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Dry eye development reaches the Eleventh hour

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A couple of years ago dry eye disease seemed to offer fertile ground for biopharma development, but improving both its signs and symptoms in a clinical trial has turned out to be a tough nut to crack.

Yesterday's pivotal study failure for Eleven Biotherapeutics' EBI-005 was the latest in a string of setbacks to hit a field that has also claimed the scalps of Mimetogen, Can-Fite and Rigel. Shire's lifitegrast is now left as one of the few late-stage hopes, notwithstanding its own mixed phase III data (see table below).

It was lifitegrast, of course, that managed to show a statistically significant effect on the tough symptom endpoint but failed to improve signs of dry eye in one pivotal trial, after a previous study had had the reverse, and more common, outcome. But Shire scored a victory last month when the US FDA accepted lifitegrast's filing, suggesting that the agency was relatively happy with the data.

The FDA has an October 23 action date, apparently without the need for an advisory committee. *EvaluatePharma's* sellside consensus data point to lifitegrast sales hitting $566m in 2020, but even so some analysts view the LFA-1 antagonist as one of the most undervalued assets in Shire's portfolio.

Attrition

The attrition in this space plays to lifitegrast's strength. Eleven's stock fell 69% yesterday when the one-asset company's EBI-005 flunked its phase III study, leaving a group that had once been capitalised at over $300m valued at just $71m.

EBI-005, an IL-1 signalling inhibitor, managed to miss both co-primary endpoints – corneal fluorescein staining score (signs) and patient-reported pain and discomfort (symptoms) – and Eleven has ditched EBI-005 in this indication. Placebo recipients actually fared numerically better than those on active treatment.

This followed the discontinuation of Can-Fite Biopharma's adenosine A3 receptor agonist CF101 in phase III – a post-hoc analysis notwithstanding – and Rigel's Jak-3 inhibitor R348 in phase II. Both projects missed primary and secondary endpoints.

Last September Mimetogen Pharmaceuticals reported what it said were positive data from a 403-patient phase III study of MIM-D3, a tyrosine kinase receptor antagonist. However, the private company only provided positive p values for secondary measures, suggesting that the co-primary endpoints – four-week sign and symptom improvement – had been missed.

The question was laid to rest days later when Valeant's Bausch + Lomb division allowed an opt-in option to lapse. There was better news last month when Kala Pharmaceuticals' nanoparticle loteprednol etabonate, KPI-121, hit a phase II signs endpoint but missed on symptoms.

Selected mid to late-stage projects targeting dry eye disease				
Project	**Type**	**Company**	**Pharmacology class**	**Status**
Lifitegrast	NME	Shire	LFA-1 antagonist	Filed
EGP-437	Drug delivery	EyeGate Pharma	Corticosteroid	Phase III
Pulmozyme ophthalmic (dornase alfa)	Drug delivery	Roche	Deoxyribonuclease I	Phase II
KCT-0809	NME (ex-US)	Kissei Pharmaceutical	Eye preparation	Phase II
ISV-101	Drug delivery	InSite Vision	NSAID	Phase II
RX-10045	NME	Auven Therapeutics	Anti-inflammatory agent	Phase II
XG-104	Drug delivery	Xigen	JNK inhibitor	Phase II
SkQ1 systemic	NME	Mitotech	Anti-oxidant	Phase II
Civanex Nasal	NME	Winston Pharmaceuticals	TRPV1 agonist & calcium channel blocker	Phase II
KPI-121	Nanoparticle formulation	Kala Pharmaceuticals	Mucosal penetrating agent	Phase II
SR Dexamethasone	Drug delivery	Ocular Therapeutix	Corticosteroid	Phase II
Source: EvaluatePharma.				

The dry eye disease market is dominated by Actavis's Restasis – one of the few agents that acts pharmacologically rather than being a tear-replacement; this became a blockbuster last year, selling $1.1bn (*Therapeutic focus – Plenty of dry eyes in the house, December 5, 2013*).

But the setbacks have left a rather bare late-stage pipeline. The table above includes only projects targeting the underlying causes of dry eye – a complex disease thought to be the final manifestation of several separate conditions – which can broadly be caused by an inflammatory mechanism or by excessive tear evaporation.

EyeGate's EGP-437 is interesting in that it uses a transscleral iontophoresis delivery system that applies a low-voltage electrical current to deliver a specified amount of drug into the eye. However, its phase III study was completed in 2011, and the private company seems to be focusing on other indications including anterior uveitis.

Eleven, too, has now turned away from dry eye – to developing EBI-005 for allergic conjunctivitis, likely a better-defined and better-understood disease. One of the problems in Eleven's pivotal trial was the widespread use of artificial tear products by patients in both arms – an issue that raises the question of whether such symptom relief could be effective beyond mild disease.

The focus on tougher ocular diseases might have come too late in the day for Eleven, however. With a valuation barely above the $59m the group has in the bank, in addition to $15m of debt, Eleven's biggest problem now is where to turn for more cash.

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