

Patience rewards Ionis and Ziarco



Jacob Plieth

Astrazeneca's four-year-old tie-up with Ionis might not have yielded any groundbreaking clinical data yet, but the UK group seems determined to press on, extending the alliance and funding its partner on several occasions.

The latest fillip came on Friday, when Ionis got \$28m on selecting a new oncology antisense project – intriguingly targeting the tough Kras oncogene – that could soon enter the clinic. And neither did a lacklustre performance dissuade Ziarco, which has attracted a buyer in the shape of Novartis even though its lead asset, the oral eczema project ZPL-3893787, failed in the clinic.

The Swiss firm obviously believes that it can carve out a niche for the first H4 receptor antagonist being developed for the skin disorder, in spite of an increasingly competitive landscape. Astra, meanwhile, is betting that antisense could hold the key to hitting tumours with Kras mutations, a target typically considered undruggable.

In fact, the partners say their project, coded IONIS-KRAS-2.5Rx or AZD4785, will be the first asset directly targeting Kras, regardless of mutation type, to enter the clinic.

Kras was one of the first oncogenes to be discovered, and the mutated protein product of this gene is thought to drive up to 30% of cancers. Because of this it is one of the most sought-after cancer targets, but owing to the lack of obvious binding pockets on the protein it has so far proved impossible to target with small molecules or antibodies.

Pronai Therapeutics is known to have worked on a Kras antisense project, while Kite Pharma recently licensed the NCI's engineered T-cell receptor project targeting tumours expressing mutated Kras antigens.

[Astra opting in to AZD4785, in return for \\$28m](#), relates to its 2012 oncology tie-up with Ionis – then known as Isis Pharmaceuticals. This has most prominently generated ISIS-STAT3Rx, an antisense against Stat3, in phase I/II; in 2014 the deal was widened to look at antisense oligonucleotide delivery, and the next year Astra paid \$65m to include cardiovascular, metabolic and renal diseases.

Skin deep

Financial terms of Novartis's Ziarco acquisition were not given, but much of the fee will surely depend on approval of ZPL-389. To get there it will need to improve on its previous performance – a proof-of-concept trial failed to meet its primary endpoint but found a benefit on secondary outcomes including the eczema area and severity index ([Ziarco lacks sparkle in atopic dermatitis, June 13, 2016](#)).

Ziarco had previously said it would start a phase IIb trial alone by the end of the year, but this will now be Novartis's responsibility.

Even if ZPL-389 succeeds in later trials and eventually gets the go-ahead, it might struggle to gain a foothold as other new players reach the market. Pfizer's topical ointment Eucrisa has just got the thumbs-up from the FDA, and there are 10 eczema candidates either filed or in phase III, according to *EvaluatePharma*. One of these, Sanofi and Regeneron's injectable antibody dupilumab, is expected to be the market leader by 2022.

However, steroid creams are still set to make up a big chunk of the sector, in spite of their side effects, so there could still be room for new products.

Top 10 eczema products in 2022

Product	Company	Description	Status	2022e sales (\$m)
Dupilumab	Sanofi/Regeneron	Injectable anti-IL-4 & IL-13 MAb	Filed	2,997
Eucrisa	Pfizer	Topical PDE4 inhibitor	Approved	1,275
Bepanthen	Bayer	Vitamin B5 cream	Marketed	571
Temovate	Glaxosmithkline	Topical corticosteroid	Marketed	99
Antebate	Torii Pharmaceutical	Topical corticosteroid	Marketed	70
Elidel	Valeant	Topical calcineurin inhibitor	Marketed	51
Nemolizumab	Chugai	Injectable anti-IL-31 MAb	Phase II	50
Cormax	Akorn	Topical corticosteroid	Marketed	48
QAW039	Novartis	Oral PD2 receptor/CRTH2 receptor antagonist	Phase II	41
Cordran	Almirall	Topical corticosteroid	Marketed	33

Source: EvaluatePharma

Ziarco's chairman, Mike Grey, previously told *EP Vantage* that he would position ZPL-389 between dupilumab, which will be reserved for the most severe patients, and Eucrisa and other topical treatments, which are more suited for milder disease.

He added that an oral product like ZPL-389 could have a convenience advantage over creams in patients with a large body surface area affected by eczema.

As well as ZPL-389, which is also in phase II in psoriasis, Ziarco has a topical eczema cytosolic phospholipase A2 (cPLA2) inhibitor, ZPL-521, in phase I/II development, and an allergic rhinitis project, ZPL-868, which it has said is "phase I ready".

It seems that both Astra and Novartis have seen enough promise to proceed with their respective assets, and they will now shoulder the risk of later-stage development.

Project	Study	Trial ID
ZPL-3893787	Phase II trial in psoriasis	NCT02618616
ZPL-5212372	Phase I/II trial in eczema	NCT02795832

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