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Summary Basis for Regulatory Action

Date:	
From:	Anna Kwilas, Chair of Review Committee, Office of Therapeutic Products (OTP), Office of Gene Therapy (OTG), Division of Gene Therapy
BLA STN:	**125774/0**
Applicant:	**Krystal Biotech, Inc**
Submission Receipt Date:	**June 20, 2022**
Action Due Date:	**May 19, 2023**
Proper Name:	**beremagene geperpavec-svdt**
Proprietary Name:	**VYJUVEK**
Indication:	**For the treatment of wounds in patients 6 months of age and older with dystrophic epidermolysis bullosa with mutation(s) in the *collagen type VII alpha 1 chain (COL7A1)* gene**

Recommended Action: The Review Committee recommends approval of this product.

_____

Acting Director, Office of Clinical Evaluation

_____

Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (Product Office and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Anna Kwilas, CBER/OTP/OGT/DGT2 Bo Liang, CBER/OTP/OGT/DGT1 Jianyang Wang, CBER/OTP/OGT/DGT1 Wei Wang, CBER/OCBQ/DMPQ Carl Perez, CBER/OCBQ/DMPQ Obinna Echeozo, CBER/OCBQ/DMPQ Iryna Zubkova, CBER/OCBQ/DMPQ Marie Anderson, CBER/OCBQ/DBSQC Tao Pan, CBER/OCBQ/DBSQC Most Parvin, CBER/OCBQ/DBSQC Claire Wernly, CBER/OCBQ/DBSQC
Clinical • Clinical (OTP/OCE/DCEGM) • Postmarketing safety Pharmacovigilance review (OBPV/DPV) • BIMO	Ning Hu, CBER/OTP/OCE/DCEGM Douglas Rouse, CBER/OBPV/DPV/PB2 Triet M. Tran, CBER/OCBQ/DIS
Statistical • Clinical data (OBPV/DB) • Non-clinical data (OBPV/DB)	Qianmiao Gao, CBER/OBPV Tianjiao Dai, CBER/OBPV
Non-clinical/Pharmacology/Toxicology • Toxicology (OTP/OPT/DPT)	Theresa Chen, CBER/OTP/OPT/DPT
Clinical Pharmacology • Clinical Pharmacology	Million Tegenge, CBER/OTP/OCE/DCEGM
Labeling • Promotional (OCBQ/APLB)	Benjamin Cyge, CBER/OCBQ/DCM/APLB
Other Review(s) not captured above categories, for example: • Consults • Devices • Software • Human Factors • FONSI	Oluchi Elekwachi, CBER/OCBQ/DCM/APLB Konstantinos Karagiannis, CBER/OBPV/ABRA Luis Santana-Quintero, CBER/OBPV/ABRA Oluwamurewa Oguntimein, CDER/OSE/OMEPRM/DMEPA
Advisory Committee Summary	N/A

Table of Contents

1. Introduction

Krystal Biotech submitted a Biologics License Application (BLA), STN 125774, for licensure of beremagene geperpavec-svdt with the proprietary name VYJUVEK. VYJUVEK is indicated for the treatment of wounds in patients 6 months of age and older with dystrophic epidermolysis bullosa, with mutation(s) in the *collagen type VII alpha 1 chain* (*COL7A1*) gene.

VYJUVEK (also known as B-VEC or KB103) is a suspension of a herpes simplex virus type 1 (HSV-1) vector-based gene therapy, mixed with the supplied sterile excipient gel

for topical application on wounds. VYJUVEK is a replication deficient HSV-1-based vector that has been genetically modified to express the human type VII collagen (COL7) protein.

Dystrophic epidermolysis bullosa (DEB) is a rare genetic disorder with significant unmet medical need. DEB is clinically and genetically heterogeneous and is characterized by fragile and blistering skin and mucosal membranes that heal with scarring. DEB is caused by mutations in the *COL7A1* gene, which results in reduced or absent levels of biologically active COL7 protein. COL7 is a structural component of anchoring fibrils (AFs), which hold the epidermis and dermis together and are essential for maintaining the integrity of the skin.

This document summarizes the basis for traditional approval of VYJUVEK. The BLA is supported primarily by two clinical studies: a Phase 1/2 study (Study KB103-001) and a Phase 3 study (Study B-VEC-03). VYJUVEK demonstrated substantial evidence of effectiveness for the treatment of wounds in patients six (6) months of age and older with DEB based on primary evidence of effectiveness from the adequate and well controlled Phase 3 study, and confirmatory evidence from the pharmacodynamic (PD) activity (expression and localization of COL7 transgene) demonstrated in the Phase 1/2 study. The risks of VYJUVEK are characterized based on a safety database of 31 subjects aged one year to 44 years in the Phase 3 study. The safety profile of two subjects aged six and seven months, respectively, in an open-label study (Study B-VEC-EX-02) supports the safety of VYJUVEK in DEB patients aged between 6 months and less than 12 months. Although the safety database is relatively small, it is acceptable considering the seriousness and rareness of the condition, the significant unmet medical need, the substantial evidence of effectiveness and the observed safety profile of VYJUVEK. The reviewed safety data do not warrant Risk Evaluation and Mitigation Strategies (REMS), or a safety postmarketing requirement (PMR) clinical study.

VYJUVEK demonstrated a favorable benefit/risk profile for the treatment of wounds in patients six months of age and older with DEB, with mutation(s) in the *COL7A1* gene. The review team recommends approval of this BLA.

2. Background

Disease background
DEB is a rare genetic disorder with significant unmet medical need. DEB is clinically and genetically heterogeneous and is characterized by fragile and blistering skin and mucosal membranes that heal with scarring. The onset of symptoms is usually at birth or in early childhood. There may be associated complications including malnutrition, anemia, infection, and skin cancer. Death may occur prematurely due to multiple causes, including infection, progression of disease, organ failure, and malignancy.

DEB is caused by mutations in the *COL7A1* gene, which results in reduced or absent levels of biologically active COL7 protein. COL7 is a structural component of anchoring fibrils (AFs), which hold the epidermis and dermis together and are essential for maintaining skin integrity. DEB can be inherited in an autosomal dominant or recessive fashion. Patients with dominant DEB (DDEB) has lower than normal functional AFs.

Patients with recessive DEB (RDEB) has no functional AFs, and therefore, more severe clinical manifestations. In the United States (US), the prevalence of RDEB and DDEB is estimated to be 1.35 and 1.49 persons per million inhabitants, respectively (Fine 2016). There is no U.S. Food and Drug Administration (FDA)-approved treatment for DEB.

Product description
The active ingredient in VYJUVEK is a recombinant, replication-deficient, non-integrating HSV-1-based gene therapy vector engineered to express full-length, functional human COL7. VYJUVEK was generated by (b) (4) Topical administration of VYJUVEK results in cell transduction and local expression of the COL7 protein.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
Pre-IND meeting	October 13, 2016
Orphan Drug designation granted	November 2, 2017
IND submission	March 20, 2018
Fast Track designation granted	May 23, 2018
RMAT designation granted	June 21, 2019
Pre-BLA meeting	March 22, 2022
BLA 125774/0 submission	June 20, 2022
BLA filed, Priority Review designation granted	August 18, 2022
Rare Pediatric Disease designation	August 22, 2022
Mid-Cycle communication	October 14, 2022
Late-Cycle meeting	December 15, 2022
Major Amendment	December 20, 2022
Action Due Date	May 19, 2023

3. Chemistry Manufacturing and Controls (CMC)

This BLA includes an adequate description of the manufacturing process and characterization of VYJUVEK. The CMC review team concludes that the manufacturing process, along with associated test methods and control measures, is capable of yielding a product with consistent quality characteristics. The CMC review team recommends approval.

a. Product Quality

Manufacturing Summary

VYJUVEK Drug Substance (DS) is manufactured by (b) (4) The DP has a nominal concentration of $5x10^9$ plaque formation unit (PFU)/mL. Filled DP vials are 100% visually inspected, frozen at (b) (4) and shipped to the packaging facility for labeling and packaging. The (b) (4) DP are manufactured at Krystal Biotech's Ancoris facility (Pittsburgh, PA).

To facilitate topical administration, KB103 is mixed with a hydroxypropyl methylcellulose (HPMC) Excipient Gel. HPMC Gel is manufactured for Krystal Biotech, Inc. by Berkshire Sterile Manufacturing (BSM). HPMC Gel is manufactured by (b) (4) HPMC in a 7.5mM Tris PBS buffer to a target concentration of 4.4% HPMC. Following dissolution, the gel is (b) (4) . The HPMC Gel is then filled into 2.0 mL (b) (4) borosilicate glass vials (b) (4) , the HPMC Gel is stored frozen at -20°C±5°C.

Following manufacture and release, the VYJUVEK DP and HPMC Gel are shipped to (b) (4) for labeling and final packaging. One vial of VYJUVEK and one vial of HPMC Gel are co-packaged into a single product carton to be stored at -20°C. At a healthcare facility, the VYJUVEK and HPMC Gel are thawed, mixed at a 1:1.5 ratio, and loaded into administration syringes for topical administration. Following preparation, the capped administration syringes are placed in a sealable plastic bag in an appropriate insulated secondary container at 2º to 8ºC for transport from the preparation site to the administration site. Administration takes place at either the healthcare facility or at the patient's home by a licensed health care provider. VYJUVEK Gel is administered within 8 hours of preparation if stored at ambient temperature and within 48 hours if stored at 2 – 8°C.

Manufacturing Control Strategy

Consistency of the VYJUVEK and HPMC Gel manufacturing processes is controlled by (b) (4) . The manufacturer accepts raw materials based on specified quality attributes, including identity, concentration, and purity. Raw materials derived from biological sources are appropriately controlled to ensure the absence of microbial contaminants and adventitious agents. In-process monitoring and controls are implemented throughout the process to support process consistency. Critical process parameters are established for unit operations based on process characterization and risk assessment studies and the Applicant's empirical experience from successful commercial scale manufacturing runs.

The control strategy also includes testing of the (b) (4) DP and HPMC Gel for microbial contaminants, identity, purity, strength, and potency. DP quality is controlled and characterized multiple quality attributes using several lot release tests (Table 2 and Table 3, respectively). The VYJUVEK lot release tests include a quantitative assay that measures the concentration of infectious virus, an assay to quantitatively measure the human COL7A1 transgene expression from virus infected cells, a potency assay that quantitatively assesses the ability of VYJUVEK expressed COL7to (b) (4) and a series of tests for impurities. The HPMC Gel lot release tests include appropriate physiochemical assessments. Lot release test methods are suitably validated or verified, except for three lot release assays that need additional validation or optimization studies, all of which will be resolved through postmarketing commitments (PMCs). VYJUVEK specifications are adequate to ensure product quality and consistency with drug product used in the clinical study. However, due to the small number of VYJUVEK lots produced to date, reevaluation of some lot release acceptance criteria is being requested through PMCs. Regarding the HPMC Gel lot release specifications, during review of the BLA, it was determined that implementation of a HPMC concentration specification was necessary for lot release of the HPMC Gel. This assay will be validated and implemented as part of the HPMC Gel lot release specification through a PMC.

Process Validation
Validation of the VYJUVEK commercial manufacturing process was performed through three consecutive process performance qualification (PPQ) runs, demonstrating the consistency of product purity and potency. A change of the (b) (4) was implemented (b) (4) validation. This finding during the pre-license inspection of the VYJUVEK manufacturing facility triggered a Major Amendment. The (b) (4) data provided in the Major Amendment indicated that the (b) (4) does not adversely impact product safety or quality. (b) (4) VYJUVEK commercial launch lots have been manufactured successfully using the commercial process with the (b) (4). A prospectively designed continued process verification plan is in place to monitor the process consistency during routine commercial manufacturing. Additional validation studies, including aseptic process simulation and shipping validation studies were also performed.

The HPMC Gel manufacturing process was also validated through the completion of three consecutive PPQ runs. Additional validation studies, including aseptic process simulation and shipping validation studies were also performed.

Impurity profile
Impurities can be classified into product-related and process-related impurities. Product-related impurities include (b) (4) . Process-related impurities may include (b) (4) Most process-related impurities are removed by the (b) (4). The residual levels of impurities are further controlled by lot release specifications.

Comparability Assessments

Throughout clinical development, the VYJUVEC manufacturing process was optimized. To support the clinical efficacy analysis, a comparability study was conducted to support comparability of VYJUVEK manufactured for the Phase 3 clinical study with the commercial DP. The Phase 3 clinical study was conducted using (b) (4) clinical lots manufactured with a process (b) (4) different from the commercial manufacturing process (b) (4) The analytical comparability assessment was conducted using (b) (4) (b) (4) lots and (b) (4) lots. This comparability assessment demonstrated that the commercial manufacturing process (b) (4) produces VYJUVEK lots with comparable critical quality attributes the VYJUVEK lots used in Phase 3 studies (manufactured using (b) (4)

The HPMC Gel manufacturing process also evolved during VYJUVEK clinical development with the manufacturing process being revised between the Phase 3 clinical study and the proposed commercial process. Analytical and non-clinical studies were performed to determine the effect of the changes implemented in the HPMC Gel manufacturing process. The results of these studies indicated that the HPMC Gel process changes had no effect on VYJUVEK titer, potency, or activity.

Stability
Long-term stability studies were conducted and support a VYJUVEK shelf life of 12 months when stored at (b) (4) -20°C. The stability studies utilized VYJUVEK manufactured using (b) (4) and (b) (4) Stability studies were also performed to support short term stability of VYJUVEK at 2-8°C for up to 1 month.

Long-term stability studies were also conducted and support a HPMC Gel shelf life of 12 months when stored at -20°C. The stability studies utilized HPMC Gel manufactured for the Phase 3 clinical study as well as the PPQ lots however did not include an assessment of HPMC concentration. HPMC concentration stability data is being requested through a PMC. When the Applicant modified the long-term storage temperature of the HPMC Gel from (b) (4) to -20°C that introduced a (b) (4) step during shipping and labeling of the filled HPMC Gel vials. The HPMC Gel batches that are used to support long-term stability did not undergo this (b) (4) step, and therefore do not represent the intended commercial process. Preliminary data were provided to support stability of the HPMC Gel through (b) (4). However, additional data supporting the intended shipping, labeling, and packaging procedures is being requested through a PMC.

In-use stability studies were also conducted to assess the stability of the VYJUVEK and HPMC Gel mixture (VYJUVEK gel) in administration syringes at ambient temperature and 2 – 8°C. The studies demonstrated that the VYJUVEK gel was stable in the filled syringes for 8 hours at ambient temperature and up to (b) (4) hours at 2 – 8°C.

Manufacturing Risks, Potential Safety Concerns, and Management
The VYJUVEK manufacturing process does not contain a (b) (4) process. This is a potential risk for microbial contamination. An (b) (4) step occurs (b) (4) to mitigate the microbial contamination risk in the (b) (4) process where all (b) (4) operations are performed. Because all process unit operations (b) (4) are performed in (b) (4) systems that

are validated for (b) (4) processing, the risk of introducing microbial contamination is relatively low. Also, the microbial contamination risk from (b) (4) to ensure the sterility of the manufacturing system is not compromised during processing. A sterility test on the final DP is also included in the DP lot release specifications. Thus, the risk of microbial contamination due to absence of a (b) (4) step is adequately mitigated and controlled.

The risk of product contamination from adventitious agents is minimized by ensuring adequate control of raw materials, especially those of biological origin that are used in (b) (4)

VYJUVEK is a replication deficient HSV-1 vector. Theoretically, there is a possibility of replication competent HSV-1 being generated through homologous recombination between viral vector sequences and the viral sequences present in the cell substrate during manufacturing. This risk is controlled by the DP lot release test for replication-competent HSV-1. The sensitivity of this assay has been validated and deemed acceptable. Furthermore, no replication competent HSV-1 has been detected in any VYJUVEK clinical trial lots.

CMC PMCs
The following issues were identified but could not be resolved during the review cycle. These issues will be resolved through PMCs.

A genetic variant with a (b) (4) is present in the current VYJUVEK (b) (4). Although this (b) (4) does not affect transgene activity or product potency based on nonclinical studies, data supporting the consistency of the presence of this (b) (4) was requested. The Applicant has initiated an analysis of the (b) (4) in the VYJUVEK Phase 3 clinical lots and PPQ lots and will submit the data in response to a PMC.

Although representative of the clinical experience, a number of VYJUVEK lot release acceptance criteria were set relatively wide because of the limited number of commercial scale lots available to establish the acceptance criteria. This included acceptance criteria for (b) (4) as well as the acceptance criterion for (b) (4) for COL7A1 expression. Though, higher residual levels are unlikely to have substantial safety impact based on clinical data, the Applicant set action limits that are lower than the acceptance criteria for the residuals to further control the manufacturing process. Additionally, PMCs were implemented requesting that the Applicant tighten these acceptance criteria when more data are collected from commercial VYJUVEK lots.

Several issues with lot release testing submitted in the BLA also could not be resolved during the BLA review. For the VYJUVEK lot release tests, these included a lack of robustness assessments for the HSV Genome Copy Number assay, a need to further

validate the COL7A1 (b) (4) assay, and a need to optimize the HSV-1 Plaque assay. For the HPMC Gel, this included the absence of a lot release assay confirming the HPMC concentration. These issues will also be resolved through PMCs.

Additional HPMC Gel stability data are also being requested though PMCs. Specifically, HPMC concentration stability data and HPMC Gel (b) (4) data in support of the current HPMC Gel storage, shipping, labeling, and packaging conditions.

b. Testing Specifications

The analytical methods and their validations and/or qualifications for VYJUVEK in-process intermediates, DP, and HPMC Gel were found to be adequate for their intended purpose. The final lot release specifications for the DP are shown in Table 2 below. The final lot release specifications for the HPMC Gel are shown in below.

Table 2. Drug Product Specifications

Attribute	**Analytical Method**	**Acceptance Criteria**
Appearance	Drug Product and Raw Material Appearance	Opalescent yellow to colorless liquid, free from extrinsic visible particulates
Identity	(b) (4)	(b) (4)
Identity	B-VEC COL7A1 (b) (4) Assay	(b) (4)
Identity	KB103 Identity (b) (4)	(b) (4)
Identity	KB103 (b) (4)	(b) (4)
Strength	Herpes Simplex Virus-1 (HSV- 1) Plaque Assay	(b) (4)
Quality	Quantification of HSV Genome Copy number by (b) (4)	(b) (4)
Quality	(b) (4)	(b) (4)
Potency	B-VEC Potency (b) (4)	(b) (4)
Purity	Quantitation of (b) (4)	(b) (4)
Purity	(b) (4) Quantification in HSV-1 Samples by (b) (4)	(b) (4)

Purity	Quantification of (b) (4) HSV-1 Samples by (b) (4)	(b) (4)
Purity	Quantification of (b) (4) in HSV-1 Samples by (b) (4)	(b) (4)
Safety	(b) (4) Quantification of Bacterial Endotoxins	(b) (4)
Safety	Sterility (b) (4)	No growth
Safety	Detection of Replication Competent HSV on (b) (4) Cells	Not Detected
Safety	BVEC (HSV-1) Virus (b) (4)	Sensitive

Table 3. HPMC Gel Specifications

Attribute	Method	Acceptance Criteria
(b) (4)	(b) (4)	(b) (4)
Visual Appearance		Clear, colorless, viscous gel, visibly free of particulates
(b) (4)		(b) (4)
(b) (4)		(b) (4)
Minimum Fill		(b) (4) 1.5mL
Bacterial Endotoxin		(b) (4)
Sterility		No Growth
Identity		Confirmed

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. Inspection histories and activities for facilities involved in the manufacture of B-VEC and excipient gel are summarized in the table below.

Table 4 Manufacturing Facilities

Name/Address	FEI Number	Waiver or Inspection	Justification and Results
Krystal Biotech, Inc. (Krystal) 2100 Wharton St Suite 701 Pittsburgh, PA 15203 *B-VEC drug substance (DS) and drug product (DP) manufacture, testing and release.* *DP vials bulk packaging.* *Working virus bank.*	3013498720	Pre-License Inspection (PLI)	CBER 11/11/2022 – 11/16/2022 Voluntary Action Indicated (VAI)
Berkshire Sterile Manufacturing (BSM) 480 Pleasant St Lee, MA 01238 *Excipient gel (co-packaged with the final DP) manufacture, vial filling and analytical services.*	3012144557	PLI	CBER 01/16/2023 – 01/20/2023 VAI
(b) (4)	(b) (4)		
(b) (4)			
(b) (4)			

CBER conducted a pre-license inspection (PLI) of the Krystal Ancoris facility in November 2022. All FDA Form 483 issues were resolved, and the inspection was classified as voluntary action indicated (VAI).

CBER conducted a PLI of the BSM facility in January 2023. All FDA Form 483 issues were resolved, and the inspection was classified as VAI.

Office of Regulatory Affairs (ORA) performed a surveillance inspection of (b) (4) . All FDA Form 483 issues were resolved, and the inspection was classified as VAI.

ORA performed a surveillance inspection of (b) (4) . All FDA Form 483 issues were resolved, and the inspection was classified as VAI.

ORA performed a surveillance inspection of (b) (4) . An FDA Form 483 was not issued, and the inspection was classified as no action indicated (NAI).

e. Container/Closure System

Sterile VYJUVEK (b) (4) The container closure integrity (CCI) of filled and (b) (4) DP vials was initially verified by using a (b) (4) method. HPMC gel is filled into 2-mL (b) (4) borosilicate glass vials, closed with conventional stoppers and aluminum crimp seals. The filled gel vials are (b) (4) . The CCI testing is performed for the stability of VYJUVEK DP vials and gel vials by using a validated (b) (4) .

f. Environmental Assessment

The applicant submitted an environmental assessment (EA) pursuant to 21 CFR part 25. The EA provided an assessment of VYJUVEK environmental exposure based on known biology of the parental virus (HSV-1 (b) (4) strain), genetic modifications made to the vector, data from biodistribution and shedding studies, waste disposal procedures, lot release testing, related nonclinical studies, and a worst-case assumption in each case. FDA determined that approval of VYJUVEK will not result in any significant environmental impact. A Finding of No Significant Impact memorandum has been prepared.

4. Nonclinical Pharmacology/Toxicology

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) and transduced with VYJUVEK. This resulted in a concentration-dependent increase in hCOL7 mRNA and protein expression, downregulation of thrompospondin-1, upregulation of lysyl hydroxylase 3, 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 3-dimensional organotypic culture 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 (HPMC) excipient gels on a skin wound in BALB/c mice at 4.8 x 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 sites. A significant reduction of vector DNA and transgene expression occurred between Days 3 and 6. Another study in comparing topical application of VYJUVEK mixed with 4% or 7% HPMC 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 x 10^6 or 4.6 x 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 the human RDEB skin xenograft at 4.6 x 10^7 pfu/application resulted in an increase in full-length hCOL7 protein and AF formation in the BMZ compared to a 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 x 10^7 pfu/mouse, 2) five repeat weekly ID administrations of VYJUVEK in BALB/c mice at 6.9 x 10^6 or 3.45 x 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 x 10^7 pfu/application. No VYJUVEK-related adverse findings were observed in these studies.

Analysis of *in vivo* biodistribution after five weekly repeat ID doses of VYJUVEK in mice at 6.9 x 10^6 or 3.45 x 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 x 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 studies were not conducted with VYJUVEK. This is acceptable based on the product characteristics and safety profile.

5. Clinical Pharmacology

Upon topical application of VYJUVEK to the wounds of patients with DEB, the proposed mechanism of action (MOA) involves the following sequential events:

- Entry into cells (e.g., keratinocytes and fibroblasts)
- Transport to nucleus and expression of COL7A1 transgenes
- Secretion of COL7 protein
- Assembly of secreted COL7 protein into anchoring fibrils.

The Phase 1/2 study explored different routes of administration (intradermal vs topical), doses and dosing frequencies. In the Phase 3 study, the unit dose administered weekly to the primary wounds was determined based on the wound area, age at baseline, and preliminary safety and efficacy information from the Phase 1/2 study.

The major clinical pharmacology findings from these two clinical studies are summarized in the following sections:

a. Pharmacokinetics: Viral vector biodistribution and shedding

- Following topical application of VYJUVEK, no viral vector DNA was detected in blood (Phase 1/2 & Phase 3).
- Viral vector was detected only in one urine sample (3.2%,1/31; Phase 3).
- Viral vector DNA was detected in skin swab samples in all treated nine subjects with maximum level ranging from $5.1x10^4$ to $4.1x10^8$ vector genomes. In 6 out of 9 subjects (67%), negative shedding was confirmed with three measurements below limit of detection within 8 weeks (Phase 1/2).
- Skin swabs from 19 out 31 subjects (61.3%) were positive for viral vector following treatment with VYJUVEK. Skin swabs from 12 out of 31 subjects (38.7%) did not show detectable viral vector at any timepoint during the 26 weeks of treatment (Phase 3).
- The skin swabs maximum viral vector ranged from $5.4x10^2$ to $5.3x10^7$ vector genomes in 19 subjects with detectable viral vectors. Negative shedding was achieved in 16 out of 19 subjects (84.2%) within six weeks following treatment with VYJUVEK (Phase 3).
- Most wound dressings (93.5%, 29/31) contained detectable vector genomes, ranging from $5.2×10^2$ to $4.2×10^8$ genome copies (Phase 3).

b. Pharmacodynamics (PD)

The expression, secretion, and localization of COL7 transgene in skin biopsies was evaluated in the Phase 1/2 study. Immunofluorescence (IF) detection of non-collagenous domain 1 (NC1) and domain 2 (NC2) of COL7, and immunoelectron microscopy (IEM) methods were used for pharmacodynamic analysis. The following is a summary of the PD results from the Phase 1/2 study:

- At baseline (pretreatment), skin biopsies (n=12) from the 9 subjects (3 subjects re-enrolled) were negative for NC2 domain of COL7. A lower expression of NC1 domain of COL7 was noted in all 12 skin biopsies.
- Following VYJUVEK application, nine skin biopsies at different timepoints were evaluated for expression of NC1 and NC2 domain of COL7 from 9 skin biopsies of 6 subjects.
    - florescence intensity for NC1 domain was increased in all 9 skin biopsies
    - NC2 domain was expressed in 8 out of 9 skin biopsies.
    - no expression of NC2 domain and a small increase in NC1 domain expression from baseline was noted in 1 subject.
- For the 3 subjects whose biopsies were analyzed by immunoelectron microscopy, < 25% of normal skin NC1 and NC2 staining was observed at

baseline. Following topical administration of VYJUVEK, immunoelectron microscopy analysis revealed detectable (>25-100% of normal skin) and appropriately localized AFs at the basement membrane zone (BMZ).

c. Immunogenicity Assessments

Antibodies against HSV:

- Antibodies against HSV-1 were evaluated using a plaque reduction neutralization test (PRNT) in a subset of subjects in the Phase 3 study.
- Antibodies against HSV-1 were detected in 7 out of 12 subjects (58%) at baseline with PRNT50 ranging from 1:80 to 1280. Post-treatment anti-HSV-1 antibodies developed in all 12 subjects (100%) with PRNT50 ranging from 1:40 to 5120. Based on the limited data, no impact of anti-HSV1 antibodies on pharmacodynamic activity of VYJUVEK (Phase 1/2) was observed.
- At baseline, 63% of subjects (14/22) had detectable anti-HSV-1 antibodies. Six of the 8 seronegative subjects seroconverted within 26 weeks following treatment with VYJUVEK.
- A post-hoc analysis of response rate in primary wound pairs among baseline anti-HSV-1 seropositive vs. seronegative subjects did not reveal any difference in the efficacy of VYJUVEK (Phase 3).

Antibodies against COL7:

- Anti-COL7 antibodies at baseline were detected in four of nine subjects, and two additional subjects developed anti-COL7 antibodies post-treatment within 34-151 days. In these 4 subjects with baseline anti-COL7, pharmacodynamic activity was demonstrated in three skin biopsies but samples from one subject did not express NC2 domain of COL7 protein with moderately increased NC1 domain (Phase 1/2).
- Anti-COL7 antibodies at baseline were detected in one of 22 subjects (4.5%). Thirteen of 18 subjects (72 %) who were seronegative at baseline developed anti-COL7 antibodies at Week 26.
- A post-hoc analysis of response rate in primary wound pairs among subjects with and without anti-COL7 antibodies did not reveal any difference in efficacy of VYJUVEK (Phase 3).
- Based on the observed clinical benefit following multiple dosing it appears that there is no significant impact of ADA on efficacy; however, data are limited to fully evaluate the impact of ADA on clinical outcome and pharmacodynamic activity.

Overall, following topical application of VYJUVEK, the COL7 transgene secretion and localization at the BMZ was demonstrated and these data provide confirmatory evidence of effectiveness of VYJUVEK.

6. Clinical/Statistical

a. Clinical Program

The Phase 3 study (Study B-VEC-03), the Phase 1/2 study (Study KB103-001), along with the safety profile of two subjects aged six and seven months, respectively, in an open-label study (Study B-VEC-EX-02), form the basis of the review team's recommendation for traditional approval of VYJUVEK for the treatment of wounds in patients six months of age and older with dystrophic epidermolysis bullosa, with mutation(s) in the *collagen type VII alpha 1 chain* (*COL7A1*) gene.

The substantial evidence of effectiveness of VYJUVEK consists of the primary evidence of effectiveness from the adequate and well-controlled Phase 3 study and the confirmatory evidence of effectiveness from the pharmacodynamic activity (expression and localization of COL7 transgene) demonstrated in the Phase 1/2 study.

The risks of VYJUVEK are characterized based on a safety database of 31 subjects aged one year to 44 years in the Phase 3 study. The safety profile of two subjects aged six and seven months, respectively, in an open-label study (Study B-VEC-EX-02) supports the safety of VYJUVEK in patients aged between 6 months and less than 12 months.

Study Description

Phase 3 study (B-VEC-03)

The study was a multicenter, intra-subject randomized, placebo-controlled, double-blind study of VYJUVEK for topical application on DEB wounds. Each subject serves as his/her own control by contributing a primary wound pair to be randomized to receive weekly topical application of either VYJUVEK or the placebo (excipient gel). The primary wound pair was selected to evaluate the primary and key secondary efficacy endpoints. The wounds in the pair were matched in size and anatomical locations. The duration of the study included a 26-week treatment period followed by an additional month of safety follow-up.

In addition to the primary wound pair, a few unmatched secondary wounds (the number of secondary wounds varied in each subject) were selected in each subject to receive VYJUVEK in an uncontrolled, open-label manner. The unmatched secondary wounds contribute to the safety evaluation.

The total dose applied to the primary and secondary wounds each week did not exceed the age-based maximum weekly dose (Table 5). Table 6 provides a reference on dose per approximate size of the wound.

Table 5 Maximum Weekly Dose Based on Age

Age Range	Maximum Weekly Dose (plaque forming units; PFU)	Maximum Weekly Volume (milliliter; mL) *
6 months to <3 years old	1.6×10^{9}	0.8

≥ 3 years old	3.2×10^9	1.6

* Maximum weekly volume is the volume after mixing VYJUVEK biological suspension with excipient gel.
Source: Adapted from the clinical study report for Study B-VEC-03 (module 5.3.5.1) page 21, submitted in BLA 125774/0 and the Applicant's response to USPI communication submitted on March 3, 2023.
Abbreviations: PFU, plaque-forming unit.

Table 6 Unit Dose Based on Wound Area

Wound Area (cm^2) *	Dose (PFU)	Volume (mL)
<20	4×10^8	0.2
20 to <40	8×10^8	0.4
40 to 60	1.2×10^9	0.6

*For wound area over 60 cm^2, recommend calculating the total dose based on this table until the maximum weekly dose is reached.

Efficacy Endpoints

Primary Endpoint:

The difference in proportion of complete wound closure (responder) in VYJUVEK-treated and placebo-treated intra-subject primary wound sites at Weeks 22 and 24 or Weeks 24 and 26.

- A responder was defined as having wounds that were closed for at least 2 consecutive weeks at defined timepoints.
- Complete wound closure was defined as 100% wound closure from the exact wound area selected at baseline, specified as skin re-epithelialization without drainage.

Key Secondary Endpoint:

The difference in proportion of complete wound closure in VYJUVEK-treated and placebo-treated intra-subject primary wound sites at Weeks 8 and 10 or Weeks 10 and 12.

Clinical Efficacy Findings

The study enrolled 31 subjects (20 males and 11 females) with clinical manifestations consistent with DEB and genetically confirmed mutations in the COL7A1 gene, including 30 subjects with autosomal RDEB and one subject with autosomal dominant DDEB. The size of the VYJUVEK gel-treated wounds ranged from 2.3 to 57.3 cm^2, with 74% of wounds < 20 cm^2 and 19% from 20 to < 40 cm^2. The size of the placebo gel-treated wounds ranged from 2.3 to 51.5 cm^2, with 71% of wounds < 20 cm^2 and 26% from 20 to < 40 cm^2. The mean age of the subjects was 17 years (1 year to 44 years), including 61% pediatric subjects (n=19, age from 1 year to < 17 years). Sixty-four percent of subjects were White; 19% were Asian, and the remainder were American Indian or Alaska Native.

Table 7 summarizes the primary efficacy endpoint analysis. Among the 31 randomized wound pairs, 20 of the 31 (64.5%) VYJUVEK-treated wounds

achieved complete closure. Eight of the 31 (25.8%) placebo-treated wounds achieve complete closure. The treatment difference was 38.7% [95% CI: 13.9, 63.5; p= 0.012].

Table 7 McNemar Test Primary Efficacy Endpoint Analysis (Primary): Primary Wound Pairs at Weeks 22 & 24 or Weeks 24 & 26 – ITT Population (N=31)

Responder/Non responder Group	VYJUVEK Responder	VYJUVEK Non-Responder	Overall	Treatment Difference (95% CI)	P-value[1]
Placebo responder	4 (12.9)	4 (12.9)	8 (25.8)	38.7 (13.9, 63.5)	0.012
Placebo non-responder	16 (51.6)	7 (22.6)	23 (74.2)	-	-
Overall	20 (64.5)	11 (35.5)	-	-	-

[1] p-value is based on exact McNemar test. The missing primary efficacy endpoints from two subjects are imputed by worst-case scenario: for the missing endpoints in VYJUVEK group, imputed as non-responder; for the missing endpoints in placebo group, imputed as responders.

Table 8 summarizes the key efficacy endpoint analysis. Among 31 randomized wound pairs, 21 of the 31 (67.7%) VYJUVEK-treated wounds achieved complete closure. Seven of the 31 (22.6%) placebo-treated wounds achieved complete closure. The treatment difference was 45.2% [95% CI: 21.8, 68.5; p= 0.003].

Table 8 McNemar Test Key Efficacy Endpoint Analysis (Sensitivity): Primary Wound Pairs at Weeks 8 & 10 or Weeks 10 & 12 – ITT Population (N=31)

Responder/Non responder Group	VYJUVEK Responder	VYJUVEK Non-Responder	Overall	Treatment Difference (95% CI)	P-value[1]
Placebo responder	4 (12.9)	3 (9.7)	7 (22.6)	45.2 (21.8, 68.5)	0.003
Placebo non-responder	17 (54.8)	7 (22.6)	24 (77.4)	-	-
Overall	21 (67.7)	10 (32.3)	-	-	-

[1] p-value is based on exact McNemar test. The missing primary efficacy endpoints are imputed by worst-case scenario: for the missing endpoints in VYJUVEK group, imputed as non-responder; for the missing endpoints in placebo group, imputed as responders.

Efficacy was established on the basis of improved wound healing defined as the difference in the proportion of complete (100%) wound closure at 24 Weeks confirmed at two consecutive study visits 2 weeks apart, assessed at Weeks 22 and 24 or at Weeks 24 and 26, between the VYJUVEK gel-treated and the placebo gel-treated wounds. Efficacy was supported by the difference in the proportion of complete wound closure assessed at Weeks 8 and 10 or at both

Weeks 10 and 12 between the VYJUVEK gel-treated and the placebo gel-treated wounds.

Phase 1/2 Study (KB103-001)

The Phase 1/2 study was a first-in-human, single-center, open-label, randomized, intra-subject, placebo (vehicle) controlled study to assess safety, molecular correction (PD activity), and preliminary efficacy of VYJUVEK for the treatment of DEB.

The study was divided into 4 phases that corresponded to protocol revisions: Phase 1, Phase 2a, Phase 2b, and Phase 2c. Phase 1 and 2b incorporated intradermal injection of VYJUVEK to intact skin for the evaluation of PD endpoints.

The study enrolled nine unique subjects. Three of the nine subjects enrolled in both Phase 2a and Phase 2b with adequate washout period between the two phases.

The efficacy assessment in the Phase 1/2 study is considered exploratory and the efficacy findings of the Phase 1/2 study are not integrated with the Phase 3 study because each subject received varying doses and dosing regimens, which were different from the weekly topical dose used in the Phase 3 study. The efficacy findings suggested clinical benefit of VYJUVEK on DEB wounds.

The PD activity (expression, secretion, and localization of COL7 transgene) of VYJUVEK was demonstrated in six subjects (9 biopsy sites) in the Phase 1/2 study. These data provide mechanistic support and serve as confirmatory evidence of effectiveness of VYJUVEK for the treatment of DEB wounds. Please refer to Section 5 Clinical Pharmacology for more detailed information.

Efficacy Conclusion

VYJUVEK demonstrated substantial evidence of effectiveness for the treatment of wounds in patients with DEB with mutation(s) in the *COL7A1* gene based on the primary evidence of effectiveness from the adequate and well controlled Phase 3 study, plus the confirmatory evidence from the PD activity (expression and localization of COL7 transgene) demonstrated in the Phase 1/2 study.

b) Bioresearch Monitoring (BIMO)

Bioresearch Monitoring (BIMO) inspections were conducted at all 3 clinical sites that participated in the conduct of Study B-VEC-03. The inspection(s) did not reveal any issues that impact the data submitted in this original BLA.

c) Pediatrics

Pediatric Research Equity Act (PREA) is not applicable to VYJUVEK for the treatment of wounds in patients with DEB because VYJUVEK was granted orphan drug designation for the indication.

The safety and effectiveness of VYJUVEK was studied in pediatric and adult patients (age 6 months and older).

d) Other Special Populations

None.

7. Safety and Pharmacovigilance

The risks of VYJUVEK are characterized based on a safety database of 31 subjects aged from one year to 44 years in the Phase 3 study. There were no deaths in the Phase 3 study. Three subjects experienced five serious adverse events (SAEs). None of the SAEs was considered related to VYJUVEK. The most frequent adverse reactions (incidence >5%) observed in the study to be included in the USPI are summarized in Table 9. There were no study discontinuations due to adverse reactions.

Table 9 Adverse Reactions (Incidence >5%) Following Treatment with VYJUVEK

Adverse Reactions	Subjects n (%), (N=31)
Itching	3 (10)
Chills	3 (10)
Redness	2 (6)
Rash	2 (6)
Cough	2 (6)
Runny nose	2 (6)

The two subjects with RDEB aged six and seven months respectively received the same weekly dose of VYJUVEK in the open-label study (Study B-VEC-EX-02) as in the Phase 3 study. The safety profile from these two subjects did not raise any new safety concerns; thus, supports the safety of VYJUVEK in patients aged between 6 months and less than 12 months.

The safety findings of the Phase 1/2 study are not integrated with the Phase 3 study because each subject received varying doses and dosing regimens, which were different from the weekly topical dose used the Phase 3 study. The route of intradermal injection of VYJUVEK to intact skin incorporated in Phases 1 and 2b was for evaluation of PD activity only. Nonetheless, the overall safety evaluation in the Phase 1/2 study did not raise any concern.

In summary, the risks that have been identified can be mitigated by routine medical management, appropriate labeling of Prescribing Information (PI), and routine pharmacovigilance plan proposed by the Applicant. The reviewed safety data do not

warrant Risk Evaluation and Mitigation Strategies (REMS), or a safety postmarketing requirement (PMR) clinical study.

The Applicant submitted a pharmacovigilance plan for VYJUVEK. There are no important identified risks associated with VYJUVEK at this time. Important potential risks include accidental exposure of healthcare providers to VYJUVEK during preparation or administration, accidental exposure of close contacts to VYJUVEK via direct contact, and immune-mediated adverse reactions. Postmarketing safety monitoring will include:

- Routine pharmacovigilance: Adverse event reporting in accordance with 21 CFR 600.80 and quarterly periodic safety reports for 3 years and annual thereafter.

Data available at this time do not suggest any safety signals that warrant a Risk Evaluation and Mitigation Strategy or safety-related postmarketing requirement study. There is no safety-related postmarketing commitment study for this product.

8. Labeling

The proposed proprietary name, VYJUVEK, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on September 8, 2022 and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on September 20,2022. The proper name suffix, -svdt, was designated on February 3, 2023.

The APLB found the prescribing information (PI) and carton/container labels to be acceptable from a promotional and comprehension perspective on May 2, 2023.

9. Advisory Committee Meeting

No advisory committee meeting was held because initial review of information submitted in the BLA did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

10. Other Relevant Regulatory Issues

This application received Orphan Drug, Fast Track, Regenerative Medicine Advanced Therapy and Priority Review designations, and a Rare Pediatric Disease Priority Review Voucher.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

Based on the treatment effect demonstrated in the Phase 3 study and supported by the Phase 1/2 study, the review team recommends traditional approval for VYJUVEK.

b. Benefit/Risk Assessment

The overall benefit/risk profile is favorable of the weekly topical application of VYJUVEK for the treatment of wounds for patients six months of age and older with DEB with mutation(s) in the *COL7A1* gene.

VYJUVEK demonstrated substantial evidence of effectiveness for the treatment DEB in promoting wound closure based on the primary evidence of effectiveness from the adequate and well-controlled Phase 3 study plus confirmatory evidence of the PD activity (expression and localization of COL7 transgene) demonstrated in the Phase 1/2 study.

The risks of VYJUVEK are characterized based on the safety database of 31 subjects in the Phase 3 study. The small safety database is acceptable taking into considerations of the seriousness and rarity of DEB, the significant unmet medical need, the substantial evidence of effectiveness and acceptable safety profile of VYJUVEK.

The safety profile of two subjects with RDEB aged six and seven months, respectively in an open-label study supports the safety of VYJUVEK in patients aged between 6 months and less than 12 months.

The overall safety findings did not raise any concern.

The risks can be mitigated by routine medical management, appropriate labeling of Prescribing Information (PI), and routine pharmacovigilance plan proposed by the Applicant. In addition, the ongoing 5-year long-term follow-up (LTFU) safety study will likely provide additional information on the risks.

c. Recommendation for Postmarketing Activities

The Applicant agreed to the following CMC PMCs:

1. Krystal Biotech commits to reassessing the commercial B-VEC (b) (4) lot release acceptance criteria after data have been collected on (b) (4) commercial lots and submit as a Postmarketing Study Commitment – Final Study Report.

   Final Report Submission: January 31, 2025

2. Krystal Biotech commits to reassessing the commercial B-VEC COL-7A1 (b) (4) lot release acceptance criterion after data have been collected on (b) (4) commercial lots and submit as a Postmarketing Study Commitment – Final Study Report.

   Final Report Submission: January 31, 2025

3. Krystal Biotech commits to assessing the consistency of the percentage of the COL7A1 transgene variant (b) (4) in the Phase 3 clinical and Process Performance Qualification (PPQ) B-VEC lots and submit as a Postmarketing Study Commitment – Final Study Report.

   Final Report Submission: November 30, 2023

4. Krystal Biotech commits to re-validating the (b) (4) COL7A1 (b) (4) Assay in support of its use for commercial B-VEC lot release. The re-validation will include validating the (b) (4) using appropriate test material and providing the validation results in copies / (b) (4) and submit as a Postmarketing Study Commitment – Final Study Report.

   Final Report Submission: November 30, 2023

5. Krystal Biotech commits to performing additional robustness assessments of (b) (4) Quantification of HSV Genome Copy Number by (b) (4) and submit as a Postmarketing Study Commitment – Final Study Report.

   Final Report Submission: November 30, 2023

6. Krystal Biotech commits to validating the HPMC concentration assay and implementing this assay, along with an appropriate acceptance criterion, as part of the commercial HPMC gel lot release specification and submit as a Postmarketing Study Commitment – Final Study Report.

   Final Report Submission: November 30, 2023

7. Krystal Biotech commits to providing HPMC concentration stability data in support of the current HPMC gel expiry date and submit as a Postmarketing Study Commitment – Final Study Report.

   Final Report Submission: May 31, 2024

8. Krystal Biotech commits to providing HPMC gel (b) (4) data in support of the current HPMC gel storage, shipping, and labeling conditions and submit as a Postmarketing Study Commitment – Final Study Report.

   Final Report Submission: November 30, 2023

9. Krystal Biotech commits to optimize the HSV-1 Plaque Assay to (b) (4) if necessary, and submit as a Postmarketing Study Commitment – Final Study Report.

   Final Report Submission: May 31, 2024

The review team agrees that the postmarketing risk mitigation plans proposed by the Applicant, including adequate information provided in the PI, routine pharmacovigilance plan (i.e., routine pharmacovigilance for adverse event reporting) and the 5-year long-term safety follow-up plan (Study KRYSLTFU01), are acceptable for monitoring postmarketing safety and no clinical PMR or REMS is required.

12. References

Fine, JD, 2016, Epidemiology of Inherited Epidermolysis Bullosa Based on Incidence and Prevalence Estimates From the National Epidermolysis Bullosa Registry, JAMA Dermatol, 152(11):1231-1238.