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A New Vision in Retinal Gene Therapy:

From Clinical Trials to Clinical Practice

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This supplement features summaries of presentations from a Novartis-sponsored symposium held at the 2019 EURETINA meeting in Paris.

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Starting With the End in Mind: Understanding the Patient Experience

Bart P. Leroy, MD, PHD

The first pediatric patient in the world to receive voretigene neparvovec did so as a child as part of the phase 1 study, which took place in Philadelphia, PA, USA. Over 10 years later, and now a young adult studying psychology at university in Belgium, he spoke with Dr. Bart P. Leroy to share his experiences.

Bart P. Leroy, MD, PhD: Prior to receiving treatment, what symptoms did you experience living with an inherited retinal disease (IRD)?

Patient: It was a long time ago, so my memories are a bit limited, but my father tells a story of being on a family holiday in Turkey. In the bright sunlight of the daytime I was able to run around the swimming pool with my sister with little sign that I had any visual impairment. However, in the evenings when we went out to eat at a restaurant, I couldn't see a thing on my plate and was basically blind. That's something that I remember quite well—when I was inside, during winter, or when it was

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– Patient

dark outside, I couldn't see anything. I was basically completely night blind.

Dr. Leroy: What do you remember about the treatment itself?

Patient: I remember that after the surgery when all the patches were removed it was painful because of the light. The doctors wanted to look into my eye using a torch, which really hurt because I wasn't used to that amount of light. Then, when we left Philadelphia, we flew out in the evening after dark. When the plane took off, I could see the lights of the city with my right eye—the eye that had received the treatment—but I wasn't able to see them with my left eye. With my left eye it was completely black.

"It took my parents 7 or 8 years just to know the name of my disease and what caused it. If you are a doctor examining a patient, and you don't know for sure what condition they have, I think referring them to someone who is a specialist in that area is one of the best things you can do."

– Patient

Dr. Leroy: How did this treatment impact what you do on a daily basis?

Patient: It has greatly affected my day-to-day life. Before the treatment, I worked completely in braille. After treatment, I started working on the computer with the aid of magnification. In my free time I use my vision to do things that I wouldn't have been able to do without having treatment. In the week I live alone, and I'm more mobile now. My visual field is still not normal, so I do use a cane, but I use my cane in a different way than a blind person. I don't follow walls or guidelines with my cane—I navigate around a city visually. I just use my cane for safety, in case of an object that I haven't seen and also as a signal to others that I'm visually impaired.

Dr. Leroy: What message would you have for clinicians who may be seeing patients with IRDs such as yours?

Patient: My message would be that this is a really important treatment for two reasons. One is the visual improvement. Although my vision is not perfect, the improvement from what it was like previously makes a huge difference in day-to-day life. The second reason is something that, in my opinion, is underestimated, which is stability. I know that without treatment I would have been completely blind by now. Comparing the vision that I have today with the prospect of complete blindness makes me really value the stability of my vision.

Dr. Leroy: Your parents have previously described to me how they had to visit many different eye specialists before finally receiving your IRD diagnosis. What do you think about being referred as a patient to a super-specialist center?

Patient: It took my parents 7 or 8 years just to know the name of my disease and what caused it. If you are a doctor examining a patient, and you don't know for sure what condition they have, I think referring them to someone who is a specialist in that area is one of the best things you can do.

Setting the Scene: Developing a Retinal Gene Therapy for *RPE65* Mutations

Mark E. Pennesi, MD, PHD

"We are entering an age of gene therapy, with multiple trials of gene therapies for IRDs ongoing," said Dr. Mark E. Pennesi. "At the same time, we are seeing a shift away from phenotypic diagnosis, such as rod-cone or cone-rod dystrophy, to defining these diseases by the gene that is involved."

RPE65 mutation-associated retinopathy is a rare autosomal recessive IRD, which usually presents very early (often before the age of 5 years), with vision loss, nystagmus, and profound nyctalopia. Patients often show pigmentary degeneration and are myopic, although many will have preserved central vision at presentation.[1,2] The natural history of the disease is for early, profound changes in VA, which worsen with age, with progressive loss of functional retina over time.[3] "What is really important to understand about this disease is that it's a progressive degeneration. By age 20, most patients are going to go legally blind and eventually they will go completely blind," said Dr. Pennesi.

In 2017, voretigene neparvovec became the first gene therapy to be approved by the US FDA for an IRD.[4] This was followed by

EMA approval in 2018.[5] In January 2018, Novartis entered into a licensing and supply agreement with Spark Therapeutics to develop, register, and commercialize voretigene neparvovec outside the United States. Spark retains the US rights under the label voretigene neparvovec-ryzl.

Voretigene neparvovec is a recombinant adeno-associated virus serotype (AAV) 2 vector used to introduce a functional copy of the *RPE65* gene into the retinal pigment epithelium (RPE) cells of patients with confirmed bi-allelic *RPE65* mutation-associated retinal dystrophy. Treatment with voretigene neparvovec drives expression of cDNA encoding human RPE65 kDa (RPE65) protein within the RPE cells.

Voretigene neparvovec is given as a subretinal injection. A dose of 0.3 mL containing 1.5 x 10^{11} vector genomes is injected beneath the retina using a fine-gauge cannula to form a bleb, which is typically resorbed within 24 hours of surgery. The location of the bleb defines the treatment area, as the treatment effect typically doesn't spread beyond the bleb, so the injection is typically directed toward the macula, although not in the immediate vicinity of the fovea.

The approval of voretigene neparvovec was based on the results of a randomized, controlled, open-label, phase 3 trial.[6] Individuals aged 3 years or older with a confirmed genetic diagnosis of bi-allelic *RPE65* mutation were randomly assigned (2:1) to treatment (voretigene neparvovec; n = 21) or control (no treatment; n = 10) (Figure 1). The primary efficacy endpoint was the change in bilateral multiluminance mobility test (MLMT) performance (change in lux score for the lowest passing light level) at 1 year relative to baseline. "The MLMT is like a maze with obstacles that the patient walks through. It's performed at various light levels from 400 lux (equivalent to a bright office environment) down to 1 lux (equivalent to a moonlit night). The score that a patient achieves is based on the light level at which they can successfully complete the maze," said Dr. Pennesi (Figure 2).[7] At 1 year, mean bilateral MLMT score improved by 1.8 light levels in the treatment group versus 0.2 levels in the control group (P = .0013).[6] It was found that 65% of participants who received treatment passed the MLMT at the lowest luminance level tested.

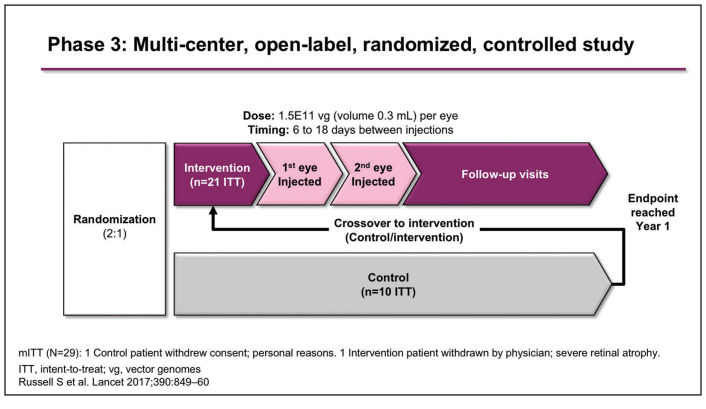


Figure 1. Design of phase 3 study of voretigene neparvovec.

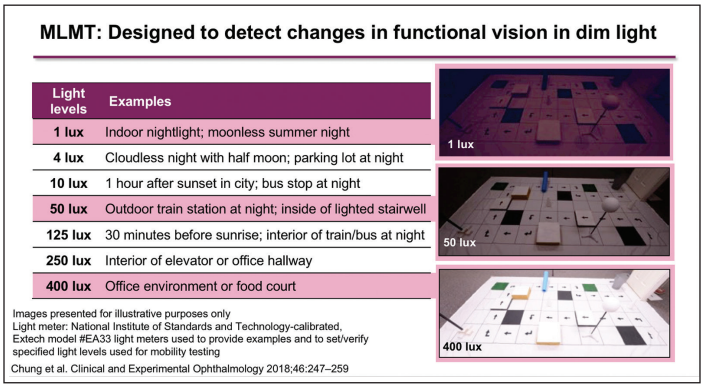


Figure 2. The MLMT.

Secondary endpoints included full-field stimulus threshold (FST) testing (averaged over both eyes) and BCVA (averaged over both eyes). Patients in the treatment group experienced a rapid improvement by day 30, which remained stable at 1 year, while the control group showed no change (P = .0004). BCVA improved by a mean of 8.1 letters in the treatment group versus 1.6 letters in the control group, but this difference was not statistically significant.[6]

These results were sustained to 4 years, with a mean change in bilateral MLMT score of 1.7 levels in the treatment group (Figure 3).[8,9] Patients who were initially randomized to the control arm were eligible to receive treatment at 1 year. These patients achieved a mean change in bilateral MLMT score of 2.4 levels at 4 years (3 years after treatment). Similar sustained results in the treatment group and improvements in the control group following crossover were seen on the secondary endpoints of FST (Figure 4) and BCVA.[8]

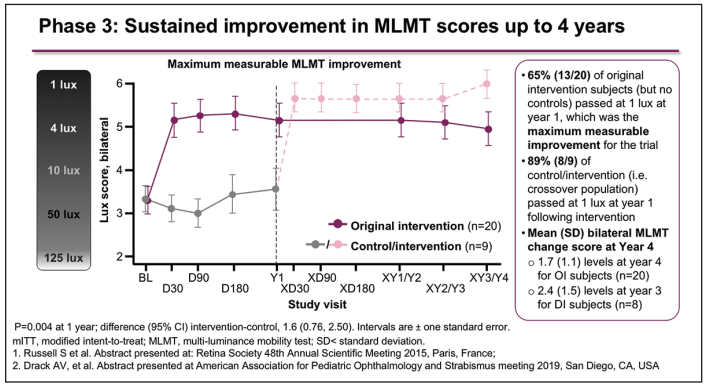


Figure 3. Mean change in bilateral MLMT scores up to 4 years in the phase 3 study.

"At the Casey Eye Institute, we have treated six patients with voretigene neparvovec as of August 2019," said Dr. Pennesi. "Of these, five were bilateral cases, with the patient ages ranging from 4 to 33 years." One example case is a 13-year-old male, who was diagnosed as a child with early-onset severe retinal dystrophy and in whom later genetic testing confirmed bi-allelic *RPE65* mutations. Before surgery, the patient presented with

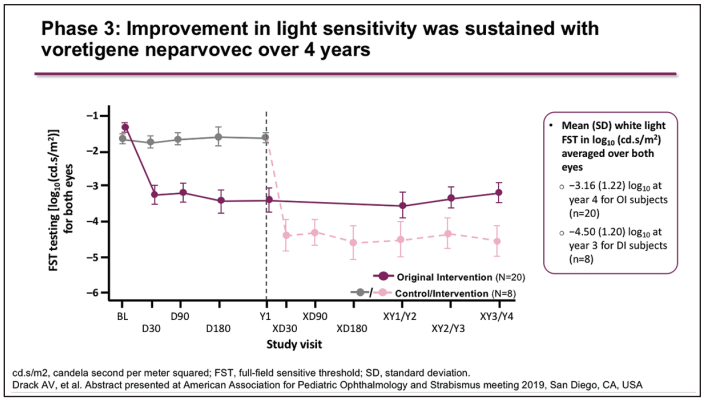


Figure 4. Change in light sensitivity up to 4 years in the phase 3 study.

BCVA of 20/400 in both eyes. Three months after treatment with voretigene neparvovec in both eyes, his VA had improved to 20/150 in the right eye and 20/200 in the left eye. FST with blue stimulus (more selective for rods) showed a one-log fold improvement in sensitivity, while FST with red stimulus (more selective for cones) showed an approximate half-log improvement. Similar results were seen with dark-adapted perimetry, which revealed a profound increase in sensitivity to blue light and a smaller, but still notable, improvement in sensitivity to red light. Improvements occurred in the approximate area that injection had taken place.

Patient Selection: Informing Diagnosis Through Relevant Testing

Bart P. Leroy, MD, PHD

IRDs are a clinically and genetically heterogeneous group of conditions.[10] Over 300 genes have been identified as being responsible for causing IRDs, defects in which can result in a wide, overlapping spectrum of conditions, including congenital night blindness, cone dysfunction syndromes, and retinitis pigmentosa.[11] These clinical phenotypes can each be caused by a number of different mutations.[12] For example, 24 genes are currently known to be involved in Leber congenital amaurosis and early onset retinal dystrophy, including *RPE65*.[13] With the advent of gene therapies specific to an individual gene or even an individual mutation,[14,15] the classification of IRDs is now moving away from a definition based on the clinical condition towards a diagnosis being based on the specific underlying gene mutation. "Gene therapy is gene specific, and there's no margin for error, so we need to know that what we are doing is right," said Dr. Leroy.

For this reason, genotyping is crucial in any patient suspected to have an IRD. Currently, the nature of the patient referral pathway means that it can take a number of years for a patient with an IRD to reach a super-specialist center where they can receive a definitive molecular diagnosis of their condition. "Ophthalmologists have a duty to recognize such disease and then not delay sending a patient for review by a specialist. Information-sharing and effective interactions between clinicians and specialists are essential," said Dr. Leroy. To help streamline the patient referral process and improve the coordination of care for patients with rare eye diseases, the European Reference Network for Rare Eye Disease (ERN-EYE), a network of 29 health care providers in 13 European Union member states, has been created. The aim of ERN-EYE is to ensure patients receive an accurate and timely diagnosis, high-quality care, access to innovation, and the opportunity to be involved in clinical trials.[16] Within ERN-EYE, rare eye disease experts integrate with their European peers and form collaborations with patient groups in order to contribute to improving patient care for individuals with IRDs. A European Union initiative, such ERNs exist for multiple types of rare diseases.

In an ocular genetics evaluation for a patient with a suspected IRD, it's important to ask the right questions about the nature of the visual complaints and the time of onset of symptoms, using language the that patient can understand. The evaluation will also entail the drawing of a pedigree, and the clinical diagnosis should be supported with specialized imaging, psychophysics, and electrophysiology (sometimes termed 'deep phenotyping'). Finally, and importantly, the diagnosis must be confirmed with molecular testing. "Often this type of detailed evaluation is not possible in a busy retinal practice, so please do refer your patients to a specialist," said Dr. Leroy.

Techniques for detecting mutations have evolved within the past decade from testing for known mutations using Sanger sequencing to next generation sequencing in which the whole exome is read in a high-throughput process (Figure 5).[17] Targeted gene testing is still performed today, but now uses panels of genes that capture exons of multiple IRD genes. This is a highly sensitive technique, which is also flexible, easy, and cost-effective.[18] With whole exome sequencing, the entire exome of an individual can be sequenced to identify causative mutations, with one

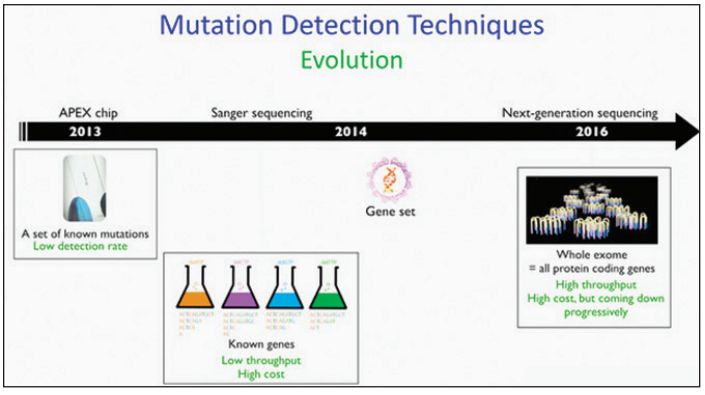
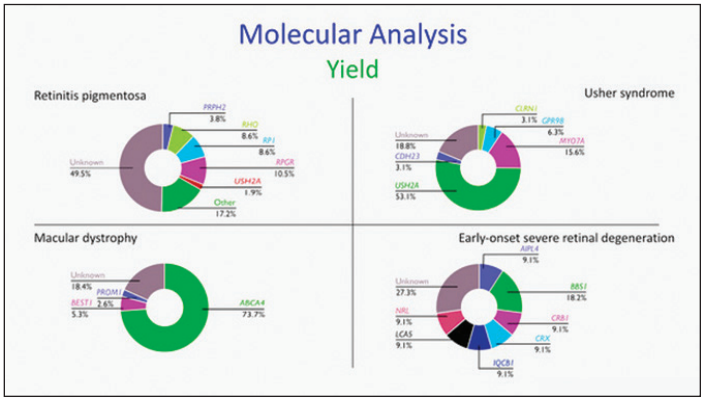


Figure 5. Evolution of mutation detection techniques.

Images provided courtesy of Caroline Van Cauwenbergh, PhD.

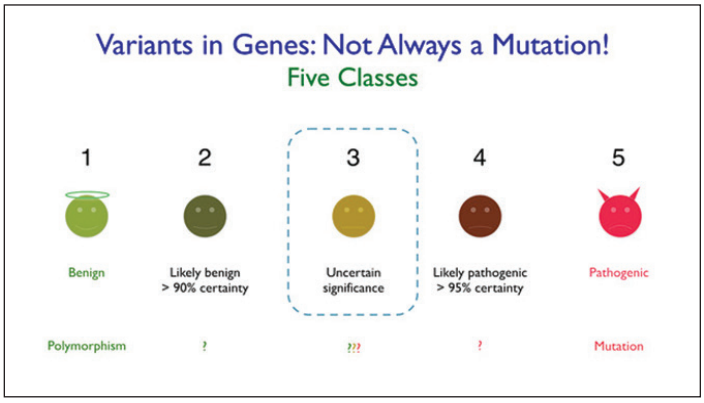


Images provided courtesy of Caroline Van Cauwenbergh, PhD.

Figure 6. Genetic variants identified in IRDs.

such sequencing procedure revealing up to 100,000 variants. Comparative genome hybridization can also be performed, which allows the detection of copy number variations.[19] However, molecular analysis alone fails to identify a causative gene in about 40% of patients, with the proportion of patients having an unsolved outcome varying between conditions (Figure 6).

Genetic variation used to be classified as either a polymorphism (implying a change with no disease-bearing importance) or a disease-causing mutation. In 2015, the American College of Medical Genetics last updated the definition for clinical significance of any given sequence variant, which actually falls somewhere along a gradient from pathogenic to benign, and they recommended the use of specific standard terminology: 'pathogenic,' 'likely pathogenic,' 'uncertain significance,' 'likely benign,' and 'benign' (Figure 7).[20] "It often takes a lot of work to determine how a variant should be classified, with treatment only possible for patients with pathogenic or likely pathogenic variants," said Dr. Leroy.



Images provided courtesy of Caroline Van Cauwenbergh, PhD.

Figure 7. American Society for Molecular Genetics classification of sequence variants.

In the case of autosomal recessive disease, which requires two mutations (one on each allele), genetic testing of the patient's parents (or if not available, their siblings or children) is vital. This is in order to unequivocally confirm that the two mutations reside on different alleles (i.e. recessive disease) rather than the two changes being carried on the same allele, which would mean that the gene was not the basis of the disease.

> "Ophthalmologists have a duty to recognize such disease and then not delay sending a patient for review by a specialist. Information-sharing and effective interactions between clinicians and specialists are essential."
>
> – Bart P. Leroy, MD, PhD

Genotyping is required to confirm eligibility for treatment with voretigene neparvovec as this gene therapy is only indicated for adult and pediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed bi-allelic *RPE65* mutations.[21] It is also necessary for the patient to have sufficient viable retinal cells. In practice, this is determined by the IRD specialist checking for the presence of outer retinal cells on SD-OCT and the presence of at least light perception upon visual testing. Some additional measurement of visual function, such as FST, is also desirable.

Retinal Gene Therapy in Clinical Practice: Perspectives From an Expert Center

José-Alain Sahel, MD

Following the approval of voretigene neparvovec for *RPE65*-related retinal dystrophy, gene therapy for IRDs is becoming a reality. "However, it's very important to realize that you cannot start treatment from scratch," said Dr. José-Alain Sahel. "Patients eligible for this treatment have been identified throughout many years of work, identification of the gene, identification of a pattern in the family history, and very deep phenotyping to identify how many cells are still viable and the status of the retina. Treatment centers must be able to handle that, and they must also have very skilled surgeons. Even with the best gene therapy, the result may be compromised if surgery is not performed as well as it can possibly be."

Treatment centers for voretigene neparvovec must fulfill a number of risk management plan criteria. The presence of an ophthalmologist with expertise in care and treatment of patients with IRDs is required, as is the presence of, or affiliation with, a retinal surgeon experienced in subretinal surgery and capable of administrating voretigene neparvovec. Finally, there must be a clinical pharmacy capable of handling and preparing AAV vector-based gene therapy products.[21]

In one such expert center, Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts in Paris, treatment with voretigene neparvovec has been ongoing since December 2018 under a temporary authorization of use. Up until September 2019, nine patients have been treated with the gene therapy. Surgical posterior vitreous detachment, subretinal injection, and air fluid exchange were performed according to the recommended surgical procedure (Figures 8 and 9). Oral prednisolone was given before and after surgery. Topical postoperative treatment was the same as any retinal surgery.

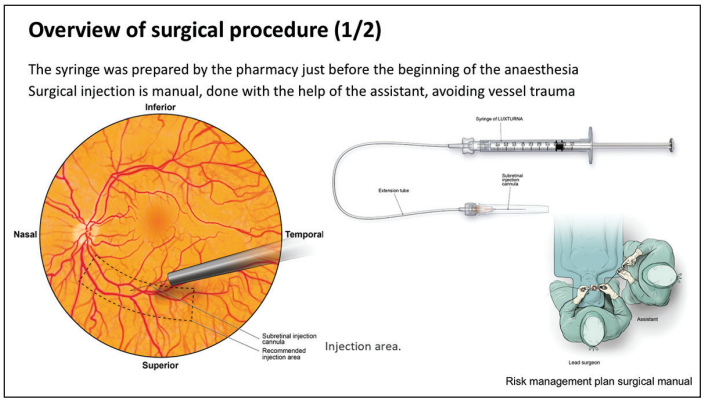


Figure 8. Surgical procedure (one of two).

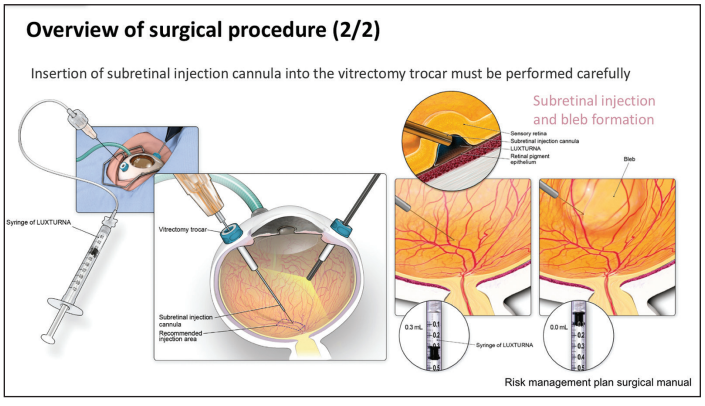


Figure 9. Surgical procedure (two of two).

"Key aspects to note in this procedure are that placement of the injection cannula has to be extremely careful to avoid any damage to the macula," said Dr. Sahel. "Also, we have experienced a level of unpredictability as to where the bleb is going to form. The surgeon has to make sure that the bleb eventually reaches the macula. Very careful fluid exchange can ensure that the bleb progressively moves beneath the macula, but it mustn't be forced as this risks damaging the photoreceptors."

The first two patients treated with voretigene neparvovec at Centre Hospitalier National d'Ophtalmologie des Quinze-Vingts were sisters who presented with Leber congenital amaurosis at the age of 10 (sister A) and 8 (sister B) years. Both sisters had

> "Patients eligible for this treatment have been identified throughout many years of work, identification of the gene, identification of a pattern in the family history, and very deep phenotyping to identify how many cells are still viable and the status of the retina. Treatment centers must be able to handle that, and they must also have very skilled surgeons."
>
> – José-Alain Sahel, MD

bi-allelic mutations of *RPE65* causing low vision, nystagmus, photophobia, hemeralopia, and night blindness. The sisters received the treatment between December 2018 and February 2019 in both eyes with a 1-week interval between eyes.

Sister A had baseline VA of 20/200 in the right eye and 20/320 in the left eye. At 6 months after treatment, this had improved to 20/125 in the right eye and 20/250 in the left eye. Goldmann visual field testing showed some improvement, while FST results showed dramatic improvements from around -4 dB at baseline in both eyes to approximately -31 dB at 6 months (Figure 10).

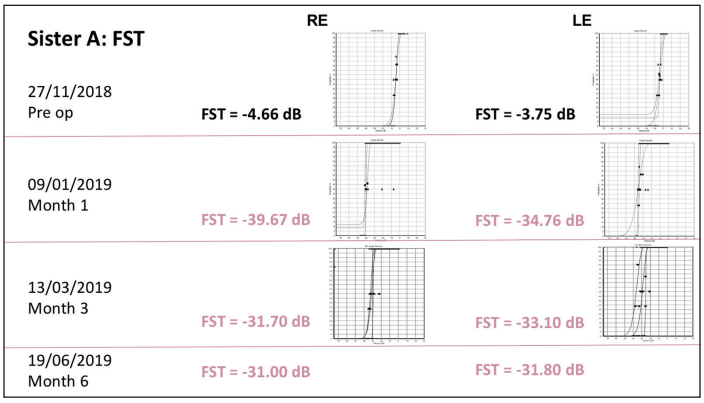


Figure 10. FST results in sister A.

Like her sibling, sister B had baseline VA of 20/200 in the right eye and 20/320 in the left eye. At 3 months after treatment, this had improved to 20/125 in the right eye and remained stable in the left eye. Improvements were again seen on Goldmann visual field testing and FST testing.

Since functional improvements achieved with voretigene neparvovec are not fully reflected by changes in BCVA, outcome measures are required that can quantify improvements in dark-adapted vision. "We have developed a platform called Streetlab, which allows us to monitor in detail the impact of low vision," said

Dr. Sahel. "The setting looks like a street, with eight randomized courses and four levels of light (2, 7.5, 50, and 500 lux). Patients are instructed to follow a delimited path while avoiding touching obstacles such as a hose, a bin, or a letterbox." The patients' movements are recorded to provide data on parameters such as course completion time, number of collisions, and preferred walking speed. In addition, patients report on their feelings about the lighting (e.g. comfortable, annoying, unbearable). Up until September 2019, seven of the nine patients treated with voretigene neparvovec had completed at least a baseline and one post-treatment visit following a prespecified protocol (Figure 11).

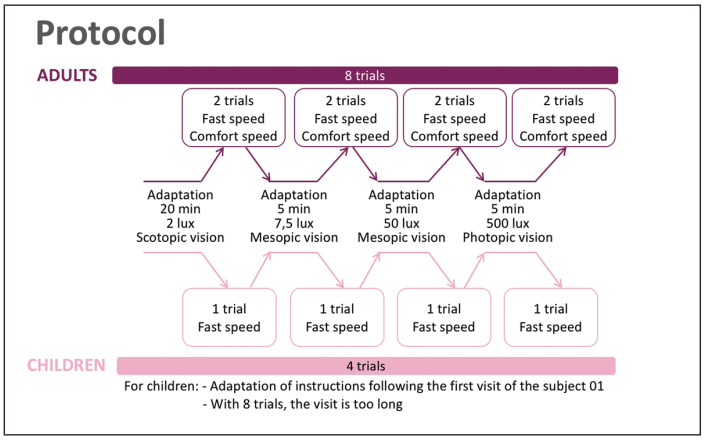


Figure 11. Streetlab study protocol.

Initial results show that course completion time and collision number at 2 lux and 7.5 lux decreased significantly following treatment in both adults and children. At 50 lux, course completion time decreased significantly after treatment when the analysis included adults (fast speed) and children, and collision number decreased significantly when the analysis included only adults (fast and comfort speed). At 500 lux, course completion time decreased significantly after treatment when the analysis included adults (fast speed) and children. Future analyses will study the correlation between visual data (VA, visual function, and FST) and mobility data.

Safety results observed to date have been in line with those from the phase 3 study,[6] with no product-related serious adverse events and no deleterious immune responses. Going forward, a post-authorization registry-based safety study will evaluate the long-term safety profile of voretigene neparvovec for 5 years post-administration in a real-world setting. ■

In collaboration with I. Audo, S. Mohand-Said, P.O. Barale, G. Bouters, C. Devisme, C. Pagot, and the teams from the National Reference Center REFERET and STREETLAB.

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Conclusion

Bart P. Leroy, MD, PHD

Although there are many ophthalmic conditions with a genetic cause, there are also numerous ongoing studies of gene therapies for IRDs. The first of these agents to receive regulatory approval was voretigene neparvovec, and learnings from the clinical trial program of voretigene neparvovec are expected to inform future development of ocular gene therapies in broader patient groups.

In the clinical management of individuals with IRDs, improvements in the identification and diagnosis of patients are needed. Options are available to IRD patients beyond gene therapy, such as prenatal or preimplantation genetic diagnosis, but in each case the identification of the causative gene is required. Referral of all IRD patients to an IRD super-specialist is therefore advisable, so that the molecular diagnosis can be confirmed and treatment provided, if available. Indeed, early clinical experience with voretigene neparvovec has demonstrated the importance of expert treatment specialist centers to provide an optimum standard of care for patients with IRDs. These experiences are applicable to the development of future ocular gene therapies.

"To conclude, voretigene neparvovec is a truly life-changing treatment which improves visual function and retinal sensitivity, which in turn improves the patient's ability to perform activities of daily living," said Dr. Leroy. "The first patients have been treated successfully in several countries. Moving forward, positive collaborations between the referring clinician and the IRD super-specialist will be required for this ground-breaking treatment to be implemented most effectively."

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