FDA Did Not Approve Corneal Crosslinking Platform Application, Requested Additional Information

The US Food and Drug Administration did not approve Avedro's combined new drug application (NDA) for its riboflavin ophthalmic solutions and ultraviolet light source for corneal collagen cross-linking. The FDA's decision was made despite a recommendation for approval from a joint advisory panel earlier this year. The agency instead identified areas of the NDA for which additional information will be required.

Avedro received a complete response letter from the FDA regarding the NDA for its riboflavin ophthalmic solution/KXL System for corneal crosslinking. The FDA does not make information raised during the review process public for unapproved applications, but Avedro told *Retina Today*'s sister publication *Cataract & Refractive Surgery Today* that none of the concerns pertain to the clinical study safety or efficacy data presented in the NDA, but rather to the design of the KXL device.

"We are disappointed with the outcome of the review and the implications this has for patients in the US 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 a 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 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 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 ultraviolet-A irradiation for performing corneal crosslinking 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 would have allowed Avedro 7 years of market exclusivity for the KXL System and certain riboflavin ophthalmic solutions for those indications, had it been approved.

Although it announced no specific timeline, Avedro said it is now working on the best way to answer the questions raised by the FDA and will continue to pursue approval.

Mediterranean Diet Associated With Improved Cognitive Function

Patients consuming a Mediterranean diet containing olive oil and mixed nuts had higher scores on cognitive tests 6 years after the start of the diet compared with patients consuming a control diet, according to a study published in *JAMA Internal Medicine*.[1]

A parallel-group, randomized clinical trial enrolled adults (n = 477) whose mean age was 66.9 years. All participants were at high cardiovascular risk. They were randomly assigned to a Mediterranean diet supplemented with 1 L of extra virgin olive oil per week and 30 g of mixed nuts per day, or to a control diet advising them to reduce dietary fat.

Researchers used a neuropsychological test battery to update cognitive change over time. Follow-up cognitive tests after a median 4.1 years were available for 334 participants. Using a multivariate analysis adjusted for confounders, participants randomized to a Mediterranean diet plus olive oil scored better on the Rey Auditory Verbal Learning Test ($P = .049$) and the Color Trails Test ($P = .04$) compared with patients in the control group. Researchers also found that all cognitive composites (memory, frontal, and global) significantly decreased from baseline for patients in the control group.

1. Valls-Pedret C, Sala-Vila A, Serra-Mir M, et al. Mediterranean diet and age-related cognitive decline: a randomized clinical trial [published online ahead of print May 11, 2015]. *JAMA Intern Med*. doi:10.1001/jamainternmed.2015.1668.

Study Found Improved Function, No Reduction in Pain for Steroid Users With Back Pain

Patients with acute radiculopathy due to a herniated lumbar disk reported improved function but no improvement in pain following a short course of oral steroids compared with placebo, according to research published in *The Journal of the American Medical Association*.[1]

A randomized, double-masked, placebo-controlled clinical trial enrolled adults (n = 269) with radicular pain for no more than 3 months, a herniated disk confirmed by magnetic resonance imaging, and an Oswestry Disability Index (ODI) score of at least 30. (ODI scores range from 0-100, with higher scores indicating greater dysfunction.) Researchers randomly assigned patients in a 2:1 ratio to receive a tapering 15-day course of oral prednisone (n = 181) or placebo (n = 88).

The treatment group showed an adjusted mean improvement in ODI score at 3 weeks of 6.4 points (95% confidence interval [CI], 1.9-10.9; *P* = .006) compared with placebo. At 52 weeks, the treatment group had a mean 7.4-point (95% CI, 2.2-12.5; *P* = .005) greater improvement compared with placebo.

In measuring pain on a 0 to 10 scale, researchers found that the treatment group, compared with placebo, showed an adjusted mean reduction of 0.3 points (95% CI, -0.4 to 1.0; *P* = .34) at 3 weeks and an adjusted mean reduction of 0.6 points (95% CI, -0.2 to 1.3; *P* = .15) at 52 weeks.

1. Goldberg H, Firtch W, Tyburski M, et al. Oral steroids for acute radiculopathy due to a herniated lumbar disk: a randomized clinical trial. *JAMA*. 2015;313(19):1915-1923.

MMR Vaccine Not Associated With Increased Risk of Autism

Regardless of whether an older sibling did or did not have autism spectrum disorder (ASD), receipt of the measles-mumps-rubella (MMR) vaccine was not associated with an increase in risk of developing ASD at any age, according to research published in *The Journal of the American Medical Association*.[1]

A retrospective cohort study examined an administrative claims database associated with a large commercial health plan. Participants (n = 95 727) with older siblings were included in the analysis. Researchers found that 994 (1.04%) participants were diagnosed with ASD and 1929 (2.01%) had an older sibling with ASD.

"Of those with older siblings with ASD, 134 (6.9%) had ASD, [versus] 860 (0.9%) children with unaffected siblings (*P* < .001)," the study authors wrote.

Researchers found that children whose older siblings did not have ASD had higher MMR vaccination rates than children with older siblings diagnosed with ASD. Of those with older siblings who did not have ASD, 78 564 (84%) children received at least one dose of MMR vaccine at 2 years; 86 063 (92%) children in that same population had the vaccine at 5 years. Children with older siblings with ASD had lower vaccination rates: 1409 (73%) of these children were vaccinated at 2 years, and 1660 (86%) were vaccinated at 5 years.

Stratifying participants by age, researchers found no association between increased risk of ASD and MMR vaccination rate. Among children with older siblings with ASD, the adjusted relative risk (RR) of ASD for one dose of MMR vaccine compared with no vaccine was 0.76 (95% CI, 0.49-118; *P* = .22) for children at age 2; at age 5, the RR of ASD for two doses compared with no doses was 0.56 (95% CI, 0.31-1.01; *P* = .052). Among children whose older siblings did not have ASD, the RR of ASD for one dose of MMR vaccine compared with no doses was 0.91 (95% CI, 0.67-120; *P* = .50) at age 2; at age 5, the RR of ASD for two doses compared to no doses was 1.12 (95% CI, 0.78-1.59; *P* = .55).

1. Jain A, Marshall J, Buikema A, et al. Autism occurrence by MMR vaccine status among US children with older siblings with and without autism. *JAMA*. 2015;313(15):1534-1540. doi:10.1001/jama.2015.3077.

Link Found Between TV Watching and Obesity in Children

Kindergartners and first graders who watched more than 1 hour of television per day were more likely to be overweight or obese compared with children who watched less than 1 hour per day, according to a presentation at the Pediatric Academic Societies annual meeting. *Newsweek* reported the story.[1]

Researchers studied three cohorts of kindergartners and first graders: those who watched less than 1 hour of television per day, those who watched 1 to 2 hours per day, and those who watched more than 2 hours per day. They found that children in the 1-hour-per-day group were at least 50% more likely to be overweight compared with those watching less than 1 hour per day. Children who watched at least 1 hour of television each day were 39% more likely to become overweight and 86% more likely to become obese between kindergarten and first grade, the researchers said. ■

1. Main D. Study shows strong, rapid TV-obesity link in children. *Newsweek*. http://www.newsweek.com/strong-tv-obestiy-link-children-325445.

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