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Amryt awaits crucial readout as it prepares rare disease push

Amy Brown

A looming interim analysis could make Amryt a player in epidermolysis bullosa – and boost its deal-making ambitions.

Later this year Amryt Pharma will learn whether it possesses the industry's most promising epidermolysis bullosa project. An interim analysis of the pivotal Ease study, the largest trial ever run in patients with this devastating inherited skin condition, will help decide whether further work on AP101 is warranted.

Given the incredibly challenging nature of the disease a green light to continue would be a huge boost for the UK-listed company, which was formed three years ago with the explicit aim of becoming a commercial-stage rare disease player. Last year's blow-up of a late-stage Amicus asset, Zorblisa – like AP101 a topical gel – showed just how tough EB is to treat, though Amryt's chief executive, Joe Wiley, tells *Vantage* that the company learned a lot from this failure.

"Amicus were incredibly generous and opened up their data for us, and we were able run our own analysis on the study," he says. "Based on what we saw we increased our sample size ... and refocused the trial onto the severe end of the spectrum, to maximise our chance of showing a treatment difference."

AP101's active ingredient is betulin, a plant extract, so it is mechanistically unrelated to Amicus's failed Zorblisa (*Amicus investors untroubled by SD-101 costs, September 13, 2017*).

The interim efficacy analysis of the Ease trial will be conducted when half of the targeted 192 patients have been treated; this is estimated to occur in the fourth quarter. Statisticians will tell the company whether the study has accumulated sufficient power to succeed.

The primary endpoint is the proportion of patients with completely healed target wounds at day 45, a shorter timeframe than the 90 days used in the failed Essence trial of Zorblisa. "We always felt that was too late" to measure the primary endpoint, Mr Wiley says.

Advice to proceed as planned would be the best outcome for Amryt, while a recommendation to increase the sample size would be a worrying sign. A ruling of futility would be a huge disappointment.

Leading the pack? Active, clinical-stage epidermolysis bullosa projects			
Project	**Company**	**Description**	**Trial ID**
Phase III			
AP101/Episalvan	Amryt Pharma	Betulin formulated as topical gel	NCT03068780
Phase II			
RGN-137	Lenus Therapeutics (Regenerx, G-treeBNT JV)	Tβ4-based dermal gel formulation	Phase III targeted to start in 2019
Diacerein	Castle Creek Pharmaceuticals	Diacerein formulated as topical gel	NCT03154333
EB-101	Abeona Therapeutics	Autologous, ex-vivo COL7A1 gene therapy	NCT01263379
KB103	Krystal Biotech	HSV vectored COL7A1 gene therapy	NCT03536143
QRX-313	Proqr Therapeutics	RNA-based oligonucleotide - skips exon 73 of COL7A1 gene	NCT03605069
FCX-007	Fibrocell Science	Lentiviral vector COL7A1 gene therapy	NCT02810951
Phase I			
BPM 31510 Topical	Berg	Topical formulation of ubiquinone (co-enzyme Q10)	NCT02793960
Source: EvaluatePharma.			

Complete lack of activity would be a surprise, as AP101 is already approved to treat partial thickness wounds in Europe, having generated three successful phase III trials in skin grafts and burns patients. Clearance here came in early 2016 when the product, branded Episalvan, was owned by Birken, a private German group that Amryt subsequently acquired. But launch in this indication has been put on hold because success in a rare condition like EB would allow for a substantially higher price tag.

However, showing efficacy in EB will be much harder. Sufferers lack a protein that holds skin together, making the skin very fragile. The healing mechanism is the same as with other wounds, Mr Wiley points out – EB effectively causes partial thickness wounds – but the added complexities of this intractable genetic disorder should not be underestimated.

Final readout from Ease is targeted for early next year, and the company hopes to file in the US and Europe on the data; recruitment at US sites will begin if the interim analysis is positive. Earlier this year the FDA granted AP101 Pediatric Rare Disease designation, meaning a priority review voucher would come Amryt's way if the drug reaches the US market.

Commercial ambitions

Amryt is committing R&D cash to EB – the company also has a gene therapy that could enter the clinic in 18 months, if all goes well – but Mr Wiley says this in-house development work is an exception. The company's ambitions are geared towards buying in commercial-stage assets, and the hunt is on for other orphan opportunities.

These would join Lojuxta, which Amryt has been selling since mid-2016, when it bought European and other regional rights from Aegerion. The treatment for extremely high cholesterol is sold as Juxtapid in the US, and in fact two of Amryt's management team have come from Aegerion.

"We're actively pursuing discussions with a number of companies," Mr Wiley says. "If you think of Lojuxta as a good example of a deal, something similar to that would be great."

Still, Lojuxta represents something of a unique situation – at the time of the Amryt deal Aegerion had been laid low by corporate scandals and missed sales expectations. No up-front fee was involved, though Amryt did commit to complete various regulatory and post-marketing obligations, as well as royalties and commercial

sales milestones.

Juxtapid was launched in the US in 2013 as a treatment for homozygous familial hypercholesterolaemia (HoFH), a very rare condition, but over-hyped, near-blockbuster expectations were ultimately dashed by the arrival of the PCSK9 inhibitors. Armed with more powerful marketing machines and much cleaner safety profiles, the injected antibodies ended Aegerion's attempts to move into broader patient populations. Amgen's Repatha also went on to win an HoFH indication.

In Europe the situation was made trickier by Juxtapid's lack of orphan designation. At the time of the application Aegerion's sights were set on bigger markets.

In Amryt's hands expectations have been reset. The company estimates a €125m ($143m) market opportunity in the regions in which it has licensed Lojuxta, including Central and Eastern Europe, North Africa and the Middle East. And Lojuxta is now positioned as a last-line therapy. About half of HoFh patients will respond to a PCSK9 inhibitor, and Lojuxta is more expensive than these already costly drugs.

"The PCSK9s have created a diagnostic test for our drug. From a reimbursement perspective physicians and payers really like that," Mr Wiley says.

Endorsement from the UK's NHS last month suggests that this strategy is working: Stifel analysts expect sales in 2018 to reach €16m, up from €7m recorded in 2016.

Mr Wiley believes that the commercial infrastructure Amryt is establishing for Lojuxta will make it an attractive partner, as it searches for other orphan disease projects. But the company will be shopping in a very competitive space, and sports a modest £51m ($65m) market value.

A phase III win in EB would improve the company's credentials enormously, making the looming readout a huge event on Amryt's horizon.