New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Vyjuvek™ (beremagene geperpavec-svdt) [Krystal Biotech, Inc.]**
Dosage Formulations:	Biological suspension mixed with excipient gel for topical application.
FDA Approval Date: **FDB File Date:**	FDA: 5/19/2023 FDB: 6/11/2023
Indication:	Treatment of wounds in patients 6 months of age and older with dystrophic epidermolysis bullosa (DEB) with mutations(s) in the *collagen type VII alpha 1 chain (COL7A1)* gene.
Mechanism of Action:	Dystrophic epidermolysis bullosa (DEB) is caused by mutation(s) in the *COL7A1* gene, which results in reduced or absent levels of biologically active COL7. Vyjuvek can transduce both keratinocytes and fibroblasts. Following entry of Vyjuvek into the cells, the vector genome is deposited in the nucleus. Once in the nucleus, transcription of the encoded human *COL7A1* is initiated. The resulting transcripts allow for production and secretion of COL7 by the cell in its mature form. These COL7 molecules arrange themselves into long, thin bundles that form anchoring fibrils. The anchoring fibrils hold the epidermis and dermis together and are essential for maintaining the integrity of the skin. Patients with autosomal dominant DEB (DDEB) have lower than normal functional anchoring fibrils, and patients with recessive DEB (RDEB) have no functional anchoring fibrils.
Dose/ Administration:	**Dosage** • The recommended dose of Vyjuvek is based on age and is administered topically to wound(s) once a week. The below table is provided by the manufacturer:

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

- It may not be possible to apply Vyjuvek gel to all the wounds at each treatment visit.
- Apply Vyjuvek gel to wounds until they are closed before selecting new wound(s) to treat. Prioritize weekly treatment to previously treated wounds if they re-open.
- If a dose is missed, apply Vyjuvek gel as soon as possible and resume weekly dosing thereafter.

Preparation

- Vials of Vyjuvek must be removed from freezer and allowed to thaw for at least 20 minutes prior to preparation.
- Prepare Vyjuvek gel by mixing the Vyjuvek biological suspension into the excipient gel for immediate use within 8 hours of application. Detailed instructions for the preparation of Vyjuvek are provided by the manufacturer. After preparation, Vyjuvek is ready to be administered in four syringes each containing 0.2 to 0.4 mL depending on the patient's age.
- Only a healthcare professional should prepare and apply Vyjuvek gel either at a healthcare professional setting or the home setting.
- Individuals who are pregnant should not prepare or apply Vyjuvek gel and should avoid direct contact with the treated wounds or dressings from treated wounds.

Administration

	• Apply Vyjuvek gel to the selected wound(s) in droplets spaced evenly within the wound, approximately 1 cm-by-1 cm apart. Avoid touching the administration syringe to the skin. • Use clean scissors to cut the non-adherent hydrophobic dressing to a size slightly larger than the wound and place the dressing atop the Vyjuvek gel droplets. • Use scissors to cut the standard dressing used by the patient to a size slightly larger than the hydrophobic dressing and place the standard dressing atop the hydrophobic dressing. • Do not change the wound dressing within approximately 24 hours after Vyjuvek gel application.

Disease State Clinical Highlights:	• Epidermolysis bullosa (EB) is a genetic skin disorder that causes abnormalities in the cohesion of the layers of the epidermis resulting in skin fragility. EB is caused by mutations involving several genes that encode for structural proteins within keratin intermediate filaments, desmosome cell junctions, and hemidesmosome attachment complexes.
	• Symptoms of EB vary widely among affected patients. Clinical manifestations include blisters, erosions, nonhealing ulcerations, and scars in response to mild skin trauma. Patients often present with extracutaneous manifestations including hair and nail abnormalities, ocular blisters, oral blisters, gastrointestinal complications, and genitourinary complications. Severe cases of EB may result in malnutrition, anemia, infection, skin cancer, and death.
	• EB is classified into four types based on skin cleavage and genetic testing:
	  ○ Epidermolysis bullosa simplex (EBS): the most common type of EB, accounting for 75 to 85% of all EB cases. Mutations in at least seven distinct genes have been associated with EBS but the vast majority of cases involve mutations in the keratin genes *KRT5* and *KRT14*. Blistering usually occurs within the uppermost layer of the skin (epidermis) and may be localized to the hand and feet.
	  ○ Junctional epidermolysis bullosa (JEB): caused by autosomal recessive mutations in the laminin-332 genes resulting in structural defects of the anchoring filaments located in the lamina lucida and superior lamina densa of the basal membrane zone. Risk of death among children with severe JEB is estimated to be approximately 45% by age 1 and 60% by age 15.
	  ○ Dystrophic epidermolysis bullosa (DEB): categorized as either recessive DEB (RDEB) or dominant DEB (DDEB) and is characterized by blistering of the skin and mucosal membranes that heal with scarring. Both types of DEB are caused by mutations in the *COL7A1* gene which encodes the alpha-1 chain of type VII collagen (COL7). COL7 is the main constituent of the anchoring fibrils located below the lamina densa of the epidermal basement membrane zone. RDEB is the more severe form of DEB due to patients having no functional anchoring fibrils.
	  ○ Kindler epidermolysis bullosa (KEB): caused by loss-of-function mutations in the *FERMT1* gene which encodes the focal adhesion protein fermitin family homolog 1 (FFH1). KEB has been reported in approximately 250 individuals worldwide and is characterized by skin blistering, photosensitivity, and extensive skin atrophy.
	• The National Epidermolysis Bullosa Registry (NEBR) estimates the incidence of EB to be approximately 20 per million live births. EB affects all genders and racial groups equally. The RDEB incidence rate is approximately 3.1 per million live births and has a prevalence of 1.4 per million population. DDEB incidence rate is approximately 2.1 per million live births and has a prevalence of 1.5 per million population.
	• Squamous cell carcinoma is a frequent complication and the leading cause of death for several EB subtypes, with the risk being highest in RDEB. Cancer generally develops in early adulthood at the sites of chronic wounds. In patients with severe RDEB, the risk of developing squamous cell carcinoma by age 55 is greater than 90%.
	• When EB is suspected in a patient, a skin biopsy is sent for immunofluorescence mapping (IFM) to identify the level of skin cleavage. Genetic testing is also strongly recommended in all patients to confirm the exact type of EB.

Drug Clinical Highlights:

- Vyjuvek is a herpes-simplex virus type 1 (HSV-1) vector-based gene therapy and is the first-in-class topical gene therapy treatment approved for DEB.
- The FDA granted Vyjuvek Orphan Drug, Fast Track, Regenerative Medicine Advanced Therapy, Priority Review, and Rare Pediatric Disease Priority Review designations.

Warnings/Precautions:

- Accidental exposure to Vyjuvek
  - Avoid direct contact with treated wounds and dressings of treated wounds for approximately 24 hours following gel application.
  - Wash hands and wear protective gloves when assisting subjects with changing the wound dressing and handling the disposal.
  - In the event of an accidental exposure, flush with clean water for at least 15 minutes.

Contraindications: None

Pregnancy/Lactation

- There are no data with Vyjuvek gel use in pregnant or lactating women to inform a drug-associated risk. If the patient becomes pregnant while being administered Vyjuvek gel, the patient should be apprised of the potential hazards to the fetus and neonate. Women of childbearing potential should be advised to use an effective method of contraception to prevent pregnancy during treatment with Vyjuvek gel.

Clinical Studies

- GEM-3 (n=31) (NCT04491604): randomized, double-blind, intra-subject placebo-controlled trial. All study subjects had clinical manifestations consistent with DEB and genetically confirmed mutation(s) in the *COL7A1* gene. Two comparable wounds in each subject were selected and randomized to receive either topical application of Vyjuvek gel or placebo weekly for 26 weeks.
  - Key Inclusion Criteria
    - Age ≥ 6 months at the time of informed consent
    - Clinical diagnosis of DEB (either DDEB or RDEB) confirmed by genetic testing including *COL7A1*.
    - Two cutaneous wounds meeting the following criteria:
      - Location: similar in size, located in similar anatomical regions, and have similar appearances.
      - Appearance: clean with adequate granulation tissue, excellent vascularization, and do not appear infected.
    - Negative pregnancy test at Visit 1 (Week 1), if applicable.
  - Key Exclusion Criteria
    - Current evidence or a history of squamous cell carcinoma in the area that will undergo treatment.
    - Subjects actively receiving chemotherapy or immunotherapy at Visit 1 (Week 1).
    - Active drug or alcohol addiction.
    - Hypersensitivity to local anesthesia.
    - Receipt of a skin graft in the past three months
    - Pregnant or nursing women.
  - Key Baseline Characteristics
    - Study enrolled 31 subjects (20 males and 11 females)
    - 30 subjects had RDEB and one subject had DDEB.
    - Size of Vyjuvek-treated wounds ranged from 2 to 57 cm^2, with 74% of wounds < 20 cm^2 and 19% from 20 to < 40 cm^2. The size of placebo-treated wounds ranged from 2 to 52 cm^2, with 71% of wounds < 20 cm^2 and 26% from 20 to < 40 cm^2.
    - The average age of subject was 17 years (1 year to 44 years). 61% of subjects were pediatric (1 to <17 years).

- 64% of patients were White, 19% were Asian, and the remainder were American Indian or Alaskan Natives.
- Primary Outcome Measure: efficacy was established on the basis of improved wound healing defined as the difference in the proportion of complete (100%) wound closure at 24 Weeks confirmed at two consecutive study visits 2 weeks apart, assessed at Weeks 22 and 24 or at Weeks 24 and 26, between the Vyjuvek-treated and the placebo-treated wounds. Efficacy was supported by the difference in the proportion of complete wound closure assessed at Weeks 8 and 10 or at Weeks 10 and 12 between the Vyjuvek-treated and the placebo-treated wounds. Complete (100%) wound closure was defined as durable wound closure evaluated at two consecutive visits two weeks apart.

Wound Closure Assessment Timepoints	Complete Wound Closure, n (%) Vyjuvek gel (N=31)	Complete Wound Closure, n (%) Placebo gel (N=31)	Treatment Difference (95% CI)	p value
Weeks 22 & 24 or Weeks 24 & 26	20 (65)	8 (26)	39% (14, 63)	0.012
Weeks 8 &10 or Weeks 10 & 12	21 (68)	7 (23)	45% (22, 69)	0.003

- Adverse Reactions (incidence > 5%) following treatment with Vyjuvek gel (n=31):

Adverse Reactions	Subjects n (%)
Itching	3 (10)
Chills	3 (10)
Redness	2 (6)
Rash	2 (6)
Cough	2 (6)
Runny Nose	2 (6)

Price Per Unit (WAC):

- $24,250 per 2.5 mL vial (1.6 mL after reconstitution)
- $630,500 - $1,261,000 per year depending on treatment duration.
  - In the GEM-3 trial, 65% of participants experienced wound closure at 26 weeks. If additional wounds are present, further treatment may be required.

Therapeutic Alternatives:

- Vyjuvek is the first FDA-approved therapy for DEB.
- Disease management is mostly supportive focusing on wound care, pain control, controlling infections, nutritional support, and prevention and treatment of complications.
- Non-pharmacologic approaches include reducing skin friction, use of non-adhesive bandages, keeping the skin cool, and use of specific clothing to reduce skin abrasions (loose-fitting, padding, etc.).

Prior Authorization Approval Criteria:

Must meet the following criteria:

Initial Therapy:

- Prescribed by or in consultation with a dermatologist or other specialist in the treated disease state **AND**
- Participant is aged 6 months or older **AND**
- Documented diagnosis of dystrophic epidermolysis bullosa (DEB) confirmed by genetic testing showing pathogenic variant(s) in the *COL7A1* gene **AND**
- Participant (female of childbearing age) is not pregnant **AND**
- Documented baseline number and size of wounds
- Initial approval: 6 months

Continuation of Therapy:

- Documented benefit of therapy defined as reduction in number or size of wounds

	• Continued approval: 1 year **Additional Provider Diagnostic/Monitoring Criteria, if desired:** • Participant (females of childbearing potential) is utilizing concurrent birth control methods

Implication to State Medicaid Program:	• LOE: 2037
	• Debcoemagene autoficel (D-Fi) (Castle Creek Biosciences)
	  ○ Locally injected gene therapy which was granted Orphan Drug, Rare Pediatric Disease, and Regenerative Medicine Advanced Therapy designations by the FDA.
	  ○ D-Fi is made up of autologously derived dermal fibroblasts genetically modified to contain the *COL7A1* gene and is administered locally via intradermal injection into wound sites.
	  ○ DEFI-RDEB (NCT04213261): ongoing Phase III randomized, open-label, intra-patient, controlled study in patients 2 years of age and older.
	  ▪ Primary outcome measure is complete wound closure of the first wound pair at Week 24. Study participants have up to three target wound pairs with 1 wound in each pair randomly assigned as the treatment wound while the other is left untreated as a control.
	  ○ D-Fi is administered locally via intradermal injection with 12 weeks between treatments.
	  ○ Phase I/II trials showed positive results with 80% of wounds closed completely compared to 0% in the untreated group.
	• EB-101 (Abeona Therapeutics)
	  ○ Autologous cell therapy which received Orphan Drug, Rare Pediatric Disease, and Regenerative Medicine Advanced Therapy designations by the FDA.
	  ○ Manufactured using patient's own skin cells which are gene-corrected with functional *COL7A1* genes using adeno-associated virus vector. Corrected cells are then transplanted onto the patient's wounds.
	  ○ Phase III VITAL trial (NCT04227106) studying patients 6 years of age and older.
	  ▪ Co-primary endpoints are proportion of RDEB wound sites with ≥ 50% wound healing compared to baseline at Week 24 and pain reduction associated with wound dressing change between treated and untreated wounds at Week 24.
	  ○ Phase I/II trial resulted in efficacious wound healing with up to 5 years of follow-up.
	• Filsuvez® (Amryt Pharma)
	  ○ Topical gel in development that has been granted Orphan Drug and Rare Pediatric Disease designations by the FDA. Contains 90% sunflower oil and 10% dry birch bark extract. Birch bark extract is mostly comprised of a compound called betulin which is the main active ingredient in Filsuvez.
	  ○ Phase III EASE trial (NCT03068780) included patients aged 21 days and older with EB types JEB, DEB, and KEB and was comprised of 223 subjects.
	  ▪ Primary outcome measure was proportion of patients with first complete closure of target wound within 45 days of treatment. The Filsuvez group saw 41.3% of patients achieving the primary endpoint while 28.9% of patients in the placebo group achieved the primary endpoint.
	  ○ Abeona Therapeutics received a CRL letter from the FDA in February 2022 indicating it needed additional confirmatory evidence of effectiveness. Filsuvez was approved in Europe in June 2022.

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