) (4) process did not significantly impact the activity of VYJUVEK (e.g., vector transduction and transgene expression, measured by mRNA and protein) in Balb/C mice after a single ID administration.

Study #7

Report Number	KB103-IVV-013
Date Report Signed	June 30, 2021
Title	Short-term In Vivo Comparison of Expression and Safety of Topical B-VEC Formulated in Different Concentrations of Gel Excipient
Testing Facility	(b) (4)
Objective(s)	<p>To compare VYJUVEK mixed with 4% or 7% HPMC** excipient gel on wounded skin of BALB/c mice via a single topical application by local vector transduction and transgene expression</p> <p>**The excipient gel of 4% HPMC is used in the Phase 3 clinical trial. Per the applicant, the excipient gel of 7% HPMC may be used in the future for open label extension and/or commercial drug product because higher viscosity may allow for better containment of VYJUVEK at the application site.</p>
Study Animals	Female BALB/c mice (8 weeks old, body weights not specified) with a full-thickness skin wound. The wounds were created by a 6-mm punch skin biopsy.
Test Article(s)	VYJUVEK GMP batch (Lot (b) (4))
Excipient Gel(s)	4% or (b) (4) HPMC
Control Article(s)	PBS + 10% glycerol
Route of Administration	Topical application to the wounded region via a topical 'well' that was adhered to the wounded region using surgical glue (application volume = 100 µl/site) on Day 1.

Study Groups and Dose Levels	Group No.:	N:	Test Article:	Excipient Gel:	Location Sites:	Termination (Hours):	Sample collection
	1	2	PBS + 10% glycerol	4% HPMC	Back; 2	24	2 skin biopsies per animal. For each skin biopsy: ½ biopsy snap frozen for qPCR/RT-qPCR; ½ biopsy for OCT embedding
	2	2	PBS + 10% glycerol	(b) (4) HPMC			
	3	3	B-VEC	4% HPMC			
	4	3	B-VEC	(b) (4) HPMC			
Source: Page 9 of ‘KB103-IVV-010 pre-clinical-study-report.pdf’ under Module 4.2.1.2 ‘Secondary Pharmacodynamics’							
Two wounds were created on each animal. VYJUVEK (33.3 µl) at 2.2 x 10 ⁸ pfu was mixed with excipient gel (66.7 µl) before application. VYJUVEK was applied at 2.2 x 10 ⁸ pfu/site.							
Dosing Regimen	Single application						
Randomization	Not described						
Description of Masking	Not described						
Scheduled Sacrifice Time Points	24 hours post-application						
Study Endpoints	Skin biopsies (8 mm) of application sites were harvested 24 hours post-application for analysis of: <ul style="list-style-type: none">Local vector transduction of hCOL7A1 DNA levels by qPCRLocal expression of hCOL7A1 mRNA by RT-qPCRLocal expression of hCOL7 protein by histology/immunofluorescence						

Key Results:

Mice that received topical application of VYJUVEK that was mixed with 4% or 7% HPMC had similar levels of local vector transduction and transgene expression, measured by mRNA and protein, at the application site.

Reviewer's Conclusion: Changing the excipient from 4% to (b) (4) Methocel did not appear to affect vector transduction and expression of hCOL7 mRNA and protein.

Study #8

Report Number	KB103-IVV-016
Date Report Signed	April 29, 2022
Title	Safety assessment of in vivo topical application of B-VEC in a mouse corneal epithelial scratch wound model
Testing Facility	(b) (4)
Objective(s)	To evaluate bioactivity and safety of VYJUVEK in a mouse corneal scratch wound model via a single topical instillation to the eyes based on local transgene (mRNA and protein) expression, Herpes Simplex Keratitis (HSK) clinical scoring, and histopathology of the eyes and off-target (mRNA) transgene expression in the trigeminal ganglion (TG)
Study Animals	Female BALB/c mice (6 weeks old, body weight not specified)
Test Article(s)	VYJUVEK (Lot # Engineering (b) (4) ; 1.9 x 10 ⁷ pfu/3µl)

Control Article(s)	<ul style="list-style-type: none">HSV wild-type (WT) vector control: HSV-1 vector (b) (4) strain (Lot # (b) (4)) (1 x 10⁵ pfu/3μl)Vehicle control: PBS+10% glycerol <p>Note: VYJUVEK originates from a non-integrating, replication incompetent HSV-1 vector. Therefore, HSV-1 related HSK is a potential concern for ophthalmic instillation. HSV-1 WT vector was used as a positive control for HSK clinical scoring.</p>																														
Route of Administration	Topical instillation of 3 μl/eye with a pipette; the eye lids were manually blinked 5 times to disperse the control and test articles.																														
Description of the Disease/Injury Model and Implant Procedure	A unilateral corneal wound was generated in the right eye of each mouse by scratching it with a 30 G needle in a crosshatch pattern under dissecting microscope on Day 0. The left eye of each mouse served as a control. <ul style="list-style-type: none">The wounded (right) eyes were instilled with test or control article on Day 0.The unwounded (left) eyes were untreated.																														
Study Groups and Dose Levels	<table><tr><th>Group No.</th><th>Total N of animals</th><th>Animal #</th><th>Test Article</th><th>Termination Day(s)</th><th>Scoring Day(s)</th></tr><tr><td>1</td><td>3</td><td>1,2,3</td><td>Vehicle</td><td rowspan="2">D1 (24h)</td><td rowspan="2">NA</td></tr><tr><td>2</td><td>3</td><td>4,5,6</td><td>B-VEC</td></tr><tr><td>3</td><td>5</td><td>7,8,9,10,11</td><td>Vehicle</td><td rowspan="3">D21</td><td rowspan="3">D10, D21</td></tr><tr><td>4</td><td>5</td><td>12,13,14,15,16</td><td>vector</td></tr><tr><td>5</td><td>5</td><td>17,18,19,20,21</td><td>B-VEC</td></tr></table> <p>Source: Page 12 of ‘KB103-IVV-016 pre-clinical-study-report.pdf’ under Module 4.2.1.2 ‘Secondary Pharmacodynamics’</p> <p>Dose level of B-VEC: 1.9 x 10⁷ pfu/eye/mouse</p>	Group No.	Total N of animals	Animal #	Test Article	Termination Day(s)	Scoring Day(s)	1	3	1,2,3	Vehicle	D1 (24h)	NA	2	3	4,5,6	B-VEC	3	5	7,8,9,10,11	Vehicle	D21	D10, D21	4	5	12,13,14,15,16	vector	5	5	17,18,19,20,21	B-VEC
Group No.	Total N of animals	Animal #	Test Article	Termination Day(s)	Scoring Day(s)																										
1	3	1,2,3	Vehicle	D1 (24h)	NA																										
2	3	4,5,6	B-VEC																												
3	5	7,8,9,10,11	Vehicle	D21	D10, D21																										
4	5	12,13,14,15,16	vector																												
5	5	17,18,19,20,21	B-VEC																												
Dosing Regimen	Single instillation on Day 0																														
Randomization	Not described																														
Description of Masking	Not described																														
Scheduled Sacrifice Time Points	Day 1 (Groups 1-5, n=3 animals/group) and Day 21 (Groups 3-5, n=2 animals/group)																														

Study Endpoints	<ul style="list-style-type: none"> • HSK clinical scorings of opacity⁸, corneal reflex⁹, and vessel ingrowth¹⁰ • Eyes and trigeminal ganglion (TG) were harvested on Day 1 for Groups 1 & 2 and eyes were harvested on Day 21 for Groups 3-5 for analyses of: • hCOL7A1 mRNA expression in the corneas and TG by RT-qPCR (Note: No individual animal data were generated because individual samples of each Study Group were pooled (e.g., right corneas, left corneas, right TGs, and left TGs) before RNA isolation for determination of hCOL7A1 mRNA levels). • For Groups 3-5 only, local histopathology and hCOL7 protein expression by histology and immunofluorescence (H&E and anti-hCOL7 stains)
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Key Results:

VYJUVEK -instilled murine eyes showed: i) increased hCOL7A1 mRNA expression locally in instilled eyes at Day 1, ii) no off-target transgene expression in (left and right) TG at Day 1, ii) no change in HSK scoring for opacity, vessel ingrowth, or corneal reflex in the instilled eyes on Days 10 and 21, iii) increased local hCOL7 protein expression in the epithelium of the cornea on Day 21, iv) no local abnormal microscopic findings in the eyes on Day 21 compared to the vehicle-instilled control eyes.

Reviewer's Conclusion: *This study is not relevant for this application because the intended clinical excipient and route of administration were not used.*

Study #9

Report Number	KB103-IVV-017
Date Report Signed	April 29, 2022
Title	Safety Assessment Of Repeated B-VEC Applications To The Scratched Murine Cornea
Testing Facility	(b) (4)
Objective(s)	To evaluate bioactivity and safety of VYJUVEK in the mouse corneal scratch wound model via single or repeat topical instillation to the eyes based on HSK clinical scoring of the eyes
Study Animals	Female BALB/c mice (6 weeks old, body weights not specified)
Test Article(s)	VYJUVEK (Lot # Engineering (b) (4) ; 1.9 x 10 ⁷ pfu/3µl)
Control Article(s)	<ul style="list-style-type: none"> • HSV WT vector control: HSV-1 (b) (4) vector (Lot (b) (4) (1 x 10⁵ pfu/3µl) • Vehicle control: PBS+10% Glycerol

⁸ The opacity score of each eye was scored on a scale of 0-4; 0=completely clear eye with increments of 0.5.

⁹ The corneal reflex of each eye was scored on a scale of 0-5; a composite core determined from 5 areas (center, top, bottom, left, and right) for negative reflex (score 0) or positive reflex (score 1).

¹⁰ The vessel ingrowth of each eye was scored on a scale of 0-4; 0=no visible vessels, 1= up to 25%; 2= up to 50%, 3=up to 75%, and 4= 100% into the center of the cornea.

Route of Administration	Topical instillation of 3 µl/eye with a pipette on Days 0, 2, and 4; the eye lids were manually blinked 5 times to disperse the control and test articles.							
Description of the Disease/Injury Model and Implant Procedure	A corneal wound was generated by scratching the mouse eye with a 30 G needle in a crosshatch pattern under a dissecting microscope on Day 0. <ul style="list-style-type: none">Groups 1 and 3 received bilateral corneal wounds.Groups 2, 4, and 5 received a unilateral corneal wound in the right eye and the left eyes were unwounded controls.							
Study Groups and Dose Levels	Grp #	Total Animal #	Animal #	TA name	Cornea	Wounding + Dosing Days	Scoring Days	Term. Day
	1	5	1, 2, 3, 4, 5	B-VEC	Right	D0	D10, D21	D21
	2	5	6, 7, 8, 9, 10			D0, D4		
	3	5	11, 12, 13, 14, 15			D0, D2, D4		
	4	5	16, 17, 18, 19, 20	Vector	Right	D0		
	5	5	21, 22, 23, 24, 25	Vehicle	Left	D0		
					Right	D0, D2, D4		
Source: Page 8 of ‘KB103-IVV-017 pre-clinical-study-report.pdf’ under Module 4.2.1.2 ‘Secondary Pharmacodynamics’								
Dose level of B-VEC: 1.9 x 10 ⁷ pfu/eye/instillation								
Dosing Regimen	Group 1 – single instillation Group 2 – repeat instillation on Days 0 and 4 Group 3 - repeat instillation on Days 0, 2, and 4.							
Randomization	Not described							
Description of Masking	Not described							
Scheduled Sacrifice Time Points	Not described							
Study Endpoints	HSK clinical scorings of opacity ¹¹ , corneal reflex ¹² , and vessel ingrowth ¹³ at Days 10 and 21.							

Key Results:

VYJUVEK -instilled murine eyes, via single or repeat instillation, showed no changes in HSK scorings for opacity, vessel ingrowth, and corneal reflex on Days 10 and 21 compared to vehicle-instilled control eyes.

Reviewer's Conclusion: *This study is not relevant for this application because the intended clinical excipient and route of administration were not used.*

¹¹ The opacity score of each eye was scored on a scale of 0-4; 0=completely clear eye with increments of 0.5.

¹² The corneal reflex of each eye was scored on a scale of 0-5; a composite core determined from 5 areas (center, top, bottom, left, and right) for a negative reflex (score 0) or a positive reflex (score 1).

¹³ The vessel ingrowth of each eye was scored on a scale of 0-4; 0=no visible vessels, 1= up to 25%; 2= up to 50%, 3=up to 75%, and 4= 100% into the center of the cornea.

Study #10

Note: In the Application Orientation Meeting held on September 16, 2022, the applicant presented nonclinical data from a murine xenograft model bearing skin from a patient with RDEB. These data have been published [Gurevich et al., NatMed, (2022)].¹⁴ However, the nonclinical study report was not submitted to the BLA. This reviewer sent an information request on September 20, 2022, and the applicant submitted Study Report Number. KB103-IVV-017 and a copy of the publication containing these data on 10/05/22 (Amendment #013). This summary is based on the submitted information.

Report Number	KB103-EXV-001
Date Report Signed	October 4, 2022
Title	Non-GLP Ex Vivo Assessment Of KB103 In An RDEB Skin Equivalent Model
Testing Facility	Stanford University School of Medicine
Objective(s)	To evaluate structural and molecular correction of the recessive DEB phenotype following topical application of KB103 on an RDEB xenograft
Animal model	NSG (NOD.CB17-PrkdcSCID/J) mice (6-8 weeks old, sex and body weights not specified) were transplanted with composite human xenografts sutured to the murine skin on the flank (2 transplants/mouse). Composite human xenograft transplants were prepared from primary human fibroblasts and keratinocytes derived from a RDEB patient lacking hCOL7 expression.
Test Article(s)	VYJUVEK (Lot (b) (4) ; 6.9 x 10 ⁸ pfu/mL) formulated in PBS + 10 % glycerol
Control Article(s)	Vehicle control: PBS+10% Glycerol
Route of Administration	Topical application - VYJUVEK was administered via injection into Telfa non-adherent pad directly in contact with the xenograft surface.
Study Groups and Dose levels	Control – Vehicle (n=2 mice/group) Treatment – VYJUVEK ** (4.6 x 10 ⁷ pfu /mouse) in an injection volume of 50 µl (n=8 mice/group) ** VYJUVECK™ was administered via injection into Telfa non-adherent pad directly in contact with xenograft surface.
Dosing Regimen	Single application
Scheduled Sacrifice Time Points	3-, 5-, and 12-days post-application
Study Endpoints	<ul style="list-style-type: none"> • Expression of a full-length of hCOL7 protein in the skin xenograft by histology/immunofluorescence (using antibodies directed against NC1 (amino-terminal) and NC2 (carboxy-terminal) epitope of COL7) 5 days post-application. • AF formation in the BMZ of the skin xenograft determined by immunoelectron microscopy of the skin xenograft 3- and 12-days post application.

Key Results:

Xenografts with VYJUVEK application showed: i) increase in expression of the full-length COL7 protein 5 days post-application, and ii) increased AF in the BMZ 3- and 12-days post application compared to vehicle-applied skin xenografts.

¹⁴ Gurevich I, et al. (2022) In vivo topical gene therapy for recessive dystrophic epidermolysis bullosa: a phase 1 and 2 trial. Nat Med 28: 780-788.

Reviewer's Conclusion: *In a mouse model with a human RDEB skin xenograft, single application of VYJUVEK resulted in increased expression of a full-length hCOL7 protein and increased AF in BMZ.*

SAFETY PHARMACOLOGY STUDIES

No safety pharmacology studies with KB-103 were performed.

PHARMACOKINETIC STUDIES⁸

No standalone biodistribution (BD) studies with VYJUVEK were performed. BD assessment was incorporated in the toxicology studies (Report Numbers 8373246 and 8420430)

TOXICOLOGY STUDIES

Summary List of Toxicology Studies

The following toxicology studies were conducted to evaluate the safety of VYJUVEK following administration in various animal species.

Toxicology Studies:

Study Number	Study Title / Publication Citation	Report Number
11	Single-Dose Toxicity Study of KB103 Following Intravenous Injection in Mice	8378961
12	Repeat Dose Toxicity and Biodistribution Study of KB103 Following Intradermal Administration in Mice	8373246
13	Repeat Dose Toxicity and Biodistribution Study of KB103 Following Intradermal Administration in Mice	8420430

Toxicology Studies

Study #11

Report Number	8378961
Date Report Signed	May 2, 2019
Title	Single-Dose Toxicity Study of KB103 Following Intravenous (IV) Injection in Mice
GLP Status	Yes With the exception of the following: – Dose formulation analysis performed by Advanced Bioscience Laboratories – Characterization and stability of the test article performed by WuXi AppTech
Testing Facility	(b) (4)
Objective(s)	To evaluate toxicity of VYJUVEK when administered by single IV injection

Study Animals	Strain/Breed	(b) (4) (a sub strain of BALB/c mice with (b) (4) mutation, which is more susceptible to (b) (4))		
	Species	Mice		
	Age	6 to 7 weeks old		
	Body Weight	Males (19.7 to 22.2 g); females (14.5 to 18.5 g)		
	#/sex/group	6/sex/group		
	Total #	24		
Test Article(s)		VYJUVEK (Lot (b) (4) ; 6.9 x 10 ⁸ pfu/mL)		
Control Article(s)		PBS + 10% glycerol (Lot # (b) (4))		
Route of Administration		IV injection (tail vein)		
Study Groups and Dose Levels		Group	Study Agent	Dose Level (pfu/animal)
		1 (vehicle)	Vehicle	0
		2 (VYJUVEK)	VYJUVEK	3.45 x 10 ⁷
				3.45 x 10 ⁸
Dosing Regimen		Single administration		
Randomization		Yes based on body weights		
Description of Masking		Not described		
Scheduled Sacrifice Time Points		Day 30 (n=6/sex/group/sacrifice time point)		

Key Evaluations and Assessments:

- Mortality/morbidity (daily)
- Clinical observations (pre-dose, days 1, 8, 15, 22, and 29)
- BWs (pre-dose, days 1, 8, 15, 22, and 29)
- Food consumption (weekly after day 1)
- Clinical pathology (not fasting) (day 30)
 - Hematology
 - Serum chemistry
- Pathology (day 30)
 - Organ weights
 - Gross pathology
 - Histopathology¹⁶

Key Results:

- Mortality/morbidity: All study animals survived until scheduled sacrifice.
- There were no consistent patterns of test article-related findings for clinical observations, body weights, food consumption, and gross pathology.
- Clinical pathology (day 30):
 - Hematology - decreased platelets in females, which was statistically significant but may not be clinically meaningful due to the magnitude of the change.

(b) (4)

¹⁶ Histopathology was performed on brain, bone marrow (sternum), heart, injection site, kidney, lesion, liver, lung with large bronchi, lymph nodes (axillary and inguinal), spleen, and testis.

- Serum chemistry -
 - Slightly elevated ALT and ALP in Group 2 females compared to Group 1
 - Slightly elevated total protein, globulin and decreased A:G ratio in Group 2 males compared to Group 1. These findings appear to be mainly caused by one male animal (M105).
- Pathology (day 30)
 - Organ weights:
 - Slightly elevated liver and spleen weights in Group 2 males and females compared to Group 1
 - Histopathology:
 - Spleen: Increased congestion (minimal to slight) in Group 2: 4/6 males, 1/6 females; hyperplasia (minimal to slight) in lymphoid, follicles, and germinal centers in Group 2: 4/6 males, 2/6 females.
 - Liver: Minimally increased extramedullary hematopoiesis in Group 2: 1/6 males, 5/6 females.
 - Testis: Minimally increased multinucleated spermatids in Group 2, 4/6 males.

Reviewer's Conclusion: *Single IV injection of VYJUVEK at 3.45×10^7 pfu/animal (1.72×10^9 pfu/kg) did not result in any consistent pattern of test article-related adverse findings. The possible test article-related abnormal microscopic findings in the liver and spleen at sacrifice were minimal in severity. This study evaluated IV administration which is not the clinical route of administration but represents the worst-case scenario of systemic VYJUVEK dissemination.*

Study #12

Report Number		8373246
Date Report Signed		July 2, 2018
Title		Repeat Dose Toxicity And Biodistribution Study Of KB103 Following Intradermal Administration In Mice
GLP Status		<p>Yes</p> <p>With the following exceptions:</p> <ul style="list-style-type: none"> - Characterization and stability of the test article performed by WuXi AppTech. - Dose formulation analysis performed by Advanced Bioscience Laboratories. - Concentration verification of samples taken from the low dose formulation were not tested until the end of the dosing phase, which constitutes a GLP deviation. - At the interim sacrifice, the initial fixative manufacturer, lot number, and expiration date for the wet tissues collected were not documented for animals assigned for qPCR tissue sampling.
Testing Facility		(b) (4)
Objective(s)		To evaluate the toxicity and BD of the test article following once weekly administration up to 5 doses by ID injections
Study Animals	Strain/Breed	(b) (4)
	Species	Mice
	Age	6 to 7 weeks old

	Body Weight	Males (15.8 to 22 g); females (15.3 to 18.9 g)		
	#/sex/group	18/sex/group		
	Total #	108		
Test Article(s)		VYJUVEK (Lot (b) (4) ; 6.9 x 10 ⁸ pfu/mL)		
Control Article(s)		PBS + 10% glycerol (Lot (b) (4)		
Route of Administration		ID administration		
Study Groups and Dose Levels	Group	Study Agent	Dose Level (pfu/animal/day)	Vector Concentration (pfu/mL)
	1 (vehicle control)	Vehicle	0	0
	2 (low dose)	VYJUVEK	6.9 x 10 ⁶	1.38 x 10 ⁸
	3 (high dose)	VYJUVEK	3.45 x 10 ⁷	6.9 x 10 ⁸
Injection Volume		50 µl/injection site		
Dosing Regimen		Five ID injections on Days 1, 8, 15, 22 and 29		
Randomization		Yes, based on body weights		
Description of Masking		Not described		
Scheduled Sacrifice Time Points		Days 4 (interim), 30 (terminal - one day after final dose), and 60 (recovery phase) (n=6/sex/group/time point)		

Key Evaluations and Assessments:

- Mortality/morbidity (daily)
- Clinical observations (pre-dose, prior to dosing on Days 1, 8, 15, 22, and 29 and days 1, 8, 15, 22, and 29 after the last injection)
- BWs (pre-dose, prior to dosing on Days 1, 8, 15, 22, and 29 and days 1, 8, 15, 22, and 29 of after the last injection)
- Food consumption (weekly after day 1)
- Clinical pathology (not fasting; at sacrifice)
 - Hematology
 - Serum chemistry
- Pathology (Days 4, 30, and 60)
 - Organ weights
 - Gross pathology
 - Histopathology¹⁷
- BD¹⁸ (Days 4, 30, and 60)

¹⁷ Histopathology was performed on brain, spleen, kidneys, liver, lungs, heart, thymus, testes, epididymis, prostate, ovaries, oviducts, uterus with cervix, bone marrow (sternum), injection site, lymph nodes (axillary and inguinal), and lesions.

¹⁸ Biodistribution was performed on blood, brain, spleen, kidney, liver, lungs, heart, testis, ovary, bone marrow, injection site, and lymph nodes (axillary and inguinal).

Blood on the day of scheduled sacrifice	brain - frontal lobe spleen kidney - left liver - left lateral lobe lungs - right lobe heart - apex	testis - left ovary - left bone marrow (femur) injection site (intradermal) ^a lymph node (axillary) lymph node (inguinal)
^a Injection site sample was collected by skin punch at least 8 mm in diameter; half of skin punch is used for histopathology and the rest is used for BD.		

Source: Page 152 of '8373246 pre-clinical-study-report.pdf' under Module 4.2.3.2 'Repeat-Dose Toxicity'

Key Results:

- Mortality/morbidity: There were no test article related findings.
- Clinical observations: Possible test article-related findings:
 - Scabbing at the injection site: 1) Group 3 (8/18 [44.4%] males and 7/18 [38.9%] females during Days 22-29 of the dosing phase, persisted in 3/4 [75%] males to Days 7-8 of the recovery phase and in 3/3 [100%] females to Day 8 of the recovery phase; 2) one female (Animal M0513) showed injection site scabbing at Day 15 of the recovery phase - clinical and microscopic findings showed an inflammatory response (increased neutrophil counts, increased mixed cell inflammation, hemorrhage and/or epidermal hyperplasia at the injection site)
 - Thinning hair coat on hind legs or hind quarters: Group 3 (3/18 males and 3/18 females)
- BWs and food consumption: There were no consistent patterns of test article-related findings.
- Clinical pathology: The results were difficult to interpret due to small sample sizes (1-2 mice/group/time point due to clotting or insufficient sample volume) and highly variable results. Results showed: 1) a trend toward increased leukocytes, neutrophils, and lymphocytes in Group 3 females at the terminal sacrifice compared to Group 1; partial resolution was observed at the recovery sacrifice, and 2) increased globulin and decreased A:G ratio in Group 3 males and females at the terminal sacrifice compared to Group 1; partial resolution was observed at the recovery sacrifice.
- Pathology:
 - Organ weights:
 - Spleen weights were increased in a dose-dependent manner in males and females which peaked at day 30, with partial resolution observed at the recovery sacrifice.
 - Gross pathology: Scabbing at the injection site was observed in two Group 3 mice (1 male and 2 females) at terminal sacrifice.
 - Histopathology:
 - Mixed cell inflammation of minimal to marked severity at the injection site in Groups 2 and 3 (males and females), in a dose-dependent manner at the interim

- and terminal sacrifices. The highest incidence and severity was observed at the terminal sacrifice. This finding had mostly resolved by the recovery sacrifice.
- Splenic hyperplasia of the follicular regions and white pulp of minimal to slight severity in Group 3 (males and females) at the terminal sacrifice, with partial resolution by the recovery sacrifice.
 - Hyperplasia of the axillary and inguinal LNs of the follicular region, cortex of minimal to slight severity in Groups 2 and 3 (males and females) at the terminal sacrifice, with partial resolution by the recovery sacrifice
- BD: VYJUVEK was primarily detected at the injection sites. All Group 2 and 3 animals examined at the interim and terminal sacrifices showed vector presence at the injection site, which declined to baseline by the recovery sacrifice. No vector was detected in the ovaries of Groups 2 and 3 females at the interim, terminal and recovery sacrifices. Some mice in Groups 2 (33.3%) and 3 (33.3% to 66.7%) had very low levels (3 to 5 logs lower compared to the injection sites) of vector in the blood, axillary and inguinal lymph nodes and spleen at Day 4 and Day 30. Very low levels of vector remained detectable in axillary and inguinal lymph nodes in 1/3 Group 3 females 30 days post last administration.

Reviewer's Conclusion: *No consistent pattern of test article-related adverse findings were observed following five weekly ID administrations of VYJUVEK at 6.9×10^6 or 3.45×10^7 pfu/animal/day (3.45×10^8 or 1.73×10^9 pfu/kg/day) resulted in. The vector was mainly detected at the administration sites. This study was used to support an early phase clinical trial which investigated the ID route of administration, which differs from the topical route of administration for the commercial product.*

Study #13

Report Number		8420430
Date Report Signed		May 20, 2021
Title		A Single Dose Biodistribution And Toxicity Study Following Topical Administration Of KB103 In Female Mice
GLP Status		Yes
Testing Facility		(b) (4)
Objective(s)		To evaluate the toxicity of the test article when administered as a single dose via topical application to a dorsal skin wound of female mice.
Study Animals	Strain/Breed	(b) (4)
	Species	Mice
	Age	6 to 7 weeks old
	Body Weight	15 to 18.1 g
	#/sex/group	12 females/group
	Total #	24

Test Article(s)	<ul style="list-style-type: none"> VYJUVEK (Lot/Batch (b) (4)) (7.3×10^9 pfu/ml) Gel excipient - 3% methylcellulose (Methocel) gel (Lot # (b) (4)) manufactured by Velesco Pharmaceuticals. 														
Control Article(s)	Vehicle control - PBS + 10% glycerol														
Route of Administration	Topical application within one hour post wound completion at Day 1														
Description of the Disease/Injury Model and Implant Procedure	<p>A single wound (open wound or abraded) was generated on mice on the mid-dorsal region on Day 1.</p> <ul style="list-style-type: none"> Open wound - The open wound was created by removal of a 5-6 mm diameter biopsy of skin using a sharp scissor Abraded - The abraded skin was created on the flank region with a mechanical drill followed by superficial perforation with 22G needle. Based on diameter of the wound (~0.6 cm), the calculated wound area is 0.28 cm^2 														
Study Groups and Dose Levels	<table border="1"> <thead> <tr> <th>Group^a</th><th>No. of Animals^b Females</th><th>Dose Level (pfu/dose)</th><th>Dose Concentration (pfu/mL)</th></tr> </thead> <tbody> <tr> <td>1 (Control)</td><td>12</td><td>0</td><td>0</td></tr> <tr> <td>2 (Test Article)</td><td>12</td><td>3.48×10^7</td><td>3.48×10^8</td></tr> </tbody> </table> <p>pfu = Plaque-forming unit.</p> <p>a Group 1 was administered vehicle control article compounded with gel excipient only.</p> <p>b Animals designated for the interim sacrifice (up to six animals/group in Groups 1 and 2) were sacrificed on Day 3 of the dosing phase.</p> <p>Source: Page 17 of '8420430 pre-clinical-study-report.pdf' under Module 4.2.3.1 'Single-Dose Toxicity'</p> <p>Prior to dosing, VYJUVEK was diluted to 6.95×10^8 pfu/ml with vehicle (PBS + 10% glycerol). The diluted VYJUVEK was then mixed with the gel excipient at a 1:1 ratio. Vehicle alone was also mixed with gel excipient at 1:1 ratio.</p> <ul style="list-style-type: none"> Dose volume = 100 μl/wound Dose level = 3.48×10^7 pfu/mouse/dose = 1.24×10^8 pfu/cm^2 surface wound area. 			Group ^a	No. of Animals ^b Females	Dose Level (pfu/dose)	Dose Concentration (pfu/mL)	1 (Control)	12	0	0	2 (Test Article)	12	3.48×10^7	3.48×10^8
Group ^a	No. of Animals ^b Females	Dose Level (pfu/dose)	Dose Concentration (pfu/mL)												
1 (Control)	12	0	0												
2 (Test Article)	12	3.48×10^7	3.48×10^8												
Dosing Regimen	Single administration														
Randomization	Yes, based on body weights														
Description of Masking	Not described														
Scheduled Sacrifice Time Points	Day 3 and Day 35 (n=6 animals/group/sacrifice time)														

Key Evaluations and Assessments:

- Cageside observations (twice/daily)
- Detailed observations (pre-dose, Days 1 (prior to dosing), 8, 15, 22, 29, and 34)
- Body weights (pre-dose, Days 1 (prior to dosing), 8, 15, 22, 29, and 34)
- Food consumption (Days 1 to 8, 8 to 15, 15 to 22, 22 to 29, and 29 to 34)
- Hematology (n=2-3 animals/group/sacrifice time point on Days 3 and 35)
- Clinical Chemistry (n=2-3 animals/group/sacrifice timepoint on Days 3 and 35)
- Necropsy, organ weights, macroscopic observations and histopathology¹⁹

¹⁹ Histopathology was performed on adrenal, application site, aorta, bone marrow, brain, cecum, duodenum, esophagus, eye, gall bladder, gut-associated lymphoid tissue/Peyer's patch, Harderian gland, heart, ileum, jejunum, kidney, lesion, liver, lungs, lymph nodes (axillary, inguinal, mandibular, and mesenteric), mammary gland, (biceps femoris) muscle, optic nerve, ovary, oviduct, pancreas, pituitary gland, rectum, salivary gland, skin/subcutis, spinal cord (cervical, thoracic, and lumbar), spleen, stomach, thymus, thyroid, tongue, trachea, urinary bladder, uterus, and vagina.

• Biodistribution by qPCR²⁰ (Day 3)

Organ/Tissue	Organ/Tissue
application/dose site (i.e., treated skin site) ^a	lung, right lobe, caudal
bone marrow (femur) ^b	lymph node, axillary
brain - frontal lobe	lymph node, inguinal
heart, apex	ovary - left and right
kidney, left	spleen
liver, left lateral lobe	

a A skin punch (at least 8 mm diameter) or equivalent sample collected manually, including the application/dose site, was collected for all scheduled sacrificed animals using clean techniques. Half of the skin punch/sample was collected for quantitative polymerase chain reaction (qPCR) analysis and the remaining half for microscopic evaluation.

Source: Page 24 of '8420430 pre-clinical-study-report.pdf' under Module 4.2.3.1 'Single-Dose Toxicity'

Key Results:

- Mortality/morbidity: There was no consistent pattern of test article-related findings.
 - One Group 2 mouse (M0104) was moribund and sacrificed on Day 1 following dosing. At necropsy, the uterus was found to be protruding through the wound generated for the study. The cause of death was determined to be an abdominal perforation, likely related to the procedure.
- There were no consistent patterns of test article-related findings for clinical observations, body weights, food consumption, clinical chemistry, macroscopic and microscopic observations.
- Hematology (pages 202): Possible test article related mild to moderate increased total white blood count, absolute neutrophils, and lymphocytes were observed in Group 2 compared to Group 1 on Day 3
 - Per the study report (page 31), hematology of Group 2 on Day 35 could not be determined because sample from Animal #M0109 was not submitted. The samples from Animals #M0107 and #M0108 could not be analyzed accurately due to technical error.

Reviewer's Comment:

- *Given that there were no other macroscopic or microscopic findings observed, the missing hematology data at Day 35 does not affect the overall conclusion of this study.*
- Organ weights (page 225): Group 2 showed possible transient test article-related reduced thymus weight on Day 3 (decrease of 0.71X by absolute weight) compared to Group 1. This finding resolved by Day 35.

²⁰ Biodistribution was performed on application site, bone marrow, brain, heart, kidney, liver, lungs, (axillary and inguinal) lymph nodes, ovary, and spleen.

- BD: The vector was mainly detected at the administration sites on Day 3. Vector was not detected in any other analyzed tissues (axillary LN, bone marrow, brain, heart, inguinal LN, kidney, liver, lung, ovary, and spleen) on Day 3. Day 35 samples were not analyzed.

Reviewer's Conclusion: Single topical application of VYJUVEK that was formulated in 3% Methocel at 3.48×10^7 pfu/administration site/mouse (1.24×10^8 pfu/cm²) did not result in any consistent pattern of test article-related adverse findings and BD data showed vector presence mainly at the injection site. Dose extrapolation is limited by the extremely small wound size in mice relative to humans and different topical application procedure used in mice (via a topical 'well' that was adhered to the wounded region using surgical glue) and humans (via topical application on the wound covered by non-adherent hydrophobic dressing).

Developmental and Reproductive (DART) Toxicology Studies⁹:

No DART studies with VYJUVEK were performed because limited systemic biodistribution of the vector was observed and no vector was detected in the reproductive organs of mice that received topical application of VYJUVEK.

Genotoxicity Studies:

No genotoxicity studies with VYJUVEK were performed because HSV-1 does not integrate into or disrupt the host genome; therefore, the risk of insertional mutagenesis of KB103 is low. The applicant cited the regulatory precedent set by FDA- and EMA- approved HSV-1 based vector talimogene laherparapvec (Imlygic®), which did not include genotoxicity studies.

Carcinogenicity/Tumorigenicity Studies:

No carcinogenicity/tumorigenicity studies with VYJUVEK were performed because available data for both KB103 and wild-type HSV-1 do not indicate a carcinogenic risk in humans. The applicant cited the public assessment report from EMA's evaluation of talimogene laherparapvec (Imlygic®)²¹ which included a risk assessment of carcinogenicity based on published articles that indicated a negligible association between HSV-1 and human cancers.

APPLICANT'S PROPOSED LABEL

- Subsections 8.1-8.3 of Section 8 ('Use in Specific Populations') should be revised to reflect available nonclinical/clinical data and comply with 21 CFR 201.56(d)(1), 201.57(c)(9), and 201.57(c)(14).²²
- Section 13 ('Nonclinical Toxicology') should be revised to contain only the necessary information.

²¹ European Medicines Agency. Public assessment report - Imlygic [internet]. Amsterdam: Committee for Medicinal Products for Human Use (CHMP); 2015 Oct 22. Available from:

https://www.ema.europa.eu/en/documents/assessment-report/imlygic-epar-public-assessment-report_en.pdf.

²² Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products - Content and Format, available at:

<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm450636.pdf>.

CONCLUSION OF NONCLINICAL STUDIES¹⁰

Review of the nonclinical studies did not identify any safety concerns that could not be addressed in the product label. The nonclinical data support approval of the license application.

KEY WORDS/TERMS

VYJUVEK, beremagen geperpavec, gene therapy, replication-defective, HSV-1 based vector, human type VII collagen, B-VEC, KB103, excipient gel, methocel, hydroxypropyl methylcellulose, topical application, dystrophic epidermolysis bullosa, recessive dystrophic epidermolysis bullosa, anchoring fibrils, hypomorphic mouse

¹ If the application is a rolling submission, cite the dates that the P/T, CMC, and clinical modules were received.

² Cite the proposed product name and description stated in bold at the beginning of the draft Package Insert (PI).

³ Cite the proposed clinical indication stated under ‘Indications and Usage’ in the draft PI.

⁴ Provide a brief summary of the findings observed in the Pharmacology and Toxicology (including Pharmacokinetics) studies. The summary should reflect the potential text in Sections 8, 12, and 13 of the draft PI. In addition, all/some of this summary will be incorporated in the Summary Basis of Regulatory Approval (SBRA).

⁵ Provide 2-3 sentences describing any deficiencies identified, need for additional non-clinical data, and your conclusion regarding the data submitted.

⁶ Include a brief description of the product (a diagram can also be included) - tissue and/or donor source, final construct formulation to include solution/suspension buffer, matrix/scaffold, encapsulation device, etc. Include information stated under ‘Dosage and Information’ and ‘Dosage Forms and Strengths’ in the draft PI.

⁷ Provide a list of each pharmacology/proof-of-concept (POC) study conducted by the study sponsor or applicant and/or the studies cited from the scientific literature that are included in the application.

⁸ Use the applicable header identification, depending on the product type (i.e., gene therapy or cell therapy). The selected studies should help inform the text in Section 12.3 of the draft PI [‘Pharmacokinetics’]

⁹ Sections 8.1-8.3 of the PI are required according to 21 CFR Part 201 titled, ‘Content and Format of Labeling for Human Prescription Drug and Biological Products: Requirements for Pregnancy and Lactation Labeling’ that was released on December 4, 2014 in Federal Register Notice No. 233 (<https://www.federalregister.gov/articles/2014/12/04/2014-28241/content-and-format-of-labeling-for-human-prescription-drug-and-biological-products-requirements-for>). Also refer to the FDA draft guidance titled, *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format* (July 2020) at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pregnancy-lactation-and-reproductive-potential-labeling-human-prescription-drug-and-biological>.

¹⁰ Provide a one-sentence summary stating if you agree or disagree that the non-clinical data provided in the submission supports licensure.