28 February 2025
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Vyjuvek (Genetically modified replication-incompetent herpes simplex virus-1 expressing collagen VII)

Treatment of epidermolysis bullosa

EU/3/18/2012

Sponsor: Krystal Biotech Netherlands B.V.

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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Table of contents

1. Product and administrative information

Product	
Designated active substance(s)	Genetically modified replication-incompetent herpes simplex virus-1 expressing collagen VII
Other name(s)	Vyjuvek, Beremagene geperpavec
International Non-Proprietary Name	Beremagene geperpavec
Tradename	Vyjuvek
Orphan condition	Treatment of epidermolysis bullosa
Sponsor's details:	Krystal Biotech Netherlands B.V. Atrium Gebouw Strawinskylaan 3051 1077 ZX Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	IDEA Innovative Drug European Associates Limited
COMP opinion	15 March 2018
EC decision	16 April 2018
EC registration number	EU/3/18/2012
Post-designation procedural history	
Transfer of sponsorship	Transfer from IDEA Innovative Drug European Associates Limited to IDEA Innovative Drug European Associates (Ireland) Limited – EC decision of 12 February 2019 Transfer from IDEA Innovative Drug European Associates (Ireland) Limited to IDEA Innovative Drug European Associates Limited – EC decision of 09 November 2022
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Joseph DeCourcey / Violaine Closson Carella
Applicant	Krystal Biotech Netherlands B.V.
Application submission	30 October 2023
Procedure start	23 November 2023
Procedure number	EMA/H/C/006330/0000
Invented name	Vyjuvek
Proposed therapeutic indication	Dystrophic epidermolysis bullosa Further information can be found in the European public assessment report (EPAR) on the Agency's website : https://www.ema.europa.eu/en/medicines/human/EPAR/Vyjuvek
CHMP opinion	27 February 2025
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Cécile Dop / Gloria Maria Palomo Carrasco
Sponsor's report submission	17 October 2024

COMP discussion	05-07 November 2024
COMP opinion (adoption via written procedure)	28 February 2025

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2018 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing genetically modified replication-incompetent herpes simplex virus-1 expressing collagen VII was considered justified based on nonclinical data in a hypomorphic collagen VII model, supporting expression of collagen VII in the treated dermal regions;
- the condition is chronically debilitating and life-threatening due to blister formation in response to minor friction or trauma, leading to the development of multiple complications including life-threatening infections, failure to thrive, and predisposition to the development of squamous cell carcinoma;
- the condition was estimated to be affecting approximately 0.7 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing genetically modified replication-incompetent herpes simplex virus-1 expressing collagen VII as an orphan medicinal product for the orphan indication: treatment of epidermolysis bullosa.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The designated orphan condition is treatment of epidermolysis bullosa (EB) and is still acceptable as an orphan condition. The therapeutic indication is treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa in patients 6 months and older. Dystrophic and junctional EB are two severe sub-forms of EB and are considered to be fully covered by the orphan

condition. EB is a heterogeneous group of genetic skin fragility disorders characterized by blistering of the skin in response to minor trauma or friction. EB is caused by mutations in one of at least 14 genes encoding anchoring proteins of the dermo-epidermal junction. EB is divided into four main categories: EB simplex, junctional EB, dystrophic EB, and Kindler syndrome, each comprising different subtypes. A common symptom for all EB subtypes is trauma-induced skin blistering and painful wounds. EB simplex (EBS) is the most common subtype of EB causing mild to moderate disease. Junctional EB (JEB) is less frequent and has a broad spectrum of severity from the lethal form of JEB Herlitz type to very mild forms often diagnosed later in life. The majority of patients encountered in specialized centres suffer from dystrophic EB (DEB). Dominant and recessive DEB forms cause moderate to severe skin fragility and scarring. Severely affected patients suffer from widespread blistering and painful wounds causing multiple secondary medical problems which often lead to physical impairment.

The approved therapeutic indication "Vyjuvek is indicated for the treatment of wounds in patients with dystrophic epidermolysis bullosa (DEB) with mutation(s) in the *collagen type VII alpha 1 chain (COL7A1)* gene, from birth*"* falls within the scope of the designated orphan condition "Treatment of epidermolysis bullosa".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

One of the most significant problems in EB is the lifelong presence of skin blistering and partialthickness wounds that result in pruritus, pain, scarring, deformity, loss of function, and immobility as well as a high risk of complications, such as infection. Patients with EB take care to minimize new wounds; however, this is particularly difficult for young children as minor trauma or friction results in partial-thickness wounds. In addition, there is an increased incidence of aggressive cutaneous SCC at a younger age than in the general population. In patients with generalized severe recessive DEB (RDEB), squamous cell carcinoma occurs in approximately 80% of patients by their mid-40s and can occur as early as adolescence. Therefore, the condition is considered to be chronically debilitating and life-threatening due to blister formation in response to minor friction or trauma, leading to the development of multiple complications including life-threatening infections, failure to thrive, and predisposition to the development of squamous cell carcinoma.

Number of people affected or at risk

The Sponsor proposes a prevalence estimate of 0.22 in 10,000 persons in the EU.

This prevalence estimate is based on a literature review conducted by the Sponsor of epidemiologic data of epidermolysis bullosa in various regions of the European Union (EU), see summarized below in Table 1. The non-weighted average prevalence of EB based on the six regions with epidemiological data is 0.22 per 10,000 persons, ranging between 0.04 to 0.54 per 10,000 persons.

Data from the German EB-Network (www.netzwerk-eb.de) and the National Epidermolysis Bullosa Registry (NEBR) indicate that about 40% of all EB patients have DEB (Bruckner-Tuderman 2010). The overall prevalence in Europe can be estimated by assuming that DEB represents 40% of all EB cases, *i.e.,* 0.40×21.9 per million = 8.8 per million. Alternatively, Orphanet indicates a DEB prevalence of 5.72 per million using European data (Orphanet 2022). By either approach, the DEB prevalence

estimate in the EU is well below the 5 per 10,000 indicated in the first paragraph of Article 3(1) (a) of Regulation (EC) No 141/2000.

Table 1. Summary of prevalence of epidermolysis bullosa in various EU regions

Country/Region	EB Prevalence (Per Million)	Reference
Germany	54	Has 2022
Italy	10.1	Tadini 2005
Croatia	9.56	Pavicic 1990
Bulgaria	8.6	Yordanova 2001
Netherlands	45	Jonkman 2003
Romania	4.2	Danescu 2015
Average	**21.9**	

The COMP noted that the Sponsor's proposed prevalence estimate of 0.22 in 10,000 persons is lower than accepted in previous designations which was approximately 0.6 in 10,000 persons. The COMP acknowledged that 0.6 in 10,000 persons is likely on the conservative end of EB prevalence in the EU, therefore the agreed prevalence estimate by the COMP was "not more than 0.6 in 10,000 persons in the European Union".

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Filsuvez was approved in the EU in June 2022 for the treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa in patients 6 months and older.

Vyjuvek on the other hand 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.

The COMP considered that Filsuvez does not cover the entirety of the population covered by the indication of Vyjuvek. In comparison to Filsuvez, Vyjuvek can be used to treat patients with DEB from birth. Furthermore, the Vyjuvek indication wording is not restricted to the treatment of partial-thickness wounds only. Therefore, the committee did not consider that Filsuvez is a satisfactory method for the purpose of the orphan maintenance evaluation for Vyjuvek. The fact that Filsuvez also covers a population subset which is not covered by the indication of Vyjuvek, i.e. patients with junctional epidermolysis bullosa, is inconsequential for the COMP decision.

Otherwise, standard of care focuses on managing the disease symptoms i.e pain, itch medications, antibiotics, surgery for scar deformities. However, none of these therapies is specifically authorized for use in EB.

Significant benefit

Not applicable.

4. COMP position adopted on 28 February 2025

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of epidermolysis bullosa (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be not more than 0.6 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating and life-threatening due to blister formation following minor friction or trauma, leading to the development of multiple complications including life-threatening infections, failure to thrive, and predisposition to the development of squamous cell carcinoma;
- at present, no satisfactory method has been authorised in the European Union for the treatment of the entirety of patients covered by the therapeutic indication of Vyjuvek.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Vyjuvek, genetically modified replication-incompetent herpes simplex virus-1 expressing collagen VII, Beremagene geperpavec for treatment of epidermolysis bullosa (EU/3/18/2012) is not removed from the Community Register of Orphan Medicinal Products.