

**Department of Health and Human Services
Food and Drug Administration (FDA)
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Epidemiology (OBPV)
Division of Epidemiology (DPV)**

PHARMACOVIGILANCE PLAN REVIEW MEMORANDUM

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Subject: Review of Pharmacovigilance Plan

Applicant: Krystal Biotech, Inc.

Product: Vyjuvek (beremagene geperpavec [B-VEC])

STN Number: 125774/0

Proposed Indication: *Treatment of wounds in patients over 6 months of age with dystrophic epidermolysis bullosa (DEB)¹.*

Submission Date: BLA: June 20, 2022

Action Due Date: 19 May 2023

¹ Except for Reviewer's Comments and subheadings, italicized statements in this memorandum indicate language quoted directly from applicant materials.

1 Objective and Scope

The purpose of this review is to assess the applicant's proposed pharmacovigilance plan (PVP) for beremagene geperpavec [B-VEC], Version 1.1, dated 9 November 2022, received 10 November 2022, submitted under BLA 125774/0.26. The BLA proposes weekly topical treatment of wounds in patients over 6 months of age with dystrophic epidermolysis bullosa (DEB). This review provides recommendations for post-authorization safety monitoring for the use of B-VEC.

2 Product Information

2.1 Product Description

Beremagene geperpavec (B-VEC) is an engineered, replication-deficient herpes simplex virus type 1 (HSV-1)-based vector encoding human COL7A1 that can be applied topically to promote functional COL7 expression in the skin. [COL7A1 = human collagen type VII alpha 1] As B-VEC is non-integrating and its genes remain physically separate from the host cell chromosome, it does not carry the potential risk of insertional mutagenesis and the resulting possibility of disrupting essential host genes and triggering oncogenesis. Through the deletion of essential viral immediate early genes, B-VEC is rendered completely replication-incompetent in non-complementing cells, thus eliminating its ability to replicate within HSV-1's natural environment, the human body.

2.2 Proposed Indication and Dosing Regimen²

Treatment of wounds in patients 6 months of age and older with dystrophic epidermolysis bullosa (DEB) with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene. VYJUVEK dose is based on age (Table 1) and wound size (Table 2). VYJUVEK is administered topically to open wound(s) once a week.

Table 1: Proposed Dose by Age For topical Application only.

Age Range	Maximum Weekly Dose (plaque forming units; PFU)	Maximum Weekly Volume (mL)*
6 months to < 3 years old	1.6×10^9	0.8
(b) (4)		
≥ 6 years old	3.2×10^9	1.6

*Maximum weekly volume is the volume after mixing VYJUVEK biological suspension with excipient gel.

Table 2: Proposed Dose by Wound Size

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

² This information is based on recent draft labeling. See the final approved U.S. Prescribing Information (USPI) for approved indications and dosing.

3 Background and Viral Vector

Dystrophic epidermolysis bullosa (DEB) is a genetic skin disorder that usually presents at birth and is divided into two major types (and subtypes) depending on inheritance pattern: recessive dystrophic epidermolysis bullosa (RDEB) and dominant dystrophic epidermolysis bullosa (DDEB)[1]. DEB is the result of “mutations in the type VII collagen gene (COL7A1), encoding a large collagenous protein that is the predominant, if not exclusive, component of the anchoring fibrils at the dermal-epidermal junction”[2]. The severity of skin manifestations can vary from dystrophic nails with/without mild blistering limited to hands, feet, knees, and elbows in DDEB to significant recurrent blistering/scarring after minimal trauma all over the body with severe complications of oral, esophageal, corneal, and hand/foot erosions and a lifetime risk of aggressive squamous cell carcinoma (SCC) of over 90% with severe generalized RDEB[1]. Cumulative risk of death from SCC by age 55 is as high as 78.7% in one subtype of RDEB[3].

B-VEC is a replication-incompetent, non-integrating HSV-1-based vector engineered to express full-length, functional human type VII collagen (COL7). The vector was generated through the deletion of key viral genes and insertion of 2 copies of the human COL7A1 gene. B-VEC is applied topically to the skin and subsequently transduces both keratinocytes and fibroblasts. B-VEC is transported to the nucleus where the episomal genome recruits the host’s transcriptional machinery to initiate expression of the human COL7A1 transgenes. The resulting transcripts allow for production of a precursor protein, Procollagen 7, that is secreted by the cell and proteolytically processed. Once these proteins are cleaved, they arrange themselves into long, thin bundles of mature COL7 that form anchoring fibrils (AFs). The AFs hold the epidermis and dermis together and are essential for maintaining the integrity of the skin.

4 Clinical Studies

4.1 Overview

The applicant reports two clinical studies have been completed for B-VEC (previously known as KB103) and two studies are ongoing (Table 3). The two completed studies along with the 120-day update on the Open-label Extension study are reviewed below.

Table 3: Clinical Studies

Study Number	Type	Objectives	Design	Status
KB103-01 (GEM-1)	Phase 1/2 safety/ efficacy	To evaluate safety, demonstrate molecular correction of the disease, and assess proportion of wounds with complete wound closure	Single-center, open-label, intrasubject randomized, placebo-controlled	Complete

B-VEC-03 (GEM-3)	Phase 3 safety/ efficacy	To determine whether administration of B-VEC in addition to standard of care improved wound healing as compared to placebo in children, adolescents, and adults with DEB	Multicenter, double-blind, intrasubject randomized, placebo-controlled	Complete
B-VEC-EX-02	Open-label extension	To provide continued use of B-VEC to subjects who completed B-VEC-03, to provide the use of B-VEC to DEB-diagnosed subjects who did not participate in B-VEC-03, and to record safety outcomes of subjects while on B-VEC	Cohort 1: open-label treatment extension for subjects who completed B-VEC-03 and naive subjects with DEB Cohort 2: continued assessment of subjects who completed B-VEC-03 (no further B-VEC treatment)	Ongoing
KRYS-LTFU-01	Long-term safety follow-up	To evaluate the long-term safety profile of the gene therapy products evaluated by Krystal Biotech, Inc. that have a shared backbone of HSV-1 in participants who received at least one dose of investigational product	Multicenter, prospective, observational, cohort study	Ongoing

Adapted from Table 1, module 2.7.4 (STN125774/0.18)

4.2 Phase 1/2 Study KB103-001 (GEM 1)

The applicant evaluated the safety and efficacy of B-VEC in a 3-month Phase 1/2, single-center, open-label, randomized, intrasubject placebo-controlled study (KB103-01) of topical B-VEC for the treatment of DEB. The Phase 1/2 study population consisted of adult and pediatric subjects with a clinical diagnosis of RDEB confirmed by genetic testing, immunofluorescence (IF), and immunoelectron microscopy (IEM). The safety hypothesis for this study is that B-VEC treated wounds would have an adverse event (AE) profile similar to placebo treated wounds. The primary and secondary safety objectives and endpoints are listed in Table 4.

Table 4: Primary and Secondary Safety Objectives/Endpoints for KB103-01

Primary	Objectives	Endpoints
Safety	To evaluate the safety through the incidence of AEs associated with B-VEC administration as compared to placebo	AEs (incidence, type, relatedness, duration, and severity)
Secondary	Objectives	Endpoints
Safety	Assessment of changes in laboratory values, HSV-1/COL7 antibodies, vital signs, and physical exam	Changes in laboratory values, HSV-1/COL7 antibodies, vital signs, and physical exam

Adapted from Table 2, module 5.3.5.1 KB103-001 Study Body Report (STN125774/0)

4.2.1 KB103-001 Study Design by Phase

Nine subjects were enrolled, but three subjects re-enrolled in a later phase of the study and were counted separately for analysis, so the total number of subjects enrolled was considered to be 12.

Phase 1 (Protocol v1.0): Two adult subjects were enrolled. Two wounds $\leq 10 \text{ cm}^2$ were selected in each subject and one was randomized to B-VEC and the other to placebo.

Phase 2a (Protocol v2.2): Two adult and 2 pediatric subjects were enrolled. Three wounds $\leq 20 \text{ cm}^2$ were selected in each subject and 2 were randomized to B-VEC and one to placebo. One adult subject withdrew from the study due to travel issues.

Phase 2b (Phase 2b (Protocol v3.0/v3.1): Three adult and 2 pediatric subjects were enrolled. Three subjects from phase 2a re-enrolled in Phase 2b. Three wounds $\leq 20 \text{ cm}^2$ were selected in each subject and 2 were randomized to B-VEC and 1 to placebo.

Phase 2c (Protocol v4.0): One pediatric subject was enrolled for treatment of large chronic wounds. Two large wounds were selected and randomized to B-VEC (65.29 cm^2) and placebo (36.17 cm^2). The subject was excluded from Intention To Treat and Per Protocol populations due to wound sizes but was observed for safety.

Safety Variables

Adverse Events (AEs) were monitored and reported. This included classification of severity (mild, moderate, severe) and relationship.

Laboratory assessments included complete blood count with differential, chemistry and electrolyte panel, pre- and post-exposure serum anti-COL7 and anti-HSV-1 antibody titers, blood, urine, and skin swabs for viral shedding. Sample collection was minimized due to skin fragility and open wounds.

Other Safety Variables

A complete physical examination and vital signs were accomplished as scheduled. New clinically relevant findings were reported. If skin cancer occurred in the region of B-VEC administration, samples were to be collected to evaluate for presence of the viral vector.

Safety Analysis

AEs were to be tabulated by category. No formal statistical analysis of laboratory results was planned.

Reviewer Comment: *The Phase 1/2 study design, safety objectives, analysis and endpoints are acceptable. There were no terminations or withdrawals due to adverse effects of B-VEC.*

4.3 Phase 3 Study B-VEC-03 (GEM-3)

B-VEC-03 is the pivotal Phase 3 randomized, multicenter, double-blind, placebo-controlled, intrasubject comparison study to evaluate the efficacy and safety of weekly topical B-VEC in patients with DEB. The study objective and endpoints are summarized in Table 5.

Table 5: B-VEC-03 Objective and Endpoints

Primary Objective	Study Endpoints	Endpoint Description
Determine whether topical administration of B-VEC in addition to standard of care improved wound healing as compared to placebo in children, adolescents, and adults with DEB.	Primary Endpoint	Proportion of DEB primary wound sites with complete wound healing from baseline in B-VEC-treated and placebo-treated intrasubject wound sites at Weeks 22 and 24 or Weeks 24 and 26 to evaluate durability of response and repeat dosing
	Key Secondary Endpoint	Proportion of primary wound sites with complete wound healing from baseline in B-VEC-treated versus placebo at Weeks 8 and 10 or Weeks 10 and 12
	Secondary Endpoints	Mean change in pain severity
	Safety Endpoints	Safety and tolerability of B-VEC was based on the assessment of AEs, clinical laboratory test results, vital signs, and physical examinations

Adapted from module 5.3.5.1 V-BEC 03 Study Body Report (STN125774/0.13)

4.3.1 B-VEC-03 Study Design

The study is a multicenter, intrasubject randomized, placebo-controlled, double-blind, Phase 3 study in which each subject served as his/her own control. The maximum weekly dose and unit dose of B-VEC was determined by baseline wound area and age of the subject. The investigator selected and randomized 2 matched wounds (primary wound pair) to receive weekly treatment with either topical B-VEC or placebo. The subject, investigator, and sub-investigator were blinded to the treatment. *No unblinding occurred during the study.* If a primary wound closed completely, weekly treatment of the wound ceased, and would resume if it opened again. If a nearby wound opened (2

to 3cm away), that wound may receive weekly treatment even if the primary wound closed.

The investigator also selected unmatched secondary wounds in each subject to receive open-label B-VEC. The weekly dose applied to the secondary wounds plus the dose applied to the primary wounds did not exceed the maximum weekly dose based on age. Similarly, if a nearby wound opened (2 to 3 cm away), that neighboring wound may have received treatment even if the original wound was closed.

Weekly visits occurred for 26 weeks followed by a Safety Follow-up Visit (SFU) 30 days after the last dose was applied. Assessments for wound closure were performed with photographs and measurements by the investigator (or trained alternate) at weeks 8, 10, 12, 22, 24 and 26 for primary and secondary endpoints. Subjects were given the option to enroll in the open label extension protocol (B-VEC-EX-02) following the SFU or early termination (ET) visit. Those who did not enroll were asked to participate in a long-term follow-up protocol (KRYIS-LTFU-01) for 5 additional years.

Since molecular correction had been demonstrated in the Phase 1/2 B-VEC study, the Phase 3 protocol limited blood draws and removed biopsies to minimize subject burden and focus on evaluation of wound healing as the primary efficacy endpoint.

Safety Variables

Adverse Events (AEs) were monitored and reported throughout the study. This included classification as an Immune Response AE, Serious AE, severity (mild, moderate, severe, life-threatening), relationship (not related, unlikely related, possibly related, related), investigational product action taken (dose not changed, drug interrupted, drug withdrawn, not applicable) and outcome (recovered/resolved, recovered/resolved with sequelae, not recovered/resolved (continuing), fatal, unknown).

Other Safety Variables

A complete physical examination was accomplished in week 1. Abbreviated examinations were scheduled for week 26 and at the 30-day SFU/ET, and at the discretion of the investigator at other visits. Vital signs were scheduled for most visits. Laboratory evaluations were scheduled for screening or week 1 and week 26 including complete metabolic panel with direct bilirubin and complete blood count with differential and platelets, urine pregnancy test, blood/urine for viral shedding, and HSV-1 and type VII collagen (COL7) antibody assay. In addition, skin swabs for viral shedding/infectivity and swabs of returned dressings for viral shedding were scheduled for weeks 1 through 26. If a skin cancer occurred in the region of B-VEC administration, samples of the skin cancer were to be collected to evaluate cells for the presence of viral vector.

Safety Analysis

Treatment-emergent adverse events (TEAEs) were recorded in summary tables by category and all AEs were provided in a listing. Incidence of TEAEs was summarized by preferred term and sorted by frequency by category. If a preferred term (PT) was

reported more than once for the same subject, the AE was counted only once for that preferred term at the highest severity and strongest relationship to treatment.

Laboratory values were flagged by subject as high or low and actual and change from baseline values were summarized. Descriptive statistics were completed on absolute and change from baseline of vital signs. Abnormalities or changes in severity on physical examinations were provided in a subject listing.

Subject Disposition

Thirty-one subjects enrolled and 28 completed the study. Three subjects discontinued as “withdrawal by subject” due to the following reasons: difficulty scheduling and missing appointments, challenges arranging air transportation during the COVID-19 pandemic, relocation for college.

Protocol Deviations

Five subjects had major protocol deviations resulting in 4 of 28 subjects being excluded from the per protocol population. Three subjects received the wrong dose, one subject was enrolled prior to meeting diagnosis inclusion criteria (diagnosis was subsequently confirmed), and one subject missed 4 visits (and withdrew prior to study completion).

Follow-Up

After the SFU/early termination (ET) visit, subjects had the option to enroll in the open label extension protocol (B-VEC-EX-02) or roll over into the long-term follow-up protocol (KRYSLTFU-01) in which they will be followed for 5 additional years.

Reviewer Comment: *The pivotal Phase 3 study design, safety objectives, endpoints, analysis, and follow-up plans are acceptable. There were no terminations or withdrawals due to adverse effects of B-VEC.*

4.4 Open Label Extension Protocol (B-VEC-EX-02)

The Open-label extension (OLE) key study objectives are:

- *To provide continued use of B-VEC to participants who participated in and completed Phase 3 Protocol B-VEC-01, upon study completion,*
- *To provide the use of B-VEC to DEB-diagnosed participants who have not participated in the Phase 3 trial, and*
- *To record safety outcomes of participants while on B-VEC.*

4.4.1 B-VEC-EX-02 Study Design

Cohort 1

Instead of treating individual wounds, the focus in this cohort is to treat entire wound areas (referred to as “Target Areas”) up to the Maximum Weekly Dose (10^9 PFU/mL) at each visit. (Target Areas are defined anatomic regions such as anterior forearm, posterior head, and neck, etc.) The volume of B-VEC investigational product (IP) administered is based on age, and wound areas are treated once a week until wound closure, for 18 months. The change to Target Area application was based on observations that adjacent wounds would often form during treatment. Thus, treating

surrounding areas in addition to targeted wounds provided additional wound healing and stability to the area. The study included those with a diagnosis of DDEB or RDEB by genetic testing including COL7A1 and age of at least (b) (4) months.

Cohort 2

Participants who completed B-VEC-03 could enroll in this cohort for observation without treatment and upload weekly images of wounds previously treated with B-VEC.

Reviewer Comment: *The basic OLE study design and safety objectives are acceptable.*

4.5 Long-Term Follow-Up (KRYS-LTFU-01)

The KRYS-LTFU-01 study will collect long-term safety follow-up information on participants who have received at least one treatment in a Krystal Biotech, Inc. sponsored study after completing or discontinuing the parent treatment protocol. Participants will be followed for 5 years from the date of last treatment to document any new serious adverse events. Only 1 participant has enrolled as of 30 June 2022. All other participants enrolled in the OLE study, remain in the long-term follow-up period of the parent protocol, or elected not to participate.

Reviewer Comment: *The Long-Term Follow-Up study design and safety objectives are acceptable.*

5 Summary of Applicant's Safety Database

5.1 Adverse Events (AEs) from Phase 1/2 study (KB103-001) and pivotal Phase 3 study (B-VEC-103).

Baseline Characteristics, Exposure and Disposition of Study Population

All AEs were treatment-emergent (newly appeared, increased in frequency, or worsened in severity on or after initiation of active treatment). An integrated database was created combining safety data from the Phase 1/2 and Phase 3 studies. Table 6 shows the baseline characteristics of the pooled Safety Population. Subjects who participated in more than one phase/protocol were analyzed as separate subjects. This resulted in an integrated safety analysis population of 43 subjects (12 in Phase 1/2 and 31 in Phase 3).

Table 6: Safety Population Baseline Characteristics (Pooled: KB 103-001/B-VEC-03)

Characteristic	(N=43)
Median Age (years), (minimum, maximum)	16.3 (1, 44)
Male/Female	29 (67.4)/14 (32.6)
Primary Wound Area (cm ²) ^a B-VEC, n	51
Median (minimum, maximum)	9.2 (1.3, 57.3)
Primary Wound Area (cm ²) ^a – Placebo, n	42
Median (minimum, maximum)	8.6 (0.9, 51.5)

Adapted from Table 5C in module 2.7.4 (STN125774/0.18); ^aOne patient was excluded for a protocol deviation of an oversized wound.

Table 7 shows the pooled disposition of subjects. A total of 35 individuals were exposed to B-VEC in one or both studies with 6 being exposed in more than one phase or protocol. For pooled B-VEC exposure from both studies, the median number of days of therapy was 175 with a range of 5 to 187.

Table 7: Summary of Safety Population Disposition (Pooled: KB-103-001/B-VEC-03)

Disposition	(N=43) n (%)
Completed	34 (79.1)
Discontinued	9 (20.9)
Reason for Discontinuation	
Other (Sponsor's Decision)	5* (11.6)
Withdrawal by subject	4 (9.3)

Adapted from Integrated Safety Summary Table 14.1.1 and Table 4C of module 2.7.4 (STN125774/0.18). *These 5 subjects were discontinued for administrative purposes but were considered to have completed the study as planned.

Adverse Events

The applicant used Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 to code AEs for the Phase 1/2 study and version 24.1 for the Phase 3 study. A summary of AEs in the safety population (pooled) is shown in Table 8. Nine subjects (75%) in the Phase 1/2 study (KB-103-001) and 18 (58.1%) subjects in the Phase 3 study (B-VEC-03) reported a total of 80 AEs.

Table 8: Applicant Reported Safety Population Adverse Events (AE) (Pooled, N=43)

Total number of adverse events (AEs)	80
Subjects with at least one: n (%)	
AE	27 (62.8)
Drug-related AE	5 (11.6)
Severe AE	2 (4.7)
Serious AE (SAE)	3 (7.0)
Drug-related SAE	0
SAE leading to death	0
AE leading to premature discontinuation of treatment	0
AE leading to premature discontinuation of study	0
Deaths	0

Adapted from Table 6C in module 2.7.4 (STN125774/0.18).

Serious Adverse Events

There were no deaths during either study. Three serious AEs were reported, all in the Phase 3 study. The investigator/applicant assessed none of the SAEs as drug-related (1 cellulitis (severe), 1 anemia and diarrhea (both severe), and 1 positive blood culture (moderate), all resolved). Skin infections are common in patients with DEB[4]. The patient with cellulitis “accidentally flipped a dirty dog water bowl on this right leg and thigh the day before symptoms began”. The patient with anemia and diarrhea had a longstanding prior history of these conditions. The patient with a positive blood culture had end-stage renal disease, a history of 8 prior central line infections and a methicillin-

resistant Staphylococcus Aureus (MRSA) skin infection. The blood culture was positive for gram positive cocci and the hemodialysis catheter was colonized with MRSA.

Other Significant Adverse Events

Three subjects in the Phase 3 study reported Squamous cell cancer (SCC) of the skin. This is a common diagnosis in patients with DEB.[4] The investigator/applicant concluded the timing and location of the cancers were not consistent with causality from B-VEC and none of the cancer sites were directly exposed to B-VEC.

Common AEs

A list of AEs occurring in more than 1 subject is shown in Table 9. The applicant indicated treatment with B-VEC was well tolerated in both studies with no treatment discontinuations or dosing changes due to AEs. No clinically significant immunologic reactions or manifestations of active herpes simplex virus (HSV) infection were reported. The applicant reported that no clinically meaningful changes in laboratory or vital sign values were noted in either study. In addition, the applicant noted that abnormal findings on physical examinations were related to DEB and no new notable findings during study treatment.

Table 9: Adverse Events Reported for More Than 1 Subject by System Organ Class and Preferred Term (Safety Population): Pooled

System Organ Class Preferred Term	(N=43) n (%)
Any AE	27 (62.8)
Skin and subcutaneous tissue disorders	
Pruritus	4 (9.3)
Erythema	3 (7.0)
Rash	3 (7.0)
General disorders and administration site conditions	
Chills	3 (7.0)
Application site pruritus	2 (4.7)
Fatigue	2 (4.7)
Pyrexia	2 (4.7)
Respiratory, thoracic and mediastinal disorders	
Cough	2 (4.7)
Rhinorrhoea	2 (4.7)
Gastrointestinal disorders	
Diarrhoea	2 (4.7)
Nausea	2 (4.7)
Investigations	
Bacterial test positive	2 (4.7)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Squamous cell carcinoma (SCC)	3 (7.0)

Adapted from module 2.7.4, Table 7C (STN125774/0.18)

Adverse Events Designated as Adverse Reactions

Adverse reactions were selected primarily based on the Phase 3 study since the Phase 1/2 study was open label, had varying doses, and most AEs were associated with intradermal injections that were only administered to establish evidence of molecular correction. The applicant noted that comparison of AEs between B-VEC and placebo was not possible given the intra-patient design since AEs were collected at the patient level. The applicant considered all treatment emergent AEs with a cumulative incidence of >5% in the Phase 3 study. The seven AEs that met the selection criterion for a potential adverse reaction are shown in Table 10. Squamous cell cancer was not included since the three cases were assessed as unrelated to B-VEC and is a common diagnosis in DEB patients[4].

Table 10: Adverse Reactions Observed in the Phase 3 Study

Adverse Reactions	Patients n (%)
Pruritus	3 (9.7)
Chills	3 (9.7)
Erythema	2 (6.5)
Rash	2 (6.5)
Cough	2 (6.5)
Rhinorrhea	2 (6.5)

Adapted from Table 8 in module 2.7.4 (STN125774/0.18).

Pregnancy and Lactation

There are no data on B-VEC use in pregnant women or presence of B-VEC in human milk. No nonclinical reproductive and developmental toxicity studies were conducted.

Reviewer comment: *There were no deaths associated with the Phase 1/2 or Phase 3 study. No treatment discontinuations due to AEs were reported. No clinical or pathologic manifestations of the wild-type viral vector were noted. No clinically significant immunologic responses to the viral vector or COL7 were reported. A review of physical examinations, vital signs, and laboratory results corroborated the assessment that there were no clinically meaningful changes associated with B-VEC. Over 60% of patients experienced AEs but most were mild. After review of each narrative for the 3 SAEs and the 3 subjects diagnosed with squamous cell cancer, the reviewer concurs these are unlikely related to B-VEC. Review of the applicant's safety data did not reveal new safety concerns that need to be addressed in the PVP beyond those already included.*

5.2 Adverse Events from the Open Label Extension (OLE) Protocol (B-VEC-EX-02) (120-Day Safety Update)

Baseline Characteristics, Disposition and Exposure

Thirty-five subjects enrolled and were treated in the OLE study, 33 were ongoing, and none had completed the study as of 30 June 2022. Twenty-three subjects were rollovers from Phase 3. One subject withdrew due to transportation issues. One subject withdrew based on investigator opinion that "it was not in the subject's best interest to continue". Demographic information is shown in Table 13.

Table 11: OLE Study: Demographic Characteristics (Safety Population)

Characteristic	N = 35
Median Age in years (Min, Max)	16.0 (1, 46)
Male	24 (68.6)
Female	11 (31.4)

Adapted from Table 13 in module 2.7.4 (STN125774/0.18).

The medical, procedural, and medication history of subjects was consistent with the diagnosis of DEB. Other frequently reported baseline conditions were constipation (42.9%), pruritus (45.7%), pain (37.1%), dysphagia (34.3%), esophageal stenosis (34.3%), and anemia (31.4%).

Exposure to B-VEC is summarized in Table 14 and is variable as the study is ongoing.

Table 12: OLE Study: Exposure (Safety Population)

Number of days of therapy:	Rollover (N = 23)	Treatment-Naïve (N = 12)	All OLE Subjects (N = 35)
Median (Min, Max)	246.0 (50.0, 401.0)	122.5 (16.0, 257.0)	234.0 (16.0, 401.0)

Adapted from Table 14 in module 2.7.4 (STN125774/0.18).

Adverse Events

Overall, 57.1% of subjects in the OLE study reported 67 AEs. This included 56.5% of rollover subjects reporting 46 AEs and 58.3% of treatment-naïve subjects reporting 21 AEs (Table 15). The investigator/applicant did not consider any AEs as related to treatment with B-VEC and did not note any clinically relevant differences in AEs by age, gender, or race, but the sample sizes were small.

Serious Adverse Events

There were no deaths during the study. No AE led to premature discontinuation of treatment or of the study. Five SAEs were reported. Four SAEs were in rollover subjects (Scrotal Cellulitis, Left Arm Cellulitis, COVID-19, and Dehydration after esophageal dilation). An SAE of Lymphadenopathy was reported in one treatment-naïve subject. Skin infections, esophageal stricture and malnutrition are commonly reported complications of DEB.[4] The investigator assessed all SAEs as unrelated to B-VEC.

Table 13: Overview of OLE AEs (Safety Population)

	AEs During Phase 3 Study	AEs During OLE Study		
	Rollover (N = 23)	Rollover (N = 23)	Treatment-Naïve (N = 12)	All OLE Subjects (N = 35)
Total number of adverse events (AEs)	33	46	21	67
Subjects with at least 1 AE, n (%)				
AE	13 (56.5)	13 (56.5)	7 (58.3)	20 (57.1)
Drug-related AE or SAE*	0	0	0	0
Severe AE	2 (8.7)	2 (8.7)	0	2 (5.7)
Serious AE	3 (13.0)	4 (17.4)	1 (8.3)	5 (14.3)

Adapted from Table 15 in module 2.7.4 (STN125774/0.18). *Of the 67 reported AEs, relationship to study drug was available for 49 at the time of data cutoff.

Common AEs

Table 16 lists AEs reported in more than 1 subject during the OLE study. The most frequently reported AEs (at least 10% of subjects) in the OLE study were Pyrexia (7 subjects, 20.0%), COVID-19 (6 subjects, 17.1%), and Rhinorrhea (4 subjects, 11.4%). Severity of AE was reported in 48 out of 67 subjects of which 37 were mild, 8 were moderate, and 3 were severe. Of the three severe AEs, 2 were reported in one subject (Cellulitis (SAE) and Pyrexia) and 1 was reported another subject (Cellulitis (SAE)).

Table 14: Adverse Events Reported for More Than 1 Subject During the OLE Study (Safety Population)

System Organ Class Preferred Term	Rollover (N = 23) n (%)	Treatment-Naïve (N = 12) n (%)	All OLE Subjects (N = 35) n (%)
Any AE	13 (56.5) 46 events	7 (58.3) 21 events	20 (57.1) 67 events
Infections and infestations			
COVID-19	4 (17.4)	2 (16.7)	6 (17.1)
Cellulitis	3 (13.0)	0	3 (8.6)
General disorders and administration site conditions			
Pyrexia	6 (26.1)	1 (8.3)	7 (20.0)

Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea	2 (8.7)	2 (16.7)	4 (11.4)
Cough	2 (8.7)	1 (8.3)	3 (8.6)
Gastrointestinal disorders			
Vomiting	2 (8.7)	1 (8.3)	3 (8.6)
Diarrhoea	2 (8.7)	0	2 (5.7)
Metabolism and nutrition disorders			
Dehydration	2 (8.7)	0	2 (5.7)
Blood and lymphatic system disorders			
Lymphadenopathy	1 (4.3)	1 (8.3)	2 (5.7)

Adapted from Table 16 in module 2.7.4 (STN125774/0.18).

For the 23 rollover subjects, Chills and Squamous cell carcinoma were reported in the Phase 3 study but not in the OLE study. Vomiting, COVID-19, and dehydration were reported in these subjects in the OLE study, but not in Phase 3. The frequency of pyrexia in these subjects was also notably higher during the OLE study as compared to Phase 3, but none were considered by the investigator to be related to B-VEC.

Table 17 lists AEs reported in at least one subject during the OLE study. The applicant did not note a meaningful difference in local AEs reported in treated vs non-treated areas.

Table 15: AEs Reported for at least One Subject in the OLE Study (Safety Population)

System Organ Class Preferred Term	Treated Target Area n/[E] (%)	Non-treated Target Area n/[E] (%)	Total (N=35) n/[E] (%)
Local AEs			
Infections and infestations	2/[2] (5.7)	4/[4] (11.4)	6/[6] (17.1)
Cellulitis	2/[2] (5.7)	1/[1] (2.9)	3/[3] (8.6)
Eye infection		1/[1] (2.9)	1/[1] (2.9)
Conjunctivitis		1/[1] (2.9)	1/[1] (2.9)
Otitis externa		1/[1] (2.9)	1/[1] (2.9)
Skin and subcutaneous tissue disorders	3/[8] (8.6)	1/[1] (2.9)	4/[9] (11.4)
Rash	1/[6] (2.9)		1/[6] (2.9)
Erythema		1/[1] (2.9)	1/[1] (2.9)
Urticaria	1/[1] (2.9)		1/[1] (2.9)
Blister	1/[1] (2.9)		1/[1] (2.9)
Eye disorders		2/[9] (5.7)	2/[9] (5.7)
Eye pain		1/[1] (2.9)	1/[1] (2.9)
Eye swelling		1/[3] (2.9)	1/[3] (2.9)

Eyelid ptosis		1/[1] (2.9)	1/[1] (2.9)
Lacrimation increased		1/[1] (2.9)	1/[1] (2.9)
Ocular hyperemia		1/[2] (2.9)	1/[2] (2.9)
Vision blurred		1/[1] (2.9)	1/[1] (2.9)
Systemic AEs			
General disorders and administration site conditions			8/[8] (22.9)
Pyrexia			7/[7] (20.0)
Pain			1/[1] (2.9)
Infections and infestations			8/[10] (22.9)
COVID-19			6/[7] (17.1)
Upper respiratory tract infection			1/[2] (2.9)
Viral upper respiratory tract infection			1/[1] (2.9)
Respiratory, thoracic, and mediastinal disorders			7/[11] (20.0)
Rhinorrhea			4/[4] (11.4)
Cough			3/[3] (8.6)
Epistaxis			1/[1] (2.9)
Respiratory disorder			1/[2] (2.9)
Sneezing			1/[1] (2.9)
Gastrointestinal disorders			4/[7] (11.4)
Vomiting			3/[3] (8.6)
Diarrhea			2/[2] (5.7)
Abdominal pain			1/[1] (2.9)
Abdominal pain upper			1/[1] (2.9)
Metabolism and nutrition disorders			3/[3] (8.6)
Dehydration			2/[2] (5.7)
Hypokalemia			1/[1] (2.9)
Blood and lymphatic system disorders			2/[2] (5.7)
Lymphadenopathy			2/[2] (5.7)
Injury, poisoning and procedural complications			1/[1] (2.9)
Ligament sprain			1/[1] (2.9)
Skin and subcutaneous tissue disorders			1/[1] (2.9)
Pruritis			1/[1] (2.9)

Adapted from Table 18 in module 2.7.4 (STN125774/0.18).

The applicant concluded the incidence of subjects reporting AEs in the OLE study was similar to the Phase 3 study with exceptions noted above. The applicant indicated most reported AEs were mild or moderate in severity and none of the SAEs were considered related to B-VEC. There were no deaths or AEs leading to discontinuation of treatment.

Reviewer comment: *There were no deaths associated with the OLE study. No treatment discontinuations due to AEs were reported. No clinical or pathologic manifestations of the wild-type viral vector were noted. Over 50% of patients experienced AEs but most were mild or moderate. Almost all the AEs could be associated with complications of the underlying condition or other conditions common in the general population (viral upper respiratory infections, allergic rhinitis, etc.). After review of each narrative for the 5 SAEs, the reviewer concurs these are unlikely related to B-VEC. Review of the applicant's safety data did not reveal new safety concerns that need to be addressed in the PVP beyond those already included.*

5.3 Compassionate Use Protocol

A 13-year-old male was treated under a compassionate use protocol for recurrent corneal conjunctivalization in the context of epidermolysis bullosa (EB). The subject underwent superficial keratectomy of the right eye with amniotic membrane transplantation. A planned esophageal dilation and gastrotomy tube (g-tube) placement was also accomplished, with complications with resulting in an extended hospitalization. The subject received topical B-VEC treatment to the right eye immediately after surgery and on 10 more occasions over 27 days. No adverse events were reported except for the g-tube complication unrelated to B-VEC. No evidence of herpes stromal keratitis or other unexpected ocular complications were observed. The subject's vision improved after surgery and no B-VEC associated safety risks were identified.

Reviewer comment: *This compassionate use case demonstrated an ocular application of B-VEC with no significant related AEs reported. The absence of signs or symptoms of herpes stromal keratitis following application of B-VEC is consistent with the viral vector being replication deficient.*

6 Pharmacovigilance Plan

6.1 Summary of Pharmacovigilance Plan (PVP)

The applicant submitted a PVP to STN 125774/0.2 on 22 July 2022 in response to an Information Request (IR) sent on 22 June 2022. A subsequent IR was sent to the applicant on 13 October 2022 requesting revisions to the PVP as follows:

1. Some elements of the Safety Specification as outlined in *Guidance for Industry: E2E Pharmacovigilance Planning* (hereafter referred to as "*Guidance*") were missing. The applicant was asked to include relevant Nonclinical and Clinical subsections to Section 1.2 Safety Specification as outlined in *Guidance*. The applicant was also asked to summarize why the following viral vector risks were considered low: a) reversion to a

replication competent form; b) infection of non-target tissues; and c) establishing latency.

2. Objectives and milestones for the studies referenced in Section 3, Action Plan for Safety Issues, and Section 4, Summary, were missing. The applicant was requested to include study objectives and milestones for the studies referenced in these sections or insert references to the module(s) in the electronic Common Technical Document (eCTD) where the objectives and milestones are listed, as outlined in *Guidance*.

The applicant submitted a revised PVP (Version 1.1) on 10 November 2022 to STN125774/0.26. An updated summary of safety concerns and proposed actions is shown in Table 18.

Table 16: Summary of Safety Concerns and Planned Pharmacovigilance Activities

Safety Concern	Actions Proposed
Important Identified Risks	
None	
Important Potential Risks	
1. Accidental exposure of healthcare provider to B-VEC during preparation or administration	<ul style="list-style-type: none"> • Thorough training and education will be made available in different formats to health care providers, patients, and close contacts. • Label Sections 5.0 (Warning and Precautions) and 5.1 (Accidental Exposure) • Label Section 2.2 (Preparation and Handling), including protective measures
2. Accidental exposure of close contacts to B-VEC via direct contact	
3. Immune-mediated adverse reactions	<ul style="list-style-type: none"> • Assessment of T cell-mediated immunity in open-label extension study (B-VEC-EX-02) • 5-year long-term follow up study (KRY5-LTFU-01) with annual assessment of product-related SAEs • Toll-free Call Center for collection of spontaneous reports • Risk communication: Label Section 6.2 (Immunogenicity)
Missing Information	
1. Pregnancy and lactating women	<ul style="list-style-type: none"> • Collect additional data through: <ul style="list-style-type: none"> ○ 5-year long-term follow up study (KRY5-LTFU-01) ○ Annual safety reports ○ Ongoing open-label extension study (B-VEC-EX-02) ○ Spontaneous adverse event reporting collected through post-approval pharmacovigilance (e.g., call center)
2. Pediatric patients <6 months of age	
3. Older adults >45 years of age	
4. Patients of black race	
5. Long-term safety data	

Adapted from applicant's Pharmacovigilance Plan, Version 1.1, Tables 1 and 2 (STN125774/0.26).

The applicant also included information addressing the questions on potential risks associated with the viral vector in the updated PVP:

Risk of reversion to a replication competent form, while theoretically possible, is considered highly unlikely. Such a reversion event would require homologous recombination between the ICP4 loci of an actively replicating wild-type HSV-1 virion and B-VEC within a single cell of a treated DEB cutaneous wound. Furthermore, the resulting theoretical recombinants (replication-deficient COL7A1+/ICP22+ and attenuated, replication-competent ICP4+/ICP22- variants) would not pose an additional safety risk to the subject beyond the already present wild-type HSV-1 (replication-competent ICP4+/ICP22+).

Risk of infection of non-target tissues is considered to be low given the lack of systemic exposure upon localized B-VEC administration demonstrated through biodistribution and vector shedding analyses conducted during nonclinical and clinical development.

Risk of establishing latency is considered extremely low because spread to, and secondary infection of, a neuron where HSV-1 latency is established requires vector replication within the primary infection site. Because B-VEC is non-replicating, cell-to-cell infection, and thus latency, is not feasible.

7 DPV Assessment of Applicant's Pharmacovigilance Plan

7.1 Important Identified Risk: None

There were no serious adverse event reports during the Phase 1/2, Phase 3, or Open-label Extension study that were considered related to B-VEC.

7.2 Important Potential Risk: Accidental exposure

1. Accidental exposure of healthcare provider to B-VEC during preparation or administration

2. Accidental exposure of close contacts to B-VEC via direct contact

The important potential risk of accidental exposure will be monitored through a Toll-Free Call Center that will be available for reporting of accidental exposures and other adverse events. Expedited cases will be reported per regulations. Data will be analyzed by the applicant and an additional action plan will be put in place if a safety signal is identified. The proposed PVP is adequate to monitor the potential risk of accidental exposure. It seems the primary potential adverse effects associated with this type of exposure would be skin irritation, other immunological response to the product, or transmission of other infectious disease organisms if the exposure was from materials contaminated with blood or body fluids from the patient.

7.3 Important Potential Risk: 3. Immune-mediated adverse reactions

The important potential risk of immune-mediated adverse reactions will be monitored through routine pharmacovigilance and ongoing studies. Risk communication is supported by label Section 6.2 (Immunogenicity). The PVP is adequate to monitor the

potential risk of immune-mediated adverse reactions through the open-label extension study (B-VEC-EX-02) and the 5-year long-term follow up study (KRYIS-LTFU-01).

7.4 Missing Information: Use in Pregnancy and lactating women

Pregnant women were excluded from studies to date and the safety profile of B-VEC in pregnant or lactating women is not known. There were no reports of pregnant or breastfeeding individuals in the studies KB103-01, B-VEC-03 or B-VEC-EX-02. Missing information on use of the product during pregnancy and lactation will be monitored through routine pharmacovigilance and ongoing studies. The lack of safety data will be communicated in product labeling (Section 8.1 Pregnancy and 8.2 Lactation). The proposed PVP is adequate to monitor for use in pregnancy and lactation.

7.5 Missing Information: Use in pediatric individuals <6 months of age

Infants less than 6 months of age were not enrolled in studies to date and the safety profile of B-VEC in this age group is not known. Missing information regarding the use of the product in infants less than 6 months of age will be monitored through routine pharmacovigilance and ongoing studies. The lack of safety data will be communicated in product labeling (Section 8.4 Pediatric Use). The proposed PVP is adequate to monitor for use in infants less than 6 months of age.

7.6 Missing Information: Older adults >45 years of age

Although not excluded, no adults over 45 years of age have enrolled in trials of B-VEC to date. The lack of safety data will be communicated in product labeling (Section 6.1 Clinical Trials Experience, Section 8.5 Geriatric Use, and Section 14 Clinical Studies). The proposed PVP is adequate to monitor use in individuals over 45 years of age.

8 DPV Conclusions

Based on review of available data, there were no safety signals among participants who received B-VEC in Studies KB103-01, B-VEC-03 or B-VEC-EX-02 (ongoing). Review of the applicant's safety data did not reveal significant safety concerns. The viral vector used appears to pose minimal risk as it is non-integrating and replication deficient. Thus, the applicant's plan to use routine pharmacovigilance for post-approval safety monitoring for B-VEC in conjunction with the 5-year long-term follow up study of clinical trial participants (KRYIS-LTFU-01) is acceptable.

Available safety data do not indicate a need for safety-related postmarketing requirement (PMR) studies or Risk Evaluation and Mitigation Strategy (REMS). There are no safety-related postmarketing commitment (PMC) studies.

9 DPV Recommendations

Should this submission be approved, the PVP (version 1.1) to monitor postmarketing safety with routine PV in accordance with 21 CFR 600.80 is acceptable. DPV will conduct routine safety monitoring for this product.

Refer to the final version of the U.S. Prescribing Information (USPI) submitted by the applicant for the final agreed-upon language for the label.

References

1. Pfendner, E.G. and A.W. Lucky, *Dystrophic Epidermolysis Bullosa*, in *GeneReviews*((R)), M.P. Adam, et al., Editors. 1993: Seattle (WA).
2. Varki, R., et al., *Epidermolysis bullosa. II. Type VII collagen mutations and phenotype-genotype correlations in the dystrophic subtypes*. J Med Genet, 2007. **44**(3): p. 181-92.
3. Fine, J.D., et al., *Epidermolysis bullosa and the risk of life-threatening cancers: the National EB Registry experience, 1986-2006*. J Am Acad Dermatol, 2009. **60**(2): p. 203-11.
4. Tang, J.Y., et al., *A systematic literature review of the disease burden in patients with recessive dystrophic epidermolysis bullosa*. Orphanet J Rare Dis, 2021. **16**(1): p. 175.

APPENDIX
Materials Reviewed

Table A1: Materials reviewed in support of this assessment

Date	Source	Document Type	Document(s) Reviewed
June 20, 2022	Applicant	STN125774/0	Module 1.14.1.3 Draft labeling text
June 20, 2022	Applicant	STN125774/0	Module 5.2, Tabular listing of all clinical studies
June 20, 2022	Applicant	STN125774/0	Module 5.3.5.1 Study reports of controlled clinical studies pertinent to the claimed indication: KB103-001 Phase 1/2 Synopsis, Study Body Report, Section 14 Tables and Figures; B-VEC 03 Synopsis, Section 14 Tables and Figures
August 1, 2022	Applicant	STN125774/0.3	Module 2.5 Clinical overview
October 11, 2022	Applicant	STN125774/0.13	Module 5.3.5.1 Study reports of controlled clinical studies pertinent to the claimed indication: Updated B-VEC Phase 3 Study Report Body
25 October 2022	Applicant	STN125774/0.18	Module 2.7.4 Summary of clinical safety (With open extension 120-day safety update)
25 October 2022	Applicant	STN125774/0.18	Module 5.3.5.3 Integrated Study of Safety
25 October 2022	Applicant	STN125774/0.18	Module 5.3.5.4 Other study reports: Tables and Listings - 120 Day Safety
July 5, 2022	Applicant	STN125774/0.2	Module 1.16.1, Draft US Pharmacovigilance Plan v1.0 (Response to Information Request)
November 10, 2022	Applicant	STN125774/0.26	Module 1.16.1, Revised US Pharmacovigilance Plan v1.1 (Response to Information Request)