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FDA APPROVES FIRST GENE THERAPY FOR PATIENTS WITH INHERITED RETINAL DISEASE

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In December, Spark Therapeutics received US Food and Drug Administration (FDA) approval for voretigene neparvovec-rzyl (Luxturna) for the treatment of an inherited retinal disease. Voretigene is a one-time gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation–associated retinal dystrophy.

The drug is the first FDA-approved gene therapy for a genetic disease, the first pharmacologic treatment for an inherited retinal disease, and the first adeno-associated virus vector gene therapy approved in the United States, according to the company. The approval may lay the groundwork for the development of gene therapies for other conditions.

"I think one of the really exciting aspects of today's approval is that there are over 220 genes involved in vision, and until today there were no treatments for any forms of inherited retinal blindness," said Katherine High, MD, co-founder, president, and chief scientific officer at Spark Therapeutics, in an interview with Eyewiretoday.com. "The approval of Luxturna signifies that there is a pathway forward for turning genes into medicines."

Voretigene should be administered only to patients with mutations on both copies of the *RPE65* gene who have sufficient viable retinal cells as determined by their treating physicians, according to the company. The drug is administered by subretinal injection to each eye on separate days within a close interval, but no fewer than 6 days apart.

"Luxturna is a gene therapy product that is delivered into the subretinal space, and it supplies a normal copy of a gene called *RPE65*, which is defective in some cases of inherited retinal dystrophy. This disease affects, we think, around 1000 to 2000 people in the United States, and they may present with visual problems very early in life, in infancy, or they may present later during childhood, but eventually most of these patients will progress to blindness," Dr. High said. "In a trial that was sponsored by Spark Therapeutics, a randomized control trial, we were able to show that the subretinal administration of this gene therapy vector resulted in improvements in the ability to navigate independently as judged by a mobility test that was developed as an endpoint for this trial. And we also showed improvement in other tests of visual and retinal function, including full field light sensitivity and visual fields."

Spark Therapeutics said it would not announce the therapy's price until January, but analysts predicted at the time of approval that the treatment would be priced at around $1 million for a patient's two eyes. Spark stated in a press release that it is committed to ensuring that eligible patients have access to voretigene and will offer patient support services for eligible patients.

The drug is expected to be available to selected retina specialists late in the first quarter of 2018. The gene therapy will be administered at treatment centers in the United States by retina surgeons who will receive surgical training provided by Spark Therapeutics on the administration procedure.

"During the more than 12 years of innovative research with dedicated

collaborators near and far, I've witnessed the dramatic improvement in vision in many patients who would have otherwise lost their sight," said Jean Bennett, MD, one of the developers of the drug. "I believe that the success of the Luxturna clinical development program will pave the way for the development of other gene therapies that may help the millions of patients with genetic diseases who currently have limited or no treatment options." Dr. Bennett, the F.M. Kirby Professor of Ophthalmology at the Perelman School of Medicine of the University of Pennsylvania and Scheie Eye Institute, was quoted in a Spark news release at the time of the drug's approval.

Voretigene was approved by the FDA under priority review and had previously received orphan drug and breakthrough therapy designations from the FDA. Spark Therapeutics' marketing authorization application for voretigene is under review with the European Medicines Agency, which has also granted orphan product designation for the drug.

WILLS EYE HOSPITAL ESTABLISHES BRADY-SHIELDS ENDOWED CHAIR IN OCULAR ONCOLOGY

During the recent Atlantic Coast Retina Conference and Macula Meeting held in Philadelphia, at Wills Eye Hospital, Jerry A. Shields, MD, (seated, at right) was honored as the inaugural recipient of the Brady-Shields Endowed Chair in Ocular Oncology. The chair is named for three pioneering physicians in ophthalmology and oncology: Luther W. Brady Jr, MD; Dr. Jerry A. Shields; and Carol L. Shields, MD. According to a press release from Wills Eye Hospital, the chair honors the Brady and Shields names and contributions in perpetuity and provides the critical research funds necessary to develop new advances and techniques in the treatment and cure of ocular oncology diseases.

Photo courtesy Roger Barone/Wills Eye Hospital

CELL THERAPY SHOWED SAFETY, POSSIBLE BENEFIT IN PATIENTS WITH RP

An investigational cellular therapy has shown a favorable safety profile and indications of potential benefit in a phase 1/2a clinical trial in patients with retinitis pigmentosa (RP). The investigational product, called jCell (jCyte), has been granted orphan drug and regenerative medicine advanced therapy (RMAT) designations by the FDA, according to a press release from jCyte.

In this 12-month open-label study, trends in improvement in best corrected visual acuity (BCVA) were seen in treated eyes compared with untreated eyes, according to the company. Several doses were evaluated, and the best results were observed in the group receiving the highest dose.

The study included 28 individuals with RP; whose BCVA was evaluated at several points during the 1-year trial. In the group receiving the lowest dose (500,000 cells), mean difference from baseline was 1 letter improvement at 12 months. At the highest dose (3 million cells), the mean difference was 9 letters. Adverse events were generally minor, transitory, and associated with the intravitreal injection. No grade 4 events were associated with the treatment.

Patients reported improved vision, including increased sensitivity to light, improved color discrimination and reading ability, and better mobility. Of the 28 patients included in the trial, 22 have received treatment in their fellow eye as part of an extension study.

The company has launched a randomized phase 2b study to evaluate efficacy of the cellular therapy, supported by the California Institute for Regenerative Medicine. Up to 85 patients with BCVA no better than 20/80 and no worse than 20/800 in their study eye will receive a single jCell injection or sham control, and efficacy will be assessed using BCVA and other means.

POTENTIAL TARGETS FOR DIABETIC RETINOPATHY, RVO THERAPIES IDENTIFIED

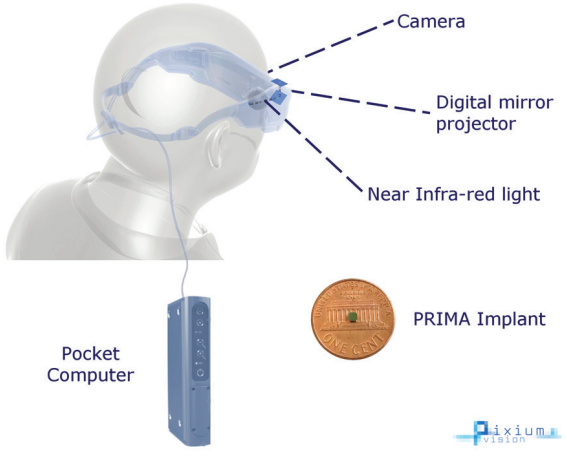
A study in mice has identified two potential molecular targets for therapies to treat diabetic retinopathy and retinal vein occlusion (RVO). The study, published in *Journal of Clinical Investigation Insight*, suggests that suppression of VEGFR1 and VCAM-1 could serve as a supplement to

anti-VEGF therapies for RVO and diabetic retinopathy.[1]

In genetically modified mice that were prompted to overexpress VEGF, the researchers found that increased VEGF levels caused leukocytes to migrate to the retina, where they adhered to retinal vascular walls and interrupted perfusion. When an antibody that suppressed VCAM-1 was administered to the mice, less clumping of leukocytes was seen, and blood flow was improved.

"These data explain the broad range of benefits obtained by VEGF suppression in patients with ischemic retinopathies, provide an important insight into the pathogenesis of RVO and diabetic retinopathy, and suggest that sustained suppression of VEGF early in the course of these diseases may prevent vessel closure, worsening ischemia, and disease progression," the authors concluded.

1. Liu Y, Shen J, Fortmann SD, Wang J, Vestweber D, Campochiaro PA. Reversible retinal vessel closure from VEGF-induced leukocyte plugging. *JCI Insight*. 2017;2(18).e95530.



**These images are for illustrative purpose and not fully representative of the actual device used in the clinical study*

US CLINICAL FEASIBILITY STUDY OF SUBRETINAL IMPLANT TO BEGIN THIS YEAR

A clinical feasibility study of the Prima subretinal implant (Pixium Vision) is set to begin in the first half of 2018, now that the company has received the go-ahead from the FDA. The study, to be conducted at the University of Pittsburgh, will seek to enroll up to five patients with vision loss due to atrophic age-related macular degeneration, according to a press release from the French company. Primary endpoints will be restoration of visual perception and safety at 12 months, and patients will be followed for a total of 36 months.

The Prima implant is a wireless photovoltaic subretinal implant, 30 µm thick, with 378 electrodes arrayed in a 2 x 2 mm area. The implant converts signals from an external camera to electrical signals that are transmitted to the brain by the optic nerve, according to the company. An earlier version of the implant, the Iris II, received the CE Mark in Europe. ■

BRIEFS

> B+L RECEIVES CE MARK FOR STELLARIS ELITE

Bausch + Lomb has received the CE Mark from European regulators for its Stellaris Elite Vision Enhancement System, including the Vitesse hypersonic vitrectomy system.

bit.ly/Brief118a

>> NDA SUBMITTED FOR 3-YEAR POSTERIOR SEGMENT UVEITIS TREATMENT

pSivida has submitted a new drug application (NDA) to the FDA for its Durasert 3-year treatment for posterior segment uveitis.

bit.ly/Brief118b

>>> WET AMD DRUG CANDIDATE FAILS TO REACH ENDPOINT

Ohr Pharmaceutical's multicenter, randomized, double-masked, placebo-controlled MAKO study evaluating the efficacy and safety of squalamine combination therapy for the treatment of wet age-related macular degeneration (AMD) did not meet its primary efficacy endpoint.

bit.ly/Brief118c

>>>> NIDEK LAUNCHES LPM

Nidek introduced a new Low Power Mode feature for its MC-500 Vixi laser photocoagulator, which, according to the company, allows better management of laser energy delivery to the retina with multiple scan patterns.

bit.ly/Brief118d