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Oleogel-S10 for inherited epidermolysis bullosa

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LAY SUMMARY

Epidermolysis bullosa (EB) is a rare lifelong inherited disease of the skin in which the outer layer of the skin separates from the inner layer. The disease is caused by abnormalities in the genes responsible for the production of the proteins that make the skin strong and elastic. EB is characterised by fragile skin with blistering of the skin following minor mechanical trauma. In some cases, internal linings of the mouth and intestinal tract and organs are also affected. EB is debilitating in the long term and in some forms is life threatening, mainly because of the severe blistering, infections of the skin and the effects on the body caused by poor nutrition. In some types of EB, an aggressive form of skin cancer also occurs in the second and third decade of life. In all forms of EB, the blistering causes pain, itch, a poor quality of life and specialist intervention and considerations are required to minimise complications and improve quality of life.

Currently there is no cure for EB and management is based on symptomatic treatment. Oleogel-S10 is a topical gel and is being developed as a prescription medicine as for EB, for which there are limited treatment options. Oleogel-S10 causes the keratinocytes (cells that regenerate the outer layer of the skin) to migrate (move across the wound) and become mature epithelial skin cells, resulting in rapid wound healing. If licensed, oleogel-S10 will offer a treatment option for wound care in patients with EB who currently have limited therapies available.

TARGET GROUP

Inherited epidermolysis bullosa (EB)

TECHNOLOGY

DESCRIPTION

Oleogel-S10 consists of the active ingredient of dry, refined extract from birch bark from two different birch species Betula pendula and Betula pubescens as well as hybrids of both species (equivalent to 0.5-1.0 g birch bark), corresponding to 72-88 mg betulin, a pentacyclic triterpene which has antifungal and antimicrobial effects. Oleogel-S10 contains 10% of birch bark extract in 90% of sunflower oil. The precise mechanism of action of the active substance in wound healing in humans is not known.[1,2,3] Betulin has been reported to promote healing in a porcine ex vivo wound healing model and to modulate inflammatory mediators and promote keratinocyte differentiation and migration in vitro[4] and in vivo, a process that is essential for re-epithelialization and maintenance of the skin barrier.[3]

In the phase III clinical trial, NCT03068780, Oleogel-S10 is given to patients with inherited epidermolysis bullosa (EB) as a topical gel application for 90 days. Patients are then treated with Oleogel-S10 in an open label extension for 24 months.[5]

The active agents present in birch bark extract, betulin, betulinic acid, lupeol, erythrodiol and oleanolic acid each influences different processes in the healing of wounds. The active ingredients have demonstrated antiviral, antibacterial, anti-inflammatory, and anti-tumoural effects. These effects and their relevance and clinical significance are yet to be demonstrated in EB patients.[6,7] The Phase III clinical study includes secondary endpoints which will explore aspects of these effects including total wound burden, itch, pain, wound infection and impact on sleep and ability to attend work / school.

Studies have been performed to demonstrate healing of partial thickness wounds in patients with split thickness skin graft donor sites and grade 2a burns.[4,8] Based on these studies, Oleogel-S10 is licensed (but not launched) in the UK for accelerated healing of partial-thickness skin wounds in adults.[9,10]

Besides EB, oleogel-S10 is in phase III trials for wound healing in split-thickness skin graft donor sites, burn wounds and actinic keratosis.[11,12]

INNOVATION and/or ADVANTAGES

Currently there are no approved wound care treatments and there is no cure for EB.[13] Oleogel-S10 is being developed as a prescription medicine for EB, for which there are limited treatment options.[14]

The product is non aqueous, oil based gel and is therefore expected to be non-sticking and potentially soothing for patients while is exerts it desired effects on accelerated wound healing. Also, at any one time approximately 10% of the active is solubilised and available to the wound bed. The other 90% is held in the “honeycomb matrix” of the gel. This, it is believed enables the product to be long acting and applied every 1-4 days. This is anticipated to reduce the frequency of dressing changes and thereby avoid unnecessary disruption of the wound bed and the associated pain of unnecessary dressing changes.[a] If licensed, Oleogel-S10 will offer a novel treatment option for people with EB.

[a] Information provided by company

DEVELOPER

Amryt Pharma plc

REGULATORY INFORMATION/ MARKETING PLANS

Oleogel-S10 was designated orphan drug in the EU for EB in February 2011.[17]

Oleogel-S10 was designated orphan drug for EB in the USA in August 2014.[15]

PATIENT GROUP

BACKGROUND

Epidermolysis bullosa (EB) is a heterogeneous group of lifelong inherited disease of the skin in which the outer layer of the skin, the epidermis, separates from the inner layer, the dermis. The disease is caused by abnormalities in the genes responsible for the production of the proteins that make the skin strong and elastic, such as collagen, laminin and keratin.[16,17]

EB is characterised by fragile skin with blistering of the skin and mucosae following minor mechanical trauma. There are four categories of EB, EB simplex, junctional EB, dystrophic EB and Kindler syndrome. These vary in their severity and associated non-cutaneous features. Milder forms result in painful blistering limited to localised areas of skin, more severe forms are associated with death in infancy, or life-long chronic skin loss, scarring, pain, systemic involvement and early death from metastatic skin cancer.[18,16]

Non-cutaneous complications, such as anaemia due to iron deficiency and chronic disease, osteoporosis, growth failure and pubertal delay further compromise wellbeing.[16]

EB is debilitating in the long term and is life threatening, mainly because of the severe blistering, which results in infections, poor quality of life, in some cases incurable squamous cell carcinoma and a significantly reduced life expectancy.[17] It requires specialist intervention and considerations to minimise complications and improve quality of life.[16]

CLINICAL NEED and BURDEN OF DISEASE

There is currently no cure for EB, so treatment aims to relieve symptoms and prevent complications.[13] The skin wounds are treated and dressed to encourage healing but despite this many wounds are chronic and fail to heal. Other areas of the body are dressed to prevent skin damage and the development of new wounds. Dressing changes are undertaken every day or every other day and can take several hours each day. Patients require a family carer or nurse to assist with dressing changes and so the disease has considerable impact on the QoL not only for the patient but also the family carer. Other treatments include management of nutrition, often through PEG feeding, management of anaemia with frequent transfusions and management of bone health to attempt to prevent osteoporosis and bone fractures.[16, 19] The causes of premature death are due to infections, chronic

renal failure, dilated cardiomyopathy and an aggressive squamous cell carcinoma with 0% survival at 5 years.[b]

In 2012, the number of people suffering from EB were estimated to be less than 0.5 in 10,000 people in the EU.[17]

According to an NHS guideline published in 2013, EB was estimated to affect 1 in 17,000 live births and there are around 5,000 people living with EB in the UK.[18]

The Hospital Episode Statistics (HES) for 2016-17 in England recorded 294 finished consultant episodes (FCEs) and 262 admissions which led to 450 FCE bed days due to epidermolysis bullosa (ICD-10 code: Q81).[20]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance identified.

NHS ENGLAND and POLICY GUIDANCE

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

OTHER GUIDANCE

- Denyer J, Pillay E, Clapham J. Best practice guidelines for skin and wound care in epidermolysis bullosa: an International Consensus. Wounds International, 2017.[16]

CURRENT TREATMENT OPTIONS

There is currently no cure for EB, so treatment aims to relieve symptoms and prevent complications.[13] Patients are advised to maintain a high standard of personal hygiene and skincare to help blisters heal, to avoid infections and to protect the skin from damage.[17] Patients are treated with a wide range of bathing agents, wound dressings, topical emollients, topical steroids, systemic and topical anti-infectives and pain control including opiates.[16]

Ideally patients should be managed in a specialist centre. Careful skin and wound assessment should be undertaken regularly. Management must be tailored to suit both the type of EB and the specific characteristics of the wound. The underlying principle of lesion management is to apply an atraumatic dressing to prevent blistering, and skin and wound bed damage leading to pain and bleeding on removal. The choice of wound management strategies should balance efficacy, patient choice and quality of life with cost effectiveness.[16]

[b] Information provided by company

EFFICACY and SAFETY

Trial	NCT03068780, EudraCT 2016-002066-32; 4 years and older; oleogel-S10 vs placebo; phase III
Sponsor	Amryt Research Limited
Status	Ongoing
Source of Information	Trial registry[5]
Location	EU (incl UK) and other countries
Design	Randomised, vehicle-controlled, double blind, parallel assignment
Participants	n=164 (planned); aged 4 years and older; male and females, inherited epidermolysis bullosa (EB)
Schedule	Not reported
Follow-up	Active treatment with Oleogel S10 or placebo gel for 90 days with an open label extension of treatment with Oleogel S10 for 24 months
Primary Outcomes	Proportion of patients with first complete closure of the EB target wound within 45 days of treatment [Time frame: 45±7 days]
Secondary Outcomes	Time to first complete closure of the EB target wound as evidenced by clinical assessment until day 90±7. [Time Frame: 90±7 days]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as Q2 2019. Study completion date reported as 4Q 2020.[c]

ESTIMATED COST and IMPACT

COST

The cost of oleogel-S10 is not yet defined.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other:

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

[c] Information provided by company

☐ Re-organisation of existing services ☐ Need for new services

☐ Other: ☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs ☐ Reduced drug treatment costs

☐ Other increase in costs: ☐ Other reduction in costs

☐ Other: *specify, e.g. uncertain unit cost compared to existing treatments* ☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified ☒ None identified

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