VOL. 15, NO.4

FDA DOES NOT APPROVE AVEDRO'S CORNEAL COLLAGEN CROSS-LINKING PLATFORM APPLICATION, REQUESTS ADDITIONAL INFORMATION

Although a joint FDA advisory panel in February recommended approval of Avedro's combined riboflavin ophthalmic solutions and ultraviolet (UV) light irradiation for corneal collagen cross-linking, the FDA did not approve the company's new drug application (NDA) and identify areas concerning the device, which require additional information.

Avedro received a complete response letter from the FDA regarding the new drug application for their riboflavin ophthalmic solution/KXL System for corneal collagen cross-linking. The FDA identified a small number of areas of the application concerning the device that require additional information, none of which pertain to the clinical study safety or efficacy data presented in the NDA, according to an Avedro news release.

"We are disappointed with the outcome of the review and the implications this has for patients in the [United States] suffering from keratoconus or corneal ectasia who remain in need of a therapeutic treatment for these sight-threatening conditions," David Muller, PhD, CEO of Avedro, said in the news release. "Despite this setback, we are diligently working to resolve these outstanding questions with the goal of making this vital treatment available as soon as possible."

On February 24, 2015, the FDA Dermatologic and Ophthalmic Drugs Advisory Committee and Ophthalmic Devices Panel of the Medical Devices Advisory Committee had voted in support of approval of the NDA for the treatment of progressive keratoconus or corneal ectasia following refractive surgery, both of which are orphan indications.

On the question, "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, "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.

The Avedro NDA submission encompassed 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 collagen 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 might have allowed Avedro 7 years of market exclusivity for the KXL System and certain riboflavin ophthalmic solutions for those indications, had it been approved.

Actavis Completes $70.5 Billion Acquisition of Allergan

Actavis announced that it has completed the acquisition of Allergan in a cash and equity transaction valued at approximately $70.5 billion. The combination creates one of the world's top 10 pharmaceutical companies by sales revenue, with combined annual pro forma revenues of more than $23 billion anticipated in 2015.

"The combination of Actavis and Allergan creates an exceptional global pharmaceutical company and a leader in a new industry model—Growth Pharma," Brent Saunders, CEO and president of Actavis, said in the news release. "Anchored by world-renowned brand franchises, a leading global generics business, a premier pharmaceutical development pipeline, and an experienced management team committed to maintaining highly efficient operations across the organization, we are creating an unrivaled foundation for long-term growth."

Actavis expects the transaction to create about $1.8 billion in operating and financial synergies within 1 year of the close. These synergies exclude any additional revenue or manufacturing synergies and are in addition to the $475 million annual savings previously announced by Allergan in connection with "Project Endurance." Actavis further expects to generate strong operating cash flow in excess of $8 billion in 2016, which would reportedly enable the company to rapidly de-lever the balance sheet.

Actavis said the combination enhances its international commercial opportunities. The company has an expanded commercial presence now, including approximately 100 countries, with an augmented presence across Canada, Europe, Southeast Asia, and Latin America and a strong footprint in China and India. According to the press release, the combined company will benefit from Allergan's global brand equity, industry-leading consumer marketing capabilities, and strong consumer awareness of key Allergan products in global markets. On a pro forma basis, the company is expected to have approximately $5 billion in 2015 international revenue, and it will have the opportunity to drive continued growth in international markets through its enhanced portfolio of brands, generics, branded-generic, and over-the-counter products.

The combined company will have a strong commitment to R&D, with an exceptional level of investment of approximately $1.7 billion expected in 2015, focused on the strategic development of innovative and durable value-enhancing products within brands, generics, biologics, and over-the-counter portfolios, according to the news release. The company has more than 20 products in near- or midterm development, including Cariprazine, Eluxadoline, Esmya, Aczone X, and Darpin AMD, among other promising candidates.

Aflibercept Approved for Diabetic Retinopathy in the Presence of Diabetic Macular Edema

The FDA has approved aflibercept (Eylea; Regeneron) for the treatment of diabetic retinopathy (DR) in patients with diabetic macular edema (DME), according to a press release. The approval is for a 2-mg dosage administered every 8 weeks following five initial monthly loading doses.

The FDA relied on data from the phase 3 VISTA-DME and VIVID-DME trials. The trials compared aflibercept 2 mg every 4 weeks, aflibercept 2 mg every 8 weeks following five initial monthly loading doses, and macular laser photocoagulation (at baseline and then as needed) in patients (n = 862) who had DME with central involvement. A prespecified secondary endpoint of the studies assessed patients' DR severity scored at year 2. In VISTA-DME, 38% of patients in the treatment groups achieved a two-step or better improvement on a DR severity scale compared with 16% of patients in the control group. In VIVID-DME, approximately 30% of patients in the treatment group achieved a two-step or better improvement on the DR severity scale compared with 8% of patients in the control group.

In addition to DR in the presence of DME, aflibercept is approved in the United States for the treatment of neovascular age-related macular degeneration, macular edema following retinal vein occlusion, and DME.

With this FDA approval, aflibercept becomes the second medication approved for DR in the presence of DME in less than 1 month. In late February, the FDA granted Genentech, maker of ranibizumab (Lucentis), approval to market the drug's 0.3-mg formulation for use in patients with DR in the presence of DME.

Iridex Granted US Patent for Disposable Device for Efficient and Predictable Wound Closure

The United States Patent and Trademark Office granted Iridex a patent for a new proprietary disposable device intended to replace certain suturing techniques for eye surgery. According to a company news release, the iClip Closure Device will initially be used for trabeculectomies, and its application will expand to a broader range of ophthalmic surgical procedures in the future.

"Eye surgery is a very delicate and precise process," coinventor Steven Vold, MD, a cataract and glaucoma specialist, said in the news release. "The new iClip technology is intended to drive efficiencies in multiple procedures with an initial focus in glaucoma."

"The iClip is a product that has a broad array of potential applications for eye surgery and is consistent with an integral part of our strategic plan: developing products that provide us new, recurring and therefore, predictable revenue streams," Will Moore, president and CEO of Iridex, said in the news release. "Furthermore, we believe ongoing investment in defensible intellectual property creates the opportunity for adding significant shareholder value."

Dr. Vold is a consultant to Iridex.

Software Tool Uses Slit-Lamp Photography for the Alignment of Toric IOLs

Eye Photo Systems, manufacturer of the EC 100 and EC 90 high-resolution anterior segment cameras, has launched the TAO (Toric Alignment by Osher) software tool to assist with intraoperative orientation of toric IOLs, according to a company news release. The new software tool reportedly provides a cost-

effective alternative to or a fail-safe backup for fully automated systems.

"The image is easily captured at the slit lamp during the initial dilated examination," Robert H. Osher, MD, the inventor of TAO, said in the news release. "The software assigns every unique iris landmark an exact number of degrees assuring accurate orientation."

"There [are] plenty of complicated, expensive technologies being released for toric alignment, but there is also a need for a simple, powerful, and affordable solution," Jeremy Graziano, OD, CEO of Eye Photo Systems, said in the news release. "I think this product hits that mark."

Dr. Osher acknowledged a financial interest in the device.

Next-Generation Humphrey Field Analyzer Introduced

At the 2015 American Glaucoma Society Annual Meeting in Coronado, California, Carl Zeiss Meditec announced the worldwide launch of the new Humphrey Field Analyzer 3 (HFA3). The device is designed to accelerate flow in the clinic while delivering the same gold-standard testing strategies and patterns. According to the company, test results on the new platform are equal to and interchangeable with results from prior generations of the HFA.

The HFA3 is the first perimeter to introduce patented Liquid Lens technology, which reportedly saves time, simplifies setup, and reduces the possibility of human error in trial lens correction. According to Zeiss, the HFA3 replaces the manual process with a patented Liquid Trial Lens, which automatically delivers the appropriate refractive correction using measurement information entered into the instrument. The available correction range is -8.00 to +8.00 D sphere and addresses spherical correction only. The Liquid Trial Lens is available on the HFA3 model 860.

The HFA3 streamlines and hastens workflow with an array of new features, including

- RelEye, which allows doctors to instantly review the patient's eye position at any stimulus point. RelEye data are available on the device and when reviewing test results with Forum Glaucoma Workplace. It may reveal common testing problems, such as droopy lids (ptosis) or misalignment of the eye relative to the trial lens holder.
- SmartTouch interface, which reduces the number of steps required for the technician to start a perimetry examination. Faster gaze tracking provides information that helps doctors assess the reliability of test results. The gaze tracker on the HFA3 provides faster initialization and works on a wider spectrum of patients compared to earlier models of the HFA.
- An easy-to-use kinetic graphical user interface with a full 180º field of view.

"The HFA3, together with the other components of the Zeiss glaucoma management offerings, delivers an unrivaled combination of seamless integration and diagnostic performance to eye professionals who diagnose and manage glaucoma," Ludwin Monz, PhD, president and CEO of Carl Zeiss Meditec, said in the news release.

The Catalys Precision Laser System Goes Mobile

ForTec Medical collaborated with Abbott Medical Optic's vision care business to mobilize the Catalys Precision Laser System for the convenience of bringing the cataract procedure directly to ophthalmology practices across the United States, according to a company news release.

"If your cataract surgical volume does not support the capital outlay, you can still leverage the finest laser cataract technology to meet your schedule," Drew Forhan, CEO of ForTec Medical, said in the news release. "And if you do have higher surgical volumes and want to prove the value of the system prior to a purchase, you can leverage the mobile option while you ramp up your patient adoption. ForTec Medical is ready to streamline the laser into your surgery schedule, support the execution of a patient marketing plan, and help you build your practice, making the laser profitable from your very first procedure."

Enhanced BLIS Reusable Injector System for enVista IOLs Available

An enhanced version of BLIS (Bausch + Lomb Injector System) is now available, according to a company news release. The injector system is designed exclusively for use with the company's enVista hydrophobic acrylic IOL. With the new enhancements, eye care practitioners reportedly will be provided even greater control, allowing safe delivery of the enVista IOL through unenlarged phaco incisions as small as 2.2 mm.

BLIS was first introduced in February 2014 and features a reusable handpiece made of high-quality titanium material. The proprietary disposable cartridge is designed for easy lens loading and wound entry and smooth delivery of enVista. Among other enhanced features, BLIS now includes a softened and tumble-polished plunger tip that is 2 mm longer than the previous design to facilitate easier placement of enVista IOLs in the capsular bag.

Grant to Advance the Study of Low Vision Rehabilitation

Envision, one of the largest employers of individuals with vision loss in the United States, has received a $300,000

challenge grant from the J. E. and L. E. Mabee Foundation to support the renovation of an entire floor of the company's headquarters in Wichita, Kansas, to house the Envision Research Institute.

"The Mabee Foundation supports many prestigious and worthwhile organizations," Michael Monteferrante, president and CEO of Envision, said in a news release. "To be numbered among them is a distinct privilege. We have already made great strides in improving the lives of those who are blind or visually impaired, and this grant will pave the way to many more advances."

Investigators at the Envision Research Institute will investigate the functional implications of vision loss as well as screening and access to treatments with the goal of optimizing rehabilitation therapies and developing accessibility technology. The researchers will also have access to an abundant pool of potential research subjects, as Envision maintains onsite facilities such as a state-of-the-art Vision Rehabilitation Center, a childcare facility, and a preschool that offers comprehensive early intervention services. The organization also has numerous connections to the broader community of individuals who are blind or have low vision. Proximity to these populations will give researchers at the Institute "a bird's-eye view" of the impact of their work, the news release said.

Envision must now raise $1.2 million by December 1, 2015, to receive the Mabee grant. The company has launched a capital campaign toward that goal. To contribute, please visit www.envisionus.com/Pages/Foundation/Give.aspx.

Phase 2 IMPACT Study: Primary Endpoint Not Met, "Clinically Meaningful Benefit" in Classic CNV

The phase 2 IMPACT study failed to reach its primary endpoint, but the study demonstrated that OHR-102 (0.2% squalamine lactate ophthalmic solution, Ohr Pharmaceuticals) combination therapy for the treatment of wet age related macular degeneration had a "positive effect on visual acuity in classic choroidal neovascularization [CNV]" early in the course of treatment and continuing through the end of the study, according to a press release.

Ohr said it plans to initiate a phase 3 study based on the outcomes of the IMPACT study.

The mean number of injections, which was the primary endpoint of the study, was similar in the combination OHR-102 and ranibizumab (Lucentis; Genentech) and ranibizumab monotherapy groups. Yet, patients with classic CNV gained 10.5 letters on combination OHR-102 and ranibizumab compared with 5.4 letters among individuals assigned ranibizumab monotherapy, demonstrating a "clinically meaningful benefit of +5.1 letters," according to a press release announcing topline data from the study.

According to the press release, 42% of individuals in the intent-to-treat population with classic-containing CNV gained three or more letters of visual acuity at 9 months compared with 28% in the monotherapy ranibizumab group. However, the press release said, "less of a benefit was seen in the overall population (classic containing and occult-only CNV lesions)."

Additional data from the study will be presented at the upcoming Association for Research in Vision and Ophthalmology scientific meeting, the press release said.

Akorn Launches Phenylephrine HCl Ophthalmic Solution

Akorn launched phenylephrine HCl ophthalmic solution, USP, 2.5% and 10%, according to a news release. The launch follows an approval of a new drug application for the product from the FDA on January 15, 2015. It further expands the company's leading generic and branded ophthalmic portfolio and brings a shelf-stable formulation of phenylephrine back to the market.

According to IMS Health, sales of phenylephrine ophthalmic solution, USP 2.5% and 10% were $24 million for the 12 months ending January 31, 2015. From prior market experience, Akorn said it estimates the total market for the product to be larger than $24 million due to direct sales to physicians and hospital systems that may not be fully captured by IMS Health.

Akorn's phenylephrine HCl ophthalmic solution, USP, is an α-1 adrenergic receptor agonist indicated to dilate the pupil. Akorn's approval represents the second new drug application approval for an ophthalmic phenylephrine product following the approval of a competing new drug application product and the subsequent withdrawal of grandfathered products from the market in 2013.

Akorn's phenylephrine HCl ophthalmic solution, USP 2.5%, available in 2-mL and 15-mL fill sizes and phenylephrine hydrochloride ophthalmic solution, USP 10%, available in a 5-mL fill size, are shelf-stable and therefore do not require refrigeration, which is an advantage over the competitor's refrigerated product, the news release stated.

Positive Topline Clinical Data Reported for OTX-DP for the Treatment of Postoperative Inflammation and Pain

Ocular Therapeutix announced positive topline data from the first of two phase 3 clinical trials evaluating the safety and efficacy of its lead product candidate, OTX-DP (dexamethasone), for the treatment of ocular inflammation and pain fol-

Renowned Cataract Surgeon Robert P. Rivera Dies at 58

Robert P. Rivera, MD, an internationally recognized authority in the field of cataract and refractive surgery, died on April 1, 2015, at the age of 58 after a battle with cancer.

Dr. Rivera, a native of southwestern New Mexico, received a bachelor's degree in biology/biological sciences from New Mexico State University. He received his Doctor of Medicine degree from the University of Utah School of Medicine in Salt Lake City, and he completed an internship and residency in ophthalmology at the Mayo Clinic in Rochester, Minnesota, according to his biography on the Hoopes Vision Correction Center, Salt Lake City, website.[1]

In 2001, Dr. Rivera practiced and was a partner at Barnet Dulaney Perkins Eye Center in Arizona, where he served for 10 years and became one of the highest-volume cataract and implantable collamer lens (Visian ICL; STAAR Surgical) surgeons in the United States. Most recently, Dr. Rivera was director of clinical research, intraocular lens & refractive surgery at Hoopes Vision Correction Center and adjunct clinical assistant professor at the John Moran Eye Center in Salt Lake City.

Dr. Rivera's main research interests were presbyopia-correcting IOLs, phakic IOLs, corneal refractive surgery, accommodation of the human crystalline lens, and femtosecond laser applications for refractive cataract and lens replacement surgery, according to Hoopes Vision.

He was board certified by the American Board of Ophthalmology, a fellow of the American Academy of Ophthalmology, and a member of the American and European societies for cataract and refractive surgery as well as the International Society of Refractive Surgery. He was also a founding member of the American-European Congress of Ophthalmology (AECOS).

In addition, Dr. Rivera taught eye surgery at numerous hospitals throughout the world, including in Paris, Tokyo, Mexico City, Stockholm, Taipei, Berlin, Cairo, Barcelona, Bangkok, Singapore, and Hong Kong.

1. Hoopes Vision. http://www.hoopesvision.com/about. Accessed April 2, 2015.

lowing cataract surgery, according to a company news release.

The phase 3a study, which enrolled 247 patients, met both primary efficacy measures, achieving a statistically significant improvement in the reduction of inflammatory cells and pain. According to the study, 33.7% of OTX-DP–treated patients showed an absence of inflammatory cells in the anterior chamber of the study eye on day 14 after the drug's insertion compared to 14.6% of those receiving a placebo vehicle control punctal plug ($P = .0015$). In addition, 76.1% of patients receiving OTX-DP reported an absence of pain in the study eye on the eighth day after the drug was inserted compared to 36.1% of those who received a placebo vehicle control punctum plug ($P < .0001$). The company said it is continuing to analyze the safety findings from the clinical trial.

OTX-DP is a product candidate placed in the canaliculus and designed to deliver dexamethasone to the ocular surface for approximately 4 weeks. After treatment, OTX-DP resorbs and exits the nasolacrimal system without the need for removal. In November 2014, the company announced encouraging data from its phase 2 clinical trial evaluating the safety and efficacy of OTX-DP in allergic conjunctivitis, and the company said it plans to initiate phase 3 clinical trials for this indication in the middle of 2015.

Ocular Therapeutix also initiated an exploratory phase 2 clinical trial of OTX-DP for the treatment of inflammatory dry eye in January 2015. The company is currently enrolling patients into a phase 2b clinical trial of its second sustained-release product candidate, OTX-TP (travoprost), for the treatment of glaucoma and ocular hypertension. Data from this trial are expected in the fourth quarter of 2015.

Heidelberg Engineering Receives the NASA Certificate of Appreciation

Heidelberg Engineering was honored with the NASA Certification of Appreciation in recognition of the company's support in placing a Spectralis OCT system on the International Space Station (ISS).

During the ceremony, the NASA guests, who included Christian Otto, MD, lead scientist for the Vision Impairment and Intracranial Pressure project, among others, described the physiological challenges encountered with long-duration space flight and the research underway to understand and ultimately address these issues. A big part of this research involves evaluating changes in ocular structures with the Spectralis.

The device, which was installed on the ISS in June 2013, is the same technology available to eye care practitioners for terrestrial use. Since initiation of this program, ISS astronauts have been undergoing baseline optical coherence tomography before flight and routine examinations with the device throughout their space station deployments.

Originally, NASA anticipated that the process of qualifying and placing the Spectralis in space would take approximately 2 years. Instead, due to efforts of the Heidelberg Engineering team, the system was delivered to the ISS within 4 months. In recognition of this effort, Heidelberg Engineering was presented with two plaques signed by Jeffrey Davis, MD, chief medical officer of NASA's Johnson Space Center, and astronaut Luca Parmitano, who was among the first crewmembers to operate the Spectralis during flight. ■