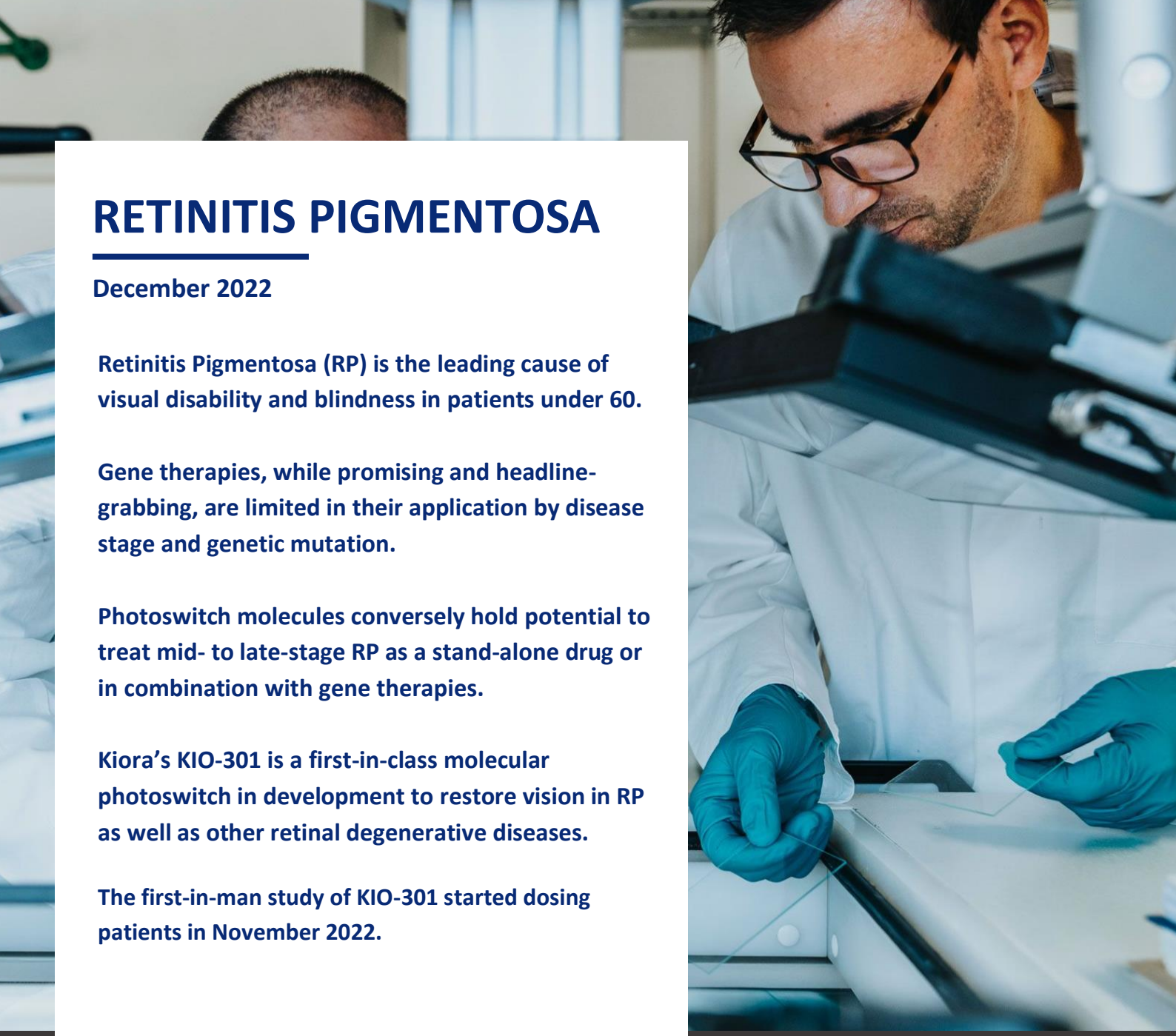

RETINITIS PIGMENTOSA

December 2022

Retinitis Pigmentosa (RP) is the leading cause of visual disability and blindness in patients under 60.

Gene therapies, while promising and headline-grabbing, are limited in their application by disease stage and genetic mutation.

Photoswitch molecules conversely hold potential to treat mid- to late-stage RP as a stand-alone drug or in combination with gene therapies.

Kiora's KIO-301 is a first-in-class molecular photoswitch in development to restore vision in RP as well as other retinal degenerative diseases.

The first-in-man study of KIO-301 started dosing patients in November 2022.

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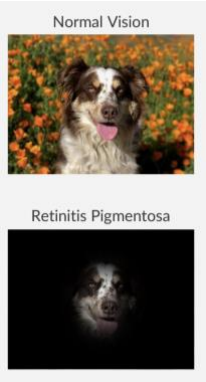
On October 19th, 2022, Stonegate Healthcare Partners held its Battling Blindness virtual investor event on Retinitis Pigmentosa. The panelists included Ben Shaberman from the Foundation Fighting Blindness, retinal surgeon Christine Kay, M.D., and Eric Daniels M.D., Chief Development Officer at Kiora Pharmaceuticals. The following are key takeaways from the event and our research on Retinitis Pigmentosa.

Significant Unmet Need in Retinitis Pigmentosa

Retinitis Pigmentosa (RP) is the leading cause of visual disability and blindness in patients under 60 years of age. There are no curative treatments for RP. Patients with RP are challenged with reduced mobility, social isolation, and increased financial burden due to difficulties performing tasks.



RP results in gradual peripheral vision loss leading to full loss of sight over time.

Upon diagnosis, patients learn that their existing vision loss will not return and that there is nothing available to slow additional vision loss that will occur. Preparing for a life without vision is all that is available. This places a great toll on the patients and families as they face the patient's progressive loss of autonomy.

As Ben Shaberman of Foundation for Blindness described, "Patients with severe vision loss are desperate for even minimal vision restoration, as this means a lot in terms of their autonomy."

Most Therapies in Clinical Trials are Restricted to a Subset of Patients

There are currently more than 100 drugs in various stages of development for RP worldwide. These assets can be separated into four general therapeutic approaches: gene therapy, cell therapy, optogenetics, and small molecules. Development of new treatments for RP is largely being advanced by innovative biotechnology companies while their work is attracting the interest of pharmaceutical companies.

Company	RetroSense Therapeutics	vedere	Ocata Therapeutics	jCyte	KIORA Pharmaceuticals
Buyer	**Allergan**	**Novartis**	**Astellas**	**Santen**	
Treatment:	Gene Therapy	Gene Therapy	Cell Therapy	Cell Therapy	Small Molecule
Valuation:	$60M + up to $495M in earnouts	$150M + up to $130M in earnouts	$379M	$62M + up to $190M in earnouts*	$5.3M
Clinical Phase at Time of Valuation:	Late Preclinical	Preclinical	Phase 1	Phase 2	Phase 1 (dosing underway)

Gene-based therapeutics are based on the delivery of a normal gene to replace the malfunction of a protein that results from a gene mutation. Each gene therapy is specific to the underlying genetic mutation and thus may only be applicable to a very small subset of patients and may not work on late-stage patients. The only gene therapy approved to date for gene mutation-associated retinal degenerative disease is Roche's Luxturna. Luxturna is approved in patients with the RPE65 gene mutation-commonly found in Leber Congenital Amaurosis 2, of which there are about 7,000 patients in the USA.

"Inherited retinal diseases (IRDs) are a clinically and genetically heterogeneous group of diseases affecting approximately 1:3,000 to 1:4,000 people worldwide" explained Dr. Kay. "316 disease-causing genes have already been identified to date for IRDs. Gene agnostic therapies will be necessary to address disease burden given the large number of genes causing disease and the prerequisite of good vision/viable cells for most forms of gene therapy."

Besides Luxturna, other products in development target mutations in the genes responsible for X-linked RP; AGTC's AGTC-50 is in phase 2/3 trial; 4D Molecular Therapeutics' 4D-125 and MeiraGTx's MGT009 are being evaluated in phase 1/2 trials.

Drugs based on Cell Therapy may require the presence of viable photoreceptors (i.e. rods and cones) to have a therapeutic effect and may have limited success in the later stages of RP after photoreceptors lose function.

These therapeutics mainly consist of the use of pluripotent stem cells that differentiate into cells of the retinal tissue to replace those cells that were lost in the course of the disease. The use of stem cells to

restore vision is complicated by potential immune rejection or oncogenic transformation. Results of such therapies are subject to varying results on an individual basis. JCyte's JCell therapy recently completed a Phase 2b trial.

Optogenetic therapies are based on the delivery of a light-sensitive protein, known as opsins, via gene therapy and are often applied in combination with an optical device such as goggles to enhance and focus the light. GenSight Biologics' GS030 is currently being evaluated in a Phase 1/2a study with some early promising outcomes. Nanoscope Therapeutics' MCO-010, Bionic Sight's BS01, RetroSense's RST-001 (acquired by Allergan), and Vedere Bio (acquired by Novartis) have similar approaches based on optogenetics.

In the webinar, Dr. Daniels explained, "Optogenetics is an attempt to make gene agnostic approach to gene therapies by adding a light sensing component using genetic engineering. We (Kiora) are not using genetic engineering but have a similar goal of making cells in the retina that are not typically light sensing into light sensing."

Small Molecules comprise the vast majority of approved medications today. Photoswitches are a novel class of small molecules that turn downstream neurons in the retina into light-sensitive cells. This is achieved by activating these cells in the presence of light to send a signal to the brain and then de-activating them when light is absent, similar to a light switch being switched on and off. **Photoswitches** are also gene mutation agnostic and have the potential to restore vision to the majority of RP patients who have some vision loss. Small molecules other than photoswitches are in development, albeit their focus is to slow disease progression and not restore the vision that was lost. These include Endogena Therapeutics' EA-2353 and Aldeyra Therapeutics' ADX-2191.

Photoswitches Have the Potential to Treat Late-Stage RP Patients As Well

In late-stage disease, when photoreceptor loss is severe, few options remain to restore vision. Retinal prosthesis devices require implants connected to a camera and video processing units to be worn by the patient and while these devices partially restore vision, they do not significantly impact the quality

of life. Photoswitchable compounds, on the other hand, are molecules that can essentially bypass damaged photoreceptors and do not rely on external devices for their ability to restore vision.

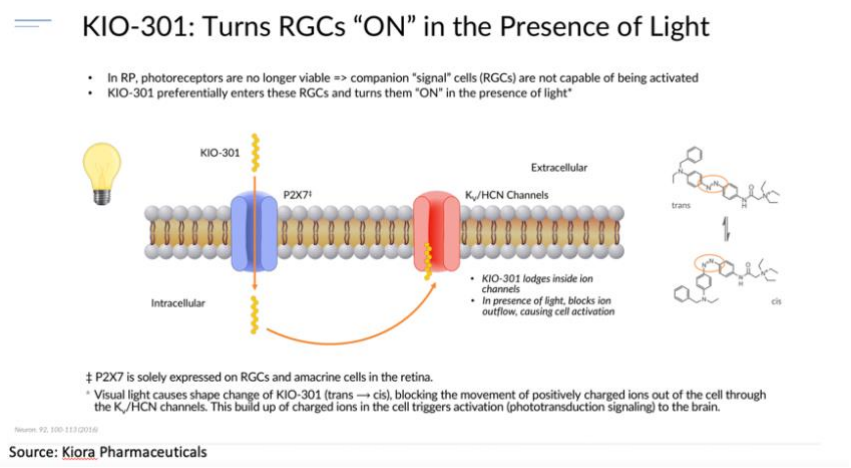
KIO-301: A Next-Generation Photoswitch That Can Potentially Restore Vision

Kiora Therapeutics' KIO-301 is a next-generation molecular photoswitch with optimized physicochemical properties making it an excellent candidate to restore vision in retinitis pigmentosa patients.

"For patients with late-stage disease, targeting photoreceptors doesn't make a lot of sense as they are mostly dead, however, downstream retinal neurons, such as retinal ganglion cells (RGCs), which remain viable, is what we are going after" explained Dr. Daniels. "KIO-301 can potentially turn RGCs into light sensing cells (in healthy retinas, RGCs are activated by photoreceptors) by actuating the flow of current into and out of RGCs in a light-dependent manner."

KIO-301 has several advantages as compared to other therapeutic approaches. Its gene-agnostic nature means it can treat more patients and the absence of stem cells eliminates the risk of potential immune rejection or oncogenic transformation. KIO-301 has no adverse impact on healthy RGCs meaning it can theoretically be used to treat patients in earlier stages of disease progression.

As illustrated below, KIO-301 can selectively enter RGCs and activate phototransduction.



A phase 1b open-label, single ascending dose, and single-site study in Australia is currently dosing patients. The study will enroll 6 patients (12 eyes) and test 3 ascending doses of the drug. Patients will be enrolled in two cohorts based on disease progression. Besides the primary objectives including safety and tolerability, the study will measure multiple functional assessments including a patient's ability to navigate a mobility course or identify objects. As described in a public communication by the company subsequent to the webinar, the principal investigator on the study, Dr. Robert Casson of the Royal Adelaide Hospital, observed that "the first patient is clinically doing well and the drug appears to be safe and well tolerated" and that "patient feedback supports improvement in vision."

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Shiv S. Kapoor
Co-Founder, Stonegate Healthcare

Shiv is a biotech veteran with over 25 years of experience in investments and the development of Oncology therapeutics. He has been rated among the top three biotechnology analysts by Forbes in the US. Shiv ran the Smith Barney Biotech fund at Citigroup and started sell-side Biotech practices at Montgomery & Co. and Morgan Joseph. His opinion on the US Biotechnology sector has been widely quoted in leading US media including CNN, CNBC, Bloomberg, and Barron's Guide.

In the past decade, Shiv led investor relations and corporate strategy at Spectrum pharmaceuticals. Shiv has a BA in Biochemistry from UC Berkeley and an MBA from the University of Chicago Booth School of Business.

Alamgir Singh Kandhari
Research Analyst, Stonegate Healthcare

Alamgir has a BA in Biology from the University of California Santa Cruz and a Master of Biotechnology from San Jose State University. Prior to his role at Stonegate Alamgir ran GMP production processes at BioMarin Pharmaceuticals, led a project at an immune-oncology start-up to target leukemia stem cells in AML, and researched aberrant pre-mRNA splicing leading to genetic diseases in the Sanford Lab at UCSC. He has experience in scientific writing, planning, presenting, GMP production, and project management.

Contact Information

Stonegate Healthcare Partners
500 Crescent Court, Suite 370
Dallas, TX 75201
Phone: (214) 987-4121
www.stonegateinc.com