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Wet AMD Market Snapshot: A High-Growth Market Poised For Change

by Jessica Merrill

Regeneron's Eylea and Roche's Lucentis currently dominate the treatment market for wet-AMD and diabetic eye disease, but biosimilar ranibizumab and new brand launches are on the horizon.

The US treatment market for wet age-related macular degeneration has been solidly established for a decade, dominated by two powerhouse anti-vascular endothelial growth factor (VEGF) brands: *Regeneron Pharmaceuticals, Inc.*'s Eylea (aflibercept) and *Roche Holding AG*'s Lucentis (ranibizumab). In the next six months, however, the market is poised for a shakeup with the potential launch of the first biosimilar version of Lucentis in the US and the first bispecific antibody for wet AMD, Roche's faricimab.

Regeneron's top priority is defending its market leadership position in the category with Eylea, the company's top-seller and a high-growth brand even after 10 years on the market. Regeneron is currently testing a high-dose version of Eylea in Phase III studies, which, if successful, could extend the duration of treatment and strengthen the brand's position against new competition.

Wet macular degeneration is a chronic eye disorder that can result in blurred vision, usually caused by abnormal blood vessels that can leak fluid or blood into part of the retina. It is considered the more serious of two types of age-related macular degeneration, the leading cause of vision loss in people over 60 (the other type is known as dry AMD). Eylea and Lucentis are also approved for various diabetic eye diseases that affect the retina, including diabetic macular edema and diabetic retinopathy.

The opportunity remains significant, despite current treatment options, partly because of the aging population and because of growth opportunities in newer indications in diabetic eye diseases, where growth rates are higher. Lucentis and Eylea work well but the biologic drugs require regular burdensome injections into the eye with varying degrees of duration, which

means drug makers see an opportunity to improve on the current treatment paradigm.

One question is how payers will perceive the value of high-cost brands that deliver more durability if a cheaper biosimilar version of Lucentis is available. Off-label use of another VEGF inhibitor, a reformulated version of Roche's Avastin (bevacizumab), is already commonplace in the category, even though it was never approved by the US Food and Drug Administration for wet AMD. Because it costs less, some insurers require its use as a step-edit before moving onto treatment with Lucentis or Eylea.

The pressure from payers to reduce spending in the category will surely be intense. Eylea is the most expensive drug reimbursed under Medicare Part B in the US, while Lucentis is the sixth most expensive, according to the Kaiser Family Foundation.

The timing for a biosimilar version of Lucentis remains uncertain, but one could launch in the US by the end of the year. (Also see "*The Drugs That Could Face US Generic/Biosimilar Competition In 2021*" - Scrip, 26 Apr, 2021.) Partners *Biogen, Inc.* and *Samsung Bioepis Co., Ltd.* have a biosimilar pending with the FDA; the same product was just approved by regulators in Europe, though a launch in Europe is not expected until 2022. (Also see "*Samsung Bioepis Scoops First EU Lucentis Biosimilar As 2022 Date Looms*" - Generics Bulletin, 24 Aug, 2021.) *(Editor's Note: Samsung Bioepsis biosimilar was approved by FDA on 20 September under the brand name Byooviz (ranibizumab-nuna).* (Also see "*FDA Approves First Ophthalmic Biosimilar With Samsung Bioepis' Lucentis Rival*" - Generics Bulletin, 20 Sep, 2021.)

Opportunity Remains

Physicians support choice in selecting the best treatment option for patients, seeing a broader benefit beyond just convenience for patients when a treatment is more durable.

Retina specialist Charles Wykoff of Houston Methodist Hospital said in an interview that while the current treatments are excellent, the outcomes seen in clinical trials do not always translate to the real-world setting.

"The problem with treatment in the real world, or routine clinical practice, is that many patients don't receive the frequency of dosing that they really need to get optimal outcomes," he said. "People go on vacation, doctors go on vacation, the clinic gets overbooked, their kids get sick. What you see in the real world is that people actually get undertreated and their outcomes are not as strong as they would have been based on the interpretation of the robust Phase III clinical trial data."

Wykoff said he is enthusiastic about some of the new options that could be on the horizon for patients, including Roche's bispecific faricimab and a new surgically implantable port delivery system Roche developed for use with ranibizumab. He has been involved as an investigator with

the clinical trials for both programs and said he has seen good outcomes for patients.

Both new products are currently under review by the FDA, with a decision on the port delivery system in wet AMD anticipated in October and a decision on faricimab for both wet AMD and diabetic macular edema (DME) expected in early 2022.

Wykoff was less enthusiastic about the launch of biosimilars in the wet AMD space, though he said he would welcome them if they expanded access to more patients.

"I hope that biosimilars don't paint us into a corner of step therapy where patients are required to fail something before they can get a newer medication that may be better for them," he said.

A Big Player Stumbles

Breaking into the market against a well-entrenched rival like Eylea won't be easy. Physicians have a heightened awareness of the safety risks associated with new treatments following *Novartis AG*'s 2019 launch of Beovu (brolucizimab), which all but crashed and burned after a sudden safety issue emerged in the real-world setting – retinal vasculitis.

Novartis most recently announced it was halting development of several ongoing clinical trials that were testing initial monthly doses of the drug after higher rates of retinal vasculitis and retinal vascular occlusion were seen. (Also see "*Blow For Novartis Eye Drug Beovu As Studies Stop On Safety Worries*" - Scrip, 1 Jun, 2021.) Beovu is still approved in the US and Europe but is not being widely used by clinicians given the safety questions and array of treatment alternatives.

For Novartis, the setback raises questions about the company's future in ophthalmology, where it has had a big presence selling Lucentis outside the US. The company had hoped to build a strong global franchise with Beovu and built a commercial infrastructure in the US to support the launch. Novartis pharmaceuticals president Marie-France Tschudin said that the company remains committed to the therapeutic area and is exploring options.

"It's an important franchise for us because we have been in ophthalmology for a long time, not so much in the US, but we have a really strong legacy in the rest of the world around our relationships with ophthalmologists and retina specialists," she told *Scrip*. "We've got an interesting pipeline. We've had obviously some setbacks, but if you asked half my team two years ago about our future in cardiology, they would have said the same thing. Things can change quickly."

"We've got some work to do to fill our pipeline and that is what we are diligently trying to do," Tschudin added.

Defending The King

Regeneron believes Eylea's safety and efficacy track record will be a big advantage competing against newer options in the market, including biosimilars.

"When we look at why physicians treat a patient, the number one driver is always vision ... and Eylea remains unbeaten from a vision perspective," Regeneron VP and head of ophthalmology Kevin Clark said in an interview. "The experience of brolucizumab ... has made the first or second thing physicians are looking at is safety, and there is an unmatched profile with Eylea."

Labeling for Eylea calls for dosing every four weeks for the first three months followed by injections every eight weeks, with an option to dose every 12 weeks after a year of effective therapy, with a caution that every 12 weeks may not be as effective. Labeling for Lucentis recommends dosing every month with an option for less frequent dosing every three months after initial monthly doses, with a caution that the regimen is less effective.

When it comes to competing against a new biosimilar rival, Clark pointed out that Eylea already faces a cheaper rival in the market in the form of off-label bevacizumab. "We continue to take share from and grow despite an already very cheap generic version of an anti-VEGF in the market," he noted.

As Regeneron hopes for a continued COVID-19 recovery in the second half of the year, the company is launching a new unbranded direct-to-consumer advertising campaign in September directed to patients with diabetic eye disease, where the company continues to see a big opportunity to drive growth.

"Less than 50% of diabetics are getting an annual eye exam," Clark said. "That is an area we are excited about." While wet AMD continues to make up the largest part of the treatment market – more than 50% – diabetic eye disease is growing at a faster rate.

Eylea generated $4.95bn in the US in 2020, growth of 6.5% in a challenging year that kept a lot of patients out of doctor's offices. Eylea’s performance has been even stronger in the first six months of 2021, with Regeneron reporting 21% growth in the US in the first half. In Europe, Eylea is marketed by Regeneron's partner *Bayer AG*. Roche’s Lucentis, meanwhile, generated CHF1.44bn ($1.56bn) in the US in 2020, a decline of 16% over 2019. In Europe, Lucentis is marketed by Novartis.

Despite its confidence, Regeneron is nonetheless looking to extend the duration of use of Eylea as it braces for new competition from Roche. Two Phase III trials are underway testing a high-dose 8 mg version of Eylea in both wet AMD and diabetic macular edema (DME). The Phase III studies, expected to report out in the second half of 2022, are testing the 8 mg dose compared to Eylea 2 mg (the current dose) at intervals of every 12 weeks and every 16 weeks, with visual acuity as the primary efficacy endpoint at 48 weeks. Safety will be key in this case, but Regeneron

reported encouraging safety data from a Phase II trial on 21 August, showing no new safety signals with the higher dose.

Innovating For The Future

Longer duration of use is where Roche could have an advantage with faricimab, which was shown in clinical trials to be non-inferior to Eylea 2mg dosed every eight weeks at intervals up to 16 weeks. (Also see "*Roche Prepares Faricimab For Filing After Phase III AMD Data*" - Scrip, 26 Jan, 2021.) The clinical trial data showed that 75% of patients were able to maintain visual acuity out to three months.

Faricimab could be the first bispecific antibody for retinal eye disease. It blocks VEGF-A like Eylea, Lucentis and Beovu but it also blocks angiopoietin-2 (Ang-2). Roche hoped that by blocking both pathways, faricimab would be more effective in stabilizing blood vessels and preserving vision.

In an interview, head of ophthalmology product development at Roche's Genentech Chris Brittain said the data were strong despite the lack of superiority versus Eylea. He highlighted the potential opportunity to improve outcomes for patients in the real-world setting with more durable treatments.

"In the Phase III trials, the vision ended up being the same, [but] I think it is important to recognize that in the real world, patients aren't coming in as frequently as they could," Brittain said. "There is an opportunity in the real world for vision outcomes to be improved."

Houston Methodist Hospital's Wykoff was also enthusiastic about the potential of the bispecific approach. "Faricimab is what I think of as the next generation," he said. "There is a real hope that by blocking both of these pathways that we can get better outcomes for patients with less injections over time."

Roche’s new port delivery system for ranibizumab would also extend the timeframe between delivering the drug to patients out to six months, but requires eye surgery to implant a port device, roughly the size of a grain of rice, that can then be refilled in the clinic.

In the Phase III ARCHWAY trial, more than 98% of wet AMD patients were able to go six months without needing treatment prior to the refill, with vision outcomes equivalent to receiving monthly ranibizumab eye injections. Eye surgery carries unique risks and costs associated with it, however, that could be among the drawbacks of the procedure.

Still, the innovation coming from Roche means while the sun may be setting on Lucentis, it does not mark the end of an era for the company in ophthalmology. In fact, quite the opposite.

"A lot of senior executives are talking about it being the year of the eye," Brittain said. "We have an incredibly strong pipeline beyond these two Phase III therapeutics. The company is extremely robustly committed to ophthalmology and retina."