Evaluate Vantage

April 28, 2021

Epidermolysis bullosa gene therapies wait in the wings

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Amryt marches ahead, but gene therapies from Krystal, Abeona and Castle Creek are heading towards data readouts.

By the end of this year, Amryt's Filsuvez could become the first approved treatment for the rare skin disorder epidermolysis bullosa. Despite mixed pivotal data, regulators in the US and Europe might be swayed by the lack of available treatments.

More durable options could come with gene therapies, and phase 3 studies of these will start to report later this year. However, gene therapy procedures can be complex, and Amryt will hope that the convenience of Filsuvez, a topical gel that can be applied at home, could make it the first-line treatment of choice.

First mover advantage

Epidermolysis bulllosa (EB) is a group of inherited skin disorders that cause fragile, blistering skin. Current treatments aim to help alleviate symptoms, including bandaging and bathing open wounds and trying to manage patients' pain.

Late last month, Amryt completed the US rolling submission for Filsuvez for junctional and dystrophic forms of EB, and the EMA began its review of the project.

The pivotal Ease study was not an emphatic victory, however. The trial met the primary endpoint, the complete closure of the target wound within 45 days, but several secondary measures were missed. These included 90-day target wound closure, and the pain endpoint.

Driving the primary treatment effect was a group of patients with the recessive form of dystrophic EB. This was the main patient group in the study, which also recruited junctional and dominant dystrophic EB patients.

Lack of available treatment options means that regulators might look favourably on Filsuvez, but restricting its use to recessive dystrophic patients cannot be ruled out.

According to Stifel analysts the recessive form makes up 15% of patients; they reckon that even if Filsuvez only gets the nod in this population it could still bring in $342m in 2027. This rises to $421m that year with a broader label.

Gene therapy race

As EB is an inherited condition, gene therapy could be the way forward in treating the underlying cause. Amryt's own topical gene therapy, AP103, is due to start clinical studies next year, but others are much further ahead, with Krystal, Abeona and Castle Creek all in phase 3.

By the fourth quarter, pivotal data should be available with Krystal Biotech's beremagene geperpavec (B-Vec), a topically applied gene therapy designed to induce local collagen production.

If the project can show strong signs of durability it could differentiate itself from Filsuvez. There are some questions about B-Vec's longevity, however, as in its phase 1/2 study some lesions that had closed later reopened *(Gene therapy's duration is less than Krystal clear, October 29, 2019)*.

The primary endpoint of the upcoming pivotal Gem-3 trial is complete wound healing at weeks 22 and 24, or weeks 24 and 26; only wounds that are completely healed for at least two weeks count as a positive response.

Approximately 30 adult and paediatric patients are being enrolled with recessive or dominant dystrophic EB. Subjects will act as their own controls, receiving either B-Vec or placebo once weekly on different wounds.

B-Vec does not represent a "once-and-done" gene therapy; due to the rapid turnover of skin cells, it still requires frequent applications.

In Gem-3, the project was administered in the clinic but Krystal is hopeful that, if approved, B-Vec could be given at home. If clinic visits are required, this could prove problematic as travel can be hard for EB patients due to their extremely fragile skin.

Complicated procedures

Further behind are Abeona and Castle Creek's EB-101 and D-Fi respectively. Both offer a personalised treatment approach that is a far cry from the ease of topical application.

With both therapies, biopsies are taken and skin cells are corrected by gene transfer. Abeona's treatment involves surgically transplanting sheets of cells onto patients' wounds while Castle Creek's uses intradermal injections.

Top-line data from Abeona's open-label phase 3 Viital study, in large chronic wounds, are due in mid-2022. The trial will enrol 10-15 recessive dystrophic EB patients with wound sites that are larger than 20cm^2, which have been present for more than six months.

The primary endpoint is the proportion of wound sites with 50% or greater healing from baseline at 24 weeks. This differs from the complete wound closure measure for competitors' treatments, presumably due to the large size of the wounds being treated.

In an earlier study run by Stanford University, wound healing of 50% or greater was present in 95% of wounds treated with EB-101 versus 0% of untreated control wounds at 24 weeks. At two years, 71% of treated wounds had 50% or greater healing compared with 17% of control wounds.

Lastly to Castle Creek's D-Fi, which was previously known as FCX-007 and originated at Fibrocell. A phase 1/2 trial found that after a single dose, 63% of treated wounds had completely closed at 12 weeks, versus none in the untreated cohort.

The phase 3 trial, DeFI-RDEB, is enrolling patients with recessive dystrophic EB, and wounds will be treated for two or more sessions. The primary endpoint is complete wound closure of the first wound pair at week 24, and the study has a primary completion date of April next year.

Selected late stage products for epidermolysis bullosa			
Product	**Company**	**Note/clinical study**	**2026 WW indication sales ($m)**
Filed			
Filsuvez/ Oleogel-S10	Amryt Pharma	Topical betulin gel, filed with the FDA and EMA, Ease study	310
Phase 3			
KB103/B-Vec (beremagene geperpavec)	Krystal Biotech	Topical HSV vectored COL7A1 gene therapy, Gem-3 data Q4'21	462
EB-101 (prademagene zamikeracel)	Abeona Therapeutics	Keratinocytes transduced with EB-101 (COL7A1 gene therapy), then applied surgically, Viital top line mid-'22	125
D-Fi (dabocemagene autoficel) (previously FCX-007)	Precigen/Castle Creek Biosciences	Fibroblasts corrected with D-Fi (lentiviral vector COL7A1 gene therapy), admin intradermally, DeFi-RDEB completes Apr '22	-
Phase 2			
Autologous Cultured Epidermal Grafts	Holostem Terapie Avanzate	Genetically corrected cultured epidermal autograft, Ph1/2 Hologene7 completes Dec '21	-
BBP-589/PTR-01	Bridgebio Pharma/Phoenix Tissue Repair	Intravenously-administered recombinant collagen 7 protein replacement therapy, data late '21/early '22	53
Source: Evaluate Pharma, clinicaltrials.gov, company releases.			