FDA ADVISORY PANEL RECOMMENDS APPROVAL OF AVEDRO'S CXL PLATFORM

A joint FDA advisory panel recommended approval of Avedro's combined riboflavin ophthalmic solutions and ultraviolet (UV) light irradiation for corneal collagen cross-linking. The recommendation is the last step before the FDA renders a decision on March 29.

The FDA's Dermatologic and Ophthalmic Drugs Advisory Committee and Ophthalmic Devices Panel heard testimony on the company's combined riboflavin solutions and UV irradiation device, which are indicated for progressive keratoconus and corneal ectasia following refractive surgery.

On the question of "Has substantial evidence of efficacy and safety been demonstrated for the drug device combination of Photrexa Viscous and Photrexa (riboflavin ophthalmic solution) and the KXL System (UVA light) to support approval for progressive keratoconus?," 10 panel members voted "yes," four voted "no," and one abstained.

On the question of "Has substantial evidence of efficacy and safety been demonstrated for the drug device combination of Photrexa Viscous and Photrexa and the KXL System to support approval for corneal ectasia following refractive surgery?," six panel members voted "yes," four voted "no," four abstained, and one member did not vote.

"Obviously, it's an important decision that allows physicians in the United States to participate in, or to benefit from, technology that's been available around the world for over 1 decade," John Vukich, MD, a partner at the Davis Duehr Dean Center for Refractive Surgery in Madison, Wisconsin, said in an interview with Eyewiretoday.com. "The ability to stabilize the cornea in patients who suffer from keratoconus is a significant advantage for us to be able to offer our patients treatment modalities, and it has been proven safe in the clinical trial, and importantly, it has been proven safe in over a decade of treatment around the world."

"[If approved], we're very enthusiastic to have this as a new addition to our treatment option and I think it is a significant benefit for patients in the United States to have this available," Dr. Vukich added.

The Avedro new drug application submission encompasses data from three prospective, randomized, parallel-group, open-label, sham-controlled, 12-month trials conducted in the United States to determine the safety and effectiveness of riboflavin ophthalmic solutions used in conjunction with UVA irradiation for performing corneal cross-linking in eyes with keratoconus and corneal ectasia following refractive surgery. The KXL System, used in combination with riboflavin ophthalmic solutions, received orphan drug designation for both keratoconus and ectasia following refractive surgery, which may allow Avedro 7 years of market exclusivity for the KXL System and certain riboflavin ophthalmic solutions for those indications, if approved.

The advisory panel will now make its recommendations to the FDA. Although the FDA is not obligated to follow the panels' recommendation, it usually does. The Prescription Drug User Fee Act action date is March 29, 2015.

Valeant To Acquire Salix Pharmaceuticals in a Deal Worth About $14.5 Billion

Valeant Pharmaceuticals International and Salix Pharmaceuticals announced that they have entered into a definitive agreement under which Valeant will acquire all of the outstanding common stock of Salix for $158 per share in cash or a total enterprise value of approximately $14.5 billion. The boards of directors of both companies approved the transaction.

Salix Pharmaceuticals is a gastrointestinal market leader with a portfolio of 22 total products, including prescription brands Xifaxan, Uceris, Relistor, and Apriso, as well as a strong near-term pipeline of innovative new assets, according to a Valeant news release.

"Salix's market-leading gastrointestinal [GI] franchise is an ideal strategic fit for Valeant's diversified portfolio of specialty products," J. Michael Pearson, Valeant's chairman and CEO, said

in the news release. "The growing GI market has attractive fundamentals, and Salix has a portfolio of terrific products that are outpacing the market in terms of volume growth. With strong brand recognition among specialist GI prescribers, a highly rated specialty sales force, and a significant product and commercial presence across the undertreated and underserved gastrointestinal market, this acquisition offers a compelling opportunity for Valeant to create a strong platform for growth and business development."

"We are pleased to have reached an agreement with Valeant, which is a logical partner and importantly, creates immediate value for our shareholders," Thomas W. D'Alonzo, chairman of the board and acting CEO of Salix, said in the news release. "Combining Salix's leading market position in gastroenterology with Valeant's scale and resources will create a stronger and more diverse business committed to providing better health solutions to health care providers and their patients. We are proud of the accomplishments of our Salix team. Together, we have built our company into the leading gastrointestinal specialty pharmaceutical company, providing solutions for patients and health care providers. We look forward to working with the Valeant team to ensure a smooth transition."

The combination is expected to yield greater than $500 million in annual cost savings from the cost base of the combined company. Synergies are expected to be achieved within 6 months of close, primarily from reductions in corporate overhead and R&D rationalization, with the cost to achieve these synergies to be approximately 65%," according to the news release. Valeant and Salix will determine how best to integrate the two companies to leverage the combined strengths of both while ensuring a smooth and orderly transition. Consistent with Valeant's approach to integrating Bausch + Lomb, there are no planned reductions to Salix's highly rated specialty sales forces or hospital, key account, and field reimbursement teams, and we will determine the optimal size of primary care sales force through the integration process.

On November 6, 2014, Salix reported 5- to 9-month wholesaler inventory levels for its top four products. Valeant has conducted extensive due diligence on Salix's stand-alone wholesaler inventory levels, stand-alone inventory work down plan, and associated potential litigation and regulatory exposure. Valeant expects to work down wholesale inventory and plans to target 2 months or less of wholesale inventory by the end of 2015. The net impact of the excess inventory on 2015 revenues is expected to be greater than $500 million.

The acquisition is structured as an all-cash tender offer for all of the outstanding shares of Salix common stock at a price of $158 per share followed by a merger in which each remaining untendered share of Salix common stock would be converted into the right to receive the same $158 cash-per-share consideration as in the tender offer.

The transaction is subject to customary closing conditions and regulatory approval.

Protocol T Comparing Three DME Agents Released

A major government-sponsored study shows that intravitreous aflibercept (Eylea; Regeneron), bevacizumab (Avastin; Genentech), and ranibizumab (Lucentis; Genentech) were effective and safe treatments for diabetic macular edema (DME), however, the relative effect correlated with patients' baseline visual acuities.

When initial visual acuity loss was mild, there was, on average, little difference in visual acuity at 1 year among the three agents. Among the subgroup of patients with baseline visual acuity worse than 20/40, aflibercept was more effective at improving vision, according to the National Institutes of Health-sponsored Protocol T study, which published its findings in the *New England Journal of Medicine* (Table).[1]

At 89 clinical sites, researchers from The Diabetic Retinopathy Clinical Research Network—the DRCR.net—randomly assigned 660 adults (mean age, 61 ±10 years) with DME involving the macular center to receive intravitreous aflibercept 2.0 mg (224 participants), bevacizumab 1.25 mg (218 participants), or ranibizumab 0.3 mg (218 participants). The study drugs were administered as often as every 4 weeks, according to a protocol-specified algorithm. The primary outcome was the mean change in visual acuity at 1 year.

From baseline to 1 year, mean visual acuity score improved by 13.3 letters among patients treated with aflibercept, by 9.7 letters in patients in the bevacizumab group, and by 11.2 letters in the ranibizumab group. Although the improvement was greater with aflibercept than with the other two drugs ($P < .001$ for aflibercept vs bevacizumab, and $P = .03$ for aflibercept vs ranibizumab), the study authors said the results were "not clinically meaningful because the difference was driven by the eyes with worse visual acuity at baseline ($P < .001$ for interaction)."

TABLE. CHANGE IN VISUAL ACUITY FROM BASELINE AMONG TREATMENT GROUPS IN THE PROTOCOL T STUDY

	Aflibercept	Ranibizumab[a]	Bevacizumab[a]
Overall	+13.3 letters	+11.2 letters ($P = .03$)	+9.7 letters ($P < .001$)
Initial visual acuity 20/32 to 20/40 (78-69 letter score)	+8.0 letters	+8.3 letters ($P > .5$)	+7.5 letters ($P > .5$)
Initial visual acuity 20/50 or worse (letter score < 69)	+18.9 letters	+14.2 letters ($P = .003$)	+11.8 letters ($P < .001$)

[a]*P* values represent interaction versus aflibercept.

Among patients whose initial visual acuity letter score was 78 to 69 (equivalent to approximately 20/32 to 20/40; n = 51% of participants), the mean improvement was 8.0 with aflibercept, 7.5 with bevacizumab, and 8.3 with ranibizumab ($P > .50$ for each pairwise comparison). When the initial letter score was less than 69 (approximately 20/50 or worse), the mean improvement was 18.9 with aflibercept, 11.8 with bevacizumab, and 14.2 with ranibizumab ($P < .001$ for aflibercept vs bevacizumab; $P = .003$ for aflibercept vs ranibizumab; and $P = .21$ for ranibizumab vs. bevacizumab).

There were no significant differences among the study groups in the rates of serious adverse events ($P = .40$), hospitalization ($P = .51$), death ($P = .72$), or major cardiovascular events ($P = .56$).

In an accompanying editorial commenting on the study, Daniel Martin, MD, of the Cole Eye Institute and Maureen Maguire, PhD, of the University of Pennsylvania noted that as much as 75% of the population seeking treatment for DME presents with a visual acuity of 20/40 or better.[2] Because of the comparable outcomes in the overall population, they said, physicians should consider the cost of treatment when choosing an appropriate agent for patients.

1. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med*. 2015; 372:8.
2. Martin DF, Maguire MG. Treatment choice for diabetic macular edema [published online ahead of print February 18, 2015]. *N Engl J Med*. doi:10.1056/NEJMe1500351.

Actavis Announces Intention to Adopt "Allergan" Corporate Name

Actavis announced that following the completion of the acquisition of Allergan, it intends to use the Allergan name as its corporate name and for its global branded pharmaceutical portfolio. It will retain the Actavis name for select geographic regions and product portfolios, according to a company news release. The change in corporate name would be subject to approval by Actavis' shareholders at its annual general meeting later this year.

"The pending combination of Actavis and Allergan will create a dynamic new breed of company—a leader in growth pharma. By adopting the Allergan name for the corporation, we will ensure that our corporate identity reflects the dramatic evolution of our company within the pharmaceutical industry," Brent Saunders, CEO and president of Actavis, said in the news release.

"Corporate names, however, represent more than heritage. They speak to the future strategic vision of an organization. Uniting under the Allergan corporate umbrella, while retaining the Allergan and Actavis identities for the two respective businesses, defines to customers, competitors, employees, and investors that this combination of two powerful, successful, and growing companies is transformational, and will reflect our position as the most dynamic growth pharmaceutical company in global health care," Mr. Saunders added. "Although we will have distinct identities to our various customers and in select geographies, we will operate the new Allergan as one company with one culture."

Stem Cells From Wisdom Teeth Can Be Transformed Into Corneal Cells

Stem cells from the dental pulp of wisdom teeth can be turned into cells of the eye's cornea and could one day be used to repair corneal scarring due to infection or injury, according to researchers at the University of Pittsburgh School of Medicine. The findings, published online in *Stem Cells Translational Medicine*, indicate they could also become a new source of corneal transplant tissue made from the patient's own cells.[1]

"Shortages of donor corneas and rejection of donor tissue do occur, which can result in permanent vision loss," senior investigator James Funderburgh, PhD, professor of ophthalmology at the University of Pittsburgh and associate director of the Louis J. Fox Center for Vision Restoration of University of Pittsburgh School of Medicine and the University of Pittsburgh, said in the news release. "Our work is promising because using the patient's own cells for treatment could help us avoid these problems."

Experiments conducted by lead author Fatima Syed-Picard, PhD, also of the University of Pittsburgh Department of Ophthalmology, and the team showed that stem cells of the dental pulp, obtained from routine human third molar, or wisdom tooth, extractions performed at the University of Pittsburgh's School of Dental Medicine, could be turned into corneal stromal cells or keratocytes, which have the same embryonic origin.

The team injected the engineered keratocytes into the corneas of healthy mice, where they integrated without signs of rejection. They also used the cells to develop constructs of corneal stroma akin to natural tissue.

"Other research has shown that dental pulp stem cells can be used to make neural, bone, and other cells," Dr. Syed-Picard noted. "They have great potential for use in regenerative therapies."

The researchers will assess whether the technique can correct corneal scarring in an animal model. The project was funded National Institutes of Health grants EY016415, EY009368, and EY008098; Research to Prevent Blindness; and the Eye and Ear Foundation of Pittsburgh. ■

1. Syed-Picard FN, Du Y, Lathrop KL et al. Dental pulp stem cells: a new cellular resource for corneal stromal regeneration [published online ahead of print February 20]. *Stem Cells Transl Med*. DOI: 10.5966/sctm.2014-0115 .

Erratum

CRST regrets the misspelling of Verus (Mile High Ophthalmics) in the sidebar *A Silicone Ring for Capsulotomy Creation* by Robert J. Cionni, MD, that appeared in our November/December 2014 edition.