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HEALTH TECHNOLOGY BRIEFING
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Beremagene geperpavec for dystrophic epidermolysis bullosa

NIHRIO ID	24253	**NICE ID**	10546
Developer/Company	Krystal Biotech Inc	**UKPS ID**	N/A

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Dystrophic epidermolysis bullosa (DEB) is caused by a mutation in a collagen gene that controls skin strength and stability. This mutation can be inherited from one or both parents, which determines the severity of the condition (those who inherit the mutation from both parents have more severe symptoms). DEB symptoms develop from birth or early childhood and is characterised by painful skin blisters and scarring. Some people with DEB can have minor blisters mainly at areas that experience trauma such as hands, feet, arms and legs, whereas other people can have blistering externally and internally, which can cause many associated issues. Most people with DEB have blistering around and inside the mouth that affects eating and dental hygiene.

Beremagene geperpavec topical gel aims to treat DEB by delivering normal, functional collagen genes to the affected skin cells, by doing so this promotes wound-healing and reduces scarring. If licenced, beremagene geperpavec will offer the first DEB-specific treatment that addresses the underlying cause of the disease for paediatric and adult patients.

PROPOSED INDICATION

For paediatric and adult patients with dystrophic epidermolysis bullosa (DEB).[1,2]

TECHNOLOGY

DESCRIPTION

Beremagene geperpavec (B-VEC; KB103) is a genetically-modified replication-incompetent herpes simplex virus-1 (HSV-1) expressing collagen VII.[3] Beremagene geperpavec is a topical gene therapy that delivers two copies of normal collagen type VII alpha 1 chain (COL7A1) genes directly to skin cells by using a modified version of HSV-1.[4] COL7A1 genes instruct the assembly of collagen VII, which plays a role in strengthening and stabilising skin, and is a major component in anchoring fibrils. Anchoring fibrils connect two layers of skin by the epidermal basement membrane and the dermis.[5]

Beremagene geperpavec is currently in clinical development for the treatment of DEB in Phase III clinical trials (NCT04491604). Three wounds are selected for each participant; beremagene geperpavec topical gel is applied to two of the wounds (please see the clinical trial section for dosage information), the other receives a placebo treatment. Administrations occur daily on days 1 through 5, and again on days 30, 60, and 90 if there is visible wound at the original administration site. Patients are on-trial for approximately 6 months: 3 months of on-site visits followed by a 3-month at-home imaging period.[1]

INNOVATION AND/OR ADVANTAGES

Current knowledge indicates that all forms of DEB are caused by mutations in the COL7A1 gene.[6] Beremagene geperpavec is a novel targeted gene therapy that delivers healthy copies of the COL7A1 gene, non-invasively to skin cells to generate COL7 protein production which anchors the epidermis and dermis together, with the aim of safely and effectively promoting wound healing in DEB patients.[7,8]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Beremagene geperpavec does not have Marketing Authorisation in the EU/UK for any indication.

Beremagene geperpavec has the following regulatory designations/awards:

- A PRIME (priority medicine) designation in the EU in March 2019 for the treatment of DEB[9]
- An Orphan Drug Designation in the EU in April 2018 for the treatment of epidermolysis bullosa (EB)[3]
- A Regenerative Medicine Advanced Therapy (RMAT) designation in the US in June 2019[10]
- A Fast Track designation in the US in May 2018 for the treatment of DEB[11]

- An Orphan Drug designation in the US in February 2017 for the treatment of DEB[12]
- A Rare Paediatric Disease designation in the US in December 2016[13]

PATIENT GROUP

DISEASE BACKGROUND

Epidermolysis bullosa (EB) is a group of rare, inherited skin disorders that cause the skin to be fragile, which results in skin blistering, scarring, and thickening. There are three main types of EB: epidermolysis bullosa simplex (EBS), dystrophic epidermolysis bullosa (DEB) and junctional epidermolysis bullosa (JEB), which vary depending on symptom severity, skin layer affected, prevalence and inheritance. EBS is most common (around 70%), affecting the epidermis, with milder symptoms and lower risk of serious complications. DEB affects the dermis and symptoms range from mild-severe. JEB is the rarest and most severe type, which affects the basement membrane.[14,15] There is no cure for EB and treatment aims on relieving and managing symptoms.[15,16]

DEB ranges from mild to severe symptoms and is categorised into dominant or recessive due to its inheritance, with both men and women being affected.[15,17] Dominant DEB (DDEB) is when someone inherits a mutated COL7A1 gene from one parent who also has DDEB, there is a 50% chance that the parent will have a child that also has DDEB. Recessive DEB (RDEB) is less frequent, as this is when a child inherits one recessive COL7A1 gene from each parent, resulting in an inability to produce normal type VII collagen. There is a 25% chance that parents with one child who has RDEB will go on to have another child with the same condition.[17,18]

Symptoms of DEB often develop at birth or shortly afterwards and depend on inheritance. Patients with DDEB have blistering in localised areas that experience trauma (such as hands, feet, arms and legs), blistering within the mouth, scarring at blister sites, milia (white spots) that form at the blister sites, thickened and abnormally shaped nails, and sometimes loss of nails. Patients with RDEB have more severe symptoms, including widespread blistering (both externally and internally) which can affect the eyes, throat, bowels and digestion, and fingers and toes can fuse together because of scar tissue attempting to heal the blisters. Other symptoms associated with RDEB include difficulty swallowing, reduced hair growth, difficulty straightening fingers due to scar tissue formation, constipation, tooth decay, anaemia, eye problems, osteoporosis, and increased risk of skin cancer. RDEB patients usually have more fragile skin than those with DDEB, with blistering caused by even the gentlest skin contact. Babies with RDEB need careful handling and specialised feeding techniques.[17,18]

CLINICAL NEED AND BURDEN OF DISEASE

One in 227 people carry a defective gene that causes EB. One in 17,000 live births will be a baby with EB and around 5,000 people in the UK live with EB.[19] 25% of the EB population have DEB.[14]

People with EB have daily limitations from painful blisters and experience distress due to the life-long nature of the disease, social isolation, discrimination, and anxiety from visible EB blisters.[16] In addition to this, one study (25 patients) found that in 82% of patients EB had a negative impact on Quality of Life (QoL) and 80% of patients experienced psychiatric symptoms.[20]

Patients with DEB have a high risk of developing an aggressive form of squamous cell carcinoma, specific to this disease.[18,21,22] It is estimated more than half of patients with RDEB will develop skin cancer by the time they are 35.[21]

Patients with DEB often have scarring in and around the mouth, which can make eating or cleaning teeth painful. In more severe cases this results in tooth decay and repeated scarring causing problems with speaking, chewing and swallowing.[21]

In England in 2019-20 there were 146 finished consultant episodes (FCE) for patients with DEB (ICD-10 code Q81.2), resulting in 100 day cases and 98 FCE bed days.[23]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There is no cure for EB so treatment aims to prevent or reduce skin damage, improve QoL and minimise the risk of developing complications, such as infection and malnutrition.[24]

After initial diagnosis parents and children are referred to one of four specialist centres in England (two in London and two in the West Midlands) where regular follow-up appointments occur to form a treatment plan. If the child's symptoms improve or stabilise then treatment may be arranged locally, with occasional specialist centre visits. However, if symptoms are severe like those in RDEB this may not be possible. As patients with EB have complex needs the specialist team who assists with treatment can include a dermatologist, oncologist, dentist, dietician, physiotherapist, play specialist and specialist nurse.[24]

Treatment includes blister lancing, controlling infection, pain relief, dental hygiene that considers the soreness caused by blisters in and around the mouth, nail care, eyecare, feeding techniques and nutrition to reduce risk of malnutrition. For severe symptoms surgery may be considered to:[24]

- Separate the skin between fingers and toes when they have become fused together by scar tissue
- Widen the oesophagus if scar tissue has narrowed the tube
- Implanting a feeding tube into the stomach if eating has become impossible due to severe symptoms

CURRENT TREATMENT OPTIONS

Pharmacological treatment options for EB include:[24]

- Pain relief, such as over-the-counter painkillers, morphine, amitriptyline or gabapentin depending on severity
- Skin infection treatments, including antiseptic creams or ointments, antibiotic creams or lotions, antibiotic tablets and impregnated dressings to stimulate healing process

PLACE OF TECHNOLOGY

There are currently no licenced treatments for DEB in the UK and EU, as such beremagene geperpavec would offer the first molecular corrective DEB-specific treatment for patients.[3,9,24]

CLINICAL TRIAL INFORMATION

Trial	NCT04491604; A Phase III Double Blinded, Placebo-Controlled, Efficacy and Safety Study of Beremagene Geperpavec (B-VEC, Previously "KB103") for the Treatment of Dystrophic Epidermolysis Bullosa (DEB) **Phase III – Recruitment completed**[a] **Location(s):** United States **Primary completion date:** Q4 2021[a]
Trial design	Randomised, quadruple masked, parallel assignment.
Population	N=30 (planned); aged ≥6 months; clinical diagnosis of DEB; confirmation of DEB diagnosis (either DDEB or RDEB) by genetic testing including COL7A1; at least two cutaneous wounds
Intervention(s)	Topical gel of beremagene geperpavec.
Comparator(s)	Matched placebo.
Outcome(s)	Complete wound healing, determined by the Investigator, as compared to baseline in B-VEC treated wounds versus placebo treated. [Time Frame: 24 weeks post-baseline] See trial record for a full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**GEM-1;** NCT03536143; A Phase II Study of Beremagene Geperpavec (KB103), a Non-Integrating, Replication-Incompetent Herpes Simplex Virus 1 (HSV-1) Vector Expressing the Human Collagen VII (COL7) Protein, for the Treatment of Dystrophic Epidermolysis Bullosa (DEB) **Phase II – Completed**[a] **Location(s):** United States **Primary completion date:** February 2020

[a] Information provided by Krystal Biotech Inc

Trial design	Open label, single group assignment.
Population	N=4 (planned); aged 5 years or older; clinical diagnosis of the recessive form of DEB; at least one wound that is between 10 and 20cm^2 in wound area.
Intervention(s)	Topical beremagene geperpavec.
Comparator(s)	No comparator
Outcome(s)	Wound Closure [Time Frame: 24 weeks post treatment] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of beremagene geperpavec is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology Appraisal proposed. Oleogel-S10 for treating skin wounds associated with epidermolysis bullosa (ID1505). Expected publication date: TBC

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Epidermolysis Bullosa Service (All Ages): A12/S(HSS)/a. June 2013
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OTHER GUIDANCE

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ADDITIONAL INFORMATION

Krystal Biotech Inc did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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