Evaluate Vantage

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Event - Regeneron's eye drug looks good for positive vote

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Excitement over Regeneron Pharmaceuticals' ophthalmology candidate Eylea reached a fever pitch in late April with presentation of detailed data in central retinal vein occlusion, and now the product awaits a US advisory committee verdict in its lead indication, macular degeneration. On safety and efficacy, the vascular endothelial growth factor (VEGF) inhibitor appears to be an approvable drug, matching up well with the incumbent, Roche's Lucentis, (*Dosing the jewel in VEGF Trap-Eye's crown, November 22, 2010*).

Anything less than a strong vote in favour would be a major surprise as Eylea showed itself the equal of Lucentis in a head-to-head trial of wet age-related macular generation (AMD) patients, with the advantage of less-frequent dosing, which in both cases involves an injection into the eye. As the use of VEGFs to treat AMD is well-validated, with Lucentis approved in 2006 and its less-expensive cousin Avastin used extensively off-label, so it seems only a previously undisclosed safety signal could derail Eylea now.

Product	Eylea (VEGF Trap-Eye)
Company	Regeneron Pharmaceuticals
Market cap	$5.04bn
Product NPV	$2.32bn
% of market cap	46%
Event type	FDA advisory committee
Indication	Wet age-related macular degeneration
Date	June 17, 2011

Well-known concept

Formerly known as VEGF Trap-Eye, Eylea is an ophthalmological formulation of aflibercept, which the New York group is testing in multiple eye and cancer indications.

In cancer, VEGF inhibitors hinder the growth of blood vessels that feed tumours; in AMD, they deter abnormal blood vessel growth that causes bleeding, fluid leakage, and eventually scarring that damages photoreceptors. It is a leading cause of blindness in the elderly – US prevalence is expected to rise to 3 million by 2020.

The pivotal View 1 and View 2 trials, the former in North America and the latter in Europe, where it is partnered with Bayer, showed that 2mg dose of Eylea every other month was non-inferior to a monthly dose of 0.5mg of Lucentis in improving visual acuity. The share of Eylea patients losing fewer than 15 letters of visual acuity was also judged as a non-inferior.

In choosing a drug, analysts from Leerink Swann write that opthalmologists find themselves overwhelmed with patients whose vision is being maintained with once-monthly injections of Lucentis and find the prospect of an equally good once-every-other-month dose preferable.

On safety, the trial did not reveal any differences between the Eylea arms and the Lucentis arm, suggesting that the adcom briefing documents due out June 15 will not contain any hidden surprises, analysts from RBC wrote in a note today, although share price volatility would not be unusual given the importance of the drug to Regeneron.

Analyst enthusiasm for its likely approval and the size of the market is reflected in the forecasts: according to *EvaluatePharma* data, $663m in US sales for Regeneron by 2016, with another $92m in partnership income

from global partner Bayer, which recently filed for approval in Europe. More than three-quarters of the sales figures are in AMD.

Leerink Swann, which initiated coverage on June 2, estimates $1.28bn in US sales by 2016, while recent positive clinical data in retinal vein occlusion and diabetic macular oedema should drive up prior forecasts for the drug.

The *EvaluatePharma* consensus, which excludes Leerink Swann, give Eylea a net present value of $2.32bn to Regeneron, 46% of its market capitalisation of $5.04bn. By comparison, Regeneron's one marketed product, Arcalyst has a net present value equal to 4% of market cap and analysts have yet to assign any value to aflibercept in its cancer indication or other pipeline products. After a number of late stage failures, use of aflibercept in cancer only recently managed to generate positive phase III data (*Regeneron, Sanofi finally get an aflibercept cancer win, April 27, 2011*).

Thus, investors have high expectations for Eylea's success. Regeneron shares touched a record high of $67.05 at the end of April and remain well above their price in November of $24.67 the day prior to the release of the View data – in morning trade today they were at $56.

Commercial concerns

However, AMD treatment is evolving quickly as specialists grasp the findings of analyses comparing the effectiveness of the Roche's pricey Lucentis and Avastin, the cancer drug used off-label in the condition (*Catt is out of bag but Lucentis-Avastin debate far from over, May 4, 2011*). Findings that suggest Lucentis could be effective with less-frequent dosing may help Roche defend its eye franchise.

Addressing physician concerns over dosing, the Catt trial also tests Lucentis and Avastin on an as-needed basis – trial coordinators National Eye Institute said an interim analysis revealed that as-needed use resulted in four to five fewer injections per year – and found visual acuity gains were equal between the two drugs and only two letters less than the drugs given monthly.

Two-year Catt data may clarify the dosing issue further. However, the View studies of Eylea against Lucentis also include a second year of treatment dosed as needed. It will provide the best picture of how all three drugs stack up in that setting, which will be welcomed by physicians and payers with ever longer patient rolls.

In addition, Roche has a phase III test of 2mg Lucentis compared with its approved dose of 0.5mg, both monthly and as needed. Data are due in the second half of the year but analysts from Leerink Swann do not expect a regulatory filing until 2013, giving Regeneron a decent head start of at least a year.

Thus Regeneron appears well on its way to getting its first drug reckoned to have blockbuster potential approved in the US. Whether it can live up to those expectations depends more on a rapidly shifting scientific and commercial landscape.