Evaluate Vantage

November 06, 2018

Clearside’s future clouds over

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After failing in retinal vein occlusion, the prospects for the eye project Xipere – and Clearside Biomedical itself – hinge on the smaller uveitis indication.

Clearside Biomedical execs claim that the company still has a future despite discontinuing its sole clinical candidate, Xipere, in its biggest potential indication, retinal vein occlusion. Investors, who sent the group’s stock below cash levels yesterday, appear to disagree.

The problem is that Clearside is now relying on the much smaller uveitis indication for all its future sales of Xipere, a corticosteroid injected into the back of the eye. Discontinuing ongoing trials should give the group enough cash to keep going until 2020, but with a sparse pipeline Clearside’s prospects look gloomy.

For now, the company is ploughing ahead with Xipere in uveitis, where it has positive data from the phase III Peachtree monotherapy trial.

Clearside plans to file for approval for macular oedema associated with non-infectious uveitis by the end of the year. But with this form of the disorder only affecting around 135,000 patients, according to Stifel analysts, this was the least valuable opportunity for Xipere.

Indeed, *EvaluatePharma's* sellside consensus puts the project’s 2024 uveitis sales at under $150m.

Clearside Biomedical's clinical-stage pipeline					
Project	**Indication**	**Status**	**2024e sales ($m)**	**Trial(s)**	**Data due**
Xipere	Retinal vein occlusion	Phase III	265	Sapphire (NCT02980874); Topaz (NCT03203447)	Failed; discontinued
	Uveitis	Phase III	146	Azalea (NCT03097315); Peachtree (NCT02595398)	Completed
	Diabetic macular oedema	Phase II	79	Tybee (NCT03126786)	Completed
Source: EvaluatePharma, company website.					

Retinal vein occlusion (RVO) could have been much more lucrative, but this is now off the table after yesterday's failure of the Sapphire study of Xipere plus Regeneron/Sanofi's Eylea versus Eylea alone at its eight-week interim analysis.

Clearside had hoped to show that the combination was superior to Eylea alone, but in the event it found a similar proportion of patients achieving the primary endpoint, at least a 15-letter improvement in vision.

The company's chief scientific officer, Glenn Noronha, blamed an "exceptional" response in the Eylea group on a conference call yesterday. This is not the first time that combinations have struggled to beat Eylea, and even Regeneron's own efforts have fallen short here (*Regeneron needs a new plan B for Eylea, 27 November 2017*).

Whatever the reason, Clearside's combo hopes in RVO are over – the company has also discontinued the Topaz trial of Xipere plus Roche's Lucentis and Avastin.

Diabetes downer

As if this were not bad enough, the latest failure raises questions about whether Xipere combos have any future in another big use, diabetic macular oedema.

Here, Clearside disappointed investors in May with data from the phase II Tybee study, again combining Xipere with Eylea. This achieved its goal, with the combo producing similar results to Eylea alone and allowing less frequent treatment, every three months versus monthly for Eylea alone.

However, efficacy looked slightly worse with the combo, and Eylea monotherapy already has approval for dosing every 12 weeks, at least in wet AMD.

To have a realistic chance of competing, Xipere needed to show superiority over Eylea alone in diabetic macular oedema in phase III – but this now looks even more unlikely after the Sapphire results.

On yesterday's conference call, Clearside execs would not give details on their phase III plans for Xipere in diabetic macular oedema, and would only say they were "evaluating options".

All of Xipere's other indications are at the preclinical stage – so the heat is now on in uveitis. It is expected to be the top drug in this indication by 2024, according to *EvaluatePharma,* but that still might not be enough to keep Clearside afloat for long.

Top five uveitis therapies in 2024				
Product	**Company**	**Mechanism of action**	**Status**	**2024e sales ($m)**
Xipere	Clearside Biomedical	Glucocorticoid receptor agonist	Phase III	146
Yutiq	Eyepoint Pharmaceuticals	Tyrosine kinase inhibitor	Approved	74
Opsiria	Santen Pharmaceutical	mTOR inhibitor	Filed	39
ADX-102 Eye Drop	Aldeyra Therapeutics	Aldehyde inhibitor	Phase III	12
Neoral	Novartis	Calcineurin subunit B type 2 inhibitor	Marketed	2
Source: EvaluatePharma.				