Closer Look

MEMORANDUM

Executive Highlights

- The FDA announced last week that it has approved Bayer/Regeneron's Eylea (intravitreal aflibercept) for diabetic retinopathy (DR) in patients with diabetic macular edema.

The FDA announced last week that it has approved Bayer/Regeneron's Eylea (intravitreal aflibercept) for diabetic retinopathy (DR) in patients with diabetic macular edema (DME). Eylea has been approved for DME without the DR indication since last July; it has been approved for wet age-related macular degeneration (wet AMD) since 2011. The product received breakthrough therapy and Priority Review designations from the FDA, which allowed it to receive expedited review. The approval was supported by two-year results from the phase 3 VISTA-DME and VIVID-DME studies, which found significantly greater improvements in DR severity with Eylea vs. control (macular laser photocoagulation). This announcement comes slightly over a month after the FDA approval of Roche/Genentech's Lucentis' (intravitreal ranibizumab) for DR; Lucentis was the first drug to receive a DR indication in the US. We are glad to see more treatment options arising in an area of such great unmet need - according to data cited in the FDA press release, 33% of adults with diabetes aged 40 years or older had some form of retinopathy as of 2008. We also imagine that other companies like Alimera Sciences (which markets Iluvien [intravitreal fluocinolone acetonide] for DME) may feel compelled to pursue DR indications in the future, if only to keep up in an increasingly competitive market. Ultimately, of course, we hope that more effective prevention and early treatment of diabetes can reduce the need for these treatments by lowering the rates of retinopathy and other debilitating complications.

- **The phase 3 VISTA-DME and VIVID-DME trials found significantly greater improvements in DR severity after two years with Eylea vs. standard laser photocoagulation.** The two similarly designed trials (VISTA-DME took place in the US and VIVID-DME in Europe, Asia, and Australia) randomized 872 patients with DME to receive either Eylea 2 mg every four weeks (2q4), Eylea 2 mg every eight weeks (2q8, following five initial monthly doses), or standard laser photocoagulation. The studies met the primary endpoint of significantly greater gains in best-corrected visual acuity (BCVA) with Eylea at one year; these results were used to support the DME approval in July. Two-year results showed significantly greater improvements in DR severity (assessed based on the degree of retinal damage) with Eylea vs. control: 38% of the 2q4 group and 30% of the 2q8 group achieved at least a two-step improvement in scores on the diabetic retinopathy severity scale, compared to 8% of the control group.
- **Eylea posted sales of $1.74 billion in the US and $1.04 billion ex-US in 2014.** As a reminder, Eylea is marketed by Regeneron in the US and by Bayer ex-US. Bayer has characterized Eylea as a strong driver of growth throughout the year, and the DR indication should certainly help spur continued growth going forward. The DME market has become increasingly competitive with the approvals for both Eylea and Iluvien in 2014 - Roche management acknowledged as much during the company's 4Q14 update, which included a more conservative outlook for Lucentis (approved for DME since 2012) in 2015. Now that both Lucentis and Eylea have been approved for DR, we wonder whether payers might attempt to pit the two drugs against each other in an attempt to keep prices low, and whether other companies like Alimera Sciences will feel compelled to pursue DR indications in order to compete. On the other hand, it is possible that high prices for Eylea and Lucentis could theoretically push some patients toward cheaper off-label options like Genentech's Avastin (bevacizumab).

- **As a reminder, the *NEJM* recently published full 52-week results of a comparative effectiveness study evaluating Eylea vs. Lucentis vs. Avastin in DME.** The NIH-sponsored study randomized 660 patients with DME to receive 2 mg Eylea, 1.25 mg Avastin, or 0.3 mg Lucentis. Topline results reported in October showed that Eylea produced significantly greater improvements in visual acuity overall than either comparator ($p<0.001$ vs. Avastin; $p=0.03$ vs. Lucentis). However, full results showed that the difference was driven entirely by the subgroup with a baseline visual-acuity letter score <69 (~20/50 vision) and that there was no significant difference between the three treatments for patients with a higher baseline score. We are curious to see what, if any, impact these results have on prescribing patterns and sales; Bayer highlighted the topline results as a positive for Eylea in its 3Q14 update, but we suspect the complexity of the full results will limit the advantages the drug can gain.

-- by Emily Regier, Adam Brown, and Kelly Close