July 7, 2025
Medical Device Evaluation Division
Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Gene Therapy Products, 2. Viral Vector Product
Non-proprietay Name	Beremagene geperpavec
Brand Name	Vyjuvek Gel
Applicant	Krystal Biotech, Inc. Freyr Life Sciences KK as the Designated Marketing Authorization Holder of Foreign-manufactured Regenerative Medical Products
Date of Application	October 29, 2024 (Application for marketing approval)

Results of Deliberation

In its meeting held on July 7, 2025, the Committee on Regenerative Medicine Products and Biotechnology reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Council.

The product may be approved. The conditional and time-limited approval is not applicable to the product. The re-examination period is 10 years.

The following approval conditions must be satisfied.

Approval Conditions

1. The applicant is required to conduct a post-marketing surveillance, etc., covering all patients treated with the product in the post-marketing setting until data from a certain number of patients have been accrued.
2. The applicant is required to take necessary measures to ensure that the product is used by individuals who have received sufficient training in its use, under a system in which adverse events can be properly managed by physicians with adequate knowledge and experience in the treatment of dystrophic epidermolysis bullosa.
3. In order to ensure that the product is used in compliance with the regulations on Type-1 Use approved under the “Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003),” the applicant is required to take necessary measures such as announcement of the regulations on Type-1 Use.

Review Report

June 27, 2025
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following regenerative medical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Vyjuvek Gel
Classification	Gene Therapy Products, 2. Viral Vector Product
Non-proprietary Name	Beremagene geperpavec
Applicant	Krystal Biotech, Inc. Freyr Life Sciences KK as the Designated Marketing Authorization Holder of Foreign-manufactured Regenerative Medical Products
Date of Application	October 29, 2024

Shape, Structure, Active Ingredients, Quantities, or Definition

The product is a regenerative medical product consisting of recombinant herpes simplex virus type 1 expressing human collagen type VII (COL7) protein (the primary component) and hydroxypropyl methylcellulose (HPMC) gel (the secondary component). The primary component is a replication-defective recombinant herpes simplex virus type 1 (derived from the KOS strain), in which one *ICP22* gene and two *ICP4* gene regions are deleted, and the two deleted *ICP4* gene regions are replaced with the human *COL7A1* gene under the control of the cytomegalovirus promoter. The secondary component is a dedicated gel formulation used to dilute the primary component prior to administration.

Application Classification	(1-1) New regenerative medical product
Items Warranting Special Mention	Orphan regenerative medical product (Orphan Regenerative Medical Product Designation No. 26 of 2023 [*R5 sai*]; PSB/MDED Notification No. 1213-1 dated December 13, 2023, by the Medical Device Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of Cellular and Tissue-based Products

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of patients with dystrophic epidermolysis bullosa, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication or performance and dosage and administration or method of use shown below, with the following approval conditions.

Indication or Performance

Dystrophic epidermolysis bullosa

Dosage and Administration or Method of Use

Usually, Vyjuvek is applied once weekly to the skin wound surface in droplets in a grid pattern of approximately 1 cm × 1 cm. The reference dose is 2×10^7 PFU (10 μL) per cm^2 wound area.

The maximum weekly dose and maximum weekly volume of Vyjuvek are calculated based on age according to the table below.

Age	Maximum weekly dose (plaque forming units: PFU)	Maximum weekly volume (mL)[Note)]
<3 years old	2×10^9	1
≥3 years old	4×10^9	2

Note) Volume after mixing the drug product with HPMC gel

Approval Conditions

1. The applicant is required to conduct a post-marketing surveillance, etc., covering all patients treated with the product in the post-marketing setting until data from a certain number of patients have been accrued.
2. The applicant is required to take necessary measures to ensure that the product is used by individuals who have received sufficient training in its use, under a system in which adverse events can be properly managed by physicians with adequate knowledge and experience in the treatment of dystrophic epidermolysis bullosa.
3. In order to ensure that the product is used in compliance with the regulations on Type-1 Use approved under the “Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003),” the applicant is required to take necessary measures such as announcement of the regulations on Type-1 Use.

Attachment

Review Report (1)

May 26, 2025

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Vyjuvek Gel
Classification	Gene Therapy Products, 2. Viral Vector Product
Non-proprietary Name	Beremagene geperpavec
Applicant	Krystal Biotech, Inc. Freyr Life Sciences KK as the Designated Marketing Authorization Holder of Foreign-manufactured Regenerative Medical Products
Date of Application	October 29, 2024

Shape, Structure, Active Ingredients, Quantities, or Definition

The product is a regenerative medical product consisting of recombinant herpes simplex virus type 1 engineered to express human collagen type VII (COL7) protein (the primary component) and hydroxypropyl methylcellulose (HPMC) gel (the secondary component). The primary component is a replication-defective recombinant herpes simplex virus type 1 (derived from the KOS strain), in which one *ICP22* gene and two *ICP4* gene regions are deleted, and the two deleted *ICP4* gene regions are replaced with the human collagen type VII alpha 1 chain (*COL7A1*) gene under the control of the cytomegalovirus promoter. The secondary component is a dedicated gel formulation used to dilute the primary component prior to administration.

Proposed Indication or Performance

Treatment of patients with dystrophic epidermolysis bullosa with mutations in the *COL7A1* gene

Proposed Dosage and Administration or Method of Use

Vyjuvek is applied once weekly to the wound in droplets in a grid pattern of approximately 1 cm × 1 cm.

The maximum weekly volume of Vyjuvek is calculated based on age according to the table below.

Age	Maximum weekly dose (plaque forming units: PFU)	Maximum weekly volume (mL)[Note)]
<3 years old	2×10^9	1
≥3 years old	4×10^9	2

Note Volume after mixing the suspension with excipient gel

The actual dose volume is calculated based on wound area according to the table below. If the total wound area exceeds 60 cm^2, the total dose volume is calculated according to the table below until the maximum weekly volume (1 or 2 mL) is reached.

Wound area (cm^2)	Dose (PFU)	Dose volume (mL)
<20	4×10^8	0.2
≥20 and <40	8×10^8	0.4
≥40 and ≤60	1.2×10^9	0.6

Vyjuvek should be applied to wounds until they are closed before selecting new wound(s) to treat.

If a previously treated wound re-opens, treatment of that wound should be prioritized (as application of Vyjuvek to all the wounds may not be possible in a single treatment session).

If a dose is missed, Vyjuvek should be administered as soon as possible and thereafter resumed on a once-weekly schedule.

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List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Outline of the proposed product

Vyjuvek is a regenerative medical product consisting of a replication-defective recombinant herpes simplex virus (HSV)-1 carrying the human collagen type VII alpha 1 chain (*COL7A1*) gene, which is the causative gene of dystrophic epidermolysis bullosa (DEB). Derived from the KOS strain of HSV-1, it incorporates a gene expression cassette composed of human cytomegalovirus (hCMV) promoter, the human *COL7A1* gene, and bovine growth hormone (BGH) polyadenylation signal sequence. When Vyjuvek is applied to the wound sites of patients, it infects human dermal fibroblasts and human epidermal keratinocytes, where its viral genome remains as an episome in the nuclei of these cells and enables the expression of functional collagen type VII (COL7) protein in both human dermal fibroblasts and keratinocytes. The expressed COL7 protein forms anchoring fibrils (AFs), which secure the epidermis to the dermis, thereby expectedly promoting wound healing in patients with DEB.

Vyjuvek was designated as an orphan regenerative medical product with the intended indication or performance for the treatment of "dystrophic epidermolysis bullosa" as of December 13, 2023 (Orphan Regenerative Medical Product Designation No. 26 of 2023 [*R5 sai*]).

1.2 Development history, etc.

DEB is one of the 4 major subtypes of the hereditary connective tissue disorder epidermolysis bullosa (EB) (simplex, junctional, dystrophic, and Kindler syndrome) and is a blistering skin disease caused by mutations in the *COL7A1* gene, which encodes COL7 protein. COL7 protein is the principal component of AFs, which play a critical role in attaching the epidermis to the dermis across the basement membrane.

DEB is broadly classified into 2 types according to the mode of inheritance, i.e., recessive dystrophic epidermolysis bullosa (RDEB) and dominant dystrophic epidermolysis bullosa (DDEB). RDEB represents a more severe phenotype compared with DDEB. RDEB is autosomal recessive, and in the skin of patients with RDEB, expression of COL7 protein is markedly reduced or completely absent due to null mutations in the *COL7A1* gene. DDEB is autosomal dominant, and in the skin of patients with DDEB, AF formation is thought to be destabilized by the presence of mutant COL7 protein. DEB can manifest at birth and is characterized by clinical features including skin fragility, separation of the epidermis and dermis (blister formation), milia, and scarring. Persistent blister formation begins at birth and contributes to a high risk of mortality from bacterial infection. Furthermore, patients with DEB are at increased risk of developing highly malignant and life-threatening squamous cell carcinoma.

In Japan, EB is designated as an intractable disease. The prevalence of RDEB and DDEB in Japan is estimated to be 2.6 to 3.6 per million population.

At present, the primary therapeutic approach for DEB is limited to supportive care, which focuses on management of multiple wound symptoms and reduction of trauma and infection.

For Vyjuvek, a foreign phase I/II study (Study KB103-001) targeting patients with RDEB aged ≥2 years was initiated in May 2018. In addition, a foreign phase III study (Study B-VEC-03) targeting patients with DEB aged ≥6 months was initiated in August 2020. Subsequently, a foreign phase III study (Study

B-VEC-EX-02) was initiated in May 2021, in which patients who had completed Study B-VEC-03 continued to receive Vyjuvek, and patients with DEB who had not previously received Vyjuvek were newly treated with Vyjuvek. In Japan, a Japanese phase III study (Study B-VEC-EX-02-JP) targeting subjects with DEB aged ≥2 months was initiated in [redacted].

In the US, on the basis of the primary results of Study B-VEC-03, an approval was granted in May 2023 with the following indication: "VYJUVEK is a herpes-simplex virus type 1 (HSV-1) vector-based gene therapy 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."

In the EU, based on the primary results of Study B-VEC-03, an approval was granted in April 2025 with the following indication: "Vyjuvek is indicated for the treatment of wounds in patients with dystrophic epidermolysis bullosa (DEB) with mutation(s) in the *collagen type VII alpha 1 chain (COL7A1)* gene, from birth."

Recently, the applicant submitted an application for marketing approval of Vyjuvek based on the primary results of Study B-VEC-03.

2. Quality and Outline of the Review Conducted by PMDA

Vyjuvek is a recombinant HSV-1 constructed using the backbone of the HSV-1 (KOS strain), carrying 2 copies of a gene expression cassette consisting of a CMV promoter, the human *COL7A1* gene, and BGH polyadenylation signal sequence.

Vyjuvek is replication-deficient due to deletion of both copies of the *ICP4* gene, which are present in duplicate in the genome of the KOS strain.[1)] A *COL7A1* gene expression cassette is inserted into each of the 2 deleted *ICP4* gene regions.[2)] In addition, the *ICP22* gene has been deleted to reduce cytotoxicity.

2.1 Drug substance

2.1.1 Generation and control of cell substrate for production of drug substance

African green monkey kidney epithelial cells (Vero cells) are used for the manufacture of the drug substance. Vero cells obtained from [redacted] were used as the original strain to generate a stable cell line expressing the [redacted] gene and *ICP4* gene. The optimal clone was selected based on the expression level of the [redacted] gene, and the master cell bank (MCB) and working cell bank (WCB) were prepared.

Characterization and purity testing of the MCB, WCB, and limit of *in vitro* cell age (LIVCA) were conducted in accordance with the ICH Q5A(R2) and Q5D guidelines. The tests for adventitious agents

1) Although multiple mutations were identified in the vector backbone sequence of Vyjuvek when compared with the reference sequence constructed from the published sequence of the wild-type KOS original strain, it was explained that none of these mutations affect the efficacy or safety of Vyjuvek.

2) For each of the *COL7A1* genes inserted into the 2 loci, a variant containing a substitution of [redacted] to [redacted] at position open reading frame (ORF) [redacted] is present at a certain frequency. This mutation results in the substitution of [redacted] with [redacted] at amino acid position [redacted] in the primary structure of the human COL7 α1 chain expressed from Vyjuvek; however, it was explained that this mutation does not affect the function of the COL7 protein. Furthermore, the proportion of variants carrying this mutation remained consistent throughout the manufacturing process from the master virus bank (MVB) to the drug product, and similar proportions were observed among the formulation batches used in the clinical studies.

performed are shown in Table 1. Within the scope of the assays conducted, no viral or non-viral adventitious agents were detected.

The MCB and WCB used for drug substance manufacture are stored in [redacted]. The MCB is [redacted], and new WCB is prepared [redacted].

Table 1. Tests for adventitious agents conducted on MCB, WCB, and LIVCA

In vitro virus tests ([redacted])
In vivo virus tests ([redacted])[*1]
Bovine virus tests ([redacted])[*1]
Porcine virus tests ([redacted])[*1]
Human virus tests ([redacted])[*2]
Monkey virus tests ([redacted])[*2]
Bovine virus test ([redacted])[*2]
Electron microscopy[*1]
Reverse transcriptase activity test[*1]
Test for mycobacteria[*1]
Sterility test[*3]
Mycoplasma test[*3]
Acholeplasma test[*2]

*1 Conducted on [redacted] and [redacted].
*2 Conducted on [redacted] only.
*3 Conducted on [redacted] and [redacted].

2.1.2 Preparation and control of virus seed stock for drug substance manufacturing

HSV-1 KOS original strain purchased from [redacted] was modified by deleting one *ICP22* gene and two *ICP4* genes, and by inserting a human *COL7A1* gene expression cassette into each of the 2 deleted *ICP4* gene regions to generate the virus. Plaques were screened using [redacted] titer, [redacted], and [redacted] as selection criteria, and the optimal plaque was selected to prepare the virus seed. By infecting MCB and WCB with the virus seed, master virus bank (MVB) and working virus bank (WVB) for drug substance manufacturing were established.

Characterization and purity testing of MVB and WVB were conducted in accordance with the ICH Q5A(R2) guideline. The tests performed for adventitious agents are summarized in Table 2. Within the scope of the assays conducted, no viral or non-viral adventitious agents were detected.

MVB and WVB are stored at ≤[redacted]°C. The MVB is [redacted], and new WVB is prepared [redacted].

Table 2. Tests for adventitious agents conducted on MVB and WVB

In vitro virus tests (, , and)
In vivo virus tests (, , , and)*1
Bovine virus tests (, , , and [ ], , , and [ ])*1
Monkey virus test ( )*1
Porcine virus tests (,)*1
(types , , , , , , , , , , and) tests*1
test*1
test
Reverse transcriptase activity test*1
Sterility test
Mycoplasma test

*1 Conducted on only.

2.1.3 Manufacturing process

The manufacturing process of the drug substance consists of WCB thawing and culture, , , , , , and , sterile filtration, , , and final filtration (filling).

, , , , , and are defined as the critical steps.

Process validation of the manufacturing process for the drug substance has been conducted at the commercial production scale.

2.1.4 Safety evaluation of adventitious agents

Table 3 shows biological raw materials other than Vero cells used in the manufacturing process of the drug substance, and compliance with the Standards for Biological Raw Materials has been confirmed for all of them.

Table 3. Biological raw materials other than Vero cells

Raw material name	Animal	Material used	Process
FBS 1	Bovine	Blood	Preparation of , , and
FBS 2	Bovine	Blood	Preparation of and and manufacturing process of drug substance ( )

In addition, in the manufacturing process of the drug substance, a mycoplasma test and an *in vitro* adventitious virus assay are performed for of the step, and a sterility test is performed for after the step.

2.1.5 Manufacturing process development

The main changes in the manufacturing processes during the development of the drug substance are as shown below (each manufacturing process is designated as Process A, B, C, D, or E [proposed process]).

- From Process A to Process B: Change in , change in , and deletion of the step
- From Process B to Process C: Change in , , change in , , change in , change in , and deletion of the step preceding step

- From Process C to Process D: Addition of the [redacted] step
- From Process D to Process E (proposed process): Change in [redacted] in [redacted] step, change in [redacted], and change in [redacted]

Table 4 shows the manufacturing processes of the drug substance used in the production of the formulation for each clinical study.

Table 4. Manufacturing processes of the drug substance used in the production of the formulation for each clinical study

Process A	Study KB103-001
Process B	Study KB103-001
Process C	Studies B-VEC-03 and B-VEC-EX-02
Process D	Study B-VEC-EX-02
Process E (proposed process)	Studies B-VEC-EX-02 and B-VEC-EX-02-JP

In association with these process changes, the comparability of quality attributes of pre- and post-change drug substances was assessed. Since Vyjuvek is continuously manufactured up to the drug product, evaluations were performed using formulations manufactured from the drug substance produced by each process.

For each process change, comparability between the formulations manufactured using the pre-change and post-change drug substances has been confirmed.

2.1.6 Characterization

2.1.6.1 Structure and characteristics

Table 5 shows characterization performed [for the characterization of biological activity, see Section 3].

Table 5. Parameters for characterization

Characteristics of viral particles	[redacted], [redacted], genome size, *COL7A1* gene sequence, [redacted]
Impurities	[redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted]

2.1.6.2 Product-related substances/Product-related impurities

From the results of the characterization analyses described in Section 2.1.6.1, Impurity 1, Impurity 2, and Impurity 3 were identified as product-related impurities. Impurity 1 is adequately controlled by the specifications for the drug product. Impurity 2 and Impurity 3 are controlled during the manufacturing process.

2.1.6.3 Process-related impurities

Host cell-derived DNA, host cell protein (HCP), Impurity 4, and Impurity 5 were identified as process-related impurities. It has been confirmed that all process-related impurities are sufficiently removed during the manufacturing process. Furthermore, all process-related impurities are adequately controlled by the specifications for the drug product.

2.1.7 Control of drug substance

Since the manufacturing process of the drug substance and the manufacturing process of the drug product are performed consecutively without long-term storage of the drug substance, specifications for the drug substance have not been established.

2.1.8 Stability of drug substance

Since the manufacturing process of the drug substance and the manufacturing process of the drug product are performed consecutively without long-term storage of the drug substance, stability studies of the drug substance have not been conducted.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a topical preparation containing 1.0 mL of drug substance at a concentration of 5×10^9 plaque forming units (PFU)/mL per vial (1 mL). The drug product contains the following excipients: glycerin, sodium chloride, disodium hydrogen phosphate dihydrate or disodium hydrogen phosphate heptahydrate,[3)] potassium chloride, potassium dihydrogen phosphate, and water for injection.

2.2.2 Manufacturing process

The manufacturing process of the drug product consists of drug substance storage, drug substance mixing, filling, stoppering and labeling, testing, and storage. From the sterile filtration process of the drug substance onward through the storage process of the drug product, the process is conducted in a closed system.

No critical steps have been specified.

The manufacturing process for the drug product has been validated on a commercial production scale.

After the manufacturing process of the drug product, steps are established for co-packaging, labeling, and storage of the drug product (the primary component) and the hydroxypropyl methylcellulose (HPMC) gel (the secondary component).

2.2.3 Manufacturing process development

The main changes in the manufacturing process during the development of the drug product are as shown below (each manufacturing process is referred to as Process I or Process II [proposed process]).

- From Process I to Process II (proposed process): Changes in [redacted], changes in [redacted], changes in [redacted], changes in [redacted], and changes in [redacted].

Table 6 shows the manufacturing process of the formulation used in each clinical study.

3) As an excipient, 10% glycerin-containing dulbecco's phosphate buffered saline (DPBS) prepared either by the [redacted] company or by the applicant is used. The 10% glycerin-containing DPBS prepared by the applicant contains disodium hydrogen phosphate [redacted], whereas the 10% glycerin-containing DPBS prepared by the [redacted] company contains disodium hydrogen phosphate [redacted]; however, the final concentration expressed as anhydrous disodium hydrogen phosphate is the same.

Table 6. Manufacturing process of the formulation used in clinical studies

Process I	Study KB103-001
Process II (proposed process)	Studies B-VEC-03, B-VEC-EX-02, and B-VEC-EX-02-JP

The change from Process I to Process II was implemented simultaneously with the change in the drug substance manufacturing process from Process B to Process C. The comparability of the quality attributes before and after the change in the drug product manufacturing process was evaluated together with that of quality attributes of the drug substances before and after the manufacturing process change [see Section 2.1.5].

2.2.4 Control of drug product

The proposed specifications for the drug product include strength, description, identification (COL7 protein expression, [redacted], [redacted], particle size), pH, purity tests (replicative HSV, host cell-derived DNA, HCP, [redacted], [redacted], total protein), bacterial endotoxin, sterility, mycoplasma test (for unprocessed bulk), adventitious viruses (for unprocessed bulk [*in vitro* virus tests ([redacted], [redacted], and [redacted])]), [redacted], HSV genome copy number, [redacted], extractable volume, [redacted] ([redacted] binding affinity), and assay (plaque formation).

2.2.5 Stability of drug product

Table 7 shows a summary of the main stability studies for the drug product.

Table 7. Summary of main stability studies for the drug product

Study	Manufacturing process for drug substance	Number of batches[*1]	Storage condition	Study period	Storage form
Long-term testing	Process D	3	-20 ± 5°C	36 months	Cycloolefin copolymer vials with thermoplastic elastomer stoppers
	Process E (proposed process)	3[*2]		[redacted] months[*3]	
	Process E (proposed process)	1		[redacted] months[*3]	
	Process D	3	-80 ± 10°C	[redacted] months	
	Process E (proposed process)	3[*2]		24 months[*3]	
Accelerated testing	Process D	3	2°C to 8°C	[redacted] months	
Stress testing	Process D	1	Freezing and sawing repeated [redacted] times		
	Process E (proposed process)	1	[redacted]°C	[redacted] months	Polypropylene tube
In-use stability testing[*4]	Process E (proposed process)	1	Stored at [redacted]°C for [redacted] days, followed by storage at 4°C for 7 days		Synthetic rubber[*5] gaskets, polycarbonate syringe, and polypropylene cap
	Process E[*6]	1	-20 ± 5°C	42 days	

*1 A drug product manufactured by Process II (proposed process) was used.
*2 A drug product stored at [redacted]°C for [redacted] to [redacted] months was used.
*3 Continued for up to [redacted] months.
*4 HPMC gel manufactured by Process 4 (proposed process) was used in the study.
*5 Polyisoprene/styrene-butadiene rubber.
*6 Drug substance manufactured using a scale [redacted] times that of Process E was used.

In the long-term testing, for 1 batch of the Process D drug product, storage at [redacted]°C for [redacted] months resulted in [redacted] falling out of the control range, and a decreasing trend was observed in other batches. The applicant considers that this deviation and decreasing trend were due to variability

in the analytical method. For other evaluation parameters, no significant changes in quality attributes were observed under any conditions throughout the study period.

The accelerated testing showed no significant changes in quality attributes throughout the study period.

In the stress testing, a decreasing trend was observed in [redacted] and [redacted] ([redacted]) at [redacted] months.

The in-use stability study showed no significant changes in quality attributes throughout the study period.

Based on the above findings, a shelf-life of 36 months has been proposed for the drug product when stored at ≤−15°C in cycloolefin copolymer vials with thermoplastic elastomer stoppers. After mixing the drug product with the HPMC gel, storage at −20°C ± 5°C for 6 weeks was feasible using synthetic rubber gaskets, polycarbonate syringes, and polypropylene caps.

2.3 HPMC gel

2.3.1 Composition and formulation development

The HPMC gel is a solution containing HPMC, trometamol, sodium chloride, disodium hydrogen phosphate heptahydrate, potassium dihydrogen phosphate, and water for injection. Each 2 mL vial contains 1.5 mL of the solution. One vial is provided per drug product.

2.3.2 Manufacturing process

The manufacturing process of HPMC gel consists of preparation, filling, sterilization/testing/storage, labeling, and storage.

[redacted], [redacted], and [redacted] are defined as the critical steps.

The manufacturing process of HPMC gel has been validated on a commercial production scale.

2.3.3 Manufacturing process development

The main changes in the manufacturing process of the HPMC gel during development are as shown below (each manufacturing process is referred to as Process 1, 2, 3, or Process 4 [proposed process]).

- From Process 1 to Process 2: Change in [redacted], change in [redacted], change in [redacted], and change in [redacted].
- From Process 2 to Process 3: Change in [redacted], change in [redacted], change in [redacted], and change in [redacted].
- From Process 3 to Process 4 (proposed process): Change in [redacted], change in [redacted], change in [redacted], addition of [redacted] process, and change in [redacted].

Table 8 shows the manufacturing processes of the HPMC gel used in each clinical study.

Table 8. Manufacturing processes of HPMC gel used in clinical studies

Process 1	Study KB103-001[*1]
Process 2	Study B-VEC-03
Process 3	Studies B-VEC-03 and B-VEC-EX-02
Process 4 (proposed process)	Studies B-VEC-EX-02 and B-VEC-EX-02-JP

*1 In phase IIa part, Plurogel commercially available in foreign countries was used.

2.3.4 Control of HPMC gel

The specifications for the HPMC gel include a description, identification ([redacted]), pH, osmolality, bacterial endotoxins, sterility, and extractable volume.

2.3.5 Stability of HPMC gel

Table 9 shows the summary of the main stability studies for the HPMC gel.

Table 9. Summary of main stability studies for HPMC gel

Study	Number of batches[*1]	Storage condition	Study period	Storage form
Long-term testing	3	-20 ± 5°C	36 months	Glass vial with bromobutyl elastomer stoppers
	3	[redacted]°C	[redacted] months	
Accelerated testing	3	[redacted]°C/[redacted]%RH ± [redacted]%RH	[redacted] months	
Stress testing	3	[redacted]°C/[redacted]%RH ± [redacted]%RH	[redacted] months	

*1 HPMC gel manufactured by the proposed process was used.

The long-term testing showed no marked changes in the quality attributes under any of the storage conditions throughout the study period.

The accelerated study showed a decrease in [redacted].

In the stress study, the changes observed in the accelerated study became more pronounced.

In light of these results, the shelf life of 36 months has been proposed for the HPMC gel when stored at ≤−15°C in glass vials with bromobutyl elastomer stoppers.

2.4 Quality control strategy

On the basis of the following investigations, the quality control strategy for Vyjuvek was established, combining control of process parameters, in-process controls, and specifications [for control of product-related impurities and process-related impurities, see Sections 2.1.6.2 and 2.1.6.3].

- Identification of critical quality attributes (CQAs):
  Based on information obtained during the development of Vyjuvek and related findings, the following CQAs were identified:
  - CQAs of the drug substance or drug product
    Sterility, bacterial endotoxins, [redacted], description, pH, identification ([redacted]), strength, [redacted]
  - CQAs of HPMC gel
    Sterility, bacterial endotoxins

- Process characterization

  Process parameters were classified according to a risk assessment based on their impact on CQAs, and characterization studies were conducted for each process.

2.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA concluded that the quality of the drug substance, drug product, and HPMC gel was appropriately controlled.

3. Primary Pharmacodynamics or Performance and Outline of the Review Conducted by PMDA

As supporting data for the efficacy or performance of Vyjuvek, the applicant submitted the following results from *in vitro* studies using the vectors for non-clinical study, as well as *in vivo* studies using BALB/c mice and *Col7a1*$^{flNeo/flNeo}$ mice. Although the vectors for non-clinical study used in these studies were derived from a different MVB than Vyjuvek, they originated from the same KOS strain with deletions in the *ICP4* and *ICP22* genes as Vyjuvek. Therefore, the applicant explained that it is possible to evaluate the efficacy or performance of Vyjuvek from the results of non-clinical pharmacological studies conducted with the vectors for non-clinical study.

3.1 *In vitro* studies

3.1.1 Studies using human dermal fibroblasts and human keratinocytes derived from patients with RDEB (CTD 4.2.1.1-1)

3.1.1.1 Expression of COL7 protein in human dermal fibroblasts and human keratinocytes derived from patients with RDEB

Human dermal fibroblasts and human keratinocytes derived from patients with RDEB were infected with the vector for non-clinical study (vehicle, a mixture of dulbecco's phosphate buffered saline [DPBS] and 10% glycerol) at multiplicity of infection (MOI) of 0.3, 1, and 3, and human COL7 protein expression at 48 hours post-infection was evaluated by immunofluorescence staining and Western blotting.

The results of immunofluorescence staining and Western blotting showed that, in cells infected with the vector for non-clinical study, the expression of human COL7 protein tended to increase at all MOI levels compared with uninfected cells.

3.1.1.2 Adhesion of human keratinocytes derived from patients with RDEB to rat-derived COL1 protein and human-derived fibronectin

Human keratinocytes derived from patients with RDEB were infected with the vector for non-clinical study (vehicle, a mixture of DPBS and 10% glycerol) or mock (a mixture of DPBS and 10% glycerol). Their adhesion to plates coated with rat tail-derived collagen type I (COL1) protein[4)] or human plasma-derived fibronectin[4)] was evaluated using a cell adhesion assay.[5)]

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4) Proteins present in the dermis that contribute to dermal–epidermal adhesion by interacting with COL7 protein.

5) Human keratinocytes infected with Vyjuvek at MOI of 0.1, 0.3, and 1, or mock-infected human keratinocytes, were seeded into 96-well plates that were either uncoated, coated with rat tail-derived COL1 protein at [redacted], [redacted], and [redacted] μg/mL, or coated with human plasma-derived fibronectin. Cells bound to COL1 protein or fibronectin were stained with crystal violet, and absorbance was measured.

Table 10 shows the results of the cell adhesion assay. In human keratinocytes derived from patients with RDEB and infected with the vector for non-clinical study, the number of adherent cells mediated by COL7 protein via rat COL1 protein and human fibronectin showed an increasing trend.

Table 10. Results of the cell adhesion assay

	COL1 protein derived from rat tail		Fibronectin derived from human plasma	
	Uncoated	[redacted] μg/mL[*1]	Uncoated	[redacted] μg/mL[*2]
Mock	0.0854 ± 0.0159	0.1409 ± 0.0078	0.0756 ± 0.0014	0.1313 ± 0.0051
MOI 0.1	0.0720 ± 0.0056	0.1950 ± 0.0252	0.0741 ± 0.0016	0.1543 ± 0.0132
MOI 0.3	0.0757 ± 0.0013	0.2436 ± 0.0385	0.0729 ± 0.0040	0.2385 ± 0.0238
MOI 1	0.0841 ± 0.0002	0.2310 ± 0.0164	0.0711 ± 0.0045	0.2319 ± 0.0027

Absorbance (mean ± standard deviation)
*1 The absorbance of plates coated with rat tail-derived COL1 protein at [redacted] and [redacted] μg/mL was similar to that of [redacted] μg/mL.
*2 The absorbance of plates coated with human plasma-derived fibronectin at [redacted] and [redacted] μg/mL was similar to that of [redacted] μg/mL.

3.2 *In vivo* studies

3.2.1 Study in BALB/c mice (CTD 4.2.1.1-2)

Male BALB/c mice received a single intradermal dose of either the vector for non-clinical study at 4.8×10^7 PFU/100 μL or a mixture of DPBS and 10% glycerol at 100 μL. In addition, in male BALB/c mice with pre-induced skin wounds,[6)] a single topical application of either the vector for non-clinical study at 4.8×10^7 PFU/120 μL or 3% HPMC at 120 μL was performed on the injured skin.

Skin biopsy specimens obtained on Day 3 and Day 6 after intradermal administration or topical application (designated as Day 1) were evaluated for *COL7A1* gene mRNA expression by real-time quantitative polymerase chain reaction (qPCR). Localization of human COL7 protein to the basement membrane was also evaluated by immunofluorescence staining.

Table 11 shows the results of real-time qPCR. In the groups administered with the vector for non-clinical study, comparable levels of mRNA expression were observed at both Day 3 and Day 6, regardless of the route of administration.

6) Wounds or scars were created. Wounds were generated by excising a 5 to 6 mm diameter area of skin tissue using sharp scissors. Scars were created by scraping the skin surface followed by superficial puncture with a 22-gauge needle.

Table 11. *COL7A1* gene mRNA levels on Day 3 and Day 6 after administration or topical application

Animal	Route of administration	Test substance	Dose (PFU/injection site)	mRNA level[*3] (copy number/100 ng RNA)	
				Day 3	Day 6
Male mice (BALB/c)	Intradermal	Vehicle[*1]	0	1.24×10^{0}	1.65×10^{-1}
		Vector for non-clinical study[*1]	4.8×10^{7}	$9.15 \times 10^{4} \pm 1.58 \times 10^{4}$	$3.30 \times 10^{3} \pm 1.29 \times 10^{3}$
	Injured skin application (wound skin)	Vehicle[*2]	0	$3.72 \times 10^{1} \pm 3.07 \times 10^{1}$	$1.47 \times 10^{2} \pm 1.36 \times 10^{2}$
	Injured skin application (wound skin)	Vector for non-clinical study[*2]	4.8×10^{7}	$1.17 \times 10^{5} \pm 3.08 \times 10^{4}$	$1.54 \times 10^{3} \pm 1.18 \times 10^{3}$
	Injured skin application (scar skin)			$3.92 \times 10^{4} \pm 1.02 \times 10^{4}$	$5.16 \times 10^{3} \pm 2.47 \times 10^{3}$

*1 Vehicle was 10% glycerol/DPBS.
*2 Vehicle was 3% HPMC.
*3 Mean ± standard error (when data from 2 or 3 animals were available; when no standard error is shown, data represent a single animal).

From the results of the immunofluorescence staining analysis, localization of human COL7 protein to the basement membrane was confirmed at all time points and by all routes of administration.

3.2.2 Study in *Col7a1*$^{flNeo/flNeo}$ mice (CTD 4.2.1.1-3)

An evaluation was conducted in 3 *Col7a1*$^{flNeo/flNeo}$ mice.[7] The administered test articles at 4 subcutaneous dorsal sites per animal and evaluation periods were as follows:

Animal 1: At 1 site, control solution (GFP-HSV[8]) and at 3 sites, the vector for non-clinical study at 4.6×10^{7} PFU were administered once intradermally (Day 1), and evaluation was performed on Day 3.

Animal 2: At 1 site, control solution (phosphate buffered saline [PBS]) and at 3 sites, the vector for non-clinical study at 4.6×10^{7} PFU were administered once intradermally (Day 1), and evaluation was performed on Day 7.

Animal 3: At 1 site, control solution (PBS) and at 3 sites, the vector for non-clinical study at 4.6×10^{7} PFU were administered intradermally in 2 doses (Day 1 and Day 3), and evaluation was performed on Day 7.

At each evaluation time point for each animal, *COL7A1* gene mRNA levels were assessed by real-time qPCR, and localization of COL7 protein to the basement membrane was evaluated by immunofluorescence staining. In Animal 1, AF formation was evaluated by immune electron microscopy (IEM) on Day 3.

Table 12 shows the results of real-time qPCR. At the injection sites that received the vector for non-clinical study, expression of *COL7A1* gene mRNA was confirmed at all evaluation time points.

7) RDEB disease-model mice with low COL7 protein expression. The sex of the animals receiving either control solution or the vector for non-clinical study was not recorded.
8) HSV carrying GFP-expressing gene

Table 12. *COL7A1* gene mRNA levels on Day 3 and Day 7 in single-dose mice and on Day 7 in repeat-dose mice

Animal	Route of administration	Treatment period (day of injection)	Animal No.	Test substance	Dose (PFU/injection site)	mRNA level[*2] (copy number/100 ng RNA)	
						Day 3	Day 7
Col7a1$^{flNeo/flNeo}$ mouse	Intradermal	Single dose (Day 1)	1	GFP-HSV[*1]	0	Below the LOD	-
				Vector for non-clinical study[*1]	4.6×10^7	3.02×10^4 to 1.84×10^5	-
			2	PBS	0	-	Below the LOD
				Vector for non-clinical study[*1]	4.6×10^7	-	2.26×10^2 to 1.03×10^4
		Repeated doses (Days 1 and 3)	3	PBS	0	-	Below the LOD
				Vector for non-clinical study[*1]	4.6×10^7	-	8.00×10^3 to 3.57×10^4

*1 Vehicle was 10% glycerol/DPBS.
*2 Values represent the mean of 3 injection sites for the vector for non-clinical study, and 1 injection site for GFP-HSV or PBS.

According to the evaluation by immunofluorescence staining, localization of human COL7 protein to the basement membrane was confirmed at the injection sites that received the vector for non-clinical study at all time points.

From the IEM evaluation, AF formation was confirmed near the basement membrane on Day 3 in the single-dose mouse.

3.R Outline of the review conducted by PMDA

The applicant's explanation about the efficacy of Vyjuvek for DEB:

In *in vitro* studies, infection with the vector for non-clinical study led to an increase in human COL7 protein in human dermal fibroblasts and human keratinocytes derived from patients with RDEB. Furthermore, human keratinocytes derived from patients with RDEB infected with the vector for non-clinical study showed a tendency toward increased adhesion to plates via rat COL1 protein and human fibronectin.

In *in vivo* studies using BALB/c mice, comparable levels of *COL7A1* gene mRNA were confirmed following both intradermal administration and topical application to injured skin, and localization of human COL7 protein to the basement membrane was also confirmed. In *in vivo* studies using *Col7a1*$^{flNeo/flNeo}$ mice, an RDEB disease model, expression of *COL7A1* gene mRNA, localization of human COL7 protein to the basement membrane, and AF formation near the basement membrane were confirmed.

Although *in vitro* and *in vivo* studies evaluating the efficacy of Vyjuvek using cells derived from patient with DDEB and DDEB model animals have not been conducted, overexpression of wild-type COL7 protein in the presence of mutant COL7 protein normalizes AF stability (*J Biol Chem.* 2009;284:30248-56). In light of this finding, Vyjuvek is considered to be effective in wound healing for patients with DDEB as well.

Taken together, topical application of Vyjuvek to the skin of patients with DEB is expected to induce COL7 protein expression in fibroblasts and keratinocytes. Localization of COL7 protein to the basement membrane is anticipated to result in AF formation, thereby anchoring the epidermis to the basement membrane and promoting wound closure in patients with DEB.

PMDA accepted the applicant's explanation.

4. Non-clinical Biological Disposition and Outline of the Review Conducted by PMDA

The applicant submitted non-clinical data on the *in vivo* disposition of Vyjuvek, in the form of results from a single percutaneous dose toxicity study and a repeated intradermal dose toxicity study, both in mice.

4.1 Analytical method

In the non-clinical evaluation of *in vivo* disposition of Vyjuvek, the concentration of genomic DNA (gDNA) of Vyjuvek was measured by qPCR.

4.2 Non-clinical biodistribution

4.2.1 Biodistribution of the vector

The studies shown in Table 13, using Vyjuvek, and those shown in Table 14, using a vector for non-clinical study, were conducted, and the distribution of gDNA of Vyjuvek to each tissue was evaluated within the toxicity studies. The vector for non-clinical study used in the repeated intradermal dose toxicity study was derived from a different MVB than Vyjuvek; however, since it was manufactured by Process C [see Section 2.1.5] and has the same vector structure as Vyjuvek (including nucleocapsid, tegument, envelope, and surface glycoproteins), the applicant explained that the results of the repeated intradermal dose toxicity study using the vector for non-clinical study can be used to evaluate the *in vivo* biodistribution of Vyjuvek.

Table 13. Single percutaneous dose toxicity study

Test system	Route of administration	Observation period	Dose (PFU/body)	Summary of results	Attached document
Female mice (BALB/c)	Injured skin[*1] application	2 days and 34 days[*2]	0,[*3] 3.48×10^{7} [*4]	On Days 2 and 34 after administration, gDNA of Vyjuvek was not detected in the blood. On Day 2, gDNA of Vyjuvek was detected in the skin at the application sites in all animals. In addition, gDNA of Vyjuvek was detected in the bone marrow; however, it was not detected in any other tissues, including the axillary lymph nodes, bone marrow, brain, heart, inguinal lymph nodes, kidneys, liver, lungs, ovaries, and spleen.	4.2.3.1-2

*1 Injuries were created by removing skin tissue approximately 6 mm in diameter using sterilized scissors.
*2 Blood was analyzed on Days 2 and 34, while other tissues (including skin at the application site) were analyzed only on Day 2.
*3 Vehicle was 10% glycerol/3.0% HPMC/DPBS.
*4 Vehicle was 10% glycerol/3.0% HPMC/DPBS; 100 μL of the test substance prepared at a concentration of 3.48×10^{8} PFU/mL was applied to the dorsal skin wound site.

Table 14. Repeated intradermal dose toxicity study

Test system	Route of administration	Administration period/ observation period	Dose (PFU/body)	Summary of results	Attached document
Male and female mice (BALB/c)	Intradermal	Single-dose administration + 3-day observation period Once weekly for a total of 5 injections + observation periods of 1 day and 30 days	0^{*1} 6.9×10^{6} *2 3.45×10^{7} *3	Single-dose administration gDNA of Vyjuvek was not detected in blood, but was detected in the skin at the application site in all animals treated. In the 6.9×10^{6} PFU/body group, gDNA of Vyjuvek was detected in the axillary lymph nodes and inguinal lymph nodes. In the 3.45×10^{7} PFU/body group, gDNA of Vyjuvek was detected in the axillary lymph nodes, brain, kidney, and testes. No gDNA was detected in other tissues (bone marrow, heart, liver, lung, spleen, or ovaries). 5 administrations In both the 6.9×10^{6} PFU/body and 3.45×10^{7} PFU/body groups, gDNA of Vyjuvek was detected in blood on Day 1, but not on Day 30. At the skin application site, gDNA of Vyjuvek was detected in all animals of both dose groups on Day 1; on Day 30, detection was observed only in the 6.9×10^{6} PFU/body group. In the 6.9×10^{6} PFU/body group, gDNA of Vyjuvek was detected in the axillary lymph nodes, inguinal lymph nodes, and spleen on Day 1, and in the kidney on Day 30. In the 3.45×10^{7} PFU/body group, gDNA of Vyjuvek was detected in the axillary lymph nodes, bone marrow, brain, inguinal lymph nodes, and spleen on Day 1, and in the axillary and inguinal lymph nodes on Day 30. No gDNA was detected in other tissues (testes and ovaries). The heart, liver, and lung were not examined on Day 30.	4.2.3.2-1

*1 Vehicle was 10% glycerol/DPBS.
*2 Vehicle was 10% glycerol/DPBS; 50 μL of the test substance prepared at a concentration of 1.38×10^{8} PFU/mL was administered intradermally.
*3 Vehicle was 10% glycerol/DPBS; 50 μL of the test substance prepared at a concentration of 6.9×10^{8} PFU/mL was administered intradermally.

4.2.2 Excretion

No non-clinical studies evaluating the excretion of Vyjuvek have been conducted.

4.R Outline of the review conducted by PMDA

The applicant's explanation about the *in vivo* disposition of Vyjuvek:

From the results of a single percutaneous dose toxicity study in which Vyjuvek was applied to injured mouse skin and a repeated intradermal dose toxicity study using a vector for non-clinical study, gDNA of Vyjuvek at levels of 10^{4} to 10^{9} copies/μg DNA was detected at the skin application site. Outside the skin application site, gDNA of Vyjuvek at levels of 10^{2} to 10^{4} copies/μg DNA was detected in lymph nodes, bone marrow, brain, kidney, spleen, and testes.

In the 3.45×10^7 PFU/body group of the repeated intradermal dose toxicity study using the vector for non-clinical study in mice, distribution to the inguinal lymph nodes—which had not been observed with single-dose administration—was detected on Day 1 and Day 30 after 5 administrations. However, except for lymph nodes, gDNA of Vyjuvek was not detected in any tissue on Day 30 after 5 administrations, and the gDNA concentration in lymph nodes on Day 30 after 5 administrations was low (<0.1% of that at the application site). These findings suggest that there is no marked accumulation of Vyjuvek in the examined tissues (axillary lymph nodes, bone marrow, brain, heart, inguinal lymph nodes, kidney, liver, lung, spleen, testes, and ovaries).

Distribution of Vyjuvek to male and female reproductive organs was investigated in the single percutaneous dose toxicity study and the repeated intradermal dose toxicity study. Results showed no distribution of Vyjuvek to the ovaries. In the testes, distribution was observed in the 3.45×10^7 PFU/body group of the repeated intradermal dose toxicity study on Day 3 after single-dose administration. However, taking account of the following points, the applicant considers that there is no marked accumulation of Vyjuvek in the testes.

- The gDNA concentration detected in the single case was low (<0.1% of that at the application site).
- In the repeated intradermal dose toxicity study, gDNA of Vyjuvek was not detected on Day 1 or Day 30 after 5 administrations.
- Among the 38 mice receiving Vyjuvek in the single percutaneous dose toxicity study and the repeated intradermal dose toxicity study, only 1 animal showed detection of gDNA of Vyjuvek in reproductive organs.

It should be noted that multiple and long-term injuring procedures in mice are technically difficult; therefore, evaluation of repeated administration of Vyjuvek was conducted by intradermal injection rather than by topical application to injured skin. In *in vivo* studies using healthy mice, comparable levels of *COL7A1* mRNA were observed following both intradermal administration and topical application to injured skin, and COL7 protein localization at the basement membrane was confirmed [see Section 3.2.1]. Thus, it is considered possible to evaluate the *in vivo* disposition of the vector in skin and non-skin tissues after administration of Vyjuvek based on the results of the repeated intradermal dose toxicity study.

Although the clinical dosing period of Vyjuvek is longer than that in the repeated intradermal dose toxicity study, the study suggested no marked accumulation of Vyjuvek in tissues. Furthermore, given that Vyjuvek is a replication-defective recombinant HSV-1, and that infected viruses are expected to be diluted by cell division, it is considered unlikely that long-term administration would lead to accumulation of the vector in skin or other organs.

PMDA's view:

In the 3.45×10^7 PFU/body group of the repeated intradermal dose toxicity study in mice receiving Vyjuvek, distribution to bone marrow, spleen, and inguinal lymph nodes—which was not observed after single-dose administration—was detected on Day 1 after 5 administrations, and distribution to inguinal lymph nodes was still observed on Day 30 after 5 administrations. However, since the blood gDNA concentration of Vyjuvek in humans remained below the limit of detection (LOD) at all evaluation time

points, systemic exposure in humans is unlikely [see Section 6.2.1], and the possibility of accumulation of Vyjuvek in systemic tissues following long-term administration is also low. Nevertheless, given that the non-clinical and clinical evaluations of *in vivo* disposition conducted to date are limited, there are limitations in assessing the accumulation potential of Vyjuvek. Therefore, the risk associated with potential accumulation of Vyjuvek will be further discussed in the clinical section as part of the assessment of its long-term safety.

5. Non-clinical Safety and Outline of the Review Conducted by PMDA

The applicant submitted the following non-clinical safety data for Vyjuvek: A single-dose toxicity study in mice receiving Vyjuvek, a single-dose toxicity study in mice receiving a vector for non-clinical study, and a repeated intradermal dose toxicity study in mice receiving the vector for non-clinical study. The vector for non-clinical study used in these studies was derived from an MVB different from that of Vyjuvek. However, it was manufactured by Process C [see Section 2.1.5], possessed the same vector structure as Vyjuvek, underwent quality attributes testing, and was confirmed to express COL7 protein. Therefore, the applicant explained that the results from studies using the vector for non-clinical study were applicable to the evaluation of the non-clinical safety of Vyjuvek.

5.1 Single-dose toxicity studies

A single intravenous dose toxicity study (28-day observation) in male and female mice receiving the vector for non-clinical study, and a single dermal dose toxicity study (2-day and 34-day observation) in female mice receiving Vyjuvek to injured skin, were conducted as shown in Table 15.

In the single intravenous dose toxicity study (28-day observation) in male and female mice, systemic effects of Vyjuvek (3.45×10^7 PFU/body) were evaluated. Changes in clinical chemistry such as increased globulin levels and effects on lymphoid tissues were observed. These findings were considered related to inflammatory responses or immune stimulation, were mild in severity, and did not affect systemic clinical signs; therefore, the applicant explained that they were not indicative of toxicity of Vyjuvek. Increased extramedullary haematopoiesis in the liver and increased testicular weight were also observed. However, in the absence of other histopathological changes, these were mild in severity and did not affect clinical signs. The applicant explained that these findings were not indicative of toxicity of Vyjuvek. From these results, the no observed adverse effect level (NOAEL) for single intravenous administration of Vyjuvek was determined to be 3.45×10^7 PFU/body.

In the single dermal dose toxicity study (2-day and 34-day observation) in female mice, the effects of topical administration of Vyjuvek (3.48×10^7 PFU/body) to injured skin were evaluated. On Day 2, haematological changes such as elevated neutrophil counts compared with the control group were observed, which were judged to be inflammatory findings attributable to Vyjuvek. Although haematology was not conducted on Day 34 due to technical issues, no histopathological findings indicating inflammation were observed at Day 34. The applicant therefore explained that the haematological changes were expected to be reversible. In addition, the slight increase in blood glucose concentration observed in the Vyjuvek group compared with controls was not accompanied by histopathological changes, and the decrease in thymus weight was not accompanied by histopathological changes and was reversible. The applicant explained that these were not considered findings of safety

concern in humans. Given the seriousness of local inflammatory reactions and related findings at the administration site and no impact of them on systemic clinical sign, the NOAEL for single dermal administration of Vyjuvek was determined to be 3.48×10^7 PFU/body.

Table 15. Single-dose toxicity studies

Test system	Route of administration	Observation period	Dose (PFU/body)	Main findings	Attached document
Male and female mice (BALB/c)	Intravenous	28 days[*1]	0,[*2] 3.45×10^7	No deaths were observed. Decreased MCHC (females), increased RDW (males), decreased platelet count (females), increased globulin concentration (males and females), decreased A/G ratio (males and females), increased total protein concentration (males and females), increased glucose concentration (males), increased spleen weight (males and females), increased liver weight (females), decreased testis weight (males), lymphocyte hyperplasia and enlargement of germinal centers in splenic lymphoid follicles (males and females), lymphocyte hyperplasia and enlargement of lymphoid follicles in the axillary and inguinal lymph nodes (males and females), and extramedullary haematopoiesis in the liver (males and females)	4.2.3.1-1
Female mice (BALB/c)	Transdermal (application to injured skin)	2 days and 34 days[*3]	0,[*4] 3.48×10^7 [*5]	No deaths were observed. Erosion and scab at the administration sites, increased total leukocyte, neutrophil, lymphocyte, and peroxidase-negative large cell counts,[*6] increased glucose concentration,[*7] increased ALP, ALT, and AST levels,[*8] decreased total protein and globulin concentrations,[*8] decreased thymus weight, and mixed inflammatory cell infiltration at the administration sites in the skin[*9] Reversibility: The findings at the administration sites in the skin and thymus weight changes had resolved. The changes in clinical chemistry persisted on Day 34.	4.2.3.1-2

*1 Haematology and clinical chemistry were conducted only on Day 28.
*2 Vehicle was 10% glycerol/DPBS.
*3 Haematology data for the Vyjuvek group on Day 34 were not obtained due to technical issues.
*4 Vehicle was 10% glycerol/DPBS/3.0% HPMC.
*5 The test substance, 100 μL prepared at a concentration of 3.48×10^8 PFU/mL, was applied to the dorsal skin wound site.
*6 Increased total leukocyte, neutrophil, lymphocyte, and peroxidase-negative large cell counts compared with controls were observed. On Day 34 in the control group, decreased platelet counts compared with Day 2 were observed and fell outside the reference range as defined in published literature. However, data for the Vyjuvek group at Day 34 were missing, and thus the toxicological significance is unclear. On Day 34 in the control group, decreased reticulocyte counts compared with Day 2 were observed. However, baseline data and historical information were not available, and data for the Vyjuvek group at Day 34 were missing; therefore, the toxicological significance is unclear.
*7 Slight increases in blood glucose concentrations compared with the control group were observed at both Day 2 and Day 34.
*8 At Day 34, increases in alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) and decreases in total protein and globulin compared with Day 2 were observed. Although AST values fell outside the reference range as defined in published literature, no histopathological changes were observed, and similar changes were seen in controls. Therefore, these were judged to be effects of procedure or vehicle administration, or changes without toxicological significance.
*9 Similar findings were observed in controls and considered to be wound-related effects. These findings were not observed at Day 34.

5.2 Repeated-dose toxicity study

A repeated intradermal dose toxicity study in male and female mice receiving the vector for non-clinical study (once weekly for 5 weeks, 30-day observation) was conducted as shown in Table 16. Repeated

long-term creation of wounds in mice for the purpose of applying Vyjuvek to injured skin was difficult; therefore, intradermal administration in healthy mice was selected as the route of administration.

In mice receiving the vector for non-clinical study, scab formation at the administration site, mixed inflammatory cell infiltration, haemorrhage, and epidermal hyperplasia at the injection site were observed. Associated increases in neutrophil counts and globulin levels were also observed. Effects on lymphoid tissues and increased circulating lymphocyte counts were observed, which were considered possibly related to inflammatory responses or immune stimulation due to administration of the vector for non-clinical study. At Day 30 after the final dose, effects on lymphocyte counts and globulin levels persisted. Since infiltration of inflammatory cells at the injection site and associated increased neutrophil counts were observed in the high-dose group, the NOAEL was determined to be 6.9×10^6 PFU/body.

Table 16. Repeated intradermal dose toxicity study

Test system	Route of administration	Administration period/ observation period	Dose (PFU/body)	Main findings	NOAEL (PFU/body)	Attached document
Male and female mice (BALB/c)	Intradermal	Single-dose administration + 3-day observation period Once weekly administration for a total of 5 doses + observation periods of 1 day and 30 days	0,[*1] 6.9×10^6, 3.45×10^7	Single-dose administration No deaths were observed. 6.9×10^6 PFU/body group: Increased spleen weight (females); mixed inflammatory cell infiltration (males and females), haemorrhage (males), and epidermal hyperplasia (males) at the administration sites 3.45×10^7 PFU/body group: Haemorrhage and erosion/ulceration at the administration sites (females) 5 administrations No deaths[*2] were observed. 6.9×10^6 PFU/body group: Increased globulin concentration and decreased A/G ratio (females), increased spleen weight (females), lymphoid follicular hyperplasia in the white pulp of the spleen (females), and lymphoid follicular hyperplasia in the cortex of the inguinal and axillary lymph nodes (males and females). 3.45×10^7 PFU/body group: Increased leukocyte, lymphocyte, and neutrophil counts (females); increased globulin concentration and decreased A/G ratio (males); increased spleen weight (males); scab formation at the administration sites (males and females); and lymphoid follicular hyperplasia in the white pulp of the spleen (males). Reversible (except for increased lymphocyte counts in females and increased globulin concentration and decreased A/G ratio in males)	6.9×10^6	4.2.3.2-1

*1 Vehicle was 10% glycerol/DPBS.

*2 On Days 7 and 8 after the final dose, death or moribund condition was observed in 2 males. These occurred during the recovery period and were accompanied by lymphocyte depletion and necrosis in the thymus, spleen, and lymph nodes, Therefore, these observations suggested that the changes were potentially attributable to stress. In the end, the study findings were considered not directly related to the vector of the clinical study.

5.3 Other safety assessments

5.3.1 Potential for chromosomal integration

The applicant's explanation:

It has been reported that wild-type HSV-1 does not possess a mechanism for integration into host chromosomes and, during latent infection, the viral genome persists as an episome without being incorporated into host cell chromosomes (*Virology.* 1987;158:265-75; *J Virol.* 1989;63:943-7, etc.). Therefore, the risk of chromosomal integration by Vyjuvek is considered low.

5.3.2 Potential for tumorigenicity and carcinogenicity

The applicant's explanation:

Taking into account the following considerations, the risks of tumorigenicity and carcinogenicity due to administration of Vyjuvek, as well as the risk of exacerbating squamous cell carcinoma that occurs frequently in DEB patients, are considered low.

- The risk of chromosomal integration by Vyjuvek is considered low [see Section 5.3.1].
- According to the following epidemiological research literature, no definitive conclusion has been reached regarding an association between wild-type HSV-1 and tumorigenicity, carcinogenesis, or tumor progression:
  - Some epidemiological studies have reported correlations between HSV-1 infection and prevalence or progression of several cancers, including squamous cell carcinoma (*Diagnostics.* 2023;13:1798, etc.). Conversely, other studies have reported no correlation between HSV-1 infection and cancer prevalence (*J Natl Cancer Inst.* 2002;94:1604-13, etc.). Therefore, no consistent conclusion has been established regarding the relationship between HSV-1 infection and cancer.
- As reported in the following literature information regarding the *COL7A1* gene and its product, COL7 protein, in relation to the malignancy of squamous cell carcinoma, overexpression of the *COL7A1* gene or COL7 protein is unlikely to be associated with carcinogenesis or tumor progression:
  - Although epidemiological studies have reported a correlation between prognosis in patients with esophageal squamous cell carcinoma and COL7 protein levels in tumor lesions (*Oncology.* 2006;71:221-8, etc.), there are currently no reports clearly demonstrating that increased COL7 protein causes carcinogenesis or contributes to tumor progression.
  - Decreased COL7 protein levels have been reported to be associated with disruption of basement membrane structure, tumor cell invasion, and enhanced differentiation. Moreover, in patients with DEB, decreased COL7 protein levels have been reported to correlate with increased incidence of squamous cell carcinoma (*J Cell Sci.* 2009;122:1788-99, etc.).
- No impact of the mutations at position open reading frame (ORF) [redacted] present in a certain proportion in the *COL7A1* gene inserted in Vyjuvek [see Section 2] on protein function is anticipated, and they are unrelated to the loss-of-function mutations of *COL7A1* gene that cause disease in patients with DEB.

5.3.3 Reproductive and developmental toxicity

The applicant's explanation:

The risk of reproductive and developmental toxicity with Vyjuvek administration is considered low in view of the following points.

- In a single intravenous dose toxicity study (28-day observation) conducted in male and female mice via a route expected to result in systemic exposure, no effects on the male or female reproductive organs were observed [see Section 5.1].
- Vyjuvek has a low risk of integration into host chromosomes [see Section 5.3.1].
- Since (i) distribution of Vyjuvek to the ovaries was not observed in mice [see Section 4.2.1] and (ii) no systemic exposure to Vyjuvek in blood was detected in clinical studies [see Section 6.2.1], the likelihood of distribution of Vyjuvek to female reproductive tissues during clinical use is considered low.
- Although the possibility of distribution of Vyjuvek to the testes during clinical use cannot be excluded, such distribution is considered transient as described below, and, together with the absence of systemic exposure to Vyjuvek in blood in clinical studies [see Section 6.2.1], the potential for effects on male germ cells or male reproductive tissues during clinical use is considered low.
  - In a repeated intradermal dose toxicity study (once weekly for 5 weeks, 30-day observation) using male and female mice, distribution of Vyjuvek genomic DNA in the testes was detected in 1 of 3 male mice in the high-dose group on Day 1 after the final dose; however, the amount was minimal, and no distribution was observed at the end of the recovery period [see Section 4.2.1].

5.3.4 Safety evaluation of excipients

The applicant's explanation:

Regarding the safety at the administration site and systemically when the excipients of the main component (drug product) and the constituents of the subcomponent (HPMC gel), namely glycerol, hypromellose, trometamol, sodium chloride, disodium hydrogen phosphate [redacted] or disodium hydrogen phosphate [redacted], potassium dihydrogen phosphate, and potassium chloride, are administered long-term to injured skin, there are no safety concerns in clinical use of Vyjuvek, based on the previous use of these substances as pharmaceutical excipients in Japan and safety information obtained from clinical studies of Vyjuvek.

5.R Outline of the review conducted by PMDA

On the basis of the submitted data and the following considerations, PMDA determined that there are no particular concerns regarding the non-clinical safety of Vyjuvek, except for the long-term safety of Vyjuvek.

5.R.1 Long-term safety

The applicant explained that, although toxicity studies with long-term administration of Vyjuvek have not been conducted, the long-term safety of Vyjuvek can be supported by clinical study results.

PMDA's view:

The findings observed in the repeated intradermal dose toxicity study in male and female mice (once weekly for 5 weeks, 30-day observation) were limited to local inflammation at the administration site

and lymphocyte increase in lymph nodes. These findings showed both limited severity and reversibility [see Section 5.2]. In addition, the potential for systemic exposure in humans upon administration of Vyjuvek is low [see Section 6.2.1], and the likelihood of increased exposure locally in the skin or systemically with long-term administration is also low [see Section 4.R]. Taken these into consideration, PMDA concluded that the emergence of new safety concerns associated with long-term administration of Vyjuvek is unlikely. Nevertheless, because the evaluation of toxicological effects of long-term administration in the non-clinical studies conducted was limited, the long-term safety of Vyjuvek will continue to be discussed in the clinical section.

5.R.2 Administration in pediatric patients

Because toxicity studies of Vyjuvek using juvenile animals have not been conducted, PMDA asked the applicant to explain the potential effects of Vyjuvek on the growth and development of pediatric patients, including neonates, based on the results of the toxicity studies that were performed.

The applicant's explanation:
The anticipated toxicological findings when Vyjuvek is administered to pediatric patients, including neonates, are considered to be limited to the observed findings of local inflammation at the administration site and lymphocyte increase in lymph nodes. There are no marked structural differences in the skin or lymphoid tissues between adults and pediatric patients. Even when considering differences in the developmental stage of immune function, there are no pediatric-specific concerns associated with the observed toxicological findings.

PMDA accepted the applicant's explanation. The safety of Vyjuvek in pediatric patients will continue to be discussed in the clinical section.

6. Clinical Biological Disposition and Outline of the Review Conducted by PMDA

The applicant submitted clinical pharmacokinetic data of Vyjuvek, in the form of the results from Studies KB103-001, B-VEC-03, and B-VEC-EX-02-JP.

6.1 Analytical methods

The gDNA of Vyjuvek in blood, urine, skin swabs, and wound dressing swabs was measured using the qPCR method. Table 17 shows the LOD of each specimen in the studies.

Table 17. LOD of specimens in each study

	Study KB103-001	Study B-VEC-03
Blood	100 copies/qPCR reaction[*1]	100 copies/qPCR reaction[*1]
Urine	100 copies/qPCR reaction[*1]	100 copies/qPCR reaction[*1]
Skin swab	100 copies/qPCR reaction[*2]	50 copies/qPCR reaction[*2]
Wound dressing swab	-	50 copies/qPCR reaction[*2]

*1 The specimen volume per qPCR reaction was 5 μL, corresponding to 0.875 μL of blood or urine.
*2 The specimen volume per qPCR reaction was 5 μL, corresponding to one-tenth of the total DNA extracted from the swab stick used for sampling.

Table 18 shows the methods for measuring antibodies against HSV-1 and antibodies against the COL7 protein and the criteria for determining positivity.

Table 18. Methods for measuring antibodies against HSV-1 and COL7 and criteria for determining positive results

	Analytical method	Criteria for positivity
Anti- HSV-1 antibody	PRNT[*1]	1:80[*2]
Anti-COL7 antibody	ELISA	20 RU/mL

*1 This method measured the percent reduction of plaque formation when serially diluted patient serum was co-cultured with Vyjuvek in virus-producing cells, and confirmed the serum dilution at which approximately 50% reduction in plaques was observed.

*2 If no plaque reduction compared with serum-negative controls was observed in any of the specimens diluted from 1:80 to 1:5,120, the result was judged negative.

Infectious viral particles in skin swabs were measured by the infectious plaque assay. The LOD was 10 plaques per swab.

6.2 Clinical pharmacokinetics

Tables 19 to 21 show the dosage regimen, specimens, and timing of specimen collection in Studies KB103-001, B-VEC-03, and B-VEC-EX-02-JP. Notably, the biodistribution of Vyjuvek in Japanese patients has not been evaluated.

Table 19. Dosage regimen, specimens, and sampling time in Study KB103-001

Part	Dosage regimen[*1]	Specimens	Sampling time[*2]
Phase I	Vyjuvek at a dose of 1×10^8 PFU per day was applied to the wound site on Day 1 (first dose) and on Days 3, 29, and 31 after the first dose. In addition, if the wound remained open on Day 43 after the first dose, an additional application to the wound site was to be performed.	Blood Urine Serum	gDNA of Vyjuvek Blood samples: Baseline and Days 3, 29, 31, and 43 after the first dose (1 subject); baseline and Days 3, 15, 29, and 31 after the first dose (1 subject). Urine samples: Baseline and Days 3 and 15 after the first dose (1 subject); baseline and Days 3, 15, 29, and 31 after the first dose (1 subject). Immune response Baseline and Days 32, 44, and 81 after the first dose (1 subject); baseline and Days 3, 16, 29, and 59 after the first dose (1 subject).
Phase IIa	Vyjuvek at a dose of 3×10^8 or 6×10^8 PFU per day was applied to the wound site once daily for 5 consecutive days. In addition, if the wound remained open on Days 30, 60, or 90 after the first dose, additional applications to the wound site were to be performed.	Skin swab Serum	gDNA of Vyjuvek Skin swab samples: Baseline and Days 2, 3, 4, 5, 34, and 49 after the first dose (1 subject); baseline and Days 2 and 5 after the first dose (1 subject); baseline and Days 2 and 37 after the first dose (1 subject); baseline and Days 2, 5, 37, 39, and 46 after the first dose (1 subject). Immune response Baseline and Month 1 after the first dose (3 subjects); baseline (1 subject).
Phase IIb	Vyjuvek at a dose of 2×10^8 PFU per day was applied to the wound site approximately every 2 to 3 days for 14 days after the first dose. In addition, if the wound remained open on Days 30, 60, or 90 after the first dose, additional applications to the wound site were to be performed.	Blood Urine Skin swab Serum	gDNA of Vyjuvek Blood samples: Day 30 after the first dose (3 subjects); Day 60 after the first dose (1 subject); Day 117 after the first dose (1 subject). Urine samples: Days 30 and 60 after the first dose (2 subjects); Day 60 after the first dose (1 subject); Day 117 after the first dose (1 subject). Skin swab samples: Baseline and Days 2, 12, and 15, and Months 1 and 2 after the first dose (3 subjects); baseline and Days 4, 6, 8, 11, 13, and 15, and Months 1, 2, and 4 after the first dose (1 subject); baseline and Days 3, 5, 9, 11, and 15, and Months 1 and 2 after the first dose (1 subject). Immune response Months 1 and 4 after the first dose (1 subject); baseline and Months 1 and 2 after the first dose (1 subject); Day 2 and Month 1 after the first dose (1 subject); baseline and Months 1, 2, and 3 after the first dose (1 subject); Day 4 and Month 1 after the first dose (1 subject).
Phase IIc	Vyjuvek at a dose of 6×10^8 PFU per day was applied to the wound site approximately every 2 to 3 days during a single cycle until wound closure. One cycle was a maximum of 3 months.	Serum	Immune response Baseline and Day 2, and Months 1 and 2 after the first dose (1 subject).

*1 The actual dosage regimen of each patient is shown in Table 24.
*2 The sampling time refers to the actual collection times, not the planned collection times.

Table 20. Dosage regimen, specimens, and sampling time in Study B-VEC-03

Dosage regimen	Specimens	Sampling time *1
Vyjuvek or placebo was applied to the wound site once weekly for 26 weeks at the following doses: Dose per wound area <20 cm^2: 4×10^8 PFU ≥20 and <40 cm^2: 8×10^8 PFU ≥40 and <60 cm^2: 1.2×10^9 PFU Maximum weekly dose ≥6 months and <3 years: 1.6×10^9 PFU ≥3 and <6 years: 2.4×10^9 PFU ≥6 years: 3.2×10^9 PFU	Blood Urine Skin swab Wound dressing swab Serum	gDNA of Vyjuvek Blood samples: Baseline and Week 26 after the first dose (18 subjects); baseline and Week 24 after the first dose (1 subject); Week 26 after the first dose (1 subject). Urine samples: Baseline and Week 26 after the first dose (24 subjects); baseline and Week 24 after the first dose (1 subject); Week 26 after the first dose (1 subject). Skin swab samples (administration site): Baseline and once weekly until 26 weeks after the first dose (31 subjects). Wound dressing swabs: 4 collections until 26 weeks after the first dose (28 subjects); 3 collections until 26 weeks after the first dose (1 subject); 2 collections until 26 weeks after the first dose (1 subject). Immune response Baseline and Week 26 after the first dose (19 subjects); baseline (3 subjects).

*1 The sampling time reflects the actual collection timing, not the planned collection schedule.

Table 21. Dosage regimen, specimens, and sampling time in Study B-VEC-EX-02-JP

Dosage regimen	Specimen	Sampling time *1
Vyjuvek was applied to the wound site once weekly for up to 52 weeks at the following doses: Dose per wound area <20 cm^2: 4×10^8 PFU ≥20 and <40 cm^2: 8×10^8 PFU ≥40 and <60 cm^2: 1.2×10^9 PFU Maximum weekly dose ≥2 months and <3 years: 2.0×10^9 PFU ≥3 years: 4.0×10^9 PFU	Serum	Immune response Baseline and Week 26 after the first dose (2 subjects); baseline (1 subject).

*1 The sampling time refers to the actual collection times, not the planned collection times.

6.2.1 Clinical pharmacokinetics of the vector

6.2.1.1 Study KB103-001

The blood concentrations of gDNA of Vyjuvek were evaluated using the following specimens collected from 1 patient each in the Phase I part: Specimens at baseline and Days 3, 29, 31, and 43 after the first dose; and specimens at baseline and Days 3, 15, 29, and 31 after the first dose. In the Phase IIb part, the concentrations were evaluated using specimens collected from 3 patients at Day 30 after the first dose, from 1 patient at Day 60, and from 1 patient at Day 117.

The concentrations of Vyjuvek gDNA were below the LOD in all blood specimens at all evaluation points.

6.2.1.2 Study B-VEC-03

The gDNA concentrations of Vyjuvek in blood were evaluated using specimens collected from 19 patients at baseline and Week 26 after the first dose (1 of these at Week 24), and specimens collected from 1 patient at Week 26 after the first dose.

The concentrations of Vyjuvek gDNA were below the LOD in all blood specimens at all evaluation points.

6.3 Excretion

6.3.1 Study KB103-001

The urinary concentrations of Vyjuvek gDNA were evaluated using specimens collected from 1 patient at baseline and Days 3 and 15 after the first dose, and from 1 patient at baseline and Days 3, 15, 29, 31, and 43 after the first dose in the Phase I part. In the Phase IIb part, the concentrations were evaluated using specimens collected from 2 patients at Days 30 and 60 after the first dose, from 1 patient at Day 60, and from 1 patient at Day 117.

The concentrations of Vyjuvek gDNA in skin swabs, in the Phase IIa part, were evaluated using specimens collected from 4 patients at each visit before administration during the 5 consecutive days of administration, and from 3 patients at the visit 1 month after the first dose, before administration. In the Phase IIb part, the concentrations were evaluated using specimens collected from 5 patients at each visit before administration during the dosing period (every 3 days), and at the visits 1 month and 2 months after the first dose, before administration.

The concentrations of Vyjuvek gDNA in urinary specimens from both the Phase I and Phase IIb parts were below the LOD at all time points. In all 4 patients in the Phase IIa part, Vyjuvek gDNA was detected in skin swab specimens during the dosing period; however, at 1 month after the first dose, its concentrations were below the LOD in 2 of 3 patients. In all 5 patients in the Phase IIb part, Vyjuvek gDNA was detected in skin swab specimens during the dosing period; however, concentrations were below the LOD in 4 of 5 patients at 1 month after the first dose, and in 4 of 5 patients at 2 months after the first dose.

6.3.2 Study B-VEC-03

The urinary concentrations of Vyjuvek gDNA were evaluated using specimens collected from 25 patients at baseline and Week 26 after the first dose (Week 24 in 1 patient), and from 1 patient at Week 26 after the first dose. In 1 patient, a low concentration of Vyjuvek gDNA was detected at Week 26 after the first dose; however, in all other urinary specimens, concentrations were below the LOD at all time points.

The concentrations of Vyjuvek gDNA in skin swabs were evaluated using specimens collected from 31 patients at baseline and weekly at each visit up to Week 26 after the first dose. In addition, infectious viral particle counts were evaluated in the skin swab specimens. Among 2,069 skin swab specimens obtained 1 week after administration, Vyjuvek gDNA concentrations ranging from 10^2 to 10^7 copies/qPCR reaction were detected in 50 specimens; in all other specimens, concentrations were below the LOD. Infectious viral particles were not detected in any of the skin swab specimens.

The concentrations of Vyjuvek gDNA in wound dressing swabs were evaluated using specimens collected from 30 patients at each visit between Weeks 2 and 22 after the first dose, 24 hours after administration. Among 713 wound dressing swab specimens, concentrations of gDNA ranging from 10^2 to 10^8 copies/qPCR reaction were detected in 483 specimens; in all other specimens, the concentrations of Vyjuvek gDNA were below the LOD.

6.4 Immune response associated with administration of Vyjuvek

The evaluation results of immune responses related to Vyjuvek were as follows:

- Antibodies against HSV-1
  - In Study KB103-001, anti-HSV-1 antibodies were positive in 5 of 8 patients at baseline. One patient tested positive for anti-HSV-1 antibodies on Day 2 after the first dose. Among the 3 patients who were negative for anti-HSV-1 antibodies at baseline, 2 patients whose antibody titers were subsequently measured became positive on Day 230 and Day 182 after the first dose.
  - In Study B-VEC-03, anti-HSV-1 antibodies were positive in 14 of 22 patients at baseline. Among 8 patients who were negative at baseline, 6 patients became positive at Week 26 after the first dose.
  - In Study B-VEC-EX-02-JP, all 3 patients were positive for anti-HSV-1 antibodies at baseline. Among the 2 patients whose sera were collected at Week 26 after the first dose, 1 patient showed a slight increase in antibody titer, while no change was observed in the other.
- Antibodies against COL7 protein
  - In Study KB103-001, anti-COL7 antibodies were positive in 2 of 7 patients at baseline. In 1 of the 2 patients, anti-COL7 antibodies were negative on Day 2 after the first dose. Among the 6 patients who were negative either at baseline or on Day 2 after the first dose, 2 patients became positive thereafter.
  - In Study B-VEC-03, anti-COL7 antibodies were positive in 1 of 22 patients at baseline. Among 18 patients who were negative at baseline and had sera collected at Week 26 after the first dose, 13 patients became positive at that time.
  - In Study B-VEC-EX-02-JP, all 3 patients were negative for anti-COL7 antibodies at baseline. In 2 patients whose sera were collected at Week 26 after the first dose, both patients remained negative at that time.

6.R Outline of the review conducted by PMDA

On the basis of the submitted data and the following considerations, PMDA determined that there were no particular safety concerns regarding the clinical pharmacokinetics of Vyjuvek.

6.R.1 Clinical pharmacokinetics of and immune response to Vyjuvek

The applicant's explanation about the evaluation of clinical pharmacokinetics of and immune responses to Vyjuvek:

- Pharmacokinetics and excretion

  The results of the evaluation of Vyjuvek gDNA concentrations in blood, urine, and skin swabs from Studies KB103-001 and B-VEC-03 were consistent, suggesting that distribution beyond the site of administration (skin) was limited. In both studies, Vyjuvek gDNA was detected in skin swabs; however, as determined from the evaluation of infectious viral particle counts in Study B-VEC-03, vectors remaining on the skin surface were considered to be noninfectious particles.
- Pharmacokinetics and excretion in Japanese patients

  In Studies KB103-001 and B-VEC-03, evaluation of Vyjuvek gDNA concentrations in blood, urine, and skin swabs showed that, except for 1 urinary specimen, Vyjuvek gDNA concentrations were below the LOD in all blood and urine specimens. Therefore, distribution and excretion of Vyjuvek

through systemic exposure is not expected, and Vyjuvek was considered to be distributed only to the administration site (skin). This was considered applicable to Japanese patients as well.

- Immune response associated with administration of Vyjuvek
  Although some patients became positive for anti-HSV-1 antibodies and/or anti-COL7 antibodies after administration of Vyjuvek, the efficacy and safety of Vyjuvek were consistent regardless of these antibodies [see Section 7.R.5.2].

PMDA accepted the applicant's explanation.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted evaluation data on efficacy and safety, in the form of the results of 4 clinical studies listed in Table 22.

Table 22. List of clinical studies on efficacy and safety

Data category	Region	Study identifier	Phase	Study population	No. of subjects enrolled	Dosage regimen	Main endpoints
Evaluation	Foreign	KB103-001	I	Patients with RDEB aged ≥18 years	2	Vyjuvek or placebo was applied to the wound site at the following doses: 1×10^8 to 6×10^8 PFU per wound	Safety Efficacy
			IIa	Patients with RDEB aged ≥5 years	4		
			IIb	Patients with RDEB aged ≥2 years	5		
			IIc	Patients with RDEB aged ≥2 years	1		
	Foreign	B-VEC-03	III	Patients with DEB aged ≥6 months	31	Vyjuvek or placebo was applied once weekly to the wound site for 26 weeks at the following doses: Dose per wound area <20 cm^2: 4×10^8 PFU ≥20 and <40 cm^2: 8×10^8 PFU ≥40 and <60 cm^2: 1.2×10^9 PFU Maximum weekly dose ≥6 months and <3 years: 1.6×10^9 PFU ≥3 and <6 years: 2.4×10^9 PFU ≥6 years: 3.2×10^9 PFU	Efficacy Safety
	Foreign	B-VEC-EX-02	III	Patients with DEB who completed Study B-VEC-03 and patients with DEB not previously treated with Vyjuvek (no age restrictions)	47 (patients with DEB who completed Study B-VEC-03, 24; patients with DEB not previously treated with Vyjuvek, 23)	Vyjuvek was applied once weekly to the wound site for up to 112 weeks at the following doses: Dose per wound area <20 cm^2: 4×10^8 PFU ≥20 and <40 cm^2: 8×10^8 PFU ≥40 and <60 cm^2: 1.2×10^9 PFU Maximum weekly dose <3 years: 2.0×10^9 PFU ≥3 years: 4.0×10^9 PFU	Safety
	Japan	B-VEC-EX-02-JP	III	Japanese patients with DEB aged ≥2 months	5	Vyjuvek was applied once weekly to the wound site for up to 52 weeks at the following doses: Dose per wound area <20 cm^2: 4×10^8 PFU ≥20 and <40 cm^2: 8×10^8 PFU ≥40 and <60 cm^2: 1.2×10^9 PFU Maximum weekly dose ≥2 months and <3 years: 2.0×10^9 PFU ≥3 years: 4.0×10^9 PFU	Efficacy Safety

7.1 Evaluation data

7.1.1 Foreign clinical studies

7.1.1.1 Foreign phase I/II study (CTD 5.3.5.1-1, Study KB103-001 [May 2018 to November 2019])

An open-label, randomized, intra-patient placebo-controlled study was conducted at a single study site in the US to evaluate the safety and efficacy of Vyjuvek in non-Japanese patients with RDEB aged ≥2 years (target sample size, 14 subjects).

Table 23 shows the main inclusion and exclusion criteria.

Table 23. Main inclusion and exclusion criteria

Inclusion criteria	Patients who met all of the following criteria: • Patients with clinical manifestations of RDEB. • Patients of the following ages ➢ Phase I part, ≥18 years; Phase IIa part, ≥5 years; Phase IIb part, ≥2 years; Phase IIc part, ≥2 years • Patients diagnosed with RDEB by IF and IEM • Patients confirmed to have recessive mutations in the *COL7A1* gene. • Patients with wounds meeting the following size/surface area criteria: ➢ Phase I part, 2 wounds ≤10 cm^2 ➢ Phase IIa and Phase IIb parts, ≥3 wounds each ≤20 cm^2 ➢ Phase IIc part, ≥2 wounds each ≤50 cm^2
Exclusion criteria	• Patients with unstable conditions who could not travel to the study site. • Patients with diseases expected to complicate participation in this study and compromise safety, such as active infections with HIV, hepatitis B, or hepatitis C. • Patients confirmed positive for anti-COL7 protein antibodies in serum by ELISA, indirect immunofluorescence microscopy, Western blot, or ELISpot (patients who tested negative within 12 months after screening were eligible). • Patients with active infection at the intended administration site. • Patients with a current or past history of squamous cell carcinoma at the intended administration site. • Patients who had received chemical or biological treatments for RDEB within the past 3 months. • Patients with wounds previously treated with gene or cell therapy study products. • Patients who had taken systemic antibiotics within 7 days.

This study consisted of 4 parts, i.e., Phase I, Phase IIa, Phase IIb, and Phase IIc.

The randomization procedure for wounds, and the dosage regimen or administration method in each part, were as follows.

Phase I part:
This part consisted of a screening period (14 days prior to the first dose of the study product [baseline]) and a treatment period (12 weeks after the first dose). For each subject, 2 wounds ≤10 cm^2 were selected by the investigator and randomized to Vyjuvek or placebo. Each wound received Vyjuvek 1×10^8 PFU or placebo on Days 1, 2, 28, and 30. If the investigator judged that a selected wound remained open on Day 42 after the first dose, Vyjuvek 1×10^8 PFU or placebo was applied. For molecular correction/mechanistic evaluation, intradermal administration of Vyjuvek to intact skin was planned.[9)]

Phase IIa part:
This part consisted of a screening period (day of the first dose [baseline]), a treatment period (90 days after the first dose), and a monitoring period (180 days after the first dose). For each subject, 3 wounds

9) No subjects actually received intradermal administration.

≤20 cm^2 were selected by the investigator and randomized such that 2 wounds received Vyjuvek and the remaining 1 received placebo. Each wound received Vyjuvek 3 × 10^8 PFU, 6 × 10^8 PFU,[10] or placebo per day for 5 consecutive days. If the investigator judged that a selected wound remained open on Day 30, 60, or 90 after the first dose, Vyjuvek 3 × 10^8 PFU, 6 × 10^8 PFU, or placebo could be applied.

Phase IIb part:
This part consisted of a screening period (day of the first dose [baseline]), a treatment period (90 days after the first dose), and a monitoring period (180 days after the first dose). For each subject, 3 wounds ≤20 cm^2 were selected by the investigator and randomized such that 2 wounds received Vyjuvek and the remaining 1 received placebo. Each wound received Vyjuvek 2 × 10^8 PFU or placebo per day. During the first 14 days after the first dose, dosing was performed approximately every 2 to 3 days. Thereafter, if the investigator judged on Day 30, 60, or 90 that a selected wound remained open, Vyjuvek 2 × 10^8 PFU or placebo was applied. After Day 14, home administration approximately every 2 to 3 days was allowed except on Days 30, 60, and 90; however, no home administrations were actually performed. For molecular correction/mechanistic evaluation, intradermal administration of Vyjuvek to intact skin was conducted.[11]

Phase IIc part:
This part consisted of a screening period (day of the first dose [baseline]) and a treatment period (up to 6 months after the first dose). For each subject, 2 wounds <50 cm^2 were selected by the investigator and randomized to Vyjuvek or placebo. Each wound received Vyjuvek 6 × 10^8 PFU or placebo per day. One cycle lasted up to 3 months, during which Vyjuvek 6 × 10^8 PFU or placebo was applied approximately every 2 to 3 days until wound closure. After the first dose in each cycle, home administration was permitted if the subject, using an image application, judged that a wound had re-opened or enlarged. However, no home administrations were actually performed.

For all of 12 subjects[12] enrolled in this study (2 in the Phase I part, 4 in the Phase IIa part, 5 in the Phase IIb part, 1 in the Phase IIc part), wounds were randomized and treated with the study product. Except for 1 subject in the Phase IIa part who discontinued the study due to difficulty traveling to the site, 11 subjects completed the study. All 12 treated subjects comprised the safety analysis set. Excluding 1 subject in the Phase IIc part with a baseline wound >50 cm^2, 11 subjects comprised the intention-to-treat (ITT) population for efficacy analysis.

Dosage regimens of Vyjuvek were prespecified as above in this study. However, in practice, doses administered differed from the protocol, and the actual administration status for each subject is shown in Table 24.

[10] The first adult and pediatric subjects received 3 × 10^8 PFU; the second adult and pediatric subjects received 6 × 10^8 PFU.
[11] Intradermal administration was performed in 5 subjects in the Phase IIb part.
[12] Initially, 9 subjects were enrolled. Among the 4 subjects enrolled in the Phase IIa part, 3 subjects were re-enrolled in the Phase IIb part after a washout period. Since each phase was analyzed separately, the total number of enrolled subjects was 12.

Table 24. Administration status of Vyjuvek in individual subjects (Study KB103-001)

Part	Patient ID	Vyjuvek dose per wound (PFU/dose)	Number of wounds treated with Vyjuvek	Day of administration[*1]
Phase I	[redacted]	8.3×10^7 to 16.6×10^7	1	1, 3, 30, 32
		8.3×10^7 to 11.6×10^7	1	1, 3, 15, 28, 30, 43
Phase IIa		3×10^8	2	1, 2, 3, 4, 5, 34, 44, 73
		6×10^8	2	1, 2, 3, 4, 5
		3×10^8	2	1, 2, 3, 4, 5, 37
		3×10^8	2	1, 2, 3, 4, 5, 37, 46
Phase IIb	[*2]	2×10^8 to 8×10^8	2	1, 4, 6, 8, 11, 13, 15, 18, 29, 71
	[*3]	1×10^8 to 1.2×10^9	2	1, 3, 5, 9, 12, 15, 17, 29
		3×10^8 to 8×10^8	2	1, 5, 8, 10, 12, 15, 33, 61
		1×10^8 to 1×10^9	2	1, 2, 5, 8, 10, 12, 15, 33, 64
	[*4]	1×10^8 to 5×10^8	2	1, 2, 5, 8, 10, 12, 15, 33, 37, 38, 60
Phase IIc		8×10^8 to 1.57×10^9	1	First cycle: 1, 2, 4, 6, 7, 9, 10, 11, 13, 14, 15, 16, 17, 18, 20, 21, 22, 23, 24, 25 Second cycle: 37, 38, 39, 40, 41, 43, 44, 45, 46, 47, 49, 50, 51, 52, 53, 54, 56, 57, 58, 59, 60

*1 Day 1 was defined as the day of the first dose.
*2 Different wound of the same patient as [redacted]
*3 Different wound of the same patient as [redacted]
*4 Different wound of the same patient as [redacted]

The primary efficacy endpoint was the proportion of target wounds with complete closure (90% closure)[13)] at Weeks 8, 10, and 12 after the first dose of the study product. The results are shown in Table 25.

Table 25. Proportion of target wounds with complete closure (90% closure) (Study KB103-001, ITT population)

Evaluation time point	Vyjuvek-treated wound	Placebo-treated wound	Between-treatment difference [95% CI]
Week 8	82.4% (14/17)	0% (0/8)	82.4% [64.2, 100.0]
Week 10	75.0% (12/16)	33.3% (2/6)	41.7% [-1.6, 84.9]
Week 12	85.7% (12/14)	14.3% (1/7)	71.4% [39.7, 100.0]

Number of wounds with complete closure (90% closure)/number of target wounds (%)

Table26 shows the time course of wound closure status in individual subjects, and Table 27 shows changes and percent changes in wound area in individual subjects. In 1 subject in the Phase IIc part who was excluded from the ITT population, the wounds were evaluated at Days 3, 5, 15, 30, and 60 after the first dose of the study product; however, neither the Vyjuvek-treated wound nor the placebo-treated wound achieved complete closure (90% closure).

13) In Study KB103-001, "complete closure" was defined as ≥90% reduction in wound area from baseline. The proportion of wounds with complete closure (90% closure) among all primary wounds in the ITT population was calculated as the "proportion of complete wound closure."

Table 26. Time course of wound closure status in individual subjects (Study KB103-001, ITT population)

Part	Patient ID	Vyjuvek-treated wound				Placebo-treated wound			
		Wound No.	Week 8	Week 10	Week 12	Wound No.	Week 8	Week 10	Week 12
Phase I	[redacted]	1	NA	NA	NA	2	NA	NA	NA
	[redacted]	2	Complete closure (90% closure)	NA	NA	1	OPEN	NA	NA
Phase IIa	[redacted]	1	Complete closure (90% closure)	Complete closure (90% closure)	Complete closure (90% closure)	2	OPEN	OPEN	OPEN
		3	OPEN	OPEN	OPEN				
	[redacted]	1	NA	NA	NA	3	NA	NA	NA
		2	NA	NA	NA				
	[redacted]	2	Complete closure (90% closure)	Complete closure (90% closure)	Complete closure (90% closure)	1	OPEN	Complete closure (90% closure)	OPEN
		3	Complete closure (90% closure)	Complete closure (90% closure)	Complete closure (90% closure)				
	[redacted]	1	Complete closure (90% closure)	Complete closure (90% closure)	Complete closure (90% closure)	2	OPEN	OPEN	OPEN
		3	Complete closure (90% closure)	Complete closure (90% closure)	Complete closure (90% closure)				
Phase IIb	[redacted]*1	1	Complete closure (90% closure)	Complete closure (90% closure)	NA	3	OPEN	OPEN	Complete closure (90% closure)
		2	Complete closure (90% closure)	Complete closure (90% closure)	NA				
	[redacted]*2	2	Complete closure (90% closure)	Complete closure (90% closure)	Complete closure (90% closure)	1	OPEN	Complete closure (90% closure)	OPEN
		3	Complete closure (90% closure)	OPEN	Complete closure (90% closure)				
	[redacted]	2	Complete closure (90% closure)	Complete closure (90% closure)	Complete closure (90% closure)	1	OPEN	OPEN	OPEN
		3	Complete closure (90% closure)	OPEN	OPEN				
	[redacted]	1	Complete closure (90% closure)	Complete closure (90% closure)	Complete closure (90% closure)	2	OPEN	NA	OPEN
		3	Complete closure (90% closure)	Complete closure (90% closure)	Complete closure (90% closure)				
	[redacted]*3	1	OPEN	OPEN	Complete closure (90% closure)	2	NA	NA	NA
		3	OPEN	Complete closure (90% closure)	Complete closure (90% closure)				

NA, Not available
*1 Different wound of the same patient as [redacted]
*2 Different wound of the same patient as [redacted]
*3 Different wound of the same patient as [redacted]

Table 27. Changes and percent changes in wound area in individual subjects (Study KB103-001, ITT population)

Part	Patient ID	Vyjuvek-treated wound					Placebo-treated wound				
		Wound No.	Baseline[*1]	Week 8[*2]	Week 10[*2]	Week 12[*2]	Wound No.	Baseline[*1]	Week 8[*2]	Week 10[*2]	Week 12[*2]
Phase I	[redacted]	1	5	NA	NA	NA	2	5.86	NA	NA	NA
		2	2.68	0 -100%	NA	NA	1	6.61	9.21 39.33%	NA	NA
Phase IIa	[redacted]	1	10.1	0 -100%	0 -100%	0 -100%	2	3.1	5.7 83.87%	0.8 -74.19%	6.5 109.68%
		3	6	3.6 -40.0%	3.55 -40.83%	3.5 -41.67%					
	[redacted]	1	12.5	NA	NA	NA	3	2.3	NA	NA	NA
		2	5	NA	NA	NA					
	[redacted]	2	15.6	0 -100%	0 -100%	0 -100%	1	3.6	22 511.11%	0 -100%	6.9 91.67%
		3	14.9	0 -100%	0 -100%	0.6 -95.97%					
	[redacted]	1	9.7	0 -100%	0 -100%	0.4 -95.88%	2	6.2	9.4 51.61%	12.1 95.16%	3.4 -45.16%
		3	15.2	0 -100%	0 -100%	0 -100%					
Phase IIb	[redacted][*3]	1	1.31	0 -100%	0 -100%	NA	3	0.89	0.12 -86.52%	0.28 -68.54%	0 -100%
		2	1.95	0 -100%	0 -100%	NA					
	[redacted][*4]	2	2	0 -100%	0 -100%	0 -100%	1	3.81	0.88 -76.90%	0.1 -97.38%	1.45 -61.94%
		3	12.91	0 -100%	2.68 -79.24%	0.58 -95.51%					
	[redacted]	2	3.16	0 -100%	0 -100%	0 -100%	1	4.65	22.21 337.63%	3.59 -22.80%	18.65 301.08%
		3	9.21	0 -100%	4 -56.57%	4 -56.57%					
	[redacted]	1	7.02	0 -100%	0 -100%	0 -100%	2	16.06	17.2 7.10%	NA	20.37 26.84%
		3	3.27	0 -100%	0 -100%	0 -100%					
	[redacted][*5]	1	2.2	0.96 -56.36%	0.55 -75.00%	0 -100%	2	1.36	NA	NA	NA
		3	3.94	1.14 -71.07%	0 -100%	0 -100%					

NA: Not available
*1 Wound area (cm^2)
*2 Upper row, wound area (cm^2); lower row, percentage change from baseline
*3 Different wound of the same patient as [redacted]
*4 Different wound of the same patient as
*5 Different wound of the same patient as

In the ITT population, the median time to complete closure (90% closure) [95% CI] was 13.5 [8, 21] days for Vyjuvek-treated wounds and 22.5 [8, 64] days for placebo-treated wounds. The median duration of complete closure (90% closure) [95% CI] was 103 [94, 118] days for Vyjuvek-treated wounds and 16.5 [0, 66] days for placebo-treated wounds.

As for safety, Table 28 shows the incidence of adverse events by study part. Adverse events observed in ≥2 subjects overall were application site pruritus and bacterial test positive in 2 subjects each. Adverse events for which a causal relationship to the study product could not be ruled out were reported in 4 of 12 subjects (19 events), all occurring in the Phase IIb part. These included application site pruritus (2 subjects) and application site erythema, application site rash, fatigue, feeling cold, injection site erythema, injection site pain, injection site swelling, pyrexia, purulent discharge, wound complication, product taste abnormal, throat irritation, and wound treatment (1 subject each). Of 19 events in 4 subjects, 12 events in 3 subjects were related to intradermal administration of Vyjuvek. All events were mild in severity and resolved.

Table 28. Adverse events by study part (Study KB103-001, safety analysis set)

	Phase I (n = 2)	Phase IIa (n = 4)	Phase IIb[*1*2] (n = 5)	Phase IIc (n = 1)	All (n = 12)
All adverse events	0	3 (75.0)	5 (100)	0	9 (75.0)
Application site pruritus	0	0	2 (40.0)	0	2 (16.7)
Application site bruise	0	0	1 (20.0)	0	1 (8.3)
Application site erythema	0	0	1 (20.0)	0	1 (8.3)
Application site rash	0	0	1 (20.0)	0	1 (8.3)
Fatigue	0	0	1 (20.0)	0	1 (8.3)
Feeling cold	0	0	1 (20.0)	0	1 (8.3)
Injection site erythema	0	0	1 (20.0)	0	1 (8.3)
Injection site pain	0	0	1 (20.0)	0	1 (8.3)
Injection site swelling	0	0	1 (20.0)	0	1 (8.3)
Pyrexia	0	0	1 (20.0)	0	1 (8.3)
Bacterial vaginosis	0	0	1 (20.0)	0	1 (8.3)
Pharyngitis streptococcal	0	1 (25.0)	0	0	1 (8.3)
Purulent discharge	0	0	1 (20.0)	0	1 (8.3)
Wound infection pseudomonas	0	0	1 (20.0)	0	1 (8.3)
Erythema	0	0	1 (20.0)	0	1 (8.3)
Pruritus	0	0	1 (20.0)	0	1 (8.3)
Rash	0	0	1 (20.0)	0	1 (8.3)
Rash generalized	0	0	0	1 (100)	1 (8.3)
Diarrhoea	0	1 (25.0)	0	0	1 (8.3)
Nausea	0	1 (25.0)	0	0	1 (8.3)
Bacterial test positive	0	0	2 (40.0)	0	2 (16.7)
Nasal congestion	0	0	1 (20.0)	0	1 (8.3)
Throat irritation	0	0	1 (20.0)	0	1 (8.3)
Gastrostomy	0	0	0	1 (100)	1 (8.3)
Wound treatment	0	0	1 (20.0)	0	1 (8.3)
Drug hypersensitivity	0	0	1 (20.0)	0	1 (8.3)
Wound complication	0	0	1 (20.0)	0	1 (8.3)
Drug taste abnormal	0	0	1 (20.0)	0	1 (8.3)

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Number of subjects (%)
*1 Three subjects from the Part IIa part also participated in the Part IIb part.
*2 Injection site pain (3 events), application site pruritus and injection site erythema (2 events each), application site erythema, fatigue, feeling cold, injection site swelling, and pyrexia (1 event each) were considered adverse events related to intradermal administration.

No deaths, serious adverse events, or adverse events leading to treatment discontinuation occurred.

7.1.1.2 Foreign phase III clinical study (CTD 5.3.5.1-2, Study B-VEC-03 [August 2020 to October 2021])

A randomized, double-blind, intra-patient placebo-controlled study was conducted at 3 study sites in the US to evaluate the efficacy and safety of Vyjuvek in non-Japanese patients with DEB aged ≥6 months (target sample size, 24 subjects[14)]).

Table 29 shows the main inclusion and exclusion criteria. In consideration of the rarity of the target disease and the possibility that wounds treated with Vyjuvek might re-open after closure and that new wounds might develop, patients who had participated in Study KB103-001 were allowed to enroll.

[14)] The sample size of 24 patients (24 pairs of primary wounds) was specified to provide 90% power at a two-sided significance level of 5%, assuming a complete healing rate at 6 months of 75% for Vyjuvek-treated wounds and 25% for placebo-treated wounds.

Table 29. Main inclusion and exclusion criteria

Inclusion criteria	Patients meeting all of the following criteria: • Patients presenting with clinical symptoms of DEB. • Patients aged ≥6 months at the time of informed consent. • Patients diagnosed with DDEB or RDEB by genetic testing including *COL7A1*. • Patients with 2 wounds meeting all of the following: ➢ Location: The 2 wounds were similar in size, anatomical location, and appearance. ➢ Appearance: Sufficient granulation tissue, good vascularization, and absence of infection.
Exclusion criteria	• Patients in an unstable condition who could not travel to the study site. • Patients judged by the investigator to have diseases or conditions that could interfere with the evaluation of the safety or efficacy of the study product, or with compliance with visits/treatment. • Patients with a current or past history of squamous cell carcinoma at the intended application site. • Patients receiving chemotherapy or immunotherapy at baseline. • Patients who had undergone skin grafting within the past 3 months. • Patients who had received investigational products other than Vyjuvek within the past 3 months. • Patients who were positive on pregnancy testing or breastfeeding.

The study consisted of a screening period (60 days prior to the first dose of the study product [baseline]) and a treatment period (26 weeks after the first dose of the study product).

Two similar wounds in each patient (primary wounds) were selected by the investigator according to size, anatomical location, and appearance, and were randomized to Vyjuvek or placebo. Under double-blind conditions, Vyjuvek at the assigned dose was applied once weekly to one wound, and placebo was applied once weekly to the paired wound until closure was achieved. When one of the primary wounds was judged by the investigator to be completely closed,[15)] application to that wound was discontinued. If subsequently the wound was judged to have re-opened, application was resumed.

In addition to the primary wound pair, up to 4 secondary wounds were selected by the investigator and treated once weekly in an open-label manner with the assigned dose of Vyjuvek. If an adjacent wound (approximately 2-3 cm from an initially selected wound) opened during treatment of the primary or secondary wounds, application of the study product to the adjacent wound was permitted, even if the initially selected wound had already been judged closed.

The dose of Vyjuvek per wound for primary and secondary wounds was determined according to baseline wound surface area, as shown in Table 30. As shown in Table 31, a maximum weekly dose was specified according to age. For secondary wounds, the dose applied was the maximum weekly dose minus the dose already applied to the pair of primary wounds, ensuring that the total weekly dose for the primary and secondary wounds did not exceed the maximum weekly dose. The dose of Vyjuvek per wound was fixed at baseline and was not to be changed during the study. After application of Vyjuvek, the wound was to be covered with a dressing for approximately 24 hours.

Table 30. Dose of Vyjuvek per wound in Study B-VEC-03

Wound area of patient (cm^2)	Dose (PFU)
<20	4×10^8
≥20 and <40	8×10^8
≥40 and ≤60	1.2×10^9

15) In Studies B-VEC-03, B-VEC-EX-02, and B-VEC-EX-02-JP, "complete closure" was defined as a 100% reduction from baseline in wound surface area with re-epithelialization of skin without drainage. "Complete healing" was defined as complete closure sustained at 2 consecutive visits.

Table 31. Maximum weekly dose in Study B-VEC-03

Age	Maximum weekly dose (PFU)
≥6 months and <3 years	1.6×10^9
≥3 and <6 years	2.4×10^9
≥6 years	3.2×10^9

All 31 enrolled patients (30 patients with RDEB, 1 patient with DDEB) with primary wounds were randomized and received the study product. Excluding 3 patients who discontinued for personal reasons, 28 patients completed the study. All 31 patients with randomized primary wounds were included in the ITT population, which was used for both efficacy and safety analyses.

Table 32 shows the primary efficacy endpoint, the proportion of primary wounds completely healed at 6 months after the first dose of the study product (defined as complete closure sustained at 2 consecutive visits at Weeks 22 and 24 or Weeks 24 and 26). A statistically significant difference was observed between Vyjuvek-treated and placebo-treated wounds.

Table 32. Proportion of primary wounds completely healed at 6 months after the first dose (Study B-VEC-03, ITT population)

Vyjuvek-treated wound (n = 31)	Placebo-treated wound (n = 31)	Between-treatment difference [95% CI] Two-sided *P*-value*1
67.4%	21.6%	45.8% [23.6, 68.0] 0.0019

Missing data were imputed by a multiple imputation method.
*1 Two-sided significance level of 5%, McNemar test.

Table 33 shows the main secondary endpoint, the proportion of primary wounds completely healed at 3 months after the first dose (defined as complete closure sustained at 2 consecutive visits at Weeks 8 and 10 or Weeks 10 and 12).

Table 33. Proportion of primary wounds completely healed at 3 months after the first dose (Study B-VEC-03, ITT population)

Vyjuvek-treated wound (n = 31)	Placebo-treated wound (n = 31)
70.6%	19.7%

Missing data were imputed by a multiple imputation method.

For safety, adverse events were reported in 18 of 31 subjects (58.1%). Adverse events occurring in ≥2 patients overall were pruritus, chills, and squamous cell carcinoma (3 patients each); and erythema, rash, cough, and rhinorrhea (2 patients each). An adverse event for which a causal relationship to the study product could not be ruled out was observed in 1 subject (erythema). However, this was reported as intermittent erythema under a wound dressing on intact, untreated skin, was not specific to the target site, and was considered a general finding.

No deaths occurred. Serious adverse events were reported in 3 subjects (cellulitis, anaemia/diarrhoea, and positive blood culture). A causal relationship to the study product was ruled out for these events, and their outcomes were all resolved. No adverse events leading to treatment discontinuation were reported.

7.1.1.3 Foreign long-term extension study (CTD 5.3.5.2-1, Study B-VEC-EX-02 [May 2021 to July 2023])

An open-label, uncontrolled study was conducted at 5 study sites in the US to evaluate the long-term safety of Vyjuvek in patients with DEB who had completed Study B-VEC-03 (hereinafter referred to as "continuing application patients") or in patients with DEB naïve to Vyjuvek (hereinafter referred to as "new patients") (target sample size, 47 subjects [24 continuing application patients, 23 new patients]).

The main inclusion criteria were patients with clinical symptoms of DEB who were diagnosed with DDEB or RDEB by genetic testing including *COL7A1*, with no age restrictions. Patients undergoing skin graft or mesh skin graft, and patients who had received any study product other than Vyjuvek within the past 3 months, were excluded.

The study consisted of a screening period and a treatment period (112 weeks after the first dose of Vyjuvek).

For each patient, multiple wounds were selected for Vyjuvek treatment by the investigator. Vyjuvek was applied once weekly at the prescribed dose until wound closure. When a wound was judged to be completely closed by the investigator or healthcare professional, application to that wound was discontinued, and when the investigator judged the wound to have re-opened, Vyjuvek treatment was resumed at that time. When a wound was judged to have been completely closed, a new wound was selected, and Vyjuvek was applied until the newly selected wound was closed. Furthermore, because it was confirmed during Study B-VEC-03 that new wounds could develop adjacent to the sites treated with the study product, Vyjuvek was also applied to adjacent areas to stabilize the treated sites. Application of Vyjuvek at medical institutions was performed by the investigator or designated healthcare professionals, and after the initial visit, home administration by healthcare professionals was also permitted.

If patients could not visit every week consecutively, adjustment of visit days was allowed.

Table 34 shows the dose of Vyjuvek. The dose was determined according to wound area at each administration. As shown in Table 35, the maximum weekly dose was determined based on age, and the total dose applied to all wounds in a week was not to exceed the maximum weekly dose.

Table 34. Dose of Vyjuvek per wound in Study B-VEC-EX-02

Wound area of patient (cm^2)	Dose (PFU)	Dose volume (mL)
<20	4×10^8	0.2
≥20 and <40	8×10^8	0.4
≥40 and ≤60	1.2×10^9	0.6

Table 35. Maximum weekly dose in Study B-VEC-EX-02

Age	Maximum weekly dose (PFU)
<3 years	2.0×10^9
≥3 years	4.0×10^9

In this study, additional specifications for dropwise application were introduced. Vyjuvek was to be applied using a syringe to deliver small droplets evenly over the wound surface in a 1 cm × 1 cm grid

pattern. After application of Vyjuvek, a hydrophobic dressing cut to be approximately 1 to 2 cm larger than the wound was applied. Subsequently, healthcare professionals or caregivers covered the wound with a standard-of-care dressing of the patient's choice over the hydrophobic dressing and left it in place for approximately 24 hours.

Among 47 patients enrolled (24 continuing application patients [23 patients with RDEB, 1 patient with DDEB,] and 23 new patients [22 patients with RDEB, 1 patient with DDEB]), 7 continuing application patients completed the study, while the remaining 40 patients discontinued. Reasons for discontinuation were study termination by the sponsor in 34 patients[16)] (15 continuing application patients, 19 new patients), withdrawal by patient decision in 5 patients (1 continuing application patient, 4 new patients), and loss to follow-up in 1 patient. All enrolled 47 patients were included in the safety analysis set.

With regard to efficacy, among 24 continuing application patients, 5 patients were excluded because they could not be evaluated due to insufficient visits for wound assessment. The remaining 19 patients received Vyjuvek in Study B-VEC-03. Table 36 shows the changes over time in rate of complete closure of primary wounds treated with Vyjuvek. The rates were maintained through 12 months after initiation of Vyjuvek in Study B-VEC-EX-02, comparable to the complete closure rates observed at 3 months (68.4%) and 6 months (73.7%) after the first dose in Study B-VEC-03.

Table 36. Changes over time in complete closure rate of primary wounds in continuing application patients

	Study B-VEC-03		Study B-VEC-EX-02				
Evaluation period*1	3 months	6 months	1 week	3 months	6 months	9 months	12 months
Complete closure rate (number of completely closed wounds/number of wounds evaluated)	68.4% (13/19)	73.7% (14/19)	89.5% (17/19)	84.2% (16/19)	61.1% (11/18)	82.4% (14/17)	62.5% (10/16)

*1 Time from first dose in each study

Table 37 shows changes over time in wound closure status in primary wounds treated with Vyjuvek in individual continuing application patients (19 patients).

16) Study B-VEC-EX-02 was terminated following approval of Vyjuvek in the US, and patients transitioned to receive the marketed product.

Table 37. Changes over time in wound closure status of primary wounds in individual continuing application patients

Patient ID	Wound area[*1] (cm^2)	Study B-VEC-03		Study B-VEC-EX-02				
		3 months[*2]	6 months[*2]	1 week[*3]	3 months[*3]	6 months[*3]	9 months[*3]	12 months[*3]
[redacted]	57.28	OPEN	OPEN	OPEN	OPEN	OPEN	OPEN	OPEN
[redacted]	10.6	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure
[redacted]	5.14	OPEN	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure
[redacted]	7.77	Complete closure	OPEN	Complete closure	Complete closure	NA	NA	NA
[redacted]	9.9	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure
[redacted]	5.64	Complete closure	Complete closure	Complete closure	OPEN	Complete closure	OPEN	OPEN
[redacted]	2.32	Complete closure	Complete closure	Complete closure	Complete closure	OPEN	Complete closure	OPEN
[redacted]	6.22	Complete closure	Complete closure	Complete closure	Complete closure	OPEN	OPEN	Complete closure
[redacted]	4.95	Complete closure	OPEN	Complete closure	Complete closure	Complete closure	Complete closure	OPEN
[redacted]	5.21	OPEN	Complete closure	Complete closure	Complete closure	OPEN	Complete closure	NA
[redacted]	27.33	OPEN	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure
[redacted]	13.02	Complete closure	Complete closure	Complete closure	OPEN	Complete closure	Complete closure	OPEN
[redacted]	16.57	OPEN	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure
[redacted]	19.31	Complete closure	OPEN	Complete closure	Complete closure	OPEN	Complete closure	Complete closure
[redacted]	4.61	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	NA	NA
[redacted]	21.74	OPEN	OPEN	OPEN	Complete closure	Complete closure	Complete closure	OPEN
[redacted]	13.24	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure
[redacted]	23.71	Complete closure	Complete closure	Complete closure	Complete closure	OPEN	Complete closure	Complete closure
[redacted]	20.71	Complete closure	Complete closure	Complete closure	Complete closure	OPEN	Complete closure	Complete closure

NA, Not available
*1 Wound area at baseline in Study B-VEC-03
*2 Time from first dose in Study B-VEC-03
*3 Time from first dose in Study B-VEC-EX-02

Regarding safety, adverse events were observed in 74.5% (35 of 47) of patients overall, 70.8% (17 of 24) of continuing application patients, and 78.3% (18 of 23) of new patients. Table 38 shows adverse events reported in ≥2 patients overall. An adverse event for which a causal relationship to Vyjuvek could not be ruled out was reported in 1 new patient (wound haemorrhage). The event was mild in severity, and the outcome of the event was reported as resolved.

Table 38. Adverse events reported in ≥2 patients overall (Study B-VEC-EX-02, safety analysis set)

	Continuing application patients (n = 24)	New patients (n = 23)	Total (n = 47)
All adverse events	17 (70.8)	18 (78.3)	35 (74.5)
COVID-19	9 (37.5)	6 (26.1)	15 (31.9)
Skin infection	4 (16.7)	2 (8.7)	6 (12.8)
Cellulitis	3 (12.5)	1 (4.3)	4 (8.5)
Rhinitis	3 (12.5)	1 (4.3)	4 (8.5)
Wound infection	2 (8.3)	1 (4.3)	3 (6.4)
Conjunctivitis	0	2 (8.7)	2 (4.3)
Ear infection	2 (8.3)	0	2 (4.3)
Gastroenteritis	0	2 (8.7)	2 (4.3)
Staphylococcal infection	1 (4.2)	1 (4.3)	2 (4.3)
Upper respiratory tract infection	1 (4.2)	1 (4.3)	2 (4.3)
Cough	6 (25.0)	3 (13.0)	9 (19.1)
Rhinorrhoea	2 (8.3)	2 (8.7)	4 (8.5)
Pyrexia	5 (20.8)	2 (8.7)	7 (14.9)
Pain	2 (8.3)	0	2 (4.3)
Vomiting	2 (8.3)	3 (13.0)	5 (10.6)
Diarrhoea	2 (8.3)	1 (4.3)	3 (6.4)
Pruritus	1 (4.2)	1 (4.3)	2 (4.3)
Rash	2 (8.3)	0	2 (4.3)
Dehydration	2 (8.3)	1 (4.3)	3 (6.4)
Anaemia	1 (4.2)	1 (4.3)	2 (4.3)
Eye pain	2 (8.3)	0	2 (4.3)

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Number of subjects (%)

No deaths occurred. Serious adverse events were observed in 14 patients overall, 9 continuing application patients (cellulitis in 2 patients, skin infection in 2 patients, dehydration, pain/gastrostomy, COVID-19, bacteraemia/pancreatitis, anaemia), and 5 new patients (stridor, haematemesis/bronchial hyperreactivity, dehydration, skin infection, oesophageal stenosis). A causal relationship to Vyjuvek was ruled out for all events, and the outcomes of the events were reported as resolved. No adverse events led to discontinuation of treatment.

7.1.2 Japanese clinical study

7.1.2.1 Japanese phase III study (CTD 5.3.5.2-2, Study B-VEC-EX-02-JP [[redacted] to [redacted])

An open-label, uncontrolled study was conducted at 2 study sites in Japan to evaluate the efficacy and safety of Vyjuvek in Japanese patients with DEB (target sample size, 3 patients).

Table 39 shows the main inclusion and exclusion criteria.

Table 39. Main inclusion and exclusion criteria

Inclusion criteria	Patients who met all of the following criteria: • Patients with clinical manifestations of DEB. • Patients diagnosed with DDEB or RDEB by genetic testing, including *COL7A1*. • Patients aged ≥2 months at the time of informed consent. • Patients with ≥1 primary wound meeting the following conditions: ➢ Wound intended for evaluation, ideally <20 cm^2 and not exceeding 40 cm^2. ➢ Wound appearing clean, with adequate granulation tissue, active neovascularization, and no evidence of infection.
Exclusion criteria	• Patients judged by the investigator to have diseases or conditions that could interfere with the evaluation of the safety and efficacy of the study product or with compliance with study visits/treatment. • Patients judged by the investigator to have active infections at the intended application site that may adversely affect Vyjuvek administration. • Patients receiving concurrent skin grafts or mesh skin grafts for the primary wound. However, for secondary wounds, patients were not excluded if, in the investigator's opinion, the graft was beginning to heal and resorb prior to initiation of Vyjuvek treatment. • Patients who had participated in a gene therapy clinical study within the past 3 months.

The study consisted of a screening period (60 days prior to the first dose of the study product [baseline]) and a treatment period (52 weeks from the first dose of Vyjuvek).

For each patient, the investigator selected the primary wound for efficacy evaluation (ideally <20 cm^2 and not exceeding 40 cm^2) and up to 6 secondary wounds,[17)] and Vyjuvek was applied once weekly at the protocol-specified dose until wound closure. The primary wound and/or its adjacent wound[18)] were to be treated with Vyjuvek prior to the secondary wounds (including its adjacent wound). When a wound was judged by the investigator to be completely closed, treatment for that wound was discontinued. If the investigator subsequently judged that the wound had re-opened and was amenable to treatment, resumption of treatment was permitted.

Up to Week 26 from the first dose, patients visited the study site once weekly for Vyjuvek application. Thereafter, visits for application were scheduled at Weeks 36, 38, 40, 48, 50, and 52; for other visits, adjustments to visit dates were permitted.

Table 34 shows the dose of Vyjuvek, and the dose was adjusted at each administration according to the wound area.

Vyjuvek was applied in small droplets using a syringe, distributed evenly over the entire wound surface in a 1 cm × 1 cm grid pattern. After application, a hydrophobic wound dressing cut to extend 1 to 2 cm beyond the wound margin was applied. Thereafter, the wound was covered for approximately 24 hours with a standard-of-care dressing chosen by the patient, applied over the hydrophobic dressing by a healthcare professional or caregiver. As shown in Table 40, the maximum weekly dose was specified according to patient age. The amount of Vyjuvek applied to secondary wounds was calculated by subtracting the dose used for the primary wound from the maximum weekly dose, ensuring that the total dose applied to both primary and secondary wounds did not exceed the maximum weekly dose.

[17)] The primary wound was predetermined and remained unchanged throughout this study; however, for secondary wounds, the investigator could select up to 6 wounds to be treated each week.

[18)] Because DEB wounds change readily, treatment of adjacent wounds (approximately 1-3 inches [2.5-7.6 cm] around the primary wound) was permitted to prevent detachment at the boundary, even if the primary wound was completely closed.

Accordingly, depending on the size of the primary wound and selected secondary wounds, the dose available for multiple secondary wounds was sometimes insufficient.

Table 40. Maximum weekly dose in Study B-VEC-EX-02-JP

Age	Maximum weekly dose (PFU)
≥2 months and <3 years	2.0×10^9
≥3 years	4.0×10^9

All of 5 enrolled patients received Vyjuvek and were included in the safety analysis set. Four patients were included in the per protocol set (PPS) and the efficacy analysis set and the remaining 1 subject who discontinued at Week 8 after the first dose due to consent withdrawal was excluded.

Table 41 shows baseline patient characteristics and target wound characteristics.

Table 41. Baseline patient characteristics and target wound characteristics (Study B-VEC-EX-02-JP)

Patient ID	Age	Sex	Diagnosis	Size of primary wound (cm^2)	Number of secondary wounds	Size of secondary wound (cm^2)
[redacted]	17	Male	RDEB	8	6	2-26
[redacted]	12	Female	RDEB	1	6	1
[redacted]	68	Female	RDEB	20	6	6-27
[redacted]	22	Female	RDEB	NA	5	NA
[redacted]	59	Female	RDEB	2	5	1-21

NA, Not available

The primary efficacy endpoint, the complete closure rate of primary wounds at 6 months after the first dose of Vyjuvek (defined as the proportion of wounds judged completely closed at Weeks 22, 24, or 26), was 100%.

The secondary endpoint, the complete closure rate of primary wounds at 3 months after the first dose of Vyjuvek (defined as the proportion of wounds judged completely closed at Weeks 8, 10, or 12), was also 100%.

Table 42 shows the time course of primary wound closure in individual patients.

Table 42. Time course of primary wound closure in individual patients (Study B-VEC-EX-02-JP, PPS)

Patient ID	Baseline	Week 8	Week 10	Week 12	Week 22	Week 24	Week 26	Week 36	Week 38	Week 40	Week 48	Week 50	Week 52
[redacted]	OPEN	Complete closure	Complete closure	OPEN	Complete closure	Complete closure	Complete closure	OPEN	OPEN	OPEN	OPEN	OPEN	OPEN
[redacted]	OPEN	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure
[redacted]	OPEN	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure
[redacted]	OPEN	OPEN	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure	Complete closure

With respect to safety, adverse events were observed in 80.0% (4 of 5) of patients. Table 43 shows adverse events observed in each patient, including nasopharyngitis (2 subjects), skin infection, diarrhoea, upper respiratory tract infection, contusion, dermatitis contact, and pruritus (1 subject each). A causal relationship to Vyjuvek was ruled out for all events. No deaths, serious adverse events, or adverse events leading to treatment discontinuation were reported.

Table 43. Adverse events observed in individual patients (Study B-VEC-EX-02-JP, safety analysis set)

Patient ID	Adverse events
[redacted]	Skin infection, nasopharyngitis, diarrhoea
[redacted]	Dermatitis contact, upper respiratory tract infection, nasopharyngitis (3 events)
[redacted]	Pruritus
[redacted]	Contusion

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7.R Outline of the review conducted by PMDA

7.R.1 Use of foreign clinical study results and review policy

For the present application, the applicant submitted the results of the following studies designed to evaluate the efficacy and safety of Vyjuvek in non-Japanese patients with DEB harboring *COL7A1* mutations: A foreign phase I/II study (Study KB103-001), a global phase III study (Study B-VEC-03), and a long-term extension study (Study B-VEC-EX-02). The only clinical study results obtained in Japanese patients with DEB were from a Japanese phase III study (Study B-VEC-EX-02-JP), which included 5 subjects.

The applicant's explanation about the appropriateness of evaluating the efficacy and safety of Vyjuvek in Japanese patients primarily on the basis of foreign clinical study results:
Because the number of Japanese patients with DEB eligible for treatment with Vyjuvek is extremely small, Study B-VEC-EX-02-JP was conducted as a small, open-label, uncontrolled study, taking feasibility into consideration. The efficacy and safety of Vyjuvek in Japanese patients were to be evaluated in conjunction with the results of the foreign Studies KB103-001, B-VEC-03, and B-VEC-EX-02, which were conducted to investigate the efficacy and safety of Vyjuvek.

For the following reasons, it was considered possible to evaluate the efficacy and safety of Vyjuvek in Japanese patients by utilizing foreign clinical study results:

- DEB is a hereditary disorder caused by mutations in the *COL7A1* gene, and there are no major differences between Japan and foreign countries in diagnostic or management practices (Research group on rare and intractable skin diseases. Guidelines for the diagnosis of epidermolysis bullosa [in Japanese]; Best Practice Guidelines: Skin and wound care in Epidermolysis Bullosa, 2017. Wounds International). Although a human (autologous) epidermal cell sheet (brand name, JACE) is approved only in Japan as a product indicated for EB, its use is limited to refractory cases.
- Vyjuvek exerts its effect by supplementing COL7 protein, regardless of the type of the *COL7A1* gene mutation causing the disease. Therefore the efficacy of Vyjuvek is not expected to differ between Japanese and non-Japanese patients.
- In light of the results of non-clinical studies and foreign clinical studies, systemic distribution and excretion of Vyjuvek through systemic exposure are not anticipated. The biodistribution of Vyjuvek is confined to the skin at the administration site, which is considered to be the case also in Japanese patients.

PMDA accepted the applicant's explanation.

7.R.2 Efficacy

PMDA's view:

The following reviews demonstrated a certain level of efficacy of Vyjuvek in patients with DEB.

7.R.2.1 Appropriateness of the study design

The applicant's explanation about the appropriateness of the study design of Study B-VEC-03:

The appropriateness of the primary endpoint

The primary endpoint of Study B-VEC-03 was the proportion of complete closure of primary wounds at 6 months after the first dose of the study product (defined as the proportion of target wounds judged to be completely closed at 2 consecutive visits). For patients with DEB, whose wounds are prone to re-opening, clinical significance lies in achieving durable wound closure that does not re-open easily, rather than transient closure. To distinguish transient wound closure from durable wound closure that resists re-opening, evaluation at 2 time points was considered necessary.

The appropriateness of conducting the study as an intra-patient randomized controlled study and selecting target ulcers

At the time of planning Study B-VEC-03, the draft FDA guidance "Human Gene Therapy for Rare Diseases," the draft FDA guidance "Epidermolysis Bullosa: Developing Drugs for Treatment of Cutaneous Manifestations. Guidance for Industry," and the draft EMA guideline "Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials" stated that, in clinical studies for rare diseases such as EB, an intra-patient randomized controlled design could be considered, as it minimizes sample size and avoids inter-patient variability. Accordingly, the study was conducted as an intra-patient randomized controlled study.

According to the judgment of the investigator, 2 wounds of similar size, anatomical location, and appearance were selected in each patient as the target wounds (a pair of primary wounds), and these wound pairs were randomized.

At the beginning of Study B-VEC-03, up to 3 pairs of primary wounds could be selected. However, in protocol version 1.3 (revised on [redacted], 20[redacted]), this was changed to allow the selection of only 1 pair of primary wounds. For 10 subjects enrolled prior to this revision, ≥2 pairs of primary wounds had been selected; for these subjects, while maintaining blinding, 1 pair of primary wounds was selected by the investigator for analysis.[19)]

The appropriateness of enrolling patients who had participated in Study KB103-001

Considering the half-life of COL7 protein expression induced by Vyjuvek and the turnover of the skin, a wound closed after treatment was expected to remain closed for at least 3 months; however, re-opening of the wound and the formation of new wounds thereafter remained possible. Taking into account both this possibility and the rarity of the disease, patients who had participated in Study KB103-001 were allowed to be enrolled in Study B-VEC-03. Among the 31 subjects enrolled in Study B-VEC-03, 5 subjects (patient IDs, [redacted], [redacted], [redacted], [redacted], and

19) Except for 3 subjects, the first numbered wound pair was selected. In 3 subjects, the second numbered wound pair was selected because size and anatomical location were more similar.

[redacted]) had previously participated in Study KB103-001. For these 5 subjects, the washout period between studies was 402 to 873 days, and enrollment of the patients previously included in Study KB103-001 was considered not to affect the efficacy evaluation in Study B-VEC-03.

PMDA's view:

The appropriateness of the primary endpoint

Regarding the choice of the primary endpoint of Study B-VEC-03 as the proportion of complete closure of primary wounds at 6 months after the first dose of the study product, the applicant's explanation is understandable from a clinical relevance perspective. Since wound status in patients with DEB is highly variable, and differences in location and size of primary wound pairs may affect wound healing after administration of Vyjuvek, PMDA determined to examine the influence of wound location and size on wound healing as well as the durability of wound healing for evaluation of the therapeutic effect in DEB.

The appropriateness of conducting the study as an intra-patient randomized controlled study and selecting target ulcers

The applicant's explanation is understandable with regard to the conduct of Study B-VEC-03 as an intra-patient randomized controlled study and the design in which 2 wounds of similar size, anatomical location, and appearance were selected in each patient as target wounds (a pair of primary wounds) and randomized.

Concerning the protocol amendment during the study, which required, in subjects enrolled before the amendment, that only 1 pair of primary wounds be selected for evaluation from multiple pairs already chosen, PMDA considered this acceptable since the study continued under blinded conditions. However, because such selection could have influenced the efficacy evaluation, PMDA decided to compare efficacy results between patients enrolled before and after the protocol amendment in order to confirm whether there was an impact on efficacy evaluation.

The appropriateness of enrolling patients who had participated in Study KB103-001

Allowing enrollment of patients who had previously participated in Study KB103-001 in Study B-VEC-03 was considered inappropriate for the evaluation of Vyjuvek's efficacy, as this involved assessing patients whose response to Vyjuvek was already known and could potentially bias the efficacy evaluation. Therefore, PMDA decided to perform an analysis comparing efficacy between the overall population of Study B-VEC-03 and a subpopulation excluding the 5 patients who had participated in Study KB103-001, to confirm the impact on the efficacy evaluation.

7.R.2.2 Results of efficacy evaluation

The applicant's explanation about the efficacy of Vyjuvek in patients with DEB:

In Study B-VEC-03, the primary endpoint was the proportion of primary wounds completely healed at 6 months after the first dose of the study product (defined as the proportion of wounds judged to be completely closed at 2 consecutive visits at Weeks 22 and 24 or Weeks 24 and 26). As shown in Table 32, this proportion was 67.4% for Vyjuvek-treated wounds and 21.6% for placebo-treated wounds, with a between-group difference [95% CI] of 45.8% [23.6%, 68.0%]. The proportion was significantly higher for Vyjuvek-treated wounds than placebo-treated wounds (McNemar test, $P = 0.0019$).

For the secondary endpoint, the proportion of primary wounds completely healed at 3 months after the first dose of the study product (defined as the proportion of wounds judged to be completely closed at 2 consecutive visits at Weeks 8 and 10 or Weeks 10 and 12) was 70.6% for Vyjuvek-treated wounds and 19.7% for placebo-treated wounds, as shown in Table 33, demonstrating a trend consistent with that at 6 months.

With respect to the effect of different location and size of primary wound pairs on efficacy, Table 44 shows the proportion of primary wounds completely healed by location and size at baseline in Study B-VEC-03. No trends were observed that would raise concerns regarding the efficacy of Vyjuvek. Although the interpretation of the results requires caution due to the small sample size, there was a tendency toward a higher proportion of complete healing in Vyjuvek-treated wounds located on the upper extremities and in wounds with an area ≥20 cm^2 and <40 cm^2. A tendency toward a higher proportion of complete healing was observed in Vyjuvek-treated wounds than in placebo-treated wounds, particularly in larger wound size.

Table 44. Proportion of primary wounds completely healed by location and size at baseline (Study B-VEC-03, ITT population[*1])

		Vyjuvek-treated wound	Placebo-treated wound
Location	Head and neck	0% (0/1 subjects)	0% (0/1 subjects)
	Trunk	66.7% (6/9 subjects)	22.2% (2/9 subjects)
	Lower extremities	69.2% (9/13 subjects)	15.4% (2/13 subjects)
	Upper extremities	83.3% (5/6 subjects)	33.3% (2/6 subjects)
Wound area[*2]	<20 cm^2	68.2% (15/22 subjects)	27.3% (6/22 subjects)
	≥20 and <40 cm^2	80.0% (4/5 subjects)	0% (0/5 subjects)
	≥40 and <60 cm^2	50.0% (1/2 subjects)	0% (0/2 subjects)
	≥60 cm^2	-	-

-, No applicable subjects
*1 Of the 31 subjects in the ITT population, 2 subjects had missing data for complete healing at 6 months.
*2 In cases where the wound size category differed between the Vyjuvek-treated and placebo-treated wounds, the category of the Vyjuvek-treated wound was applied.

Regarding the durability of wound healing, in Study B-VEC-03, the proportion of wounds completely healed both at 3 months and 6 months after the first dose of the study product within the same patients (defined as complete closure at 2 consecutive visits at Weeks 8 and 10 or Weeks 10 and 12, and at 2 consecutive visits at Weeks 22 and 24 or Weeks 24 and 26) was 49.7% in Vyjuvek-treated wounds (31 subjects) and 7.1% in placebo-treated wounds (31 subjects).

In Study B-VEC-EX-02, the change over time in the complete closure rate for primary wounds was assessed in subjects who had received Vyjuvek in Study B-VEC-03 and continued treatment (19 subjects out of 24, excluding the 5 subjects who lacked sufficient visits for wound evaluation). As shown in Table 36, a comparable rate of complete closure was maintained up to 12 months after administration of Vyjuvek.

Table 45 shows comparisons of efficacy between patients enrolled before and after the protocol amendment regarding the number of primary wound pairs selected in Study B-VEC-03. Table 46 shows comparisons of efficacy between the overall ITT population and the population excluding the 5 subjects

who had participated in Study KB103-001. These results indicate that the protocol amendment did not lead to overestimation of the efficacy of Vyjuvek.

Table 45. Proportion of primary wounds completely healed at 3 and 6 months after the first dose of the study product:
Comparison between patients enrolled before and after the protocol amendment (Study B-VEC-03, ITT population)

Evaluation period	Subjects enrolled before protocol amendment (n = 10)		Subjects enrolled after protocol amendment (n = 21)	
	Vyjuvek-treated wound	Placebo-treated wound	Vyjuvek-treated wound	Placebo-treated wound
3 months	80.0%	20.0%	66.2%	20.2%
6 months	88.0%	12.0%	57.1%	25.2%

Missing data were imputed using a multiple imputation.

Table 46. Proportion of primary wounds completely healed at 3 and 6 months after the first dose of the study product:
Comparison between the population excluding the 5 subjects who participated in Study KB103-001 and the overall population (Study B-VEC-03, ITT population)

Evaluation period	Population excluding the 5 subjects who participated in Study KB103-001 (n = 26)		Overall population (Study B-VEC-03, ITT population) (n = 31)	
	Vyjuvek-treated wound	Placebo-treated wound	Vyjuvek-treated wound	Placebo-treated wound
3 months	64.6%	19.6%	70.6%	19.7%
6 months	60.4%	19.2%	67.4%	21.6%

Missing data were imputed using a multiple imputation.

The applicant' explanation about efficacy in Japanese patients:
Based on the results of Study B-VEC-03 in non-Japanese patients and Study B-VEC-EX-02-JP in Japanese patients, Table 47 shows the wound closure status of primary wounds at Weeks 8, 10, 12, 22, 24, and 26 after the first dose of Vyjuvek. Although the small number of Japanese patients limits the interpretation of results, no markedly different trends between Japanese and non-Japanese patients were observed.

Table 47. Comparison of complete closure rates of primary wounds between Study B-VEC-03 (ITT population) and Study B-VEC-EX-02-JP (PPS)

Evaluation time point	Study B-VEC-03 (non-Japanese patients: N = 31)	Study B-VEC-EX-02-JP (Japanese patients N = 4)
Week 8	51.6% (16)	75.0% (3)
Week 10	71.0% (22)	100% (4)
Week 12	74.2% (23)	75.0% (3)
Week 22	67.7% (21)	100% (4)
Week 24	64.5% (20)	100% (4)
Week 26	64.5% (20)	100% (4)

Proportion of wounds with complete closure (number of subjects achieving complete closure)

Although the primary endpoint of Study B-VEC-EX-02-JP was the complete closure rate of primary wounds and did not include complete healing as an endpoint, the proportion of primary wounds with complete healing at 6 months after the first dose of Vyjuvek (defined as the proportion of wounds with complete wound closure confirmed at 2 consecutive visits at Weeks 22 and 24 or Weeks 24 and 26), and at 3 months after the first dose of Vyjuvek (defined as the proportion of wounds with complete wound closure confirmed at 2 consecutive visits at Weeks 8 and 10 or Weeks 10 and 12), were both 100%, as

shown in Table 42. No markedly different trends between Japanese and non-Japanese patients were observed.

PMDA's view:
The above explanation by the applicant is understandable. Taking the following points into account, the results of Studies B-VEC-03, B-VEC-EX-02, and KB103-001 demonstrated certain efficacy of Vyjuvek in patients with DEB:

- In Study B-VEC-03, the proportion of primary wounds with complete healing at 6 months after the first dose of the study product, which was the primary endpoint, was statistically significantly higher in Vyjuvek-treated wounds than placebo-treated wounds.
- No results suggesting doubts regarding the efficacy of Vyjuvek with respect to wound location or size were obtained.
- The results of Studies B-VEC-03 and B-VEC-EX-02 suggested the durability of wound closure following treatment with Vyjuvek over an extended period.

In addition, as demonstrated by the results of Study B-VEC-EX-02-JP in Japanese patients, the efficacy of Vyjuvek can be expected also in Japanese patients. However, because the number of Japanese patients in clinical studies was extremely limited, information on the efficacy of Vyjuvek in Japanese patients should be collected in the post-marketing setting.

7.R.3 Safety

7.R.3.1 Safety profile of Vyjuvek and differences between Japanese and non-Japanese patients

The applicant's explanation about the safety profile of Vyjuvek drawing on safety information from patients treated with Vyjuvek in Studies KB103-001, B-VEC-03, B-VEC-EX-02, and B-VEC-EX-02-JP:
Tables 48 to 50 show summaries of safety in Studies KB103-001, B-VEC-03, and B-VEC-EX-02. No deaths or events leading to treatment discontinuation were observed.

Table 48. Summary of safety (Study KB103-001, safety analysis set)

	Phase I part (N = 2)	Phase IIa part (N = 4)	Phase IIb part[*1*2] (N = 5)	Phase IIc part (N = 1)	Total (N = 12)
All adverse events	0	3 (75.0)	5 (100)	1 (100)	9 (75.0)
Adverse events for which a causal relationship to Vyjuvek could not be ruled out	0	0	4 (80.0)	0	4 (33.3)
Serious adverse events	0	0	0	0	0
Severe adverse events	0	0	0	0	0
Adverse events leading to treatment discontinuation	0	0	0	0	0
Adverse events resulting in death	0	0	0	0	0

n (%)
*1 Three subjects in the Phase IIa part also participated in the Phase IIb part.
*2 Adverse events related to intradermal administration were observed in 3 subjects.

Table 49. Summary of safety (Study B-VEC-03, safety analysis set)

	All subjects (N = 31)
All adverse events	18 (58.1)
Adverse events for which a causal relationship to Vyjuvek could not be ruled out	1 (3.2)
Serious adverse events	3 (9.7)
Severe adverse events	2 (6.5)
Adverse events leading to treatment discontinuation	0
Adverse events resulting in death	0

n (%)

Table 50. Summary of safety (Study B-VEC-EX-02. Safety analysis set)

	Continuing application patients (N = 24)	New patients (N = 23)	All patients (N = 47)
All adverse events	17 (70.8)	18 (78.3)	35 (74.5)
Adverse events for which a causal relationship to Vyjuvek could not be ruled out	0	1 (4.3)	1 (2.1)
Serious adverse events	9 (37.5)	5 (21.7)	14 (29.8)
Severe adverse events	8 (33.3)	2 (8.7)	10 (21.3)
Adverse events leading to treatment discontinuation	0	0	0
Adverse events resulting in death	0	0	0

n (%)

With regard to long-term safety, the incidence of adverse events was similar between continuing application patients and new patients in Study B-VEC-EX-02. A causal relationship to Vyjuvek was ruled out for all serious adverse events and severe adverse events, and no concerns about the long-term safety of Vyjuvek were identified.

Regarding age-specific safety, Tables 51, 52, and 53 show summaries of safety in Studies KB103-001, B-VEC-03, and B-VEC-EX-02, respectively. Although the number of subjects in each age subgroup was small, limiting interpretation, no differences in the safety profile attributable to age were observed.

Table 51. Safety by age group (Study KB103-001, safety analysis set)

	<3 years (N = 0)	≥3 and <12 years (N = 1)	≥12 and <18 years (N = 4)	≥18 years (N = 7)
All adverse events	0	1 (100)	3 (75.0)	5 (71.4)
Adverse events for which a causal relationship to Vyjuvek could not be ruled out	0	0	2 (50.0)	5 (41.7)
Serious adverse events	0	0	0	0

n (%)

Table 52. Safety by age group (Study B-VEC-03, safety analysis set)

	<3 years (N = 3)	≥3 and <12 years (N = 7)	≥12 and <18 years (N = 9)	≥18 years (N = 12)
All adverse events	1 (33.3)	5 (71.4)	4 (44.4)	8 (66.7)
Adverse events for which a causal relationship to Vyjuvek could not be ruled out	1 (33.3)	1 (14.3)	1 (11.1)	0
Serious adverse events	0	1 (14.3)	0	2 (16.7)

n (%)

Table 53. Safety by age group (Study B-VEC-EX-02, safety analysis set)

	Continuing application patients (N = 24)				New patients (N = 23)			
	<3 years (N = 1)	≥3 and <12 years (N = 8)	≥12 and <18 years (N = 4)	≥18 years (N = 11)	<3 years (N = 4)	≥3 and <12 years (N = 5)	≥12 and <18 years (N = 4)	≥18 years (N = 10)
All adverse events	1 (100)	6 (75.0)	4 (100)	6 (54.5)	4 (100)	4 (80.0)	2 (50.0)	8 (80.0)
Adverse events for which a causal relationship to Vyjuvek could not be ruled out	0	0	0	1 (9.1)	0	2 (40.0)	0	3 (30.0)
Serious adverse events	0	4 (50.0)	2 (50.0)	3 (27.3)	3 (75.0)	0	0	2 (20.0)

n (%)

Regarding safety in Japanese patients, adverse events observed in Study B-VEC-EX-02-JP were judged to be causally unrelated to Vyjuvek. No severe adverse events, serious adverse events, or adverse events leading to treatment discontinuation were observed. As shown in Table 43, contusion occurred only in Study B-VEC-EX-02-JP; however, the outcome of the event was reported as resolved, and the severity was mild. Although the small number of Japanese patients limited the interpretation of the results, no new safety concerns specific to Japanese patients were identified.

PMDA's view:
In Studies KB103-001, B-VEC-03, B-VEC-EX-02, and B-VEC-EX-02-JP, no relevant adverse events for which a causal relationship to Vyjuvek could not be ruled out were observed, and Vyjuvek was considered tolerable. Although only 5 Japanese patients have been treated with Vyjuvek, no events specific to Japanese patients have been identified at present.

The following sections present the results of assessments of adverse events occurring at the administration site in clinical studies of Vyjuvek, and adverse events requiring attention with administration of Vyjuvek (immunogenicity and tumorigenicity).

7.R.3.2 Adverse events related to the administration site

The applicant's explanation about adverse events related to the administration site of Vyjuvek:
Table 54 shows the incidence of adverse events[20)] that occurred in the primary wound sites (Vyjuvek administration sites and placebo administration sites), secondary wound sites, and other skin areas in Study B-VEC-03. A causal relationship to Vyjuvek was ruled out for all adverse events that occurred at the Vyjuvek administration sites of the primary and secondary wounds.

[20)] From the site of occurrence recorded in the EDC, the site was identified. Events recorded as "Systemic" or "Not collected" were excluded.

Table 54. Adverse events related to the administration site (Study B-VEC-03, safety analysis set)

	Vyjuvek application site (N = 31)	Placebo application site (N = 31)	Secondary wounds (N = 31)	Other skin areas (N = 31)	All (N = 31)
All adverse events	0	1 (3.2)	1 (3.2)	4 (12.9)	6 (19.4)
Squamous cell carcinoma	0	0	0	3 (9.7)	3 (9.7)
Cellulitis	0	1 (3.2)	0	0	1 (3.2)
Hand dermatitis	0	0	0	1 (3.2)	1 (3.2)
Skin lesion	0	0	0	1 (3.2)	1 (3.2)
Skin plaque	0	0	0	1 (3.2)	1 (3.2)
Xanthoma	0	0	0	1 (3.2)	1 (3.2)
Wound drainage	0	0	1 (3.2)	0	1 (3.2)

n (%)
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Table 55 shows the incidence of adverse events[21)] occurring at the administration site, in other skin areas, in organs other than the skin, and at unknown locations in Study B-VEC-EX-02. The incidence of adverse events was similar between the administration site and other skin areas. Events corresponding to the system organ class (SOC) "Infections and infestations" were most frequent, and their incidence was similar between the administration site and other skin areas. A causal relationship to Vyjuvek was ruled out for all adverse events occurring at the administration site.

Table 55. Adverse events related to the administration site occurring in ≥5% of patients overall (Study B-VEC-EX-02, safety analysis set)

	Administration site (N = 47)	Other skin areas (N = 47)	Other than skin (N = 47)	Unknown locations (N = 47)	All sites (N = 47)
All adverse events	8 (17.0) 22	6 (12.8) 6	5 (10.6) 20	18 (38.3) 32	25 (53.2) 80
Skin infection	2 (4.3) 3	1 (2.1) 1	0 0	4 (8.5) 4	6 (12.8) 8
Cellulitis	0 0	1 (2.1) 1	0 0	3 (6.4) 4	4 (8.5) 5
Wound infection	2 (4.3) 3	0 0	0 0	1 (2.1) 1	3 (6.4) 4

Upper row, n (%); lower row, number of events
MedDRA ver.25.0

PMDA's view:
In the clinical studies of Vyjuvek, no relevant adverse events related to the administration site were identified. However, since the submitted data are limited, information on the incidence of adverse events related to the administration site should be collected continuously in the post-marketing setting.

7.R.3.3 Immunogenicity

The applicant's explanation about the risk of immunogenicity associated with administration of Vyjuvek:
In Studies B-VEC-03, B-VEC-EX-02, KB103-001, and B-VEC-EX-02-JP, no immunogenicity-related adverse events[22)] attributable to Vyjuvek were observed. In foreign post-marketing surveillance (data cutoff date, August 18, 2024), no clinically significant adverse events were reported.

[21)] From the site of occurrence recorded in the EDC, the site was specified. Events recorded as "Systemic" or "Not collected" were excluded.
[22)] Adverse events judged by the investigator to be attributable to immunogenicity of Vyjuvek.

PMDA's view:
In clinical studies of Vyjuvek and in foreign post-marketing use, no clinically significant immunogenicity-related adverse events have been observed. However, given the limited information available, information on the incidence of immunogenicity-related adverse events should be collected continuously in the post-marketing setting.

7.R.3.4 Tumorigenicity

The applicant's explanation about the risk of tumorigenicity associated with administration of Vyjuvek:
As tumorigenicity-related events, squamous cell carcinoma was observed in 3 patients in Study B-VEC-03. Among these patients, 2 patients had the event 65 days after the first dose of Vyjuvek, and the remaining 1 patient had event 43 days after the first dose. All events developed early after the first dose and at sites not directly exposed to Vyjuvek; therefore, a causal relationship to Vyjuvek was ruled out. In Study B-VEC-EX-02, squamous cell carcinoma was observed in 1 patient. This event also occurred at a site not directly exposed to Vyjuvek. Thus, a causal relationship to Vyjuvek was ruled out. No malignant tumors were observed in other clinical studies. Squamous cell carcinoma reported in the clinical studies is frequently diagnosed in patients with DEB, with nearly all patients developing at least 1 squamous cell carcinoma by mid-adulthood (*J Am Acad Dermatol*. 2009;60:203-11).

In foreign post-marketing surveillance (data cutoff date, August 18, 2024), no tumorigenicity-related events were reported.

Given the characteristics and mechanism of action of Vyjuvek, there is no evidence suggesting tumor formation, oncogenic transformation, or exacerbation of squamous cell carcinoma [see Section 5.3.2]. Therefore, the administration of Vyjuvek is unlikely to lead to the risk of tumor formation, oncogenic transformation, or exacerbation of squamous cell carcinoma occurring frequently in patients with DEB. Nevertheless, because the impact of Vyjuvek on malignant tumors has not yet been fully elucidated at present, the package insert will include a precaution advising that Vyjuvek should not be applied to wounds in which squamous cell carcinoma has been definitively diagnosed or is suspected.

PMDA's view:
In clinical studies of Vyjuvek, the incidence of malignant tumors was low, and no tumorigenicity-related adverse events for which a causal relationship to Vyjuvek could not be ruled out were observed. However, information from clinical studies evaluating the effect of Vyjuvek on malignant tumors is limited. The package insert should include a precaution advising against the application of Vyjuvek to wounds in which squamous cell carcinoma has been definitively diagnosed or is suspected, and information on the occurrence of malignant tumor-related adverse events should be collected continuously in the post-marketing setting.

7.R.4 Clinical positioning of Vyjuvek

The applicant's explanation about the clinical positioning of Vyjuvek in the treatment of DEB:
DEB is an inherited blistering disorder caused by mutations in the *COL7A1* gene encoding the COL7 protein (*J Med Genet.* 2007;44:181-92), and is characterized by clinical manifestations such as skin fragility, blistering, milia, and scar formation (*J Eur Acad Dermatol Venereol.* 2004;18:649-53).

Persistent blistering begins at birth and partly contributes to a high risk of death due to bacterial infections. In addition, patients are at high risk of developing highly aggressive and life-threatening squamous cell carcinoma. Current treatment for DEB remains supportive and is primarily limited to symptomatic management. In Japan, as a treatment option beyond supportive care, a human (autologous) epidermal cell sheets (brand name, JACE) have been approved. However, challenges such as the difficulty of obtaining donor tissue remain, and the development of new therapies is needed.

The results of Studies KB103-001, B-VEC-03, B-VEC-EX-02, and B-VEC-EX-02-JP demonstrated the efficacy and safety of Vyjuvek in patients with DEB caused by *COL7A1* gene mutations [see Sections 7.R.2 and 7.R.3]. Therefore, Vyjuvek is considered to provide a new therapeutic option for these patients.

PMDA accepted the above explanation of the applicant. The appropriateness of the "Indication or Performance" of Vyjuvek will be further evaluated in Section "7.R.5 Indication or performance."

7.R.5 Indication or performance

The proposed "Indication or performance" of Vyjuvek was "Treatment of patients with dystrophic epidermolysis bullosa with mutations in the *COL7A1* gene." The "Precautions Concerning Indication or Performance" were specified as follows:

- Vyjuvek should be used in patients with a *COL7A1* gene mutation confirmed by genetic testing.

With reference to Sections "7.R.2 Efficacy," "7.R.3 Safety," and "7.R.4 Clinical positioning of Vyjuvek," as well as the reviews described below, PMDA concluded that the Indication or Performance and the Precautions Concerning Indication or Performance should be revised as follows:

Indication or Performance (Strikethrough denotes deletions.)
~~Treatment of patients with d~~Dystrophic epidermolysis bullosa~~ with mutations in the *COL7A1* gene~~

Precautions Concerning Indication or Performance (Underline denotes additions and strikethrough denotes deletions.)

- Vyjuvek should be used <u>only</u> in patients~~ with a COL7A1 gene mutation confirmed by genetic testing~~ <u>who have been definitively diagnosed with dystrophic epidermolysis bullosa</u>.

7.R.5.1 Necessity of confirming *COL7A1* gene mutations before administration of Vyjuvek

In the Precautions Concerning Indication or Performance of Vyjuvek, it is specified that Vyjuvek should be used in patients with a *COL7A1* gene mutation confirmed by genetic testing. Because diagnostic modalities other than genetic testing are also used in the diagnosis of DEB, PMDA asked the applicant to explain the necessity of requiring genetic confirmation of *COL7A1* gene mutations prior to administration of Vyjuvek.

The applicant' response:
For the following reasons, it is not mandatory to confirm *COL7A1* mutations by genetic testing prior to administration of Vyjuvek. Instead, such testing may be performed, if necessary, in cases where

definitive diagnosis cannot be made by immunofluorescence mapping (IFM) or transmission electron microscopy (TEM).

- Although DEB is caused by mutations in the *COL7A1* gene encoding COL7 protein, the subtype of suspected epidermolysis bullosa is usually determined by clinical features and/or family history, supported by clinical diagnostic tests. Definitive diagnosis is made by (1) IFM using skin biopsy, (2) skin ultrastructure analysis using TEM, and/or (3) *COL7A1* gene testing. If DEB can be definitively diagnosed by IFM and TEM, genetic testing is not necessarily required (*British Journal of Dermatology.* 2020;183:614-27).
- While neither IFM nor TEM can directly confirm mutations in the *COL7A1* gene, IFM can demonstrate reduced or absent deposition of the COL7 protein along the basement membrane, and TEM can identify separation between the dermis and epidermis beneath the basement membrane. Therefore, the likelihood of misdiagnosis with other subtypes of epidermolysis bullosa that involve different causative genes (simplex type, junctional type, or Kindler syndrome) is low. When an accurate diagnosis of DEB cannot be established by IFM and TEM alone, genetic testing is performed as necessary.

PMDA's view:

The applicant's explanation is considered acceptable. While the requirement that "Vyjuvek should be used in patients with a *COL7A1* gene mutation confirmed by genetic testing" is unnecessary in the Precautions Concerning Indication or Performance section, it is important to ensure that Vyjuvek is administered only after differentiation from other EB subtypes with distinct causative genes, given that Vyjuvek exerts efficacy by supplementing functional COL7 protein that is deficient in patients with DEB. Therefore, the Precautions Concerning Indication or Performance section should specify that Vyjuvek should be used in patients with a confirmed diagnosis of DEB. Furthermore, since the causative gene of DEB is limited to *COL7A1*, cases arising from mutations in other genes correspond to other EB subtypes, not DEB. Accordingly, the phrase "with mutations in the *COL7A1* gene" in the Indication or Performance section is unnecessary, and the indication should be stated simply as "Dystrophic epidermolysis bullosa."

7.R.5.2 Necessity of confirming anti-HSV-1 and anti-COL7 antibody titers prior to administration of Vyjuvek

PMDA asked the applicant to explain whether it is necessary to confirm anti-HSV-1 and anti-COL7 antibody titers prior to administration of Vyjuvek.

The applicant's response:

For the following reasons, confirmation of anti-HSV-1 and anti-COL7 antibody titers before administration of Vyjuvek is not considered necessary.

(a) Impact on efficacy

The following findings demonstrated that efficacy of Vyjuvek did not differ significantly, regardless of antibody status for anti-HSV-1 and anti-COL7 antibodies.

- In Study KB103-001, both antibody-positive and antibody-negative patients at baseline were identified for anti-HSV-1 and anti-COL7 antibodies. As shown in Table 27, no clear differences in

the course of closure of Vyjuvek-treated wounds were observed between antibody-positive and antibody-negative patients at baseline.

- Five patients positive for anti-HSV-1 antibody at baseline (patient IDs, [redacted], [redacted], [redacted], [redacted], and [redacted])
- Three patients negative for anti-HSV-1 at baseline (patient IDs, [redacted], [redacted], and [redacted])
- Two patients positive for anti-COL7 antibody at baseline (patient IDs, [redacted] and [redacted])
- Five patients negative for anti-COL7 antibody at baseline (patient IDs, [redacted], [redacted], [redacted], [redacted], and [redacted])

• Table 56 shows the proportion of primary wounds achieving complete healing at 6 months after the first dose in antibody-positive patients compared with that in antibody-negative patients at baseline for both anti-HSV-1 and anti-COL7 antibodies in Study B-VEC-03. No significant differences were observed in the proportion of primary wounds with complete healing according to baseline antibody status.

Table 56. Comparison of the proportion of primary wounds with complete healing at 6 months after the first dose, classified by the presence or absence of antibodies at baseline (Study B-VEC-03, ITT population[*1])

		Vyjuvek-treated wound	Placebo-treated wound
Anti-HSV-1 antibody	No	62.5% (5/8 subjects)	12.5% (1/8 subjects)
	Yes	69.2% (9 /13 subjects)	30.8% (4/13 subjects)
Anti-COL7 antibody	No	65.0% (13/20 subjects)	25.0% (5/20 subjects)
	Yes	100% (1 /1 subject)	0% (0/1 subject)

*1 In patients with DEB, blood sampling is often difficult due to skin fragility; therefore, baseline serum samples could not be obtained in 9 of the 31 subjects in the ITT population. Among the 22 patients with baseline measurement, data at 6 months were missing for 1 patient.

(b) Impact on safety

Tables 57 and 58 show the incidence of adverse events by presence or absence of anti-HSV-1 antibody and anti-COL7 antibody at baseline in Studies KB103-001 and B-VEC-03, respectively. Although the sample size was small and interpretation is limited, no meaningful differences in incidence of adverse events were observed between antibody-positive and antibody-negative patients.

Table 57. Incidence of adverse events by presence or absence of antibody at baseline (Study KB103-001, safety analysis set)

	Anti-HSV-1 antibody		Anti- COL7 antibody	
	No (N = 3)	Yes (N = 6)	No (N = 7)	Yes (N = 2)
All adverse events	3 (100)	4 (66.7)	6 (85.7)	1 (50.0)

n (%)

Table 58. Incidence of adverse events by presence or absence of antibody at baseline (Study B-VEC-03, safety analysis set)

	Anti-HSV-1 antibody			Anti- COL7 antibody		
	No (N = 8)	Yes (N = 14)	Unknown[*1] (N = 9)	No (N = 21)	Yes (N = 1)	Unknown[*1] (N = 9)
All adverse events	5 (62.5)	8 (57.1)	5 (55.6)	12 (57.1)	1 (100)	5 (55.6)

n (%)

*1 In patients with DEB, blood sampling is often difficult due to skin fragility; therefore, baseline serum samples could not be obtained in 9 subjects.

PMDA's view:

Because no notable differences in the efficacy or safety of Vyjuvek were observed according to baseline anti-HSV-1 or anti-COL7 antibody status in clinical studies, the applicant's view that confirmation of these antibody titers is unnecessary prior to administration of Vyjuvek is acceptable. Because information on the efficacy and safety of Vyjuvek in patients who were antibody-negative at baseline but seroconverted after administration is limited, the impact of post-administration seroconversion cannot be evaluated directly. However, it was confirmed that the development of antibodies did not affect the efficacy or safety of Vyjuvek.

7.R.5.3 Administration of Vyjuvek in patients with dominant dystrophic epidermolysis bullosa (DDEB)

The applicant's explanation about the administration of Vyjuvek in patients with DDEB:

Patients with DDEB have autosomal dominant mutations in the *COL7A1* gene, and expression of mutant COL7 protein is considered to destabilize the formation of AF, leading to the pathology of EB. Compared with RDEB, which is the most serious subtype of DEB, symptoms in DDEB are generally milder; however, patients with DDEB also experience blister formation and recurrent wounds as clinical issues (*Pediatr Dermatol.* 2021;38:1198-1201), and they are at increased risk of developing squamous cell carcinoma (*Orphanet J Rare Dis.* 2016;11:117).

Overexpression of wild-type COL7 protein in the presence of mutant COL7 protein restores the stability of COL7 protein molecule assemblies, suggesting that inducing wild-type COL7 protein expression in the skin of patients with DDEB may represent an effective therapeutic strategy (*J Biol Chem.* 2009;284:30248-56). Since Vyjuvek exerts its efficacy by inducing expression of wild-type COL7 protein in the skin, regardless of DEB genotype, it is considered to be an effective therapy for DDEB as well.

In clinical studies, 1 patient with DDEB was enrolled in Study B-VEC-03 (patient ID, [redacted]). In the primary wound treated with Vyjuvek, complete healing (defined as complete closure confirmed at 2 consecutive visits) was achieved at 6 months after the first dose, and complete closure was maintained at Weeks 22, 24, and 26. In contrast, in the primary wound of the same patient treated with placebo, complete closure was observed at Week 24 but not at Weeks 22 and 26, failing to achieve complete healing. Evaluation of the primary wound treated with Vyjuvek in this patient continued in Study B-VEC-EX-02 (patient ID, [redacted]), and complete closure was again observed at 9 and 12 months after the first dose in that study. Furthermore, in another newly enrolled patient with DDEB in Study B-VEC-EX-02 (patient ID, [redacted]), photographs of 3 wounds at baseline and at 3, 6, and 18 months after the first does of Vyjuvek demonstrated results for which efficacy could be expected. In these 2 patients, no safety concerns considered attributable to Vyjuvek were observed.

In light of these findings, the efficacy of Vyjuvek in patients with DDEB is suggested. Since no safety concerns have been identified, Vyjuvek would be indicated for patients with DEB, regardless of genotype, including those with DDEB.

PMDA's view:
Given the mechanism of action of Vyjuvek, the applicant's explanation is understandable. However, since clinical experience with Vyjuvek in patients with DDEB is extremely limited, information on the efficacy and safety of Vyjuvek in patients with DDEB should be collected continuously in the post-marketing setting.

7.R.5.4 Use of Vyjuvek in pediatric patients aged <6 months

The applicant's explanation about the use of Vyjuvek in pediatric patients aged <6 months:
Patients aged <6 months were excluded from Study B-VEC-03. In Study B-VEC-EX-02, enrollment was allowed from birth, and in Study B-VEC-EX-02-JP, from 2 months of age; however, no patients aged <6 months were actually enrolled in any of the clinical studies conducted.

In the foreign post-marketing setting (from May 19, 2023, when Vyjuvek was launched in the US, to November 22, 2024), administration of Vyjuvek to patients aged < 6 months was reported, as shown in Table 59.

Table 59. Summary of patients aged <6 months treated with Vyjuvek (foreign post-marketing surveillance reports, through November 22, 2024)

Patient ID	Age (months) at the first dose of Vyjuvek	Diagnosis	Duration of treatment with Vyjuvek (weeks)	Number of Vyjuvek applications
[redacted]	0.33	DDEB	21	20
[redacted]	2.89	RDEB	23	24
[redacted]	5.06	RDEB	8	8
[redacted]	0.51	RDEB	63	47
[redacted]	0.61	RDEB	75	42

According to the report, 5 patients were treated with Vyjuvek at the same dose[23)] as used in patients aged ≥6 months and <3 years in the US, and no safety concerns have been identified to date.

From these findings, pediatric patients aged <6 months were included as eligible for Vyjuvek treatment, allowing initiation of therapy at birth. The 9.7 Pediatric Use section in the package insert will include a precaution stating that no clinical studies have been conducted in infants aged <6 months.

PMDA's view:
Although the use of Vyjuvek in pediatric patients aged <6 months has not been studied in clinical studies, overseas post-marketing reports on the use of Vyjuvek in such patient population are available. Furthermore, the use of Vyjuvek at an early stage before skin damage due to *COL7A1* gene mutations progresses may be considered appropriate. Therefore, with a precaution in the package insert stating that no clinical studies have been conducted in infants aged <6 months, it is acceptable not to exclude this population from treatment eligibility, thereby providing a therapeutic option. However, because clinical experience with Vyjuvek in pediatric patients aged <6 months is extremely limited, information on the efficacy and safety of Vyjuvek in this population should be collected continuously in the post-marketing setting.

[23)] The dose per wound of Vyjuvek was the same as in Study B-VEC-EX-02, as shown in Table 34. The maximum weekly dose was the same as that for patients aged ≥6 months and <3 years in Study B-VEC-03, with an upper limit of 1.6×10^9 PFU.

7.R.6 Dosage and administration or method of use

The proposed Dosage and Administration or Method of Use of Vyjuvek was as shown below. Precautions Concerning Dosage and Administration or Method of Use were not specified.

Dosage and Administration or Method of Use

Vyjuvek is applied once weekly to the wound in droplets in a grid pattern of approximately 1 cm × 1 cm.

The maximum weekly volume of Vyjuvek is calculated based on age according to the table below.

Age	Maximum weekly dose (plaque forming unit [PFU])	Maximum weekly volume (mL)[Note)]
<3 years old	2×10^9	1
≥3 years old	4×10^9	2

Note Volume after mixing the suspension with excipient gel

The actual dose volume is calculated based on wound area according to the table below. If the total wound area exceeds 60 cm^2, the total dose volume is calculated according to the table below until the maximum weekly volume (1 or 2 mL) is reached.

Wound area (cm^2)	Dose (PFU)	Dose volume (mL)
<20	4×10^8	0.2
≥20 and <40	8×10^8	0.4
≥40 and ≤60	1.2×10^9	0.6

Vyjuvek should be applied to wounds until they are closed before selecting new wound(s) to treat.

If a previously treated wound re-opens, treatment of that wound should be prioritized (as application of Vyjuvek to all the wounds may not be possible in a single treatment session).

If a dose is missed, Vyjuvek should be administered as soon as possible and thereafter resumed on a once-weekly schedule.

With reference to Sections "7.R.2 Efficacy," "7.R.3 Safety," and "7.R.4 Clinical positioning of Vyjuvek," as well as the review results described below, PMDA concluded that the Dosage and Administration or Method of Use and Precautions Concerning Dosage and Administration or Method of Use of Vyjuvek should be modified as follows.

Dosage and Administration or Method of Use (Underline denotes additions or changes. Strikethrough denotes deletions.)

Usually, Vyjuvek is applied once weekly to the skin wound surface in droplets in a grid pattern of approximately 1 cm × 1 cm. The reference dose is 2×10^7 PFU (10 μL) per cm^2 wound area.

The maximum weekly dose and maximum weekly volume of Vyjuvek are calculated based on age according to the table below.

Age	Maximum weekly dose (plaque forming unit [PFU])	Maximum weekly volume (mL)[Note)]
<3 years old	2×10^9	1
≥3 years old	4×10^9	2

Note) Volume after mixing the ~~suspension with excipient gel~~ drug product with HPMC gel

~~The actual dose volume is calculated based on wound area according to the table below. If the total wound area exceeds 60 cm^2, the total dose volume is calculated according to the table below until the maximum weekly volume (1 or 2 mL) is reached.~~

~~Wound area (cm^2)~~	~~Dose (PFU)~~	~~Administration volume (mL)~~
~~<20~~	~~4×10^8~~	~~0.2~~
~~≥20 and <40~~	~~8×10^8~~	~~0.4~~
~~≥40 and ≤60~~	~~1.2×10^9~~	~~0.6~~

~~Vyjuvek should be applied to wounds until they are closed before selecting new wound(s) to treat.~~

~~If a previously treated wound re-opens, treatment of that wound should be prioritized (as application of Vyjuvek to all the wounds may not be possible in a single treatment session).~~

~~If a dose is missed, Vyjuvek should be administered as soon as possible and thereafter resumed on a once-weekly schedule.~~

Precautions Concerning Dosage and Administration or Method of Use (Underline denotes additions.)

- Vyjuvek should be used until wound closure. However, if the physician judges that another wound should be prioritized, this does not apply.
- When a wound has closed, administration to that wound should be discontinued and treatment should be initiated for the next new wound.
- If a closed wound re-opens, treatment of that wound should, in principle, be prioritized.
- If a dose is missed, Vyjuvek should be administered as soon as possible and thereafter resumed on a once-weekly schedule.

7.R.6.1 Dosage and administration or method of use of Vyjuvek

Dose per wound of Vyjuvek

The applicant's explanation about the dose per wound of Vyjuvek:

In Study B-VEC-03, the dose of Vyjuvek was specified as shown in Table 30, and the dose was determined according to baseline wound area. In Study B-VEC-EX-02, the dose of Vyjuvek was specified as shown in Table 34, with the dose adjusted at each administration according to the wound area. Vyjuvek was applied evenly over the wound in small droplets using a syringe in a 1 cm × 1 cm grid pattern. Vyjuvek was administered at these doses, and efficacy outcomes were obtained as described in Sections 7.1.1.2, 7.1.1.3, and 7.R.2.2.

Although the dosage and administration or method of use of Vyjuvek was determined based on the results of Studies B-VEC-03 and B-VEC-EX-02, the number and size of wounds vary among the target patient population. Moreover, from post-marketing administration experience of Vyjuvek in foreign

countries, it was found that the fixed 3-tiered non-linear dose defined by wound size in clinical studies could cause confusion. Therefore, the marketed dose regimen in Japan was modified to a simplified regimen applicable, regardless of the number or size of wounds. Specifically, Vyjuvek is applied to the skin wound in droplets in an approximately 1 cm × 1 cm grid pattern, enabling uniform distribution over the entire wound when covered with a hydrophobic dressing. The average droplet volume is assumed to be approximately 10 μL, applied to an approximately 1 cm^2 wound. Although the doses per wound in Studies B-VEC-03 and B-VEC-EX-02 (Tables 30 and 34) followed a non-linear regimen, the application dose is essentially linear per an approximately 1 cm^2 wound in the proposed regimen, resulting in differences in per-area dosing, strictly speaking. However, since Study KB103-001 demonstrated wound closure across various doses administered (Table 24 and Table 27), a strict dose-response relationship by wound area was not observed. Therefore, these differences are not considered to affect the efficacy or safety of Vyjuvek.

Results of the human factors study (Study PRO-HF-02) conducted after regulatory submission [see Section 7.R.6.2] indicated that inclusion of non-linear dosing tables such as those in Tables 30 and 34 would be inconsistent with the above linear grid-based method, potentially leading to dosing errors or confusion. Therefore, descriptions of such tables are to be deleted from the Dosage and Administration or Method of Use section.

Since no efficacy data for wounds >60 cm^2 were available from clinical studies, PMDA asked the applicant to explain the appropriateness of the application of Vyjuvek to the larger wounds and its dose.

The applicant's response:
In Study B-VEC-03, Vyjuvek was applied to 12 secondary wounds >60 cm^2 in 11 subjects, with the largest wound being 229.78 cm^2, although Vyjuvek-treated wound area and closure outcomes were not recorded. In Study B-VEC-EX-02, photographic data (at baseline and at the end of Study B-VEC-EX-02) from newly enrolled subjects (patient IDs B-VEC-EX-02-01-05 and B-VEC-EX-02-03-10) indicated that efficacy could be expected even in wounds >60 cm^2 when the same dosing as for ≤60 cm^2 wounds was used. Therefore, Vyjuvek can be expected to have efficacy in wounds >60 cm^2 when administered at the same dose as for ≤60 cm^2 wounds.

PMDA's view:
Although the proposed per-area dose technically differs from the clinical study dose, the applicant's explanation that this difference would not affect the efficacy or safety of Vyjuvek is understandable. Given that a simplified regimen applicable regardless of wound number or size is desirable, the grid-pattern droplet application of approximately 1 cm × 1 cm to the skin wound surface is acceptable. Although no efficacy data are available in clinical studies for wounds larger than 60 cm^2, the applicant's explanation that efficacy can be expected even in wounds exceeding 60 cm^2, as evidenced by wound photographs presented as reference information, is understandable. Therefore, it is acceptable to apply the same dosage regimen to larger wounds. However, to ensure uniform per-area dosing, the droplet volume and the approximate content of Vyjuvek per droplet should be specified in the Dosage and Administration or Method of Use section. Accordingly, specifying the reference dose of Vyjuvek per cm^2 wound area in the Dosage and Administration or Method of Use section is appropriate.

Maximum weekly dose

The applicant's explanation about the maximum weekly dose of Vyjuvek:

In Study B-VEC-03, considering that the mean body surface area is smaller in younger patients (*J Dermatolog Treat.* 2006;17:224-8), the following maximum weekly dose was selected according to patient age: 1.6×10^9 PFU for patients aged ≥6 months and <3 years, 2.4×10^9 PFU for patients aged ≥3 years and <6 years, and 3.2×10^9 PFU for patients aged ≥6 years. As a result, efficacy outcomes were as shown in Sections 7.1.1.2 and 7.R.2.2, and there were no concerns regarding the safety profile.

In Study B-VEC-EX-02, taking account of the variability of measurements in the quantitative assay (plaque assay) used to determine the dose of Vyjuvek, the necessity of strictly defining the maximum weekly dose across 3 age categories was considered to be low. Therefore, the maximum weekly dose was 2.0×10^9 PFU for patients aged <3 years and 4.0×10^9 PFU for patients aged ≥3 years. As a result, efficacy outcomes were as shown in Sections 7.1.1.3 and 7.R.2.2, and there were no concerns regarding the safety profile.

From these findings, the maximum weekly dose was determined according to Study B-VEC-EX-02.

Although there was no clinical study experience in patients aged <6 months, doses up to 1.6×10^9 PFU, the same as the upper limit for patients aged <3 years, were administered in foreign post-marketing settings [see Section 7.R.5.4]. Considering the variability of measurements in the quantitative assay (plaque assay), there would be little need to establish different upper limits for patients aged <6 months and those aged ≥6 months and <3 years. Therefore, the maximum weekly dose of 2.0×10^9 PFU was also selected for patients aged <6 months.

PMDA's view:

Although the maximum weekly dose of Vyjuvek in Study B-VEC-EX-02 differs from that in Study B-VEC-03, which was a confirmatory study, efficacy results consistent with those of Study B-VEC-03 were maintained in Study B-VEC-EX-02 which included patients from Study B-VEC-03, and there were no concerns regarding the safety profile. Furthermore, the same dose was used in Study B-VEC-EX-02-JP, which enrolled Japanese patients. Therefore, it is acceptable to specify the maximum weekly dose on the basis of that used in Study B-VEC-EX-02. The use of the same dose for pediatric patients aged <6 months as that for patients aged ≥6 months and <3 years is also acceptable, given the experience in the overseas post-marketing setting.

Dosage and administration or method of use in Japanese patients

The applicant's explanation about the dosage and administration or method of use of Vyjuvek in Japanese patients:

In Study B-VEC-EX-02-JP in Japanese patients, Vyjuvek was administered with the same per-wound dose and the same maximum weekly dose as in Study B-VEC-EX-02. Efficacy results were generally consistent with those of Study B-VEC-03, and no safety concerns specific to Japanese patients were observed. From these findings, the same dosage and administration or method of use should be established in Japanese patients as in non-Japanese patients.

PMDA accepted the applicant's explanation.

Priority of wounds to be treated

The applicant's explanation about the priority of wounds to be treated:

The results of Study B-VEC-03 demonstrated that once-weekly administration was the dosing frequency at which efficacy of Vyjuvek could be expected. Therefore, once-weekly administration of Vyjuvek to a given wound site should be continued until wound closure. If Vyjuvek was administered to a different wound site each week, efficacy might not be expected. It is recommended that once initiated, treatment of a wound be continued until its closure before beginning treatment of another wound.

If a previously treated and closed wound re-opens, prompt treatment of that wound to maintain closure is considered most effective. It is recommended that re-opened wounds be prioritized for treatment.

It is also conceivable that circumstances may arise, such as the occurrence of a new wound, that necessitate initiation of treatment of a new wound site before the ongoing wound is completely closed. In such cases, the patient and the treating physician are not precluded from discussing and selecting which wound should be prioritized.

In view of the above, the Dosage and Administration or Method of Use section should stipulate that, when a wound is under treatment, treatment of new wounds should begin only after closure of the ongoing wound, and that when previously treated wound re-opens, re-opened wounds should be prioritized.

PMDA's view:

The following applicant's explanation is understandable: Treatment of new wounds should begin only after closure of the wound under treatment, and that when previously treated wound re-opens re-opened wounds should be prioritized. But it is conceivable that other wounds may arise that should be prioritized. In this case, a provision should be added allowing physicians to select other wounds deemed more appropriate to prioritize. To clarify when administration of Vyjuvek to a wound should be discontinued, a provision should specify that administration should continue until wound closure. These provisions should be described under the Precautions Concerning Dosage and Administration or Method of Use section.

7.R.6.2 Home administration

The applicant's explanation about home administration of Vyjuvek:

The necessity of home administration

Weekly hospital visits for the administration of Vyjuvek impose a substantial burden on patients and their family members. In particular, patients are at high risk of symptom exacerbation, such as blister or erosion formation, due to external mechanical forces during hospital visits. Allowing home administration of Vyjuvek is expected to reduce the burden of weekly hospital visits on patients and their family members, while decreasing the risk of symptom exacerbation in patients. Even when

hospital visits are not feasible due to the circumstances of patients or their family members, home administration would remain possible, which is expected to improve treatment adherence.

Personnel responsible for preparation and administration of Vyjuvek

For home administration, Vyjuvek is to be prepared at medical institutions or dispensing pharmacies by physicians or pharmacists, whereas Vyjuvek is to be administered by healthcare professionals such as visiting nurses, or by non-healthcare professionals including patients or their family members, after receiving appropriate education and training. Home administration by patients or their family members is permitted only when physicians provide education and training regarding appropriate administration procedures of Vyjuvek and confirm that the patient or family member is capable of performing the procedure properly.

Efficacy and safety during home administration

In the US, a human factors study (Study PRO-HF-02) was conducted to evaluate the feasibility of home administration. In Study PRO-HF-02, healthcare professionals and non-healthcare professionals were divided into 3 groups (A, B, and C) as shown in Table 60. After reviewing the US labeling and instructional video provided, participants were assessed on whether they could apply a simulated solution in an appropriate dose to simulated wounds.[24)]

Table 60. Information on subjects, sample size, and reference materials used for administration in each group (Study PRO-HF-02)

Group	Target population	N	Documents supplied
A	Healthcare professionals	17	US labeling
B	Healthcare professionals	18	US labeling and instructional video[*1]
C	Non-healthcare professionals	14	US labeling and instructional video[*1]

*1 In addition to these materials, it was allowed to make inquiries in advance if there were any questions. Moreover, some subjects were given an opportunity to practice beforehand, and some subjects were provided with an opportunity to observe a demonstration of the administration procedure.

Each subject was assigned 1 simulated wound of <20 cm^2, ≥20 cm^2 and <40 cm^2, and ≥40 cm^2 and <60 cm^2. Subjects were instructed to apply droplets of the simulated solution in a grid-like pattern (approximately 1 cm × 1 cm) to each simulated wound. The number of droplets applied by each subject to each simulated wound was recorded. Passing criteria were defined as 3 to 28 droplets for wounds <20 cm^2, 19 to 45 droplets for wounds ≥20 cm^2 and <40 cm^2, and 38 to 76 droplets for wounds ≥40 cm^2 and <60 cm^2.

Table 61 shows the pass rates calculated from the number of droplets applied by each group, indicating that both healthcare professionals and non-healthcare professionals achieved higher pass rates when they had observed a prior live demonstration of administration and practiced the procedure in advance. Training was shown to enable non-healthcare professionals to administer with accuracy comparable to that of healthcare professionals.

[24)] A sheet containing 3 types of simulated wounds (<20 cm^2, ≥20 cm^2 and <40 cm^2, and ≥40 cm^2 and <60 cm^2).

Table 61. Pass rates calculated from the number of droplets applied in each group[*1] (Study PRO-HF-02)

Group	Demonstration	Practice	<20 cm^2 (pass by 3-28 droplets)	≥20 and <40 cm^2 (pass by 19-45 droplets)	≥40 and <60 cm^2 (pass by 38-76 droplets)
A	No	No	11/12 subjects (91.7%)	5/15 subjects (33.3%)	3/15 subjects (33.3%)
B	No	No	7/7 subjects (100%)	5/7 subjects (71.4%)	5/7 subjects (71.4%)
	No	Yes	6/6 subjects (100%)	5/6 subjects (83.3%)	3/6 subjects (50.0%)
	Yes	Yes	5/5 subjects (100%)	4/5 subjects (80.0%)	4/5 subjects (80.0%)
C	No	No	6/6 subjects (100%)	4/6 subjects (66.7%)	4/6 subjects (66.7%)
	No	Yes	2/3 subjects (66.7%)	1/3 subjects (33.3%)	1/3 subjects (33.3%)
	Yes	Yes	5/5 subjects (100%)	4/5 subjects (80.0%)	4/5 subjects (80.0%)

*1 When droplets had coalesced or when the covering material had been applied before recording the droplets, the number of droplets could not be counted, and such cases were excluded from the denominator.

In addition, in the US post-marketing surveillance (from May 19, 2023 to February 24, 2025 after approval), among 458 patients who received Vyjuvek application, Vyjuvek was applied to wounds in 15 patients at medical institutions and in 443 patients at home. In the 15 patients applied at medical institutions, administration was performed exclusively by healthcare professionals. Among the 443 patients applied at home, Vyjuvek was applied to wounds in 225 patients by healthcare professionals, and in 218 patients by patients themselves or non-healthcare professionals including caregivers. In the foreign periodic safety report (from May 19, 2023 to November 18, 2024), no adverse events related to home administration were reported, and no safety concerns specific to home administration were identified.

PMDA's view:

Although there has been no experience with home administration of Vyjuvek in Japan, the following considerations suggest that home application of Vyjuvek is acceptable:

- Weekly hospital visits for administration of Vyjuvek impose a substantial burden on patients and their family members, with concerns regarding deterioration of wound condition and treatment adherence.
- Results from the human factors study (Study PRO-HF-02) demonstrated that both healthcare professionals and non-healthcare professionals could apply Vyjuvek appropriately at home after receiving training.
- In US post-marketing use, home administration by both healthcare professionals and non-healthcare professionals has been performed, and no particular safety or efficacy concerns have been suggested to date.
- Appropriate training materials will be provided in Japan as well.

However, initiation of home administration should be carefully considered by physicians. In addition, it should only be implemented after sufficient education and training on appropriate administration procedures of Vyjuvek have been provided to the healthcare professionals or patients/family members who will perform home administration, and after confirming that they can reliably use Vyjuvek. If wound improvement is not observed after initiation of home administration, or if events suggestive of adverse reactions to Vyjuvek occur and continuation of home administration becomes difficult, home administration should be immediately discontinued. In addition, precautions should be taken, such as close monitoring, under the supervision of a physician. Furthermore, because there is no experience with home administration of Vyjuvek in Japan, information on the safety and efficacy of home administration should be collected in post-marketing surveillance.

7.R.6.3 Administration to sites other than the skin

The applicant's explanation about administration of Vyjuvek to sites other than the skin:
In DEB, extensive blistering and scarring of the skin and mucosa are observed. In the eye, corneal erosion and other lesions leading to visual impairment are major concerns. Based on the mechanism of action of Vyjuvek and the structural similarities between the skin and cornea, the potential of treating ocular manifestations of patients with DEB was explored. Under humanitarian use, Vyjuvek was administered following corneal surgery to a 13-year-old male with bilateral symblepharon and blindness secondary to corneoconjunctival epithelial invasion. As a result, improvement in visual acuity was observed, and no signs or symptoms of ocular complications, such as herpetic interstitial keratitis, were reported. Based on these results, a clinical study is currently ongoing to evaluate local ocular administration of Vyjuvek for the treatment of ocular disease in DEB. However, administration to mucosal sites other than the eye has not been studied at present. Given that the current evaluation of the risk-benefit balance remains insufficient, administration of Vyjuvek to sites other than the skin is not recommended.

PMDA's view:
In DEB, not only cutaneous but also mucosal lesions, including ocular involvement, are problematic. Although the mechanism of action of Vyjuvek suggests potential efficacy in mucosal lesions including the eye, the applicant's explanation that administration to sites other than the skin is not recommended due to insufficient evaluation of the risk-benefit balance at this time is understandable. Accordingly, the Dosage and Administration or Method of Use section should specify that Vyjuvek is to be used for cutaneous wounds.

8. Risk Analysis and Outline of the Review Conducted by PMDA

The applicant's explanation about the post-marketing surveillance plan of Vyjuvek:
Following marketing authorization of Vyjuvek, the applicant plans to conduct a post-marketing surveillance covering all patients treated with Vyjuvek to evaluate its safety and efficacy in clinical practice.

Safety specifications will include the following, considering the incidences of adverse events observed in clinical studies and foreign post-marketing experience, as risks expected to occur in the post-marketing setting: "Accidental exposure of Vyjuvek to healthcare professionals and persons related to the patient during preparation and administration" and "accidental exposure of Vyjuvek to close contacts or healthcare professionals through direct contact with body fluids or treated lesions." As missing information, "long-term safety" will be monitored. Efficacy specifications will include the following: In relation to wound healing, "≥50% reduction in the size of the target wound," and in relation to treatment satisfaction, "change in the treatment satisfaction questionnaire for medication (TSQM-9) score," both of which will be defined as "long-term efficacy."

The planned sample size for surveillance is 200, considering the expected number of patients who use Vyjuvek in the post-marketing setting.

The observation period will be 5 years from the first dose of Vyjuvek to evaluate each specification of the surveillance.

PMDA's view:
Since clinical experience of Vyjuvek in Japanese patients is extremely limited, post-marketing surveillance should be conducted covering all patients treated with Vyjuvek in order to rapidly and unbiasedly collect safety and efficacy information of Vyjuvek, and the obtained safety information should be promptly provided to healthcare professionals.

For safety specifications, based on the considerations described in Section "7.R.3 Safety," "adverse events related to the application site," "adverse events related to immunogenicity," and "squamous cell carcinoma" should also be evaluated.

For efficacy specifications, based on the investigations described in Section "7.R.2 Efficacy," "complete closure of the target wound" should also be investigated as part of the "long-term efficacy." The planned sample size and observation period are d acceptable.

The details of the post-marketing surveillance will be finalized, taking account of comments from the Expert Discussion.

9. Regulations on Type-1 Use of Living Modified Organisms under Article 4 of the Act on Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms ("the Cartagena Act")

Use of Vyjuvek is classified as Type-I Use of Living Organisms under Article 4 of the Cartagena Act, and the Regulations on Type-I Use of Living Organisms has been approved under the same article of the Act.

10. Results of Compliance Assessment Concerning the New Regenerative Medical Product Application Data and Conclusion Reached by PMDA

10.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new regenerative medical product application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

10.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new regenerative medical product application data (CTD 5.3.5.2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. PMDA concluded that the clinical studies overall were conducted in compliance with GCP and that there were no obstacles to conducting its review using the application documents submitted. PMDA identified the following problems to be

solved by the sponsor (Clinical Trial In-Country Representative), although they had no significant impact on the overall evaluation of the clinical studies. PMDA notified the sponsor (Clinical Trial In-Country Representative) of the findings requiring corrective action.

Finding requiring corrective action

Sponsor (Clinical Trial In-Country Representative)

- No standard operating procedure had been prepared for the development of the study protocol.

11. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that Vyjuvek has a certain level of efficacy in the treatment of dystrophic epidermolysis bullosa, and that Vyjuvek has acceptable safety in view of its benefits. PMDA considers it meaningful to provide Vyjuvek to clinical settings as a new therapeutic option for patients with DEB.

PMDA has concluded that Vyjuvek may be approved if Vyjuvek is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

June 27, 2025

Product Submitted for Approval

Brand Name	Vyjuvek Gel
Non-proprietary Name	Beremagene geperpavec
Applicant	Krystal Biotech, Inc. Freyr Life Sciences KK as the Designated Marketing Authorization Holder of Foreign-manufactured Regenerative Medical Products
Date of Application	October 29, 2024

List of Abbreviations
See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

As a result of the review in Section "7.R.2 Efficacy" of the Review Report (1), the following findings were obtained: (1) In Study B-VEC-03 in non-Japanese patients with DEB, a statistically significant difference was observed for the proportion of primary wounds with complete closure at 6 months after the first dose of the study product, the primary endpoint, between Vyjuvek-treated and placebo-treated wounds; (2) in Study B-VEC-EX-02 in patients with DEB who completed Study B-VEC-03, persistence of wound healing was observed up to 12 months after administration of Vyjuvek; and (3) in Study B-VEC-EX-02-JP in Japanese patients with DEB, the proportion of primary wounds with complete closure at 6 months after the first dose of Vyjuvek, the primary endpoint, demonstrated results for which efficacy could be expected. Taken together, these results indicate that Vyjuvek has demonstrated certain efficacy in DEB.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

The expert advisors commented that the results of the primary endpoint in Study B-VEC-03 (Table 32) should also present the correspondence of complete and incomplete healing between Vyjuvek-treated wounds and placebo-treated wounds within the same patient, for the following reasons:

- Although Study B-VEC-03 was conducted as an intra-patient randomized controlled study, the presentation in Table 32 may cause misunderstanding as a conventional randomized controlled study.
- McNemar's test was used to compare Vyjuvek with placebo, but the *P*-value of McNemar's test cannot be reproduced from the information provided in Table 32 alone.

Reflecting the comments from the expert advisors, Table 62 shows the results of the primary endpoint in Study B-VEC-03 (proportion of primary wounds with complete healing at 6 months after the first dose of the study product).

Table 62. Proportion of primary wounds with complete healing at 6 months after the first dose of the study product (Study B-VEC-03, ITT population)

		Vyjuvek-treated wound		Total
		Complete healing	Incomplete healing	
Placebo-treated wound	Complete healing	4.4 subjects (14.2%)	2.3 subjects (7.4%)	6.7 subjects (21.6%)
	Incomplete healing	16.5 subjects (53.2%)	7.8 subjects (25.2%)	24.3 subjects (78.4%)
Total		20.9 subjects (67.4%)	10.1 subjects (32.6%)	31 subjects (100%)

Because the multiple imputation method was used for the missing cases, the number of subjects in the table may include decimal values.

1.2 Safety

As a result of the review in Section "7.R.3 Safety" of the Review Report (1), PMDA concluded that no problematic adverse event for which a causal relationship to Vyjuvek could not be ruled out was observed throughout the clinical studies, and Vyjuvek was tolerable.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.3 Indication or performance

As a result of the review in Section "7.R.5 Indication or performance" of the Review Report (1), PMDA has concluded that the Indication or Performance and Precautions Concerning Indication or Performance sections should be described as per the relevant sections of the Review Report (1).

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.4 Dosage and administration or method of use

As a result of the review in Section "7.R.6 Dosage and administration or method of use" of the Review Report (1), PMDA concluded that the Dosage and Administration or Method of Use and Precautions Concerning Dosage and Administration or Method of Use sections should be specified as described in the corresponding sections of the Review Report (1).

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

Additionally, the expert advisors commented that since some patients may require several hours, including wound care procedures before and after application of Vyjuvek, enabling home administration of Vyjuvek is important.

1.5 Post-marketing surveillance plan (draft)

At the time of regulatory submission, the applicant proposed a plan for post-marketing surveillance covering all patients treated with Vyjuvek to evaluate the safety and other aspects of Vyjuvek used in clinical settings. The planned sample size was 200. The planned observation period was 5 years.

As a result of the review in Section "8. Risk Analysis and Outline of the Review Conducted by PMDA" of the Review Report (1), PMDA has concluded that the following items should be added to the post-marketing surveillance: "Adverse events related to the administration site," "adverse events related to immunogenicity," and "squamous cell carcinoma" for the safety specifications; and "complete closure of treated wounds" for the efficacy specifications.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion. At the same time, the following comment was raised from the expert advisors.

- Because the clinical studies with Vyjuvek in patients with DDEB is very limited in the clinical studies of Vyjuvek, information on the genotypes (RDEB or DDEB) of patients should be collected in the post-marketing surveillance in order to assess the safety and efficacy of Vyjuvek in patients with DDEB.

PMDA requested the applicant to revise the post-marketing surveillance plan in light of the results of the Expert Discussion. The applicant appropriately responded and submitted the outline (draft) of the revised post-marketing surveillance plan as shown in Table 63, and PMDA accepted the draft plan.

Table 63. Outline of post-marketing surveillance plan (draft)

Objective	To evaluate the safety and other aspects of Vyjuvek in clinical practice
Survey method	All-case surveillance
Population	Japanese patients with DEB (RDEB or DDEB)
Observation period	5 years
Planned sample size	All patients receiving Vyjuvek during the enrollment period (3 years and 6 months) (Expected sample size, 200)
Main survey items	Safety specifications: Accidental exposure of Vyjuvek to healthcare professionals and persons related to the patient during preparation and administration, accidental exposure of Vyjuvek to close contacts or healthcare professionals through direct contact with patient body fluids or the treated wound after administration, long-term safety, adverse events related to the application site, adverse events related to immunogenicity, squamous cell carcinoma Efficacy specifications ≥50% reduction in the area of the target wound, complete closure of the target wound, changes in TSQM-9 scores

1.6 Others

1.6.1 Designation of specified regenerative medical product

On the basis of "Principles for designation of biological products, specified biological products, and specified regenerative medical products" (PFSB/ELD Notifications No. 1105-1 and No. 1105-2, dated November 5, 2014), PMDA has concluded that Vyjuvek need not be designated as a specified regenerative medical product for the following reasons: (1) The risk of infection by adventitious agents derived from biological components of human or animal origin used for the manufacture of Vyjuvek is negligible; and (2) the risk of infection propagation caused by the use of Vyjuvek in the open system is negligible.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication or performance as well as dosage and administration or method of use as shown below, with the following approval conditions, on the premise that the cautionary statement is provided in the package insert and the information on the proper use of the product is appropriately disseminated in the post-marketing setting. Because the product is designated as an orphan regenerative medical product, the re-examination period should be 10 years. The product need not be designated as a designated regenerative medical product.

Indication or Performance

Dystrophic epidermolysis bullosa

Dosage and Administration or Method of Use

Usually, Vyjuvek is applied once weekly to the skin wound surface in droplets in a grid pattern of approximately 1 cm × 1 cm. The reference dose is 2×10^7 PFU (10 μL) per cm^2 wound area.

The maximum weekly dose and maximum volume of Vyjuvek are calculated based on age according to the table below.

Age	Maximum weekly dose (plaque forming unit: PFU)	Maximum weekly volume (mL)[Note)]
<3 years old	2×10^9	1
≥3 years old	4×10^9	2

Note) Volume after mixing the drug product with HPMC gel

Approval Conditions

1. The applicant is required to conduct a post-marketing surveillance, etc., covering all patients treated with the product in the post-marketing setting until data from a certain number of patients have been accrued.
2. The applicant is required to take necessary measures to ensure that the product is used by individuals who have received sufficient training in its use, under a system in which adverse events can be properly managed by physicians with adequate knowledge and experience in the treatment of dystrophic epidermolysis bullosa.
3. In order to ensure that the product is used in compliance with the regulations on Type-1 Use approved under the "Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003)," the applicant is required to take necessary measures such as announcement of the regulations on Type-1 Use.

Appendix

List of Abbreviations

[redacted]	[redacted]
[redacted]	[redacted]
AF	anchoring fibril
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
[redacted]	[redacted]
A/G ratio	albumin/globulin ratio
[redacted]	[redacted]
BGH	bovine growth hormone
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Cartagena Act	Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms
CMV	cytomegalovirus
COL1	collagen type I
COL7	collagen type VII
COVID-19	coronavirus disease
CQA	critical quality attribute
DDEB	dominant dystrophic epidermolysis bullosa
DEB	dystrophic epidermolysis bullosa
DPBS	Dulbecco's phosphate buffered saline
EB	epidermolysis bullosa
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunosorbent spot
[redacted]	[redacted]
FBS	fetal bovine serum
gDNA	genomic DNA
HCP	host cell protein
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
HPMC	hydroxypropyl methylcellulose
HSV	herpes simplex virus
[redacted]	[redacted]
IEM	immune electron microscopy
IF	immunofluorescence
IFM	immunofluorescence mapping
ITT	intention-to-treat
LIVCA	limit of *in vitro* cell age
[redacted]	[redacted]
LOD	limit of detection
[redacted]	[redacted]
MCB	master cell bank
MCHC	mean corpuscular hemoglobin concentration

MedDRA	Medical Dictionary for Regulatory Activities
MOI	multiplicity of infection
[redacted]	[redacted]
MVB	master virus bank
ORF	open reading frame
[redacted]	[redacted]
PBS	phosphate buffered saline
[redacted]	[redacted]
PFU	plaque forming units
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	per protocol set
[redacted]	[redacted]
PRNT	plaque reduction neutralization test
[redacted]	[redacted]
[redacted]	[redacted]
qPCR	quantitative polymerase chain reaction
RDEB	recessive dystrophic epidermolysis bullosa
RDW	red blood cell distribution width
Regulatory submission	Submission of application for marketing approval
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
SOC	system organ class
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
TEM	transmission electron microscopy
[redacted]	[redacted]
[redacted]	[redacted]
TSQM-9	treatment satisfaction questionnaire for medication
Vero cells	African green monkey kidney epithelial cell
Vyjuvek	Vyjuvek Gel
WCB	working cell bank
WVB	working virus bank