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Sponsor

Spark Therapeutics (US MAH)

Generic Drug Name

voretigene neparvovec

Trial Indication(s)

Inherited Retinal Dystrophy Due to RPE65 Mutations; Leber Congenital Amaurosis

Protocol Number

AAV2-hRPE65v2-301 (CLTW888A12301)

Protocol Title

A Safety and Efficacy Study in Subjects with Leber Congenital Amaurosis (LCA) Using Adeno-Associated Viral Vector to Deliver the Gene for Human RPE65 to the Retinal Pigment Epithelium (RPE)

Clinical Trial Phase

Phase III

Phase of Drug Development

Phase III

Study Start/End Dates

15-Nov-2012 to 16-Jul-2015 cutoff for presented results

Reason for Termination

Not applicable.

Study Design/Methodology

This was a Phase 3 open label, randomized controlled trial of gene therapy intervention by subretinal administration of AAV2-hRPE65v2. At least twenty-seven subjects, three years of age or older, were to be recruited at either The Children's Hospital of Philadelphia or University of Iowa to provide for complete data in at least twenty-four subjects. Subjects randomized to the Intervention group (n ≥ 16) were to receive non-simultaneous injections of 1.5E11 vector genomes (vg) AAV2-hRPE65v2 to each eye; sequential subretinal injections were to occur within an eighteen-day period. Subjects randomized to the Control group (n ≥ 8) were not to receive AAV2-hRPE65v2 for a period of at least one year from Baseline evaluation. Following retinal and visual function analysis, including mobility testing, at one year's time, subjects in the Control group were to receive non-simultaneous injections of 1.5E11 vg AAV2-hRPE65v2 to each eye (also within eighteen days), provided they still met all study eligibility criteria.

Centers

2 centers in 1 country: United States (2)

Objectives:

Primary objective(s)

Primary Objective: The primary objective was to determine whether non-simultaneous, bilateral subretinal administration of AAV2-hRPE65v2 improves the ability to navigate (as measured by standardized mobility testing) in adults and children with LCA due to RPE65 mutations, three years of age or older.

Secondary objective(s)

Secondary efficacy endpoints included full-field light sensitivity threshold (FST) testing and visual acuity (VA) testing. Additional efficacy endpoints included pupillary light reflex (PLR) testing, independent orientation and mobility assessments, and other evaluations/measurements of visual and retinal function including a visual function questionnaire, visual field testing (Humphrey and/or Goldmann), and contrast sensitivity.

Test Product (s), Dose(s), and Mode(s) of Administration

AAV2/2.CMV.CβA.hRPE65: Adeno-associated viral type 2 vector with cytomegalovirus (CMV) enhancer, chicken beta actin (CβA) promoter driving expression of human retinal pigment epithelium 65 kDa protein (RPE65) gene with an optimized Kozak sequence.

Statistical Methods

Full statistical methodology was developed in a formal statistical analysis plan. Subjects were randomized to either the Intervention or the Control group stratified by Screening age category (≥ 10 years or < 10 years) and Screening mobility testing passing level (≥ 125 lux or < 125 lux) in a 2:1 ratio of Intervention to Control. Within each age and mobility testing stratum, randomized blocks

governed the allocation to treatment group. Descriptive statistics were to be tabulated for the study population. Subject disposition, demographic and baseline characteristics, extent of exposure, and information on study termination and withdrawal were to be summarized and presented by the means, standard deviation (SD) or standard error (SE), and ranges for continuous variables, as well as by counts and percentages for categorical variables. The efficacy analyses included all randomized subjects (intent to treat, or ITT, population). The safety analyses (adverse event data and labs) included all subjects who received injection for the Intervention group, and all Control subjects who did not withdraw prior to Baseline.

Primary efficacy endpoint analyses: The primary efficacy endpoint was the mobility test change score. Specifically, the study was to measure the ability of vector administration to increase visual function, as evidenced by an increase relative to controls in mean mobility test change score at one year after Baseline. The analysis was to use a non-parametric permutation test based on a Wilcoxon Rank-Sum as the observed test statistic and an exact method for the corresponding p-value. Additional analyses were performed with the modified ITT (mITT) and per protocol (PP) populations. Additional sensitivity analyses were performed to determine the robustness of the results of the primary analysis.

Second efficacy endpoint analyses: The secondary efficacy endpoints of FST and visual acuity were to be analyzed based on longitudinal repeated measures models that provided estimates of the difference between Baseline and Year 1 between the two treatment groups. For the monocular mobility testing, analyses were to use models analogous to the model described for the primary outcome. The secondary outcomes were only to be formally tested statistically if the primary outcome was statistically significant; testing of the secondary outcomes was to be performed using a hierarchical ordering.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Willingness to adhere to protocol and long-term follow-up as evidenced by written informed consent or parental permission and subject assent (where applicable).
- Diagnosis of LCA due to RPE65 mutations; molecular diagnosis is to be performed, or confirmed, by a CLIA-approved laboratory.
- Age three years old or older.
- Visual acuity worse than 20/60 (both eyes) and/or visual field less than 20 degrees in any meridian as measured by a III4e isopter or equivalent (both eyes).
- Sufficient viable retinal cells as determined by non-invasive means, such as optical coherence tomography (OCT) and/or ophthalmoscopy. Must have either: 1) an area of retina within the posterior pole of >100 μm thickness shown on OCT; 2) ≥ 3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole; or 3) remaining visual field within 30 degrees of fixation as measured by a III4e isopter or equivalent.

- Subjects must be evaluable on mobility testing (the primary efficacy endpoint) to be eligible for the study. Evaluable is defined as: 1) The ability to perform mobility testing within the luminance range evaluated in the study. Individuals must receive an accuracy score of ≤ 1 during screening mobility testing at 400 lux or less to be eligible; individuals with an accuracy score of > 1 on all screening mobility test runs at 400 lux, or those who refuse to perform mobility testing at screening, will be excluded. 2) The inability to pass mobility testing at 1 lux. Individuals must fail screening mobility testing at 1 lux to be eligible; individuals that pass one or more screening mobility test runs at 1 lux will be excluded.

Exclusion Criteria:

- Unable or unwilling to meet requirements of the study, including receiving bilateral subretinal vector administrations.
- Any prior participation in a study in which a gene therapy vector was administered.
- Participation in a clinical study with an investigational drug in the past six months.
- Use of retinoid compounds or precursors that could potentially interact with the biochemical activity of the RPE65 enzyme; individuals who discontinue use of these compounds for 18 months may become eligible.
- Prior intraocular surgery within six months.
- Known sensitivity to medications planned for use in the peri-operative period.
- Pre-existing eye conditions or complicating systemic diseases that would preclude the planned surgery or interfere with the interpretation of study. Complicating systemic diseases would include those in which the disease itself, or the treatment for the disease, can alter ocular function. Examples are malignancies whose treatment could affect central nervous system function (for example: radiation treatment of the orbit; leukemia with CNS/optic nerve involvement). Subjects with diabetes or sickle cell disease would be excluded if they had any manifestation of advanced retinopathy (e.g., macular edema or proliferative changes). Also excluded would be subjects with immunodeficiency (acquired or congenital) as there could be susceptibility to opportunistic infection (such as CMV retinitis).
- Individuals of childbearing potential who are pregnant or unwilling to use effective contraception for four months following vector administration.
- Individuals incapable of performing mobility testing (the primary efficacy endpoint) for reason other than poor vision, including physical or attentional limitations.
- Any other condition that would not allow the potential subject to complete follow-up examinations during the course of the study or, in the opinion of the investigator, makes the potential subject unsuitable for the study.
- Subjects will not be excluded based on their gender, race, or ethnicity.

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Participant Flow Table

Disposition of Subjects (ITT)

Category, n (%)	Intervention (N = 21)	Control (N = 10)	Total (N = 31)
Randomized	21 (100%)	10 (100%)	31 (100%)
Injected in both eyes	20 (95%)	N/A	20 (65%)
Injected in one eye only	0	N/A	0
Completed one-year assessment	20 (95%)	9 (90%)	29 (94%)
Death	0	0	0
Discontinued early	1 (5%)	1 (10%)	2 (6%)
Pre-any intervention	1 (5%)	1 (10%)	2 (6%)
Post-any intervention	0	0	0
Reason for discontinuing early			
Physician decision	1 (5%)	0	1 (3%)
Withdrawal by subject	0	1 (10%)	1 (3%)

Column header counts and denominators are subjects in the ITT population.

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Baseline Characteristics

Demography (ITT)

Parameter/Category/Statistic	Intervention (N = 21)	Control (N = 10)	Total (N = 31)
Age at Randomization (years)			
N	21	10	31
Mean (SD)	14.7 (11.8)	15.9 (9.5)	15.1 (10.9)
Range (min, max)	4, 44	4, 31	4, 44
Quartiles (25th, median, 75th)	6, 11, 18	9, 14, 24	6, 11, 20
Male, n (%)	9 (43%)	4 (40%)	13 (42%)
Race, n (%)			
White	14 (67%)	7 (70%)	21 (68%)
Asian	3 (14%)	2 (20%)	5 (16%)
American Indian or Alaska Native	2 (10%)	1 (10%)	3 (10%)
Black or African American	2 (10%)	0	2 (6%)
Ethnicity, n (%)			
Not Hispanic or Latino	16 (76%)	9 (90%)	25 (81%)
Hispanic or Latino	5 (24%)	1 (10%)	6 (19%)
Country, n (%)			
United States	17 (81%)	6 (60%)	23 (74%)
Netherlands	1 (5%)	2 (20%)	3 (10%)
Belgium	0	1 (10%)	1 (3%)
Canada	1 (5%)	0	1 (3%)
India	1 (5%)	0	1 (3%)
Italy	0	1 (10%)	1 (3%)
Mexico	1 (5%)	0	1 (3%)

Column header counts and denominators are subjects in the ITT population.

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Primary Outcome Result(s)

Bilateral Mobility Testing Change Score, Year 1 Compared to Baseline (ITT)

MT Change Score	Intervention (N = 21)	Control (N = 10)	Difference (95% CI) (Intervention-Control)	Observed *p*-value	Permutation Test *p*-value
Mean (SD)	1.8 (1.1)	0.2 (1.0)	1.6 (0.72, 2.41)	0.001	0.001
Range (min, max)	0, 4	-1, 2			
Quartiles (25th, median, 75th)	1, 2, 3	-1, 0, 1			

Column header counts are subjects in the ITT population. The observed two-sided *p*-value is from a Wilcoxon rank-sum test using an exact method. The permutation test *p*-value was computed from all possible permutations.

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Secondary Outcome Results

Full-Field Light Sensitivity Threshold (FST), First Eye Mobility Test Score, and Visual Acuity

Outcome/Parameter	Intervention (N = 21)			Control (N = 10)			Difference (95% CI) (Intervention-Control)	*p*-value
	Baseline	Year 1	Change	Baseline	Year 1	Change		
Full-field light sensitivity testing: white light [Log10(cd.s/m^2)] [a]								
N	20	20	19	9	9	9		
Mean (SE)	-1.29 (0.09)	-3.36 (0.28)	-2.08 (0.29)	-1.65 (0.14)	-1.61 (0.42)	0.04 (0.44)	-2.11 (-3.19, -1.04)	< 0.001
First eye: lux score [b]								
N	21	21	21	10	10	10		
Mean (SD)	2.2 (1.8)	4.1 (2.7)	1.9 (1.2)	2.4 (1.5)	2.6 (1.7)	0.2 (0.6)	1.7 (0.89, 2.52)	0.001
Visual acuity (LogMAR) [a]								
N	21	20	20	10	9	9		
Mean (SE)	1.18 (0.14)	1.03 (0.17)	-0.16 (0.07)	1.29 (0.21)	1.30 (0.25)	0.01 (0.10)	-0.16 (-0.41, 0.08)	0.17

Column header counts are subjects in the ITT population. *P*-values are presented based on their hierarchical order.

a. All measures are averaged over both eyes and then analyzed. Changes, 95% confidence intervals, and *p*-values were estimated using a repeated measures model with time, treatment, and time by treatment interaction as specified in the SAP.

b. Baseline and Year 1 present means of the lowest passing lux levels for the first eye. The *p*-value is from a permutation test.

Safety Results

Summary of Treatment Emergent Adverse Events (Safety)

Category	Intervention (N = 20)	Control (N = 9)	Overall (N = 29)
Subjects with at Least One TEAE	20 (100%)	9 (100%)	29 (100%)
Subjects with any Study Drug Related TEAE	0	NA	0
Subjects with any Administration Procedure Related TEAE	13 (65%)	NA	13 (65%)
Subjects with any Serious TEAE	2 (10%)	0	2 (7%)
Subjects Discontinued Study Due to TEAE	0	0	0
Deaths	0	0	0

NA, not applicable; TEAE, treatment-emergent adverse event.

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Summary of Treatment-Emergent Adverse Events Reported in More than One Subject (Safety)

MedDRA System Organ Class/ Preferred Term, n (%)	Intervention (N = 20)			Control (N = 9)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
ANY EVENT	4 (20%)	13 (65%)	3 (15%)	5 (56%)	4 (44%)	0
INFECTIONS AND INFESTATIONS	5 (25%)	6 (30%)	0	4 (44%)	0	0
Nasopharyngitis	3 (15%)	4 (20%)	0	2 (22%)	0	0
Upper respiratory tract infection	1 (5%)	1 (5%)	0	3 (33%)	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4 (20)	6 (30%)	0	5 (56%)	0	0
Oropharyngeal pain	2 (10%)	4 (20%)	0	4 (44%)	0	0
Cough	3 (15%)	3 (15%)	0	1 (11%)	0	0
Epistaxis	1 (5%)	1 (5%)	0	0	0	0
Nasal congestion	1 (5%)	1 (5%)	0	0	0	0
GASTROINTESTINAL DISORDERS	7 (35%)	3 (15%)	2 (10%)	3 (33%)	0	0
Vomiting	5 (25%)	1 (5%)	2 (10%)	2 (22%)	0	0
Nausea	4 (20%)	0	2 (10%)	1 (11%)	0	0
Diarrhoea	0	2 (10%)	0	1 (11%)	0	0
Abdominal pain upper	1 (5%)	1 (5%)	0	0	0	0
NERVOUS SYSTEM DISORDERS	4 (20%)	5 (25%)	1 (5%)	2 (22%)	1 (11%)	0
Headache	3 (15%)	4 (20%)	0	1 (11%)	1 (11%)	0
EYE DISORDERS	7 (35%)	3 (15%)	0	1 (11%)	0	0
Cataract	3 (15%)	0	0	0	0	0
Eye inflammation	2 (10%)	0	0	0	0	0
Retinal tear	1 (5%)	1 (5%)	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (10%)	6 (30%)	2 (10%)	1 (11%)	0	0
Pyrexia	0	7 (35%)	0	1 (11%)	0	0
Adverse drug reaction	0	0	2 (10%)	0	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	8 (40%)	1 (5%)	0	0	0	0
Leukocytosis	8 (40%)	1 (5%)	0	0	0	0
INVESTIGATIONS	7 (35%)	0	0	1 (11%)	0	0

MedDRA System Organ Class/ Preferred Term, n (%)	Intervention (N = 20)			Control (N = 9)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Intraocular pressure increased	4 (20%)	0	0	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2 (10%)	3 (15%)	0	2 (22%)	0	0
Animal bite	1 (5%)	1 (5%)	0	0	0	0
RENAL AND URINARY DISORDERS	3 (15%)	0	0	1 (11%)	0	0
Haematuria	3 (15)	0	0	1 (11%)	0	0
VASCULAR DISORDERS	1 (5%)	0	0	1 (11%)	0	0
Hypertension	1 (5%)	0	0	1 (11%)	0	0

For SOC, N (%) includes any subject with an AE in that SOC; listed PTs only include those experienced by more than one subject overall.

Summary of Treatment-Emergent Serious Adverse Events (Safety)

MedDRA System Organ Class/ Preferred Term, n (%)	Intervention (N = 20)	Control (N = 9)	Overall (N = 29)
Subjects with at Least One SAE	2 (10%)	0	2 (7%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (10%)	0	2 (7%)
Adverse drug reaction	2 (10%)	0	2 (7%)
NERVOUS SYSTEM DISORDERS	1 (5%)	0	1 (3%)
Convulsion	1 (5%)	0	1 (3%)

No deaths were reported in this study

Conclusion:

Subretinal injection of AAV2-hRPE65v2 was safe and well-tolerated. The retinal and visual function changes observed through one year following bilateral administration of AAV2-hRPE65v2 suggest durable improvements in visual performance. These improvements contrast with the progressive nature of inherited retinal degenerative conditions in which subjects face an inexorable deterioration of retinal and visual function, which progresses until no useful vision remains.

Date of Clinical Trial Report

13 December 2016 (as amended by CSR AMENDMENT 003, EU, dated 12 June 2017)

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Marketing Authorization Rest of World
Novartis Pharmaceuticals

Swiss Authorization date and authorization number
Swissmedic Approval Number: 67371

Swissmedic Approval Date 14.02.2020

Novartis Study Code

CLTW888A12301

EudraCT Number

2016-002109-20

Planned and Actual Number of Patients
Planned: ≥ 27 (Intervention ≥ 18; Control ≥ 9)
Actual: 31 (Intervention = 21; Control = 10)

Batch Numbers
The AAV2-hRPE65v2 used was Lot 142-07001 (DOM: 03-Jan-2007).

Information on comparators drug dosage, route of administration, batch numbers
Control group subjects who did not receive AAV2-hRPE65v2 for a period of at least one year from Baseline evaluation.

Publication(s)

1 RUSSELL, S., BENNETT, J., WELLMAN, J. A., et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. Lancet. 2017 Aug 26;390(10097):849-860.[1]

2 CHUNG, D. C., RUSSELL, S. & BENNETT, J. Correlation of multi-luminance mobility testing with visual function tests in a phase 3 trial of voretigene neparvovec for biallelic RPE65-mediated inherited retinal disease. Presented at: The Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting, May 7-11 2017 Baltimore, MD

3 CHUNG, D.C., HIGH, K.A., RUSSELL, S. et al. Correlation between multi-luminance mobility testing and visual function tests in a Phase 3 trial of voretigene neparvovec for biallelic RPE65-mediated inherited retinal disease. Presented at 13th Asia-Pacific Vitreo-retina Society (APVRS) Congress, November 22–24, 2019, Shanghai, China.

4 CHUNG, D. C., DRACK, A. V., BENNETT, J. et al. Four-year results of a phase 3 voretigene neparvovec trial in biallelic RPE65-associated inherited retinal disease. 13th Asia-Pacific Vitreo-retina Society (APVRS) Congress, November 22–24, 2019, Shanghai, China.

5 DRACK, A. V., BENNETT, J., RUSSELL, S., et al. How long does gene therapy last? 4-year follow-up of phase 3 voretigene neparvovec trial in RPE65-associated LCA/inherited retinal disease. JAAPOS, August 2019 Volume 23, Issue4, Page e7.

6 HALLER, J., RUSSELL, R. LEROY, B.P. et al. PO225 Cone-Mediated Outcomes in the Voretigene Neparvovec Phase 3 Trial. American Academy of Ophthalmology 2018 Scientific Sessions, October 27–30, 2018, Chicago, Illinois.

7 HALLER, J., RUSSELL, S., MAHAJAN, V. B., et al. Change in Legal Blindness Status During the Phase 3 Voretigene Neparvovec-rzyl Study in Biallelic RPE65 Mutation–Associated Inherited Retinal Disease. Presented at Macula Society Annual Meetings, 2019 Bonita Springs, FL, US.

8 HUI, D. J., CHEN, Y., ANTRILLI, T., et al. Safety study by validated immunoassays in a phase III study of subjects with inherited retinal dystrophy due to mutations in the gene encoding human retinal pigment epithelium-specific protein 65 (RPE65) injected with adeno-associated viral vectors. Molecular Therapy, 2016 May, Vol.24 Suppl 1, pp.S72-S73.

[1] Erratum : In this Article (published Online First on July 13, 2017), the affiliation for Francesca Simonelli should have been Eye Clinic, Multidisciplinary Department of Medical, Surgical and Dental Sciences, University of Campania Luigi Vanvitelli, Naples, Italy. This correction has been made to the online version as of Aug 24, 2017, and the printed version is correct.

9 LEROY, B. P., MAGUIRE, A. M., RUSSELL, S. R., et al. Phase 3 efficacy and safety study of voretigene neparvovec (AAV2-HRPE65V2) in subjects with RPE65-mediated inherited retinal dystrophy. Ophthalmologica, 2016, Vol.236 Suppl 1, pp.2-2

10 LEROY, B. P., HALLER, J., CHUNG, D. C., et al. A. Year 1 time to mobility test completion in a voretigene neparvovec trial in subjects with RPE65 mutation–associated inherited retinal disease. 18th EURETINA Congress, 20–23 September 2018 Vienna, Austria.

11 LEROY, B. P., RUSSELL, S., WELLMAN, J., et al. Year 3 Results and Age-Stratified Analyses for a Phase 3 Trial of Voretigene Neparvovec in RPE65 Mutation–Associated Inherited Retinal Disease. 18th EURETINA Congress, 20–23 September 2018 Vienna, Austria.

12 LEROY, B., DRACK, A., BENNETT, J., et al. Duration of effect of ocular gene therapy: 4 year follow-up data from the phase III voretigene neparvovec trial in patients with biallelic RPE65 mutation associated retinal dystrophy. Encore presentation at the 19th EURETINA Congress 5-8 September 2019 Paris, France.

13 LEROY B.P., RUSSELL, S., MAGUIRE, A.M., et al. Vision-dependent Activities of Daily Living After Ocular Gene Therapy: Visual Function Questionnaire Responses in the Voretigene Neparvovec Phase 3 Trial. 19th EURETINA Congress, 5-8 September 2019 Paris, France.

14 MAGUIRE, A. M., BENNETT, J., WELLMAN, J. A., et al. Phase 3 trial update of voretigene neparvovec in biallelic RPE65 mutation-associated inherited retinal disease [oral presentation]. Presented at: The American Academy of Ophthalmology (AAO) Annual Meeting, November 10-14, 2017; New Orleans, Louisiana.

15 MAGUIRE, A., RUSSELL, S., LEROY, B.P. et al. PA074 - Visual Acuity Outcomes in the Voretigene Neparvovec-rzyl Phase 3 Trial. American Academy of Ophthalmology annual meeting; 2018 27-30 October; Chicago, US. 2018.

16 MAGUIRE, A. M., RUSSELL, S., WELLMAN, J. A., et al. Efficacy, Safety, and Durability of Voretigene Neparvovec-rzyl in RPE65 Mutation–Associated Inherited Retinal Dystrophy: Results of Phase 1 and 3 Trials. Ophthalmology. 2019 Sep;126(9):1273-1285.

17 MAHAJAN, V.B., BENNETT, J., MAGUIRE, A. PO220 RPE65 Mutation Subtype Effect on Baseline Visual Function and Treatment Response in Phase 3 Voretigene Neparvovec Trial. American Academy of Ophthalmology Annual Meeting, October 27–30, 2018, McCormick Place, Chicago, IL.

18 RUSSELL, S., BENNETT, J. & WELLMAN, J. Year 2 results for a phase 3 trial of voretigene neparvovec in biallelic RPE65-mediated inherited retinal disease. Investigative Ophthalmology & Visual Science, 2017 Jun, Vol.58(8).

19 RUSSELL, A., BENNETT J., WELLMAN, J. et al. Three-year update for the phase 3 voretigene neparvovec study in biallelic RPE65 mutation-associated inherited retinal disease. Investigative Ophthalmology & Visual Science, 2018 Jul, Vol.59(9).

20 RUSSELL, S., MAGUIRE, A.M., BENNETT, J. Visual Function Questionnaire Responses in the Voretigene Neparvovec Phase 3 Trial. Presented at: ARVO 2019 Annual Meeting, April 28-May 2, 2019, Vancouver, BC.

Investigators & Information on Study Centers

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