EU RISK MANAGEMENT PLAN (RMP) FOR VYJUVEK (BEREMAGENE GEPERPAVEC [B-VEC])

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QPPV oversight declaration: The content of this RMP has been reviewed and approved by Krystal's QPPV.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse drug reaction
AEs	Adverse Events
aRMM	Additional Risk Minimisation Measures
ATC	Anatomical Therapeutic Chemical Classification System
B-VEC	Beremagene geperpavec
DDEB	Dominant DEB
DEB	Dystrophic epidermolysis bullosa
EB	Epidermolysis bullosa
EEA	European Economic Area
EU	European Union
FAQ	Frequently asked questions
HCP	Healthcare provider/professional
HSV-1	Herpes simplex virus type 1
INN	International Nonproprietary Names
MAH	Marketing Authorisation Holder
OLE	Open Label Extension
PFU	Plaque Forming Units
PI	Product Information
PL	Patient Leaflet
PPE	Personal Protective Equipment
PSUR	Periodic safety update report
QA	Quality Assurance
QPPV	Qualified Person Responsible for Pharmacovigilance
QR Code	Quick-response code
RDEB	Recessive DEB
RMP	Risk Management Plan
RWE	Real World Evidence
SAE	Serious Adverse Event
SCC	Squamous Cell Carcinoma
SD	Standard Deviation
SmPC	Summary of Product Characteristics

PART I: PRODUCT(S) OVERVIEW

Table Part I.1: Product(s) Overview

Active substance(s) (INN or common name)	beremagene geperpavec
Pharmacotherapeutic group(s) (ATC Code)	dermatologicals D03AX16
Marketing Authorisation Applicant	Krystal Biotech Netherlands, B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Vyjuvek (beremagene geperpavec)
Marketing authorisation procedure	Centralised

Brief description of the product	Vyjuvek (beremagene geperpavec [B-VEC]) is an engineered non-replicating herpes simplex virus (HSV) type 1-based vector coding human COL7A1 that can be applied cutaneously to promote functional COL7 expression in the skin. As Vyjuvek is non-integrating and its genes remain physically separate from the host cell chromosome, it does not carry the potential risk of insertional mutagenesis and the resulting possibility of disrupting essential host genes and triggering oncogenesis. Upon application to cutaneous wounds, Vyjuvek transduces both keratinocytes and fibroblasts. Following entry into the cell, Vyjuvek is transported down microtubules using microtubule cargo proteins like dynein to reach the nucleus, and the viral genome is deposited therein. Once in the nucleus, the episomal genome recruits the host's transcriptional machinery to initiate expression of the human COL7A1 transgenes. The resulting transcripts allow for production of a precursor protein, Procollagen 7, that is secreted by the cell and proteolytically processed. Once these proteins are cleaved, they arrange themselves into long, thin bundles of mature COL7 that form anchoring fibrils (AF). The AFs hold the epidermis and dermis together and are essential for maintaining the integrity of the skin.
Hyperlink to the Product Information	Not applicable at this time; will provide at the time of MAA submission.
Indication(s) in the EEA	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.
Dosage in the EEA	Recommended once weekly dose of Vyjuvek is: • 4×10^9 plaque forming units (PFU) for ages 3 years and older • 2×10^9 PFU for ages less than 3 years
Pharmaceutical form(s) and strengths	Suspension and gel for gel for cutaneous use; 5×10^9 PFU/mL per vial (1mL withdrawable) and 1.5mL per vial of excipient gel
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

Vyjuvek (beremagene geperpavec [B-VEC], in this document for consistency and previously known as KB103), is an engineered non-replicating herpes simplex virus (HSV) type 1-based vector coding human *COL7A1* that can be applied cutaneously to promote functional COL7 expression in the skin. As Vyjuvek is non-integrating and its genes remain physically separated from the host cell chromosome, it does not carry the potential risk of insertional mutagenesis and the resulting possibility of disrupting essential host genes and triggering oncogenesis.

Vyjuvek is a gene therapy indicated for the treatment of wounds in patients with dystrophic epidermolysis bullosa (DEB), from birth. Based on data from the clinical development program, weekly treatment with Vyjuvek for 26 weeks was well tolerated overall with few adverse reactions. As a cutaneous treatment, biodistribution is restricted to the site of application without evidence of significant systemic exposure. Vector shedding from wounds was minimal and considered non-infectious. No serious or severe adverse reactions were observed. Erythema was the only symptom that was deemed causally related and was mild or moderate in nature and did not result in discontinuation of treatment.

Treatment with Vyjuvek led to detectable antibodies to HSV-1 and COL7 in some subjects but was not associated with any safety events or clinically relevant immunologic reactions.

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Vyjuvek is a gene therapy indicated for the treatment of wounds in patients with DEB, from birth.

DEB is a serious, ultra-rare genetic blistering disease caused by mutations in *COL7A1*, the gene encoding type VII collagen (COL7) (Uitto 1994, Varki 2007). DEB is inherited in an autosomal dominant or autosomal recessive pattern depending on the subtype. The disease, which can present as early as birth, is characterized by skin fragility, separation of the epidermis from the dermis (blister formation), milia, and scarring (Bruckner 2020, Intong 2012). DEB-associated blisters and erosions affect skin as well as certain mucosa exposed to disruptive external environments, including the oropharynx, esophagus, rectum, genitourinary system, and eyes.

Healing of erosions can result in debilitating scarring.

As this is an autosomal inherited disease, both genders have an equal probability of inheritance and therefore the proportion of male:female affected by the disease is generally considered to be 1:1 (Has 2020). The majority of patients present with symptoms within the first year of life.

Regardless of the timing of appearance of symptoms, there may be a delay in accurate diagnosis due to the rarity of the disease (Feinstein 2019). It is not well understood whether this disease is more prevalent in specific racial or ethnic groups.

The most reliable estimates of the prevalence of epidermolysis bullosa (EB) are derived from the National Epidermolysis Bullosa Registry, a cross-sectional and longitudinal epidemiological study of 3,300 patients with confirmed EB across the entire continental United States (US) from 1986 to 2002 (Fine 2016). Based on this 16-year analysis of registry data, the prevalence of recessive DEB (RDEB) in the US was estimated to be 1.35 persons per million inhabitants and the prevalence of dominant DEB (DDEB) was estimated to be 1.49 persons per million inhabitants.

The most severe form of DEB is RDEB, in which COL7 protein expression is severely diminished or completely absent in the patient's skin due to null mutations in the *COL7A1* gene. A systematic literature review of the disease burden in patients with RDEB that included 65 studies was recently published (Tang 2021). It was reported that 60% of patients had wounds covering more than 30% of their bodies, with pain and itch seen with the larger wounds.

Commonly reported symptoms and complications included lesions and blistering, anemia, nail dystrophy and loss, milia, infections, musculoskeletal contractures, strictures or stenoses, constipation, malnutrition/nutritional problems, pseudosyndactyly, ocular manifestations, and dental caries.

Persistent blistering begins at birth and contributes to the high mortality risk due to bacterial infection. In a study of 41 RDEB patients, pneumonia and sepsis resulted in the death of 14.6% and 9.8% of these patients, respectively (Fine 2010). Patients who survive bacterial sepsis during early infancy are at a high risk of later developing severe complications such as growth retardation due to gastrointestinal involvement (Fine 2008), multifactorial anemia, esophageal strictures, corneal scarring and/or progressive blindness (Fine 2004), post streptococcal glomerulonephritis, renal failure, progressive hand and foot deformities such as pseudosyndactyly (Fine 2005), muscle contractures that restrict movement, microstomia, obliteration of the oral vestibule, dysphagia, rapid tooth decay, nail deformities, and hair loss.

Additionally, patients suffering from RDEB have a high risk of developing squamous cell carcinoma (SCC), which is highly aggressive and life-threatening. The risk of SCC was 76%, with mortality from SCC reaching 84% by age 40 (Tang 2021). There is significant mortality associated with RDEB; nearly 10% of the patients died before age 10, almost 40% by age 20, and 72% before the age of 30 (Varki 2007). These deaths occur despite aggressive tumor resection. While not as prevalent as in RDEB, SCC also poses a significant risk for patients with DDEB (Montaudié 2016), with tumors occurring later in life and tending to be less aggressive.

There are no approved corrective treatment options for DEB patients. Currently, management of DEB is supportive in nature and limited to palliative care. Standard of care is tailored to reduce trauma and infections while managing the symptoms associated with multiple wounds of varying duration, size, and healing stage (Rashidghamat 2016). Regimented personal hygiene and skincare are necessary to promote wound healing and to prevent infection and wound growth (Bruckner 2020, Denyer 2017). Pain medications are commonly used. Surgery is indicated for co-morbidities such as pseudosyndactyly, esophageal strictures, and skin cancer.

DEB patients in general, and RDEB patients in particular, require a broad spectrum of medications, specialized care, and nutritional support. The specific approach to wound care for RDEB is dependent on a number of variables and usually consists of a combination of therapies including medicated ointments, functional wound dressings, foams, and gauzes (Bruckner 2020). The burden of wound care for RDEB is substantial, requiring daily changes of wound dressings that can take several hours (Hsu 2014). Thirteen to 54% of patients report daily dressing changes and 15% to 40% report spending up to 3 hours per change. The estimated annual US costs for wound dressings ranged from $4,000 to $245,000 (Tang 2021).

One advance is the use of gastrostomy tubes, which allow feeding at night (Ingen-Housz-Oro, 2004). Frequently RDEB patients are unable to eat during the day because of painful erosions and blisters in the mouth and esophagus. Pain control is often used during daily dressing changes. As the surface area of the wounds increases, patients suffer more severe pain and immobility and may require narcotics

(Herod 2002). Overall, this is a devastating and life-threatening disease with little hope for the individual or the family.

Other than Vyjuvek, there is one other approved therapy for DEB, Filsuvez, (a topical gel formulation containing birch triterpene extract made from dried birch bark) that has been investigated in a double-blind study of patients with EB, including DEB. The birch triterpene extract showed 41% wound closure within 45 days of treatment compared to 29% with placebo (Murrell 2020). The exact mechanism of action remains unclear, although is purported to be associated with general anti-inflammatory properties of the extract. Filsuvez was approved in the EU on 21 June 2022 for the treatment of partial thickness wounds associated with DEB and junctional EB (JEB) in patients 6 months and older (Filsuvez assessment report EMA/260035/2022, Procedure No. EMEA/H/C/005035/0000, European Medicines Agency, 22 April 2022). Filsuvez was approved by the USFDA on 18 December 2023 for the treatment of wounds associated with dystrophic and junctional epidermolysis bullosa in adult and pediatric patients 6 months of age and older.

Earlier attempts at corrective therapy for RDEB have faced substantial challenges (Marinkovich 2019, Bruckner-Tuderman 2019, Lwin 2022). Bone marrow transplantation promoted COL7 expression and wound healing but was associated with a mortality rate approaching 30% (Wagner 2010). Alternatively, autologous cell-based *ex vivo* gene therapy methods have been explored in patients with DEB (Siprashvili 2016, Lwin 2019). Such *ex vivo* approaches require integrating viral transfer of the *COL7A1* gene into keratinocytes or fibroblasts harvested from patients, which are then transplanted back as an epidermal graft or by intradermal injection.

Drawbacks to previously explored therapies include the need for complex manufacturing and product handling processes, potential for oncogenesis due to non-specific integration of the transgene into the host genome, extended travel of fragile patients to specialized centers, risks associated with general anesthesia, and prolonged immobilization for graft integration.

Given the severity of DEB, its associated mortality and morbidity, and the lack of effective treatment options, there exists a clear need for therapies that focus on the root cause of the debilitating symptoms and that can be administered in a minimally invasive way.

Part II: Module SII - Nonclinical part of the safety specification

Single-Dose Toxicity and Biodistribution (Topical Administration)

Female BALB/cAnNCrl mice received CCI PFU of B-VEC (or vehicle) mixed with a methylcellulose gel excipient via topical administration to a skin wound on Day [redacted] and underwent toxicity assessments at Day [redacted] and CCI based on mortality, clinical observations, body weights, food consumption, and clinical and anatomic pathology. No B-VEC-related effects on clinical observations, body weights, or food consumption, were observed. No B-VEC-related mortality or macroscopic or microscopic observations were noted. Vyjuvek related clinical pathology changes were limited to minimally higher blood glucose concentrations and mildly to moderately higher total white blood cell count and absolute neutrophil, lymphocyte, and large unstained cell counts, suggestive of mild, Vyjuvek-associated inflammation two days post administration. B-VEC-related lower thymus weights occurred on Day [redacted] but were not noted on Day CCI, which indicated reversibility. Due to the mild severity of findings and the lack of impact on the health and well-being of animals administered CCI PFU B-VEC, effects for this dose were considered non-adverse.

B-VEC vector DNA was detected in all B-VEC-treated skin dose sites with values between

CCI and CCI copies/µg DNA. Most other samples from B-VEC-treated animals were negative. These data indicate that there was no pronounced accumulation of B-VE in analyzed tissues other than the B-VEC-treated skin dose site.

Repeat Dose Toxicity and Biodistribution

Male and female BALB/cAnNCr1 mice were assigned to three groups, and animals were administered low (CCI PFU) or high (CCI PFU) dose B-VEC or vehicle control once weekly for CCI weeks (Days CCI , and CCI) via intradermal injection into intact skin of the dorsal thoracic region. Toxicity assessments were conducted at Days CCI and CCI for subsets of these animals. Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, and clinical and anatomic pathology. B-VEC-related dose site scabbing was noted for animals administered the high dose (CCI PFU/day) of B-VEC. Formulations of the low dose CCI PFU/day) of B-VEC were tolerated when administered via intradermal injection once weekly for CCI or CCI doses. Due to the lack of impact on the health and well-being of animals administered the low dose (CCI PFU/day) of B-VEC, effects for this dose were considered non-adverse.

Blood and tissue samples were tested by qPCR for biodistribution of the vector genome upon intradermal injection. The vector was detected in the injection sites sampled during the dosing phase from animals administered B-VEC, with values between CCI and CCI copies/µg of DNA. No pronounced accumulation of B-VEC in analyzed tissues other than the site of injection was noted, and vector genome persistence in mouse skin was minimal, as indicated by low copy numbers obtained in samples analyzed from recovery phase animals.

The genotoxic potential of B-VEC has not been evaluated in long-term animal or human studies. Because HSV-1 does not integrate into, or otherwise disrupt, the host genome, the risk of insertional mutagenesis of B-VEC is negligible. The sufficiency of this assessment is in line with the regulatory precedent set by a previously FDA- and EMA- approved HSV-1-based vector, talimogene laherparepvec (Imlygic®), which did not include studies on the vector's potential for genotoxicity. The carcinogenic potential of B-VEC has not been evaluated in long-term animal or human studies. However, available data for both B-VEC and wild-type HSV-1 do not indicate a carcinogenic risk in humans.

Additionally, because HSV-1 remains episomal and does not integrate into, or otherwise disrupt, the host genome (Zhou 1999, Lachmann 2004), the risk of insertional mutagenesis of B-VEC is negligible, and the encoded transgene (human *COL7A1*) is not a known oncogene, so treatment- emergent tumorigenicity was unlikely. Moreover, histopathological evaluations from the standard toxicity studies for B-VEC did not indicate any findings of interest in relation to potential tumor induction. Finally, the intended patient population for B-VEC (those with DEB) are not immunocompromised by either the disease state or concurrent palliative therapy. As such, specific tumorigenic or oncogenic studies of B-VEC were not conducted, in consideration of ICH guideline S6, given the product's identity, mechanism of action, and intended patient population.

The potential for reproductive and development toxicity of B-VEC has not been evaluated in long-term animal or human studies. However, there were no significant impacts to male or female reproductive tissues or accumulation of vector therein following treatment of adult mice by intravenous, topical, or intradermal routes of administration, irrespective of dose frequency. In addition, no significant systemic vector exposure was observed (blood or urine samples) after local B-VEC administration in the Phase 1/2 or 3 clinical trials, suggesting containment of the product to

cutaneous wounds. In addition, no adverse developmental findings were reported to- date in any adolescent subjects (those <18 years of age) that received B-VEC as part of clinical development.

Part II: Module SIII - Clinical trial exposure

The Phase 1/2 study (KB103-001) enrolled 9 individual subjects, 3 of whom re-enrolled in a later phase of the study for different wounds after a washout period. For purposes of analysis these subjects were counted separately in the different phases, so the total number of subjects enrolled is considered to be 12. All subjects were considered to have completed the study except one study subject who withdrew after 4 weeks due to an inability to travel.

The Phase 3 study (B-VEC-03) enrolled 31 subjects, 5 of whom were rolled over from KB103-001 with different wounds studied after an adequate washout. Twenty-eight (28) subjects completed the study, and 3 subjects withdrew from the study for reasons unrelated to treatment.

A total of 35 individuals were exposed to B-VEC in one or both of the randomized studies. Of these, 6 subjects were exposed in more than one phase/protocol, with treatment to different wounds in different treatment durations.

Table SIII.1: Duration of exposure Study Treatment B-VEC Exposure (Safety Population)

	KB103-001 (N=12)	**B-VEC-03 (N=31)**	**Pooled (N=43)**
Number of days of therapy			
Mean (SD)	52.3 (27.07)	166.7 (32.08)	134.8 (60.18)
Median	53.0	176.0	175.0
Min, Max	5, 96	40, 187	5, 187
Number of weeks of therapy (weeks only), N (%)			
0	0	0	0
1-4	3 (25.0)	0	3 (7.0)
5-8	3 (25.0)	1 (3.2)	4 (9.3)
9-12	4 (33.3)	1 (3.2)	5 (11.6)
13-16	2 (16.7)	0	2 (4.7)
17-20	0	2 (6.5)	2 (4.7)
21-24	0	3 (9.7)	3 (7.0)
25-26	0	24 (77.4)	24 (55.8)

SD = standard deviation

Table SIII.2: Age Group and Gender Exposure

	Age (Years)			Gender	
Characteristics	**≤ 12 (N=10)**	**>12 and ≤ 18 (N=9)**	**>18 (N=12)**	**Male (N=20)**	**Female (N=11)**
Number of days of therapy					
n	10	9	12	20	11
Mean (SD)	171.1 (16.34)	158.2 (46.10)	166.5 (30.50)	173.1 (11.72)	152.0 (49.69)
Median	177.0	176.0	176.0	176.0	176.0
Min, Max	126, 183	40, 187	70, 178	126, 187	40, 183
Number of weeks of therapy (weeks only), N (%)					
0	0	0	0	0	0
1-4	0	0	0	0	0
5-8	0	1 (11.1)	0	0	1 (9.1)
9-12	0	0	1 (8.3)	0	1 (9.1)
13-16	0	0	0	0	0
17-20	1 (10.0)	1 (11.1)	0	1 (5.0)	1 (9.1)
21-24	2 (20.0)	0	1 (8.3)	3 (15.0)	0
25-26	7 (70.0)	7 (77.8)	10 (83.3)	16 (80.0)	8 (72.7)
>26	0	0	0	0	0

Note: Percentages are based on the number of subjects in the Safety population.

Table SIII.3: Maximum Weekly Dose Exposure

	Max Weekly Dose (PFU)		
Characteristics	**1.2×10^9 (N=2)**	**4×10^8 (N=23)**	**8×10^8 (N=6)**
Number of days of therapy			
n	2	23	6
Mean (SD)	177.0 (1.41)	166.2 (30.37)	159.5 (43.95)
Median	177.0	176.0	175.5
Min, Max	176, 178	40, 187	70, 183
Number of weeks of therapy (weeks only), N (%)			
0	0	0	0
1-4	0	0	0
5-8	0	1 (4.3)	0
9-12	0	0	1 (16.7)
13-16	0	0	0
17-20	0	2 (8.7)	0
21-24	0	3 (13.0)	0
25-26	2 (100)	17 (73.9)	5 (83.3)
>26	0	0	0

PFU= plaque-forming units
Note: Percentages are based on the number of subjects in the Safety population

Table SIII.4: Ethnicity Exposure

Characteristics	Hispanic or Latino (N=16)	Not Hispanic or Latino (N=15)
Number of days of therapy		
n	16	15
Mean (SD)	164.9 (35.63)	166.3 (28.52)
Median	176.0	175.0
Min, Max	40, 178	70, 187
Number of weeks of therapy (weeks only), N (%)		
0	0	0
1-4	0	0
5-8	1 (6.3)	0
9-12	0	1 (6.7)
13-16	0	0
17-20	1 (6.3)	1 (6.7)
21-24	0	3 (20.0)
25-26	14 (87.5)	10 (66.7)
>26	0	0

Note: Percentages are based on the number of subjects in the Safety population.

Part II: Module SIV - Populations not studied in clinical trials

The populations that were not studied in clinical trials included pregnant and lactating women, and older patients >45 years of age. Pregnant women, lactating women were excluded from the clinical trials. Although not excluded, there were no pediatric patients <6 months of age or adults >45 years of age in the studies. Due to the mechanism of action of Vyjuvek, there is no reason to believe that pediatric patients <6 months of age, and older patients >45 years of age would respond any differently than those who participated in the studies The use of Vyjuvek is not recommended during pregnancy. For lactating women, a risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Vyjuvek therapy considering the benefit of breast feeding for the child and the benefit of therapy for the woman.

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Pregnant patients

Reason for exclusion: There is no data from the use of Vyjuvek in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. The use of Vyjuvek is not recommended during pregnancy. Until a broader safety profile is established, this patient population was excluded to avoid exposing fetuses in utero and young infants through breast feeding.

Considered to be included as missing information: No

Rationale: The use of Vyjuvek is not recommended during pregnancy and therefore information will remain unavailable.

Lactating patients

Reason for exclusion: It is unknown whether Vyjuvek is excreted in human milk. A risk to the newborns/infants cannot be excluded. Until a broader safety profile is established, this patient population was excluded to avoid exposing fetuses in utero and young infants through breast feeding.

Considered to be included as missing information: No

Rationale: A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Vyjuvek considering the benefit of breast feeding for the child and the benefit of therapy for the woman.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions due to the limited number of subjects, adverse reactions caused by prolonged exposure greater than 26 weeks, or adverse reactions with long latency of onset. Due to the intra-patient design of the Phase 3 study, all subjects received both Vyjuvek and placebo.

Therefore, it was not possible to differentiate whether a systemic AE (such as chills) was related to Vyjuvek or placebo.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of Special Population	Exposure
Pregnant Patients	Not included in clinical development program. There are no available data regarding the use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.
Lactating Patients	Not included in clinical development program. There is no information available on the presence of Vyjuvek in human milk, the effects on the breastfed infant, or the effects on milk production. Vyjuvek is not detected systemically following cutaneous application.
Pediatric patients <6 months of age	No pediatric patients <6 months of age were enrolled in clinical studies.
Older Patients >45 years of age	No patients >45 years of age were enrolled in clinical studies.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Vyjuvek Real World Evidence (RWE) is based on the US Open Label Extension (OLE) study (NCT04917874), US post-marketing experience, and one patient from EU early access program. As of 22-NOV-2024, the RWE of Vyjuvek includes CCI treated patients and 273.9 patient-years of experience. This is over 13 times greater than the number of patients enrolled in the GEM-3 trial (31) and is adequately distributed over subgroups of interest, as summarized in the tables below.

Table 1 Vyjuvek Real-World Evidence

Patient Subgroup	Patient Count	Total wks (yrs) [Min wks, Max wks]	Age Range (yrs)	Sex Ratio M : F
All	CCI	14,242 (273.9) [1, 177]	CCI	CCI

DDEB/RDEB distribution in RWE

Across CCI Vyjuvek treated patients in the US and EU real-world settings, CCI patients were DDEB, CCI patients were RDEB, and CCI patients were unknown type.

Table 2 Vyjuvek Real-World Evidence by Diagnosis

Diagnosis	Patient Count	Total wks (yrs) [Min wks, Max wks]	Age Range (yrs)	Sex Ratio M : F
DDEB	CCI	1,847 (35.5) [1, 84]	CCI	CCI
RDEB	CCI	11,943 (229.7) [1, 177]	CCI	CCI
Unknown	CCI	452 (8.7) [1, 55]	CCI	CCI

Age distribution in RWE

In the real-world setting, Vyjuvek has been administered to patients ages ranging from CCI days to over CCI years. Each age group considered includes both RDEB and DDEB diagnoses as well as balanced representation between patient sexes (Table 3).

Table 3 Vyjuvek Real World Evidence by Age Group and Diagnosis

Age Subgroup* (yrs)	Diagnosis	Patient Count	Total wks (yrs) [Min wks, Max wks]	Age Range (yrs)	Sex Ratio M : F
<1	DDEB	[redacted]	50 (1.0) [11, 20]	[redacted]	[redacted]
<1	RDEB	[redacted]	367 (7.1) [3, 112]	[redacted]	[redacted]
1 to <3	DDEB	[redacted]	164 (3.2) [4, 57]	[redacted]	[redacted]
1 to <3	RDEB	[redacted]	1050 (20.2) [4, 131]	[redacted]	[redacted]
1 to <3	Unknown	[redacted]	18 (0.3) [18, 18]	[redacted]	[redacted]
3 to <46	DDEB	[redacted]	1083 (20.8) [1, 84]	[redacted]	[redacted]
3 to <46	RDEB	[redacted]	9931 (191.0) [1, 177]	[redacted]	[redacted]
3 to <46	Unknown	[redacted]	332 (6.4) [1, 55]	[redacted]	[redacted]
>=46	DDEB	[redacted]	550 (10.6) [1, 62]	[redacted]	[redacted]
>=46	RDEB	[redacted]	595 (11.4) [1, 56]	[redacted]	[redacted]
>=46	Unknown	[redacted]	102 (2.0) [2, 41]	[redacted]	[redacted]

* At the time of first treatment

Greater than 104 weeks of Vyjuvek treatment

Certain patients who initiated Vyjuvek treatment during the US OLE and continued with US post-marketing have received greater than 104 weeks of treatment. Cumulatively, these [redacted] patients contribute 57.4 patient-years of experience.

Table 4 Vyjuvek Real World Evidence by Treatment Duration and Diagnosis

Treatment Duration	Diagnosis	Patient Count	Total wks (yrs) [Min wks, Max wks]	Age Range (yrs)	Sex Ratio M : F
>= 104 wks	RDEB	[redacted]	2,984 (57.4) [104, 177]	[redacted]	[redacted]

Summary

As seen in the extrapolation concept plan, for an ultra-rare disorder, Vyjuvek DEB patient experience based on US OLE, US post-marketing, and EU early access program is robust, significant, and broad with adequate patient counts and experience for subgroups of interest. The Vyjuvek patient experience

profile reported in the extrapolation concept plan will continue to improve based on the ongoing, successful US Vyjuvek post marketing experience.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Vyjuvek does not have characteristics that would make it attractive for use for illegal purposes; therefore, the potential for misuse of the product for illegal purposes is highly unlikely**.**

SVII Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Immune-mediated adverse reactions were not observed in clinical studies and therefore are not categorized as an important potential risk.

Antibodies against HSV-1 and COL7 were present in a subset of patients after treatment with Vyjuvek; however, their presence was not associated with any observable difference in treatment efficacy or any immune related adverse reactions. Notably, anti-HSV- 1 antibodies are detectable in more than half of the US population, therefore, seroconversion alone, in the absence of an adverse reaction, is not considered an important risk.

Overall, levels of the antibodies (HSV-1 and COL7) are not expected to have a significant impact on the benefit-risk profile of Vyjuvek. However, out of an abundance of caution, in addition to routine pharmacovigilance, if any immune related adverse events are reported, then the healthcare provider (HCP) will be asked to collect blood samples to evaluate antibodies against HSV-1 and COL7 to evaluate its impact.

Infections in the home setting are not considered important for inclusion in the list of safety concerns because the precautions used to administer Vyjuvek would be the same in a home setting as in the healthcare setting. Patients and caregivers will follow the instructions for PPE as described in SmPC and the patient leaflet. In the event of an infection, it is unlikely that the cause of infection can be attributed to Vyjuvek because this patient population can have routine infections from their open wounds. In addition, routine standard of care topical ointments such as Vaseline and Aquaphor are used and administered in this patient population in a non-sterile manner. In any case, the occurrence of any treatment related infections will be captured as part of routine pharmacovigilance and is already covered in the primary objective of the PASS, where treatment related adverse events will be captured.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Descriptions of the initially proposed important identified risks, important potential risks, and missing information are provided herein; changes will be captured in Section SVII.2.

SVII1.2.1 Important Identified risk

None

SVII 1.2.2 Important Potential Risk -Exposure of health care providers (HCP) and caregivers to Vyjuvek during preparation or administration

Benefit-Risk Impact

To date, there have been no reported exposures/adverse events related to mixing and/or administration, in the clinical setting nor the commercial setting that includes home dosing. However, exposure to Vyjuvek during these procedures is possible, and is considered as a potential risk.

SVII 1.2.3 Important Potential Risk – Accidental exposure of Vyjuvek from patient to close contacts or HCP via direct contact with administered wounds or body fluids

Benefit-Risk Impact

To date, there have been no reported exposures/adverse events related to mixing and administration in the clinical setting nor the commercial setting that includes home dosing. However, exposure to Vyjuvek during these procedures is possible, and is considered as a potential risk.

SVII 1.2.4 Important Potential Risk – Medication errors in the clinical and home setting

Benefit-Risk Impact

As of November 2024, around CCI patients have been dosed at a home setting with commercial Vyjuvek in the US with no reported medication errors. However, medication errors in the home setting are possible, and considered a potential risk.

SVII.1.2.5 Missing Information – Long-term safety

Benefit-Risk Impacts

As of 22-NOV-2024, exposure data as referenced in Table 4, provides exposure data on subjects treated with Vyjuvek. Vyjuvek is intended as a chronic treatment. Hence, further monitoring is needed to continue to evaluate safety of chronic use.

SVII.1.2.6 Missing Information –Safety in patients less than 6 months of age

Benefit-Risk Impacts

See Table 3 for data on exposure for patients on commercial Vyjuvek ages 6 months and below. However, this data is limited. Hence, further characterisation is needed to continue to evaluate safety in patients less than 6 months of age.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not Applicable in initial version of EU RMP.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1 Important Identified Risks

None

SVII 3.1.2 Important Potential Risk -Exposure of HCP and caregivers to Vyjuvek during preparation or administration

Potential Mechanisms

The likelihood of exposure to the HCP/caregiver increases during preparation and administration of Vyjuvek. However, this risk is minimal-to-none unless, in the event of exposure to the HCP/caregiver the contact area is compromised (such as a break in their skin or if exposure to the mucus membrane).

Evidence source(s) and strength of evidence

Vyjuvek does not penetrate intact skin and stays locally in the exposed area with no risk of systemic exposure. The vector upon transfecting cells does not replicate or integrate and is transient and clears with turnover of the cells. There has been no reporting of this exposure to HCP/caregivers to date in the clinical or commercial setting.

Characterisation of the risk

In the event of exposure, the vector will be localized to the exposed area. Based on the mechanism of action, the vector cannot penetrate intact skin. In the event of exposure through compromised skin, then the safety concern is minimal because of the localized, transient, non-replicating nature of the vector. There was no systemic exposure of the vector detected in patients treated with Vyjuvek. In the clinical and commercial setting, there have been no reported exposure to HCP or caregivers

Risk factors and risk groups

HCPs, patient caregivers, and close contacts.

Preventability

HCPs and caregivers will be provided risk minimisation tools outside of the SmPC to ensure proper handling of Vyjuvek.

Impact on the benefit-risk balance of the product

To date, there have been no reports of events related to exposure.

Public health impact

Since treatment is contained to the clinical or home setting, there are no public health impacts.

SVII 3.1.3 Important Potential Risk - Accidental exposure of Vyjuvek from patient to close contacts or HCP via direct contact with administered wounds or body fluids

Potential Mechanisms

The likelihood of exposure from wounds treated with Vyjuvek to close contacts or HCP is minimal-to-none unless the location of contact area is compromised (such as a break in their skin or if exposure to the mucus membrane).

Evidence source(s) and strength of evidence

Vyjuvek does not penetrate intact skin and stays locally in the exposed area with no risk of systemic exposure. The vector upon transfecting cells does not replicate or integrate and is transient and clears with turnover of the cells. There has been no reporting of this exposure of Vyjuvek from patient to close contacts or HCP via direct contact with administered wounds or body fluids to date in the clinical or commercial setting.

Characterisation of the risk

In the event of exposure, the vector will be localized to the exposed area. Based on the mechanism of action, the vector cannot penetrate intact skin. In the event of exposure through compromised skin, the safety concern is minimal because of the localized, transient, non-replicating nature of the vector. There was no systemic exposure of the vector detected in patients treated with Vyjuvek. In the clinical and commercial setting, there have been no reported exposure from patients to close contacts or HCP via direct contact.

Risk factors and risk groups

HCPs, patient caregivers, and close contacts.

Preventability

HCPs and caregivers will be provided risk minimisation tools outside of the SmPC to ensure proper handling of Vyjuvek.

Impact on the benefit-risk balance of the product

To date, there have been no reports related to exposure. Also, there were no exposure-related adverse events in the clinical and commercial setting.

Public health impact

Since treatment is contained to the clinical or home setting, there are no public health impacts.

SVII 3.1.4 Important Potential Risk -Medication errors in the clinical and home setting

Potential Mechanisms

Mistakes in the storage of Vyjuvek could lead to a decrease in the potency of the product.

Improper administration could affect the optimal use of the dose volume to treat the maximum available wounds at the time of administration.

Evidence source(s) and strength of evidence

Based on the stability data of Vyjuvek following the recommended storage (See SmPC section 6.3) is necessary to maintain the potency of the product. Failure to maintain the storage condition could result in a potentially sub-potent product.

Due to the fixed weekly maximum dose and the waxing and waning nature of the wounds in this patient population, there may be variability in Vyjuvek administered to the wound area from week to week. Differences in dosing are not expected to increase risk to the patient or impact the overall efficacy or safety of the product.

Characterisation of the risk

This administration approach was used in clinical studies and is currently used in the commercial setting. There have been no reported medication errors in the commercial setting, including the home setting.

Risk factors and risk groups

Patients receiving Vyjuvek

Preventability

HCPs and caregivers will be provided with risk minimisation tools outside of the SmPC to ensure proper handling and administration of Vyjuvek.

Impact on the benefit-risk balance of the product

To date, there have been no reports of medication error events in the commercial setting. In the event of a medication error, it is unlikely to be significant given the safety profile of Vyjuvek. The benefit to patients outweighs any potential risk.

Public health impact

Since treatment is contained to the clinical or home setting, no public health impact is anticipated.

SVII.3.2.1 Missing Information – Long-term safety

Evidence source

Data on long-term exposure are provided in Table 4. However, long-term safety data are considered missing and further information/characterisation is needed.

Population in need of further clarification

Long-term safety data continues to be collected under post-marketing routine surveillance and proposed post-authorisation studies.

SVII.3.2.2 Missing Information – Safety in patients less than 6 months of age

Evidence source

Patients less than 6 months were not included in the clinical studies. Limited commercial data in this population is available (see Table 3). However, this patient population is eligible to receive Vyjuvek in the commercial setting. The benefit of early treatment outweighs the risks because the severity of the disease increases with age. Based on this, safety data within the age group is considered missing information. Further characterization is needed.

Population in need of further clarification

Patients less than 6 months of age will be evaluated and monitored through post-authorisation studies and routine surveillance.

SVIII Summary of Safety Concerns

Table SVIII.1 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• None

Important potential risks	• Exposure of HCP and caregivers to Vyjuvek during preparation or administration • Accidental exposure of Vyjuvek from patient to close contacts or HCP via direct contact with administered wounds or body fluids • Medication errors in the clinical and home setting
Missing information	• Long-term safety • Safety in patients less than 6 months of age

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

The safety of Vyjuvek will be monitored via routine pharmacovigilance activities including the following:

- Krystal has well established systems and processes for the collection, review, analysis and submission of adverse event reports
- Preparation of reports to regulatory authorities: Expedited safety reports, Aggregate reports [Periodic Benefit Risk Evaluation Reports (PBRERs)/Periodic Safety Update Reports (PSURs)]
- Continuous monitoring of the evolving safety profile of Vyjuvek through signal detection and evaluation of safety issues
- Updates to label when required and prompt communication to regulatory authorities, prescribers, caregivers and patients

III. 2 Additional Pharmacovigilance Activities

III. 2.1 Post surveillance safety study (PASS)

PASS-01 is a prospective, non-interventional, multi-country study to confirm the long-term safety profile, including in paediatric patients less than 6 months of age, receiving Vyjuvek for the treatment of DEB wounds, in a real-life clinical setting.

Rationale and Study Objectives

The **primary objective** of the study is to evaluate the occurrence of treatment related adverse events in patients with DEB treated with Vyjuvek, in a long-term follow-up study, as ascertained by the treating healthcare professional. This will include the assessment of the safety of Vyjuvek in patients with DEB with less than 6 months of age, the occurrence of adverse events with delayed manifestation, and treatment discontinuations/interruptions due to safety reasons.

As **secondary objectives**, this study will evaluate:

- the occurrence of medication errors;
- the occurrence of accidental exposure of Vyjuvek from patient to close contacts or HCP via direct contact with administered wounds or body fluids;
- the effectiveness of the additional Risk Minimization Measures (aRMM), as defined in the Risk Management Plan, aimed at reducing accidental exposure and medication errors, particularly in the home setting;
- the effectiveness of Vyjuvek in real-life clinical practice.

Study design:

PASS-01 is a prospective, non-interventional, multi-country and multi-centre study, based on primary data collection, to be conducted in the U.S., Germany and France (additional countries may be added if needed to achieve the projected sample size). The study will have a 2-year enrolment period, followed by a 5-year follow-up period.

All patients with DEB receiving treatment with Vyjuvek and meeting the inclusion/exclusion criteria will be documented in the study. The prescribing physician's decision that Vyjuvek treatment is in the patient's best interest is to be made before and independently of his/her decision to invite the patient to participate in the study. At all times during the study, patients will be treated and monitored according to the approved Vyjuvek label (Summary of Product Characteristics in EU and Prescribing Information in US), the prescribing physician's routine clinical practice and no additional clinical visits or invasive tests will be performed.

To fulfil the primary and secondary objectives of the study, data will be collected on all variables of interest when patients attend their standard of care visits, which are expected to occur approximately every 3 to 6 months.

Study Population:

Patients with DEB receiving treatment with Vyjuvek and close contacts such as treating HCPs and caregivers.

Milestones:

- Protocol submission within 3 months after the Marketing Authorisation
- Registration in the European (EU) PAS register: Within 30 days after protocol endorsement by European Medicines Agency (EMA)
- Anticipated start of data collection: Q4 2025
- Anticipated end of data collection: Q4 2032
- An interim report will be generated when approximately 50 patients have completed a 1-year follow-up.
- Final Study Report: Q4 2034

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.1: Ongoing and planned additional pharmacovigilance activities

Study/Status	Summary of objectives	Safety concerns addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit-risk)				
PASS-01 A prospective, non-interventional, multi-country study to confirm the long-term safety profile, including in paediatric patients less than	The study primary objective will include the monitoring of: • long-term safety • safety in patients less than 6 months The secondary objectives of the study are to assess:	Long-term safety Safety in patients less than 6 months of age Exposure of HCP and caregivers to Vyjuvek during preparation or administration Accidental exposure of Vyjuvek from patient to close contacts or HCP	Registration in the European (EU) PAS register	Within 30 days after protocol endorsement by European Medicines Agency (EMA)
			Anticipated start of data collection	31-DEC-2025
			Anticipated end of data collection	31-DEC-2032
			Progress reports	With every PSUR

6 months of age, receiving Vyjuvek for the treatment of DEB wounds, in a real-life clinical setting. Planned	• the occurrence of medication errors; • the occurrence of accidental exposure of Vyjuvek to HCPs, caregivers and close contacts; • the effectiveness of the aRMM • the effectiveness of Vyjuvek in real-life clinical practice.	via direct contact with administered wounds or body fluids Medication errors in the clinical and home setting	Interim report(s)	Once when approximately 50 patients have completed a 1-year follow-up
			Final Study Report	31-DEC-2034

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no post-authorisation efficacy studies planned at this time.

Table Part IV.1: Planned and ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations

There are no post-authorisation efficacy studies planned at this time.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V.1 Routine Risk Minimisation Measures

Careful consideration of the benefit-risk balance for Vyjuvek leads one to conclude that routine risk minimization activities are sufficient to manage the majority of the safety concerns associated with the drug. Routine risk communication primarily through product labeling describes the safety profile for the product and communicates to healthcare professionals the appropriate actions to prevent or mitigate risks, where those recommendations exist. In addition to the routine risk minimization measures, Educational Materials including training guides and videos will be provided to HCPs and patients/caregivers to support home administration of Vyjuvek (Section V.2) by a HCP or the caregiver/patient.

Routine pharmacovigilance activities are summarized in Section III.1, and if through routine pharmacovigilance new risks are identified, the risk communication and minimization measures will be updated as necessary.

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety Concern	Risk Minimisation Activities
Exposure of HCP and caregivers to Vyjuvek during	**Routine Risk Communication:** SmPC Section 4.2, 4.6 and 6.6 Package Leaflet (PL) Sections 2 and 6

Safety Concern	Risk Minimisation Activities
preparation or administration	**Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Section 4.2 describes the precautions to be taken before manipulating or administering Vyjuvek • Further details on precautions, handling and disposal of Vyjuvek are listed in Section 4.6 in the SmPC • Section 6.6 provides details on appropriate PPE that should be worn and the measures to take if there is accidental exposure and precautions with waste disposal • PL Section 2 and 6 provides information on accidental contact with Vyjuvek
	Other routine risk minimisation measures beyond the Product Information: B-VEC handling and administration should be conducted by a trained HCP/patient/caregiver.
Accidental exposure of Vyjuvek from patient to close contacts or HCP via direct contact with administered wounds or body fluids	**Routine Risk Communication:** SmPC Section 4.2, 4.6 and 6.6 PL Section 2 and 6.
	Routine risk minimisation activities recommending specific clinical measure to address the risk: • Section 4.2 in the SmPC describes the precautions to be taken before manipulating or administering Vyjuvek • Further details on precautions, handling and disposal of Vyjuvek are listed in Section 4.6 in the SmPC • Section 6.6 provides details on appropriate PPE that should be worn and the measures to take if there is accidental exposure and precautions with waste disposal • PL Section 2 and 6 provides information on accidental contact with Vyjuvek
	Other routine risk minimisation measures beyond the Product Information:

Safety Concern	Risk Minimisation Activities
	Vyjuvek handling and administration should be conducted by a trained HCP/patient/caregiver.
Medication errors in the clinical and home setting	**Routine Risk Communication:** SmPC Section 4.2 and 4.6 PL Sections 3 and 5
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • Posology and method of administration is outlined in Section 4.2 of the SmPC. • Further details on precautions, handling and disposal of Vyjuvek are listed in Section 4.6 in the SmPC • Section 3 in the PL describes how Vyjuvek is given to the patient • Section 5 in the PL describes how Vyjuvek is stored
	Other routine risk minimisation measures beyond the Product Information: B-VEC handling and administration should be conducted by a trained HCP/patient/caregiver.
Long-term safety	**Routine Risk Communication:** SmPC Section 4.4 PL Section 2
	Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation for long-term follow up is provided in SmPC Section 4.4 • Expectation for long-term monitoring are described in PL Section 2
	Other routine risk minimisation measures beyond the Product Information: B-VEC handling and administration should be conducted by a trained HCP/patient/caregiver.

Safety Concern	Risk Minimisation Activities
Safety in Patients Less Than 6 Months of Age	**Routine Risk Communication:** SmPC Section 4.8
	Routine risk minimisation activities recommending specific clinical measures to address the risk: As Vyjuvek has not been studied in patients <6 months in the clinical studies, recommendation to consider the benefits of treatment against the risks provided in SmPC Section 4.8.
	Other routine risk minimisation measures beyond the Product Information: B-VEC handling and administration should be conducted by a trained HCP/patient/caregiver.

V.2 Additional Risk Minimisation Measures

The effectiveness of the risk minimisation measures put in place will be evaluated via the PASS-01 study as well as aggregate safety data review. All reported treatment related adverse events will be reflected in the Periodic Safety Update Report (PSUR).

Additional Risk Minimisation Measures (aRMM) beyond product label will include training regarding preparation and administration of Vyjuvek as listed below:

- Guide for HCPs
- Guide for Patients and caregivers
- Vyjuvek dose preparation video
- Vyjuvek administration video

Each of these 4 additional risk minimization measures will address the 4 safety concerns: Exposure of HCP and caregivers to Vyjuvek during preparation or administration, accidental exposure of Vyjuvek from patient to close contacts or HCP via direct contact with administered wounds or body fluids, medication errors in the clinical and home setting, and long-term safety.

These aRMMs have been developed on the basis of preparation of the drug in pharmacies and administration in a healthcare setting or at the patient home by a HCP or the patient or his/her caregiver.

V2.1 Guide for HCPs

Objectives

The objective of the proposed aRMM is to inform HCPs (pharmacists, prescribing physicians, and/or nurses) of safe handling of the drug and guide the prescribing physicians on decision criteria with regards to home setting administration and caregiver administration to avoid accidental exposure or medication errors, and ensure long term safety. In addition, this guide will provide responses to commonly asked questions, tested hydrophobic dressing options, administration best practices and

wound management expectations to better train, and provide support to patients to ensure optimal use of Vyjuvek. The guide will also provide information for the prescribing physicians and nurses to counsel patients/caregivers regarding the risks and missing information. It also aims at providing additional information to the pharmacists and other HCPs for securing the logistical aspects of the mixed product to the healthcare setting or the patient home and waste management. Additionally, there is limited information regarding long-term safety of Vyjuvek. Therefore, prescribing physicians should encourage patients to participate in the long-term safety study PASS-01.

Rationale for the additional risk minimisation activity

Additional awareness and knowledge of HCPs (pharmacists, prescribing physicians and nurses) about the risks and best practices help to mitigate potential risks.

The information within the planned guide will address all elements related to the

Preparation and administration:

- Training on how to prepare and administer Vyjuvek, including a QR code with access to a preparation and administration video.
- Ability for the HCP to order a demonstration kit to facilitate the training of the HCP, patient, or caregiver.

Storage and transport:

- Appropriate storage conditions prior to and after mixing of Vyjuvek and handling of the drug
- Requirements for transport of prepared syringes to the setting of administration (including surveillance of temperature and timeline)

Administration objectives and patient/caregiver counselling:

- The appropriate dosing and treatment plan
- Detailed information on treated wound(s) dressings
- Steps to consider to prevent accidental exposure
- Actions to take in the event of an accidental exposure and in case of emergency
- Appropriate biological waste management
- The HCP should provide and discuss the patient and caregiver guide with the patient/caregiver
- HCPs should encourage patients to participate in the long-term safety study PASS-01

Home setting:

- Requirements for home administration, including availability and timely administration
- In case of in-home administration, the prescribing physician should establish a treatment plan, indicating the appropriate dose and prioritizing wounds to treat initially and sequential wounds to treat afterwards
- Suitability of the patient for home administration by HCP:

  - Training of HCP who will administer the product in home setting
  - Educating / counselling of patient and caregiver on home administration and discuss and provide the patient and caregiver guide

- Suitability of the patient for home administration by caregiver or patient:

  Requirement of at least one application of Vyjuvek to be administered by patient/caregiver (or as many times as needed to be compliant with all steps) to take place under the supervision of a HCP in a healthcare setting

Target Audience and planned distribution path

The target audience includes prescribing physicians, nurses, and pharmacists. Krystal Biotech will provide the guide prior to treatment. A replacement guide is available via a QR code or a new hard copy may be provided. The Krystal Medical Affairs team will provide training, if requested.

Plans to evaluate the effectiveness of the interventions and criteria for success

Krystal proposes to evaluate the effectiveness of the aRMM via the PASS-01 study as well as routine pharmacovigilance and will be reported in PSURs.

V2.1 Guide for Patients/Caregivers

Objectives

The objective of the proposed aRMM is to inform patients/caregivers on:

- how to administer Vyjuvek
- how to prevent accidental exposure of close contacts via direct contact with administered wounds
- the essential product information as per the patient leaflet
- commonly asked questions, administration best practices, and wound management expectations to ensure safe use of Vyjuvek

Additional information will also be provided to ensure safe handling and disposal of administration materials, potential left over Vyjuvek, and bandages/ dressings from the first dressing change. Additionally, because there is limited information regarding the long-term effects of Vyjuvek, patients are encouraged to work with their HCP to participate in the long-term study PASS-01.

Rationale for the additional risk minimisation activity

Additional awareness and knowledge of patients and caregivers about the risks, as well as providing the best practices to help mitigate potential risks.

The information within the planned guide should address the following elements:

- Training administration video (including a QR code with access to administration video)
- How to administer Vyjuvek
- Steps to prevent accidental exposure
- Actions to take in the event of an accidental exposure and in case of emergency

- Detailed information on treated wound dressings, including changing and disposing of wound dressings
- Appropriate biological waste management
- Encouraging the patient to participate in the long-term study PASS-01

Home setting:

- Requirements for home administration, including availability and timely administration
- Requirements for transport of prepared syringes to the setting of administration (including storage conditions and timeline)
- Appropriate storage conditions of Vyjuvek and handling of the drug
- In case of home administration by caregiver or patient, a requirement of at least one application of Vyjuvek to be administered by patient/caregiver under the supervision of a HCP in a healthcare setting (or as many times as needed to be compliant with all steps) A treatment plan established by the prescribing physician indicating the appropriate dose and prioritizing wounds to treat initially and sequential wounds to treat afterwards

Target Audience and planned distribution path

The intended audience is patients and caregivers. The HCPs will provide the guide prior to treatment and a replacement is available via QR code or a new hard copy may be provided.

Plans to evaluate the effectiveness of the interventions and criteria for success

Krystal proposes to evaluate the effectiveness of the aRMM via the PASS-01 study as well as routine pharmacovigilance and will be reported in PSURs.

V2.1 Vyjuvek Dose Preparation Videos

Objectives

The objective of the proposed aRMMs is to provide appropriate visual tools designed to enhance the users understanding of the written information located with the SmPC and PL, to ensure safe and accurate execution of Vyjuvek preparation. To accomplish the objective, the videos were validated as educational tools in the PRO-HF-02 study.

Rationale for the additional risk minimisation activity

Additional visual clarification and label training to help mitigate risks of accidental exposure to Vyjuvek.

The video includes all steps necessary for mixing and preparing the Vyjuvek syringes for administration, including transport conditions of the prepared syringes to the setting for administration in accordance with the EU SmPC and PIL.

Target Audience and planned distribution path

The intended audience is HCPs (pharmacists, prescribing physicians, and/or nurses). Access to Dose Preparation Videos will be provided through a QR code.

Plans to evaluate the effectiveness of the interventions and criteria for success

The videos were validated as educational tools in the PRO-HF-02 study demonstrating 95% accuracy for demonstrating ability to locate and comprehend the label to properly complete tasks including but not limited to, storage, mixing, and disposal. Krystal proposes to evaluate the effectiveness of the aRMM via the PASS-01 study as well as routine pharmacovigilance and will be reported in PSURs.

V2.1 Vyjuvek Dose Administration Videos

Objectives

The objective of the proposed aRMMs is to provide appropriate visual tools designed to enhance the users understanding of the written information located with the SmPC and PL, to ensure safe and accurate execution of Vyjuvek administration. To accomplish the objective, the videos were validated as educational tools in the PRO-HF-02 study.

Rationale for the additional risk minimisation activity

Additional visual clarification and label training to help mitigate risks of accidental exposure to Vyjuvek or medication errors in the home setting.

The video includes all steps of administration including wound dressing and waste disposal in accordance with the EU SmPC and PIL and national guidelines on genetically modified and biological material.

Target Audience and planned distribution path

The intended audience is HCPs, patients, and caregivers. Access to the Dose Administration videos will be provided through a QR code.

Plans to evaluate the effectiveness of the interventions and criteria for success

The videos were validated as educational tools in the PRO-HF-02 study demonstrating 95% accuracy for demonstrating ability to locate and comprehend the label to properly complete tasks including but not limited to, storage, administration, disposal. Krystal proposes to evaluate the effectiveness of the aRMM via the PASS-01 study as well as routine pharmacovigilance and will be reported in PSURs.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risk		
None	NA	NA
Important Potential Risks		
Exposure of HCP and caregivers to Vyjuvek during preparation or administration	**Routine risk minimization measures:** SmPC Sections 4.2, 4.6, and 6.6 • Section 4.2 describes the precautions to be taken before	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:** • None

	manipulating or administering Vyjuvek • Further details on precautions, handling and disposal of Vyjuvek are listed in Section 4.6 in the SmPC • Section 6.6 provides details on appropriate PPE that should be worn and the measures to take if there is accidental exposure and precautions with waste disposal <u>PL Sections 2 and 6</u> • PL Section 2 and 6 provides information on accidental contact with Vyjuvek B-VEC handling and administration should be conducted by a trained HCP/patient/caregiver. **Additional risk minimization measures:** • Guide for HCPs • Guide for patients and caregivers • Vyjuvek dose preparation video • Vyjuvek administration video	**Additional Pharmacovigilance activities:** • PASS-01 Study Progress Report: With every PSUR Interim Report: Once approximately 50 patients have completed a 1-year follow-up Final Report: 31-DEC-2034 **Efficacy studies that will provide relevant safety results:** • None
Accidental exposure of VYJUVEK from patient to close contacts or HCP via direct contact with administered wounds or body fluid	**Routine risk minimization measures:** <u>SmPC Sections 4.2, 4.6, and 6.6</u> • Section 4.2 describes the precautions to be taken before manipulating or administering Vyjuvek • Further details on precautions, handling and disposal of Vyjuvek are listed in Section 4.6 in the SmPC • Section 6.6 provides details on appropriate PPE that should be worn and the measures to take if there is accidental exposure and precautions with waste disposal	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:** • None **Additional Pharmacovigilance activities:** • PASS-01 Study Progress Report: With every PSUR Interim Report: Once approximately 50 patients have completed a 1-year follow-up Final Report: 31-DEC-2034 **Efficacy studies that will provide relevant safety results:** • None

	PL Sections 2 and 6 • PL Section 2 and 6 provides information on accidental contact with Vyjuvek B-VEC handling and administration should be conducted by a trained HCP/patient/caregiver. **Additional risk minimization measures:** • Guide for HCPs • Guide for patients and caregivers • Vyjuvek dose preparation video • Vyjuvek administration video	
Medication Errors in the clinical and home setting	**Routine risk minimization measures:** SmPC Sections 4.2 and 4.6 • Section 4.2 describes the precautions to be taken before manipulating or administering Vyjuvek • Further details on precautions, handling and disposal of Vyjuvek are listed in Section 4.6 in the SmPC PL Sections 3 and 5 • Section 3 in the PL describes how Vyjuvek is given to the patient • Section 5 in the PL describes how Vyjuvek is stored B-VEC handling and administration should be conducted by a trained HCP/patient/caregiver. **Additional risk minimization measures:** • Guide for HCPs • Guide for patients and caregivers • Vyjuvek dose preparation video • Vyjuvek administration video	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:** • None **Additional Pharmacovigilance activities:** • PASS-01 Study Progress Report: With every PSUR Interim Report: Once approximately 50 patients have completed a 1-year follow-up Final Report: 31-DEC-2034 **Efficacy studies that will provide relevant safety results:** • None

Missing Information		
Safety in patients <6 months of age	**Routine risk minimization measures:** SmPC Section 4.8 • As Vyjuvek has not been studied in patients <6 months in the clinical studies, recommendation to consider the benefits of treatment against the risks provided in SmPC Section 4.8. B-VEC handling and administration should be conducted by a trained HCP/patient/caregiver. **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:** • None **Additional Pharmacovigilance activities:** • PASS-01 Study Progress Report: With every PSUR Interim Report: Once approximately 50 patients have completed a 1-year follow-up Final Report: 31-DEC-2034 **Efficacy studies that will provide relevant safety results:** • None
Long-term safety	**Routine risk minimization measures:** SmPC Sections 4.4 • Recommendation for long-term follow up is provided in SmPC Section 4.4 PL Section 2 • Expectation for long-term monitoring are described in PL Section 2 **Additional risk minimization measures:** • Guide for HCPs • Guide for patients and caregivers • Vyjuvek dose preparation video • Vyjuvek administration video	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:** • None **Additional Pharmacovigilance activities:** • PASS-01 Study Progress Report: With every PSUR Interim Report: Once approximately 50 patients have completed a 1-year follow-up Final Report: 31-DEC-2034 **Efficacy studies that will provide relevant safety results:** • None

PASS: Post-authorisation safety study; PL: Package Leaflet; SmPC: Summary of Product Characteristics; Periodic Safety Update Report (PSUR).

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

This is a summary of the risk management plan (RMP) for Vyjuvek. The RMP details important risks of Vyjuvek, how these risks can be minimised, and how more information will be obtained about Vyjuvek's risks and uncertainties (missing information).

I. The medicine and what it is used for

Vyjuvek is indicated for the treatment of wounds in patients from birth with dystrophic epidermolysis bullosa (DEB) with mutation(s) in the *collagen type VII alpha 1 chain (COL7A1)* gene. It contains beremagene geperpavec as the active substance and it is given cutaneously.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Vyjuvek, together with measures to minimise such risks and the proposed studies for learning more about Vyjuvek's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks

Together, these measures constitute *routine risk minimisation* measures.

In the case of Vyjuvek, these measures are supplemented with with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities.*

If important information that may affect the safe use of Vyjuvek is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Vyjuvek are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Vyjuvek. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not yet been established and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• Exposure of HCP and caregivers to Vyjuvek during preparation or administration • Accidental exposure of Vyjuvek from patient to close contacts or HCP via direct contact with administered wounds or body fluids • Medication errors in the clinical and home setting
Missing information	• Long-term safety • Safety in patients less than 6 months of age

II.B Summary of important risks

No Important Identified Risk.

II.B.2 Important Potential Risk: Exposure of HCP and caregivers to Vyjuvek during preparation or administration

Evidence for linking the risk to the medicine	Vyjuvek does not penetrate intact skin and stays locally in the exposed area with no risk of systemic exposure. The vector upon transfecting cells does not replicate or integrate and is transient and clears with turnover of the cells. There has been no reporting of this exposure to Pharmacists, HCP (prescribing physicians or nurses)/caregivers to date in the clinical or commercial setting.
Risk factors and risk groups	Pharmacists, HCPs, patient caregivers, and close contacts.
Risk minimisation measures	**Routine risk minimization measures:** SmPC Sections 4.2, 4.6, and 6.6 • Section 4.2 describes the precautions to be taken before manipulating or administering Vyjuvek • Further details on precautions, handling and disposal of Vyjuvek are listed in Section 4.6 in the SmPC • Section 6.6 provides details on appropriate PPE that should be worn and the measures to take if there is accidental exposure and precautions with waste disposal

	PL Sections 2 and 6 • PL Section 2 and 6 provides information on accidental contact with Vyjuvek B-VEC handling and administration should be conducted by a trained HCP/patient/caregiver. **Additional risk minimization measures:** • Guide for HCPs • Guide for patients and caregivers • Vyjuvek dose preparation video • Vyjuvek administration video
Additional pharmacovigilance activities	• PASS-01 Study Progress Report: With every PSUR Interim Report: Once approximately 50 patients have completed a 1-year follow-up Final Report: 31-DEC-2034

II.B.3 Important Potential Risk: Accidental exposure of Vyjuvek from patient to close contacts or HCP via direct contact with administered wounds or body fluids

Evidence for linking the risk to the medicine	Vyjuvek does not penetrate intact skin and stays locally in the exposed area with no risk of systemic exposure. The vector upon transfecting cells does not replicate or integrate and is transient and clears with turnover of the cells. There has been no reporting of this exposure of Vyjuvek from patient to close contacts or HCP via direct contact with administered wounds or body fluids to date in the clinical or commercial setting.
Risk factors and risk groups	HCPs, patient caregivers and close contacts
Risk minimisation measures	**Routine risk minimization measures:** SmPC Sections 4.2, 4.6, and 6.6 • Section 4.2 describes the precautions to be taken before manipulating or administering Vyjuvek • Further details on precautions, handling and disposal of Vyjuvek are listed in Section 4.6 in the SmPC • Section 6.6 provides details on appropriate PPE that should be worn and the measures to take if there is accidental exposure and precautions with waste disposal PL Sections 2 and 6

	• PL Section 2 and 6 provides information on accidental contact with Vyjuvek B-VEC handling and administration should be conducted by a trained HCP/patient/caregiver. **Additional risk minimization measures:** • Guide for HCPs • Guide for patients and caregivers • Vyjuvek dose preparation video • Vyjuvek administration video
Additional pharmacovigilance activities	• PASS-01 Study Progress Report: With every PSUR Interim Report: Once approximately 50 patients have completed a 1-year follow-up Final Report: 31-DEC-2034

II.B.4 Important Potential Risk: Medication errors in the home or clinical setting

Evidence for linking the risk to the medicine	Based on the stability data of Vyjuvek following the recommended storage is necessary to maintain the potency of the product. Failure to maintain the storage condition could result in a potentially sub-potent product. Due to the fixed weekly maximum dose and the waxing and waning nature of the wounds in this patient population, there may be variability in Vyjuvek administered to the wound area from week to week. Differences in dosing are not expected to increase risk to the patient or impact the overall efficacy of the product, therefore this is considered a potential risk.
Risk factors and risk groups	Patients receiving Vyjuvek
Risk minimisation measures	**Routine risk minimization measures:** <u>SmPC Sections 4.2 and 4.6</u> • Section 4.2 describes the precautions to be taken before manipulating or administering Vyjuvek • Further details on precautions, handling and disposal of Vyjuvek are listed in Section 4.6 in the SmPC <u>PL Sections 3 and 5</u> • Section 3 in the PL describes how Vyjuvek is given to the patient • Section 5 in the PL describes how Vyjuvek is stored

	B-VEC handling and administration should be conducted by a trained HCP/patient/caregiver. **Additional risk minimization measures:** • Guide for HCPs • Guide for patients and caregivers • Vyjuvek dose preparation video • Vyjuvek administration video
Additional pharmacovigilance activities	• PASS-01 Study Progress Report: With every PSUR Interim Report: Once approximately 50 patients have completed a 1-year follow-up Final Report: 31-DEC-2034

II.B.5 Missing Information: Long-term safety

Evidence for linking the risk to the medicine	Data on long-term exposure are provided in Table 4. However, long-term safety data are considered missing and further information/characterisation is needed.
Risk factors and risk groups	Patients receiving Vyjuvek
Risk minimisation measures	**Routine risk minimization measures:** SmPC Sections 4.4 • Recommendation for long-term follow up is provided in SmPC Section 4.4 PL Section 2 • Expectation for long-term monitoring are described in PL Section 2 **Additional risk minimization measures:** • Guide for HCPs • Guide for patients and caregivers • Vyjuvek dose preparation video • Vyjuvek administration video
Additional pharmacovigilance activities	• PASS-01 Study Progress Report: With every PSUR Interim Report: Once approximately 50 patients have completed a 1-year follow-up Final Report: 31-DEC-2034

II.B.6 Missing Information: Safety in Patients Less Than 6 Months of Age

Evidence for linking the risk to the medicine	Patients less than 6 months were not included in the clinical studies. Limited commercial data in this population is available (see Table 3). However, this patient population is eligible to receive Vyjuvek in the commercial setting. The benefit of early treatment outweighs the risks because the severity of the disease increases with age. Based on this, the age group is considered missing information. Further characterization is needed.
Risk factors and risk groups	Patients less than 6 months of age receiving Vyjuvek
Risk minimisation measures	**Routine risk minimization measures:** SmPC Section 4.8 • As Vyjuvek has not been studied in patients <6 months in the clinical studies, recommendation to consider the benefits of treatment against the risks provided in SmPC Section 4.8. B-VEC handling and administration should be conducted by a trained HCP/patient/caregiver. **Additional risk minimization measures:** • None
Additional pharmacovigilance activities	• PASS-01 Study Progress Report: With every PSUR Interim Report: Once approximately 50 patients have completed a 1-year follow-up Final Report: 31-DEC-2034

II.C Post-authorisation development plan

II.C.1 Studies that are conditions of the marketing authorization

The following study is a condition of the marketing authorisation:

Study short name: Post authorization safety study (PASS-01)

Purpose of Study: The study is a prospective, non-interventional, multi-country study to confirm the long-term safety profile, including in paediatric patients less than 6 months of age, receiving Vyjuvek for the treatment of DEB wounds, in a real-life clinical setting.

Rationale and Study Objectives

The **primary objective** of the study is to evaluate the occurrence of treatment related adverse events in patients with DEB treated with Vyjuvek, in a long-term follow-up study, as ascertained by the treating healthcare professional. This will include the assessment of the safety of Vyjuvek in patients with DEB with less than 6 months of age, the occurrence of adverse events with delayed manifestation, and treatment discontinuations/interruptions due to safety reasons.

As **secondary objectives**, this study will evaluate:

- the occurrence of medication errors;
- the occurrence of accidental exposure of Vyjuvek to HCPs, caregivers and close contacts;
- the effectiveness of the additional Risk Minimization Measures (aRMM), as defined in the Risk Management Plan, aimed at reducing accidental exposure and medication errors, particularly in the home setting.
- the effectiveness of Vyjuvek in real-life clinical practice.

See Part III.2.1 for a full description of this study.

II.C.2 Other studies in post-authorisation development plan

There are no additional planned post-authorisation studies.

PART VII: ANNEXES

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ANNEX 4 - SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable

ANNEX 6 - DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Prior to the launch of Vyjuvek in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where Vyjuvek is marketed, all HCPs (pharmacists, prescribing physicians, and/ or nurses) and patients/carers who are expected to prescribe,-use, or oversee the administration of Vyjuvek have access to/are provided with the following educational packages aimed at highlighting the important potential risks of Vyjuvek. These packages will be translated into the local language to ensure understanding of proposed mitigation measures by all users.

HCPs educational materials consist of

- Guide for HCPs
- Vyjuvek dose preparation video
- Vyjuvek administration video

Patient/Caregiver educational materials consist of:

- Guide for patients and caregivers
- Vyjuvek administration video

Guide for HCPs

The guide will explain the following:

Preparation and administration:

- Training on how to prepare and administer Vyjuvek, including a QR code with access to a preparation and administration video.
- Ability for the HCP to order a demonstration kit to facilitate the training of the HCP, patient, or caregiver.

Storage and transport:

- Appropriate storage conditions prior to and after mixing of Vyjuvek and handling of the drug
- Requirements for transport of prepared syringes to the setting of administration (including surveillance of temperature and timeline)

Administration objectives and patient/caregiver counselling:

- The appropriate dosing and treatment plan
- Detailed information on treated wound dressing
- Steps to prevent further accidental exposure

- Actions to take in the event of an accidental exposure and in case of emergency
- Appropriate biological waste management
- The HCP should provide and discuss the patient and caregiver guide with the patient/caregiver
- HCPs should encourage patients to participate in the long-term study PASS-01

Home setting:

- Requirements for home administration, including availability and timely administration
- In case of in-home administration, the prescribing physician should establish a treatment plan, indicating the appropriate dose and prioritizing wounds to treat initially and sequential wounds to treat afterwards
- Suitability of the patient for home administration by HCP:
    - Training of HCP who will administer the product in home setting
    - Educating / counselling of patient and caregiver on home administration and discuss and provide the patient and caregiver guide
- Suitability of the patient for home administration by care giver or patient:

Requirement for at least one application of Vyjuvek to be administered by patient/caregiver under the supervision of a HCP in a healthcare setting (or as many times as needed to be compliant with all steps).

Guide for patients and caregivers

<u>The guide will explain the following:</u>

- Training administration video (QR code with access to administration video)
- How the administration of Vyjuvek is performed
- Steps to prevent accidental exposure
- Actions to take in the event of an accidental exposure and in case of emergency
- Detailed information on treated wound dressing, including changing and disposing of wound dressings
- Appropriate biological waste management
- Encourage the patient to participate in the long-term study PASS-01

Home setting:

- Requirements for home administration, including availability and timely administration
- Requirements for transport of prepared syringes to the setting of administration (including storage conditions and timeline)
- Appropriate storage conditions of Vyjuvek and handling of the drug

- In the case of home administration by a caregiver or patient, there will be a requirement for at least one application of Vyjuvek to be administered by patient/caregiver to take place under the supervision of a HCP in a healthcare setting (or as many times as needed to be compliant with all steps). The prescribing physician has established a treatment plan, indicating the appropriate dose and prioritizing wounds to treat initially and sequential wounds to treat afterwards

Vyjuvek dose preparation video

The video will explain: all steps necessary for mixing and preparing the Vyjuvek syringes for administration, including transport conditions of the prepared syringes to the setting for administration in accordance with the EU SmPC and PIL.

Vyjuvek administration video

The video will explain: all steps of administration including wound dressing and waste disposal in accordance with the EU SmPC and PIL and national guidelines on genetically modified and biological material.

ANNEX 7 - OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

Bardhan 2020

Bardhan A, Bruckner-Tuderman L, Chapple ILC, Fine JD, Harper N, Has C, et al. Epidermolysis bullosa. Nat Rev Dis Primers. 2020;6(1):78.

Bodemer 2022

Bodemer C, Soussand L, Sandrin A, Khatim A, Sauvestre A, Elarouci N, et al. French data on the epidemiology and expert healthcare network for epidermolysis bullosa. J Eur Acad Dermatol Venereol. 2022; 37(5):e597-e599.

Bruckner 2020

Bruckner AL, Losow M, Wisk J, Patel N, Reha A, Lagast H, et al. The challenges of living with and managing epidermolysis bullosa: insights from patients and caregivers. Orphanet J Rare Dis. 2020;15(1):1-4.

Bruckner-Tuderman 2019

Bruckner-Tuderman L. Newer treatment modalities in epidermolysis bullosa. Indian Dermatol Online J. 2019;10(3):244.

Denyer 2017

Denyer J, et al. Best Practice Guidelines: Skin and wound care in Epidermolysis Bullosa 2017. Wound International. Accessed 27 May 2022. Available from: https://www.woundsinternational.com/resources/details/best-practice-guidelines-skin-and- wound-care-in-epidermolysis-bullosa.

Fine 2004

Fine J-D, Johnson LB, Weiner M, Stein A, Cash S, Deleoz J, et al. Eye involvement in inherited epidermolysis bullosa: experience of the National Epidermolysis Bullosa Registry. Am J Ophthalmol. 2004;138(2):254-62.

Fine 2005

Fine, JD, Johnson LB, Weiner M, Stein A, Cash S, Deleoz J, et al. Pseudosyndactyly and musculoskeletal contractures in inherited epidermolysis bullosa: experience of the national epidermolysis bullosa registry, 1986-2002. J Hand Surg Br. 2005;30(1):14-22.

Fine 2008

Fine JD, Johnson LB, Weiner M, Suchindran C. Cause-specific risks of childhood death in inherited epidermolysis bullosa. J Pediatr. 2008;152(2):276-80.

Fine 2010

Fine JD. Inherited epidermolysis bullosa. Orphanet J Rare Dis. 2010;5(1):12.

Fine 2016

Fine JD. Epidemiology of inherited epidermolysis bullosa based on incidence and prevalence estimates from the National Epidermolysis Bullosa Registry. JAMA Dermatol. 2016;152(11):1231-8.

Feinstein 2019

Feinstein JA, Jambal P, Peoples K, Lucky AW, Khuu P, Tang JY, et al. Assessment of the timing of milestone clinical events in patients with epidermolysis bullosa from North America. JAMA dermatology. 2019;155(2):196-203.

Has 2020

Has C, Bauer JW, Bodemer C, Bolling MC, Bruckner-Tuderman L, Diem A, et al. Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility. British Journal of Dermatology. 2020;183(4):614-27.

Herod 2002

Herod J, Denyer J, Goldman A, Howard R. Epidermolysis bullosa in children: pathophysiology, anaesthesia and pain management. Paediatr Anaesth. 2002;12(5):388-97.

Hsu 2014

Hsu C-K, Wang S-P, Lee JY-Y, McGrath JA. Treatment of hereditary epidermolysis bullosa: updates and future prospects. Am J Clin Dermatol. 2014;15(1):1-6.

Ingen-Housz-Oro, 2004

Ingen-Housz-Oro S, Blanchet-Bardon C, Vrillat M, Dubertret L. Vitamin and trace metal levels in recessive dystrophic epidermolysis bullosa. J Eur Acad Dermatol Venereol. 2004;18(6):649- 53.

Intong 2012

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

Lachmann 2004

Lachmann RH. Herpes simplex virus-based vectors. Int J Exp Path. 2004;85(4):177-190.

Lwin 2019

Lwin SM, Syed F, Di W, Kadiyirire T, Liu L, Petrova A, et al. Safety and early efficacy outcomes for lentiviral fibroblast gene therapy in recessive dystrophic epidermolysis bullosa. JCI Insight. 2019;4(11): e126243.

Lwin 2022

Lwin SM, McGrath JA. Restoring type VII collagen in skin. Med. 2022;3(5):273-5.

Marinkovich 2019

Marinkovich MP, Tang JY. Gene therapy for epidermolysis bullosa. J Invest Dermatol. 2019;139(6):1221-26.

Montaudié 2016

Montaudié H, Chiaverini C, Sbidian E, Charlesworth A, Lacour J-P. Inherited epidermolysis bullosa and squamous cell carcinoma: a systematic review of 117 cases. Orphanet J Rare Dis. 2016;11(1):117.

Murrell 2020

Murrell DF, Sprecher E, Bruckner A, et al. Efficacy and safety of topical Oleogel-S10 for epidermolysis bullosa – results of 3 months double-blind treatment during the phase 3 study "EASE". Presented at: EADV Virtual Congress; October 29-31, 2020. D3T03.3B.

Petrof 2022

Petrof G, Papanikolaou M, Martinez AE, Mellerio JE, McGrath JA, Bardhan A, et al. The epidemiology of epidermolysis bullosa in England and Wales: data from the national epidermolysis bullosa database. Br J Dermatol. 2022;186(5):843-848.

Rashidghamat 2016

Rashidghamat E, Mellerio JE. Management of chronic wounds in patients with dystrophic epidermolysis bullosa: challenges and solutions. Chronic Wound Care Management and Research. 2017;4:45-54.

Siprashvili 2016

Siprashvili Z, Nguyen NT, Gorell ES, Loutit K, Khuu P, Furukawa LK, et al. Safety and wound outcomes following genetically corrected autologous epidermal grafts in patients with recessive dystrophic epidermolysis bullosa. JAMA. 2016;316(17):1808-17.

Tang 2021

Tang JY, Marinkovich MP, Lucas E, Gorell E, Chiou A, Lu Y, et al. A systematic literature review of the disease burden in patients with recessive dystrophic epidermolysis bullosa. Orphanet J Rare Dis. 2021;16(1):175.

Uitto 1994

Uitto J, Christiano AM. Molecular basis for the dystrophic forms of epidermolysis bullosa: mutations in the type VII collagen gene. Arch Dermatol Res. 1994;287(1):16-22.

Varki 2007

Varki R, Sadowski S, Uitto J, Pfendner E. Epidermolysis bullosa. II. Type VII collagen mutations and phenotype-genotype correlations in the dystrophic subtypes. J Med Genet. 2007;44(3):181-92.

Wagner 2010

Wagner JE, Ishida-Yamamoto A, McGrath JA, Hordinsky M, Keene DR, Woodley DT, et al. Bone marrow transplantation for recessive dystrophic epidermolysis bullosa. N Engl J Med. 2010;363(7):629-39.

Zhou 1999

Zhou ZH, Chen DH, Jakana J, Rixon FJ, Chiu W. Visualization of tegument-capsid interactions and DNA in intact herpes simplex virus type 1 virions. J Virol. 1999;73(4):3210-8.