30 April 2020
EMADOC-628903358-1929

Public summary of opinion on orphan designation

Autologous skin equivalent graft composed of keratinocytes and fibroblasts genetically corrected by CRISPR/Cas9-mediated excision of mutation-carrying *COL7A1* exon 80 for the treatment of epidermolysis bullosa

On 28 February 2020, orphan designation EU/3/20/2253 was granted by the European Commission to Consorcio Centro de Investigación Biomédica en Red, M.P, Spain, for autologous skin equivalent graft composed of keratinocytes and fibroblasts genetically corrected by CRISPR/Cas9-mediated excision of mutation-carrying *COL7A1* exon 80 for the treatment of epidermolysis bullosa.

What is epidermolysis bullosa?

Epidermolysis bullosa is a group of inherited diseases in which the skin is very fragile and forms severe blisters after even minor friction (rubbing) or injury. In most cases, symptoms of epidermolysis bullosa appear from birth, but for some forms, symptoms may not occur until adulthood. The diseases are caused by mutations (changes) in the genes responsible for the production of certain proteins that make the skin strong and elastic, such as collagen or keratins.

Epidermolysis bullosa is a long-term debilitating and life-threatening condition because the severe blistering and associated scarring and deformities result in poor quality of life and may reduce life expectancy.

What is the estimated number of patients affected by the condition?

At the time of designation, epidermolysis bullosa affected less than 0.9 in 10,000 people in the European Union (EU). This was equivalent to fewer than 47,000 people*, and is below the ceiling for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and the knowledge of the Committee for Orphan Medicinal Products (COMP).

What treatments are available?

At the time of designation, no satisfactory methods were authorised in the EU to treat epidermolysis bullosa. Good personal hygiene and skincare were recommended to help blisters heal, to avoid

*Disclaimer: For the purpose of the designation, the number of patients affected by the condition is estimated and assessed on the basis of data from the European Union (EU 28), Norway, Iceland and Liechtenstein. This represents a population of 519,200,000 (Eurostat 2020).

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infections and to protect the skin from damage. Painkillers were also used. Surgery was sometimes necessary for complications such as deformed hands or skin cancer.

How is this medicine expected to work?

The medicine is a skin graft containing the patient's own cells with an abnormal gene 'edited' so that the cells can produce a skin protein (called collagen 7) that was previously not produced correctly. The skin graft is expected to behave like healthy skin and no longer form blisters and cause other symptoms of the condition.

The modification of the cells is made using CRISPR-Cas9, a method for editing genes that uses an enzyme combined with a small piece of genetic material (RNA), which allows the precise modification of the abnormal gene (*COL7A1)*.

What is the stage of development of this medicine?

At the time of submission of the application for orphan designation, the evaluation of the effects of the medicine in experimental models was ongoing.

At the time of submission of the application for orphan designation, no clinical trials in patients with epidermolysis bullosa had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for the treatment of epidermolysis bullosa or designated as an orphan medicinal product elsewhere for this condition.

In accordance with Regulation (EC) No 141/2000, the COMP adopted a positive opinion on 22 January 2020, recommending the granting of this designation.

Opinions on orphan medicinal product designations are based on the following three criteria:

- the seriousness of the condition;
- the existence of alternative methods of diagnosis, prevention or treatment;
- either the rarity of the condition (affecting not more than 5 in 10,000 people in the EU) or insufficient returns on investment.

Designated orphan medicinal products are products that are still under investigation and are considered for orphan designation on the basis of potential activity. An orphan designation is not a marketing authorisation. As a consequence, demonstration of quality, safety and efficacy is necessary before a product can be granted a marketing authorisation.

For more information

Sponsor's contact details:

Contact details of the current sponsor for this orphan designation can be found on EMA website.

For contact details of patients' organisations whose activities are targeted at rare diseases see:

- Orphanet, a database containing information on rare diseases, which includes a directory of patients' organisations registered in Europe;

- European Organisation for Rare Diseases (EURORDIS), a non-governmental alliance of patient organisations and individuals active in the field of rare diseases.

Translations of the active ingredient and indication in all official EU languages[1], Norwegian and Icelandic

Language	Active ingredient	Indication
English	Autologous skin equivalent graft composed of keratinocytes and fibroblasts genetically corrected by CRISPR/Cas9-mediated excision of mutation-carrying *COL7A1* exon 80	Treatment of epidermolysis bullosa
Bulgarian	Автоложна еквивалентна кожна присадка, съставена от кератиноцити и фибробласти, генетично коригирани чрез CRISPR / Cas9-медиирана ексцизия на екзони, пренасящи мутации, в колагенен домейн *COL7A1* екзон 80	Лечение на булозна епидермолиза
Croatian	Autologni graft ekvivalentan koži koji se sastoji od keratinocita i fibroblasta genetički ispravljenih CRISPR / Cas9 posredovanom ekscizijom egzona 80 gena *COL7A1* koji nosi mutaciju	Liječenje bulozne epidermolize
Czech	Autologní kůži ekvivalentní štěp složený z keratinocytů a fibroblastů geneticky upravených CRISPR/Cas9-zprostředkovanou excizí *COL7A1* exonu 80 nesoucího mutaci	Léčba bulózní epidermolýzy
Danish	Autolog hudækvivalent transplantat sammensat af keratinocytter og fibroblaster genetisk korrigeret ved CRISPR / Cas9-medieret excision af mutationsbærende *COL7A1* ekson 80	Behandling af epidermolysis bullosa
Dutch	Autologe huid equivalent transplantaat samengesteld uit keratinocyten en fibroblasten genetisch gecorrigeerd door CRISPR / Cas9-gemedieerde excisie van mutatie-dragende *COL7A1* exon 80	Behandeling van epidermolysis bullosa
Estonian	Autoloogse nahaga ekvivalentne siirik, mis koosneb keratinotsüütidest ja fibroblastidest, millest on CRISPR/Cas9 meetodil eemaldatud mutatsiooni kandva *COL7A1* ekson 80	Bulloosse epidermolüüsi ravi
Finnish	Autologinen ihoa vastaava siirre, joka koostuu keratinosyyteistä ja fibroblasteista, jotka ovat geneettisesti korjattu CRISPR / Cas9-välitteisesti mutaatiota kantavan *COL7A1* eksonin 80 poistolla	Epidermolysis bullosan hoito

[1] At the time of designation

Language	Active ingredient	Indication
French	Greffon équivalent de peau autologue composé de kératinocytes et de fibroblastes génétiquement corrigés par excision médiée par CRISPR / Cas9 d'exons porteurs de mutations dans le domaine collagénique *COL7A1*	Traitement de l'épidermolyse bulleuse
German	Autologes hautäquivalentes Transplantat aus Keratinozyten und Fibroblasten, das durch CRISPR / Cas9-vermittelte Entfernung des mutationstragender Exons 80 innerhalb der *COL7A1*-Kollagendomäne genetisch korrigiert wurde	Behandlung der Epidermolysis bullosa
Greek	Ανθρώπινο ισοδύναμο μόσχευμα δέρματος αποτελούμενο από κερατινοκύτταρα και ινοβλάστες γενετικώς διορθωμένων με CRISPR / Cas9 εκτομή του φέροντος μετάλλαξη εξωνίου 80 του *COL7A1*	Θεραπεία της πομφολυγώδους επιδερμόλυσης
Hungarian	A mutációt hordozó *COL7A1* exon 80 CRISPR/Cas9-mediált kimetszésével genetikailag korrigált, keratinocitákból és fibroblasztokból álló autológ bőrazonos graft	Epidermolysis bullosa kezelése
Italian	Innesto autologo equivalente di pelle composto da cheratinociti e fibroblasti geneticamente corretti mediante escissione mediata da CRISPR / Cas9 di esone 80 portatore di mutazione all'interno del dominio collageno *COL7A1*	Trattamento della epidermolisi bollosa
Latvian	Autologs ādas ekvivalenta transplantāts, kas sastāv no keratinocītiem un fibroblastiem, kas ir ģenētiski koriģēti, ar CRISPR / Cas9 starpniecību veicot mutāciju pārnēsājoša *COL7A1* eksona 80 ekscīziju	Bulozās epidermolīzes ārstēšanai
Lithuanian	Autologinis, odą atitinkantis transplantatas iš genetiškai koreguotų keratinocitų ir fibroblastų, naudojant CRISPR/Cas9 iškirpti *COL7A1* 80 egzoną	Pūslinės epidermolizės gydymas
Maltese	Trapjant ekwivalenti tal-ġilda awtoloġika kompost minn keratinoċiti u fibroblasti ġenetikament ikkoreġuti minn eċiżjoni medjata ta' CRISPR/Cas9 ta' eżoni 80 li jġorru mutazzjoni *COL7A1*	Kura tal-epidermolisi bullosa

Language	Active ingredient	Indication
Polish	Autologiczny przeszczep równoważny ze skórą złożony z keratynocytów i fibroblastów genetycznie skorygowanych za pośrednictwem CRISPR / Cas9 przez wycięcie zawierającego mutacje eksonu 80 genu *COL7A1*	Pęcherzowe oddzielanie się naskórka
Portuguese	Enxerto autólogo equivalente à pele composto por queratinócitos e fibroblastos geneticamente corrigidos por excisão mediada por CRISPR / Cas9 dos exões 80 portadores de mutação no domínio colágeno *COL7A1*	Tratamento da epidermólise bulhosa
Romanian	Grefon echivalent autolog al pielii compus din keratinocite și fibroblaste corectate genetic prin excizie mediată de CRISPR / Cas9, a exonului 80 purtătoare a mutației *COL7A1*	Tratamentul epidermolizei buloase
Slovak	Autológny koži ekvivalentný štep z keratinocytov a fibroblastov geneticky korigovaný CRISPR/Cas9 excisiou mutácie v *COL7A1* exóne 80	Liečba epidermolysis bullosa
Slovenian	Avtologen kožni ekvivalent , sestavljen iz keratinocitov in fibroblastov, genetsko popravljenih s pomočjo ekscizije mutacije CRISPR/Cas9, ki nosi *COL7A1* ekson 80	Zdravljenje bulozne epidrmolize
Spanish	Injerto autólogo equivalente de piel compuesto de queratinocitos y fibroblastos genéticamente corregidos por escisión mediada por CRISPR/Cas9 de exones portadores de mutación dentro del dominio colágeno *COL7A1*	Tratamiento de la epidermolisis bullosa
Swedish	Autolog hudekvivalent transplantat sammansatt av keratinocyter och fibroblaster genetiskt korrigerade med CRISPR / Cas9-medierad excision av mutationsbärande *COL7A1* exon 80	Behandling av epidermolysis bullosa
Norwegian	Autologt hudekvivalent transplantat sammensatt av keratinocytter og fibroblaster genetisk korrigert ved CRISPR/Cas9-mediert eksisjon av mutasjonsbærende *KOL7A1* ekson	Behandling av epidermolysis bullosa
Icelandic	Sjálfgena ígræðsla húðígilda sem eru samsett úr keratínfrumum og trefjakímfrumum sem eru erfðafræðilega lagaðar með CRISPR / Cas9-miðluðum brottskurði á *COL7A1* táknröð 80sem ber stökkbreytingu	Meðferð á epidermolysis bullosa